A step towards

personalized care for psoriasis

Celine I.M. Busard

A step towards personalized care for psoriasis

Celine Ingrid Michelle Busard

A step towards personalized care for psoriasis patients
PhD thesis, University of Amsterdam, Amsterdam, the Netherlands

Author: Celine I.M. Busard
Cover design: Evelien Jagtman
Layout: Yasmin Katlich, Persoonlijk Proefschrift
Printed by: Ridderprint

Financial support for printing this thesis was supported by: BAP Medical bv, Eurocept Homecare, Galderma Benelux bv, Huidstichting Chanfleury van Ijsselsteijn, LEO Pharma bv, La Roche-Posay, Mylan bv, Olmed, Pfizer, Psoriasispatiënten Nederland, UCB Pharma bv, Van der Bend bv

A step towards personalized care for psoriasis

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 27 januari 2021, te 11.00 uur

door Celine Ingrid Michelle Busard
geboren te Nijmegen

Promotiecommissie

Promotor:

Prof. dr. P.I. Spuls	AMC-UvA

Copromotor:

Dr. B.A. Hutten	AMC-UvA

Overige leden:

Prof. dr. M.A. de Rie	AMC-UvA
Prof. dr. D.L.P. Baeten	AMC-UvA
Prof. dr. H.J.C. de Vries	AMC-UvA
Dr. M.W. Langendam	AMC-UvA
Prof. dr. T. Rustemeyer	Vrije Universiteit Amsterdam
Dr. D.M.W. Balak	LangeLand Ziekenhuis
Dr. L.L.A. Lecluse	Bergman Clinics

Faculteit der Geneeskunde

Table of contents

CHAPTER 1

General introduction and outline of the thesis

Psoriasis

Psoriasis is a complex multifactorial condition related to a combination of genetic, environmental and immunological factors which was first described as a specific clinical entity around 1809. Although initially mixed up with leprosy, "lepra" was eliminated from the clinical description of psoriasis in 1841, separating it from leprosy for all time.

The disease affects around 1.3-2.2% of the world population. Prevalence rates vary according to geographic region, from 0.91% (United States) to 8.5% (Norway), being more frequent in countries more distant from the equator.[1]

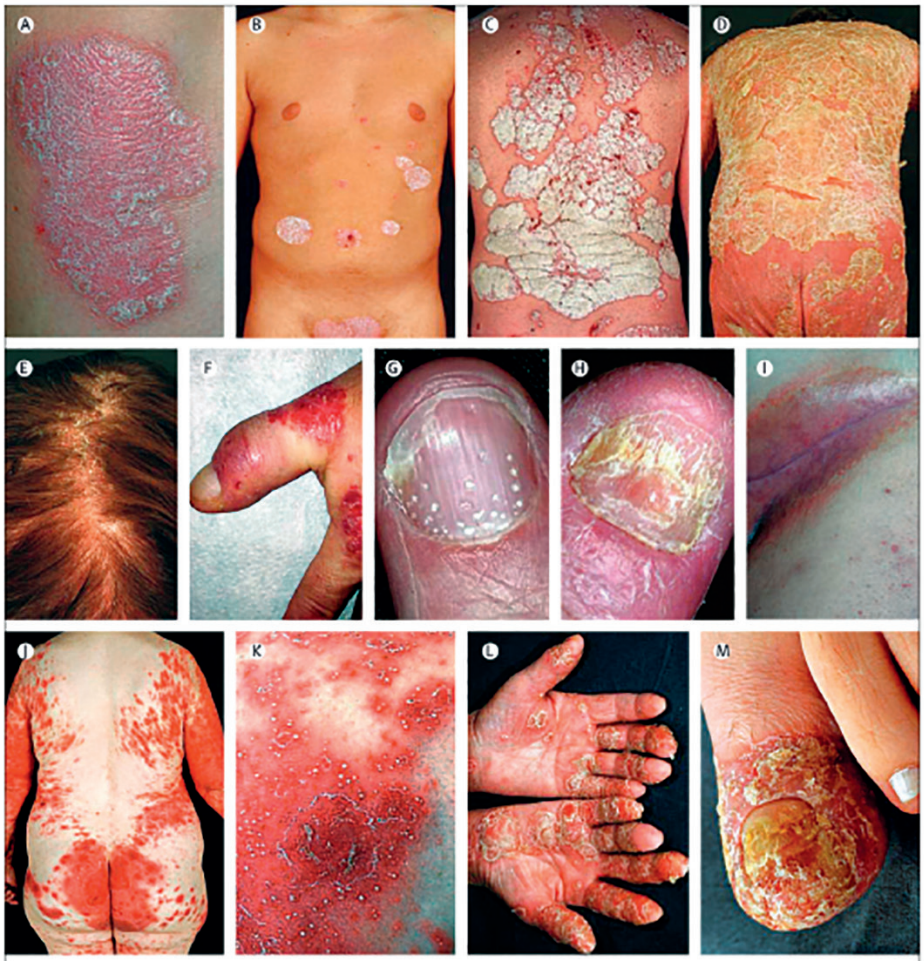
Morphological manifestations are heterogeneous, with clearly defined clinical subtypes including chronic plaque psoriasis, guttate psoriasis, and generalized or localized (pustular) psoriasis. Chronic plaque type is most common (85-90%). Clinical features include well-demarcated, symmetrical erythematous plaques with adherent silvery scale. Common affected sites include the scalp, elbows, knees, nails and the pre-sacral area of the back. Disease severity can range from a single plaque to involvement of more than 90% of the skin surface. There are no validated diagnostic criteria for psoriasis.[2]

Psoriasis can cause a significant burden on quality of life. Many patients experience physical complaints and restrictions in daily life activities. Approximately two-thirds of patients with psoriasis report itching and flaking, and skin pain is reported by up to 45% of patients.[3] Studies also demonstrate that psoriasis related skin symptoms are associated with sleep disturbance and can have a negative impact on patients ability to work.[4] Unemployment has been reported to occur in up to 40% of psoriasis patients, which represents a significant social-economic problem.[5]

Involvement of the immune system in psoriasis is now widely accepted.[2] Genome-wide scans for psoriasis-associated genes have identified predominantly immune related genes, providing a mechanistic link between genetics and immunity. The functional mechanism by which disease associated alleles confer susceptibility to psoriasis is unknown. However, expression of HLA-Cw6 on antigen-presenting cells enables a potential regulatory role of the innate and adaptive immune system, which may contribute to the immune dysregulation in psoriasis.[6]

Psoriatic skin lesions originate as a result of dysregulated interactions of innate and adaptive components of the immune system with resident cutaneous cell types.[2, 6, 7] Innate immune cells induce a pro-inflammatory cytokine cascade. Interferon alpha released from plasmacytoid dendritic cells is a crucial cytokine in the initiation phase of psoriasis. Myeloid dendritic cells are key immune system sentinels that drive the adaptive immune response in psoriasis.

Figure 1. Clinical manifestations of psoriasis



Plaque-psoriasis (A-C), erythrodermic psoriasis (D), psoriasis of the scalp (E), psoriatic arthritis (F), nail changes psoriasis (G-H), psoriasis inversa (I), generalized pustular psoriasis (J-K), localized pustular psoriasis (L-M).

Their numbers are increased in psoriatic plaques and can induce auto-proliferation of T-cells when activated. Activated myeloid dendritic cells function as antigen-presenting cells and secrete cytokine mediators including interleukin (IL)-12 and IL-23 which drive differentiation of T-cells into Type 1 and Type 17 T-helper cells respectively. These pathways lead to keratinocyte proliferation and production of pro-inflammatory cytokines (IL-1, IL-6, tumour necrosis factor (TNF) alpha), chemokines and anti-microbial peptides. A positive feedback loop exists to attract other innate and adaptive immune cells and further potentiate the inflammatory

process. The inflammatory cascade also activates mediators of angiogenesis, and induces endothelial adhesion molecules that stimulate further migration of immune cells into psoriasis lesions.

Psoriasis can be induced or exacerbated by trauma (Koebner phenomenon), streptococcal pharyngitis, stress and drugs including lithium, beta-blockers, chloroquine, and non-steroidal anti-inflammatory drugs.[6] Besides, paradoxical psoriasis has been described e.g. when treating patients for rheumatoid arthritis or inflammatory bowel diseases with anti-TNFα blockers.[8] Moreover, evidence suggests smoking as an independent risk factor for the development of psoriasis.[9] Environmental triggers are probably most relevant in patients with a genetic predisposition to developing psoriasis.

Patients with psoriasis have a higher risk to develop other (comorbid) diseases compared to the general population. Comorbid diseases such as psoriatic arthritis, Crohn's disease and metabolic syndrome contribute substantially to morbidity and mortality in patients with psoriasis.[10] A genetic basis of these diseases might (partly) explain the association between psoriasis and these comorbid diseases.[11]

Treatment for moderate to severe plaque psoriasis

Due to its chronic character, psoriasis often requires long-term therapy. Treatment objectives have historically evolved from the reduction of symptoms and disease severity to more stringent outcomes incorporating patients functional level and overall well-being.[12] Regarding choice of therapy, it is important to match patient expectations and practical considerations.[13, 14] Non-adherence has been shown to occur when patient's preferences, expectations and beliefs have not been considered sufficiently in the prescribing process.[15]

Other factors that are taken into account in clinical decision making include disease related factors (disease severity, previous treatments, body location, involvement of nails and/or joints), patient characteristics (age, comorbidity, pregnancy), treatment aspects (e.g. mode and frequency of administration, screening and monitoring and treatment costs). Generally, a step up approach is used with the prescription of the least toxic, but also least potent, drugs for mild disease and stronger immunosuppressant therapy for moderate to severe and therapy resistant disease.[16]

Topical agents are the cornerstone of psoriasis treatment.[17] They are available in many strengths and formulations. Topical treatment alone is generally not sufficient if the area affected by psoriasis reaches 10-15% of the body surface.[18] In this case, patients depend upon phototherapy, systemic therapy or combination therapy to achieve and sustain disease remission. Historically, systemic treatments for psoriasis included methotrexate, ciclosporin, fumaric acid and the oral retinoid acitretin.[19]

Although these systemic agents may be effective for many patients, long-term treatment can be limited by insufficient effectiveness, safety concerns, or both.

In the quest for more effective and safer treatments, the identification of specific pro-inflammatory cytokines that are involved in the pathogenesis of psoriasis has resulted in the development of innovative targeted biologic therapies.[20]

Biologics are usually expensive and therefore in many countries criteria are developed that patients need to fulfil to get approved for reimbursement of these therapies.[21] Since their introduction in 2005, many biologics have been registered for the treatment of plaque-psoriasis such as: TNF antagonists adalimumab, certolizumab pegol, infliximab, golimumab and etanercept, IL-17 inhibitors secukinumab, brodalumab and ixekizumab, IL-12/23 inhibitor ustekinumab and the IL-23 inhibitors guselkumab and tildrakizumab. To facilitate cost-effective use of health resources 'biosimilars' have been introduced for some of the biologics.[22] They are not identical, but have essentially the same biological substance, though there may be minor differences due to their complex nature and production methods.[23] Compared to conventional systemic agents, biologics have several advantages. The action of biologics is highly specific, as such, they have less potential to exert non-target toxicity. Moreover, biologic therapies are generally more effective than conventional systemic agents. The introduction of biologics has revolutionized the treatment of psoriasis with achievement of treatment goals (Psoriasis Area and Severity Index (PASI) 90, remission) that are not usually met with conventional systemics.[24] Finally, dosing is less frequent with biologic therapy compared to conventional systemic due to differences in elimination half-lives, promoting compliance to patients who need long-term therapy.[25]

Another novel systemic agent for the treatment of plaque psoriasis includes the small molecule orally administered phosphodiesterase 4 inhibitor apremilast.[26, 27]
With the introduction of immunological based therapies, psoriasis management greatly advanced with considerable improvements on disease severity and quality of life.[20, 28, 29] However, some patients still fail to achieve desired outcomes (defined as primary non-responders) or fail to maintain efficacy improvements over time (defined as secondary non-responders).[19]

Combination treatment

Several strategies have been proposed to overcome and prevent primary or secondary non-response in patients treated with biologic agents. These include dose escalations, switch to another systemic agent with different mechanisms of action or addition of a second systemic agent or phototherapy.[30-32] Combination of two systemic agents is suggested to be beneficial due to enhanced efficacy, acceleration of onset of disease remission and the potential to reduce the dose

of individual agents, thereby decreasing toxicity and improving tolerability and compliance. There are reasons to believe that specific combinations, the addition of methotrexate (MTX) to a biological, can reduce immunogenicity and promote increased drug concentrations with subsequent maintained improvements in clinical response over time.[25, 33, 34] On the other hand, combination therapy may lead to enhanced immune suppression which can theoretically increase the risk of more severe side effects compared to monotherapy.[19]

Immunogenicity, pharmacokinetics and pharmacogenetics of biologic therapy

A treatment to which all patients respond adequately or a reliable test that predicts individual response to treatment, is not yet available. Identification of biomarkers which allow for personalized treatment algorithms would support long-term effective treatment. Several pharmacogenetic studies using single nucleotide polymorphisms (e.g. HLA-Cw6) to predict treatment response have been performed but the clinical implications of these investigations remain uncertain.[35]

Another concept that has been investigated to help tailor individualized treatment algorithms includes therapeutic drug monitoring.[36] Currently, standardized dosing and interval schedules are the base of biologic therapies. With these fixed-dosing regimens, a wide variety in clinical response and serum drug concentrations have been observed in several observational cohorts, with significantly higher serum drug concentrations in good responders compared with non and moderate responders in adalimumab and infliximab treated patients.[37] Analogous to recent findings in rheumatoid arthritis RA, this possibly implies that

a substantial part of psoriatic patients are under- or overtreated.[37, 38] Overtreatment with biologics results in a substantial waste of healthcare resources and a potential higher risk on toxicity and safety concerns while under treatment results in poor clinical response. A therapeutic algorithm based on monitoring serum drug concentrations tailored to patients individual needs may have the potential to improve health care from both a clinical and cost-effectiveness perspective.

Formation of anti-drug antibodies that interfere with the biological agent's binding activity (neutralizing antibodies) have been identified as an important factor contributing to lower serum concentrations and inefficacy of biologic agents [39]. The extent to which it is clinically relevant to monitor the formation of anti-drug antibodies has not yet been established for drugs such as ustekinumab.

Management of patients with nail psoriasis

Nail psoriasis is estimated to be present in 50 to 80% of patients with plaque psoriasis and can be associated with substantial restrictions in daily life activities.[40] Treatment can be challenging due to limited penetration through the nail plate and slow regeneration of the nail.[41] Moreover, patients with nail psoriasis are often undertreated.[42] Fortunately, scientific interest in the field of nail psoriasis has increased over the last couple of years and important new data on (systemic and combined) nail psoriasis interventions have emerged. In 2013, de Vries *et al.* published a Cochrane systematic review on nail psoriasis interventions.[43] Although a comprehensive overview of available nail psoriasis treatment options could be provided, data synthesis was limited due to substantial heterogeneity in outcome measurement instruments.

Based on the anatomical structure of the nail that is affected, different morphological changes can be detected. Nail matrix psoriasis is characterized by nail plate changes of pitting, leukonychia, red spots in the lunula and nail plate crumbling. Nail bed psoriasis shows onycholysis, oil-drop dyschromia, splinter haemorrhages and subungual hyperkeratosis. The most common nail sign in psoriasis is pitting, which affects approximately 68% of patients with psoriasis and nail changes.[44] Assessment of nail psoriasis severity is currently based on objective (physician-assessed; the presence or absence of morphological changes) and subjective (patient-assessed; e.g. pain) outcome measurement instruments, although recent advances in the field of imagining are generating growing interest in the use of ultrasound as a tool for diagnosis, prognosis, and treatment monitoring of nail psoriasis.[45]

The number of different outcome measurement instruments for nail psoriasis, including the Nail Psoriasis Severity Index (NAPSI),[46] has been expanding over the

past decades and so far standardization of outcome reporting in clinical trials on nail psoriasis is lacking.

In recent years, there has been a movement toward standardization of outcome reporting and the development of core outcome sets (COSs). A COS is defined as an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. Initiatives are ongoing to develop a COS for psoriasis and psoriatic arthritis in which nail psoriasis is incorporated. The International Dermatology Outcome Measures (IDEOM) group published an iterative Delphi process and identified nail psoriasis as an important outcome domain that should be strongly considered in psoriasis trials. However, it was not selected as one of the six core domains that are considered required to measure in every psoriasis clinical trial.[47] The Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) selected nail psoriasis (as part of the domain 'skin disease activity') to be measured in all randomized controlled trials and longitudinal observational studies.[48]

Standardization of outcome reporting is important to improve trial integrity and data interpretation and to ensure that only valid, reliable and relevant outcome measurement instruments are used. As currently no comprehensive overview of nail psoriasis outcome measurement instruments is available, the first step towards standardization of outcome reporting includes the identification of all instruments (previously) used in clinical trials.

Moreover, an update on available nail psoriasis interventions is desired because new treatment options (e.g. apremilast, ixekizumab) and an expanded number of trials on biologics became available since the Cochrane systematic review in 2013 was published. As clinical therapeutic decision are adjusted based on to the extent of dermal, articular and ungual psoriasis lesions it is helpful to know whether and which (combined) systemic interventions are effective and safe for treating nail psoriasis.

Outline of this thesis

Part I: Treating psoriasis with combinational therapies

In this part of the thesis we examine the evidence and extent of using combinational therapy with systemic agents. **Chapter 2** presents a comprehensive overview of all randomized controlled trials that have been undertaken to investigate systemic combination therapy. **Chapter 3** reports on the use and persistence of biologic combination treatment among different European countries. **Chapter 4** discusses the protocol of a randomized controlled trial that we conducted to determine the efficacy and safety of adalimumab and methotrexate combination treatment compared to adalimumab monotherapy. **Chapter 5** reports on the results of this trial.

Part II: Immunogenicity, pharmacokinetics and pharmacogenetics of biologic therapy
In this second part we seek for tests/biomarkers to help tailor individualised treatment algorithms by examining the role of serum concentrations, anti-drug-antibodies and HLA-Cw6 status in patients treated with ustekinumab (**Chapter 6**).

Part III: (Gaps in) the management of patients with nail psoriasis
In this final part, we aim to increase the knowledge on available evidence of nail psoriasis interventions, with a focus on systemic agents. **Chapter 7** introduces a first step towards harmonization of outcomes by providing an overview of outcome measurement instruments used in randomized controlled trials on nail psoriasis to measure clinically relevant outcome domains. **Chapter 8** presents available evidence for (mostly systemic) nail psoriasis interventions. In **Chapter 9** and **Chapter 10** the main findings of this thesis are summarized and discussed.

References

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification, Management of P, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85.
2. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983-94.
3. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014;70(5):871-81 e1-30.
4. Gupta MA, Simpson FC, Gupta AK. Psoriasis and sleep disorders: A systematic review. Sleep Med Rev. 2015;29:63-75.
5. Vanderpuye-Orgle J, Zhao Y, Lu J, Shrestha A, Sexton A, Seabury S, et al. Evaluating the economic burden of psoriasis in the United States. J Am Acad Dermatol. 2015;72(6):961-7 e5.
6. Alwan W, Nestle FO. Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine. Clin Exp Rheumatol. 2015;33(5 Suppl 93):S2-6.
7. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496-509.
8. Munera-Campos M, Ballesca F, Carrascosa JM. Paradoxical Reactions to Biologic Therapy in Psoriasis: A Review of the Literature. Actas Dermosifiliogr. 2018;109(9):791-800.
9. Armstrong AW, Armstrong EJ, Fuller EN, Sockolov ME, Voyles SV. Smoking and pathogenesis of psoriasis: a review of oxidative, inflammatory and genetic mechanisms. Br J Dermatol. 2011;165(6):1162-8.
10. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-71.
11. Gupta Y, Moller S, Zillikens D, Boehncke WH, Ibrahim SM, Ludwig RJ. Genetic control of psoriasis is relatively distinct from that of metabolic syndrome and coronary artery disease. Exp Dermatol. 2013;22(8):552-3.
12. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.
13. Meredith F, Ormerod AD. Patient preferences for psoriasis treatment: process characteristics considered more important than outcome attributes. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):145-7.
14. Umar N, Yamamoto S, Loerbroks A, Terris D. Elicitation and use of patients' preferences in the treatment of psoriasis: a systematic review. Acta Derm Venereol. 2012;92(4):341-6.

15. Augustin M, Holland B, Dartsch D, Langenbruch A, Radtke MA. Adherence in the treatment of psoriasis: a systematic review. Dermatology. 2011;222(4):363-74.

16. van der Kraaij GE, Balak DMW, Busard CI, van Cranenburgh OD, Chung Y, Driessen RJB, et al. Highlights of the updated Dutch evidence- and consensus-based guideline on psoriasis 2017. Br J Dermatol. 2019;180(1):31-42.

17. Mason A, Mason J, Cork M, Hancock H, Dooley G. Topical treatments for chronic plaque psoriasis: an abridged Cochrane systematic review. J Am Acad Dermatol. 2013;69(5):799-807.

18. Gardinal I, Ammoury A, Paul C. Moderate to severe psoriasis: from topical to biological treatment. J Eur Acad Dermatol Venereol. 2009;23(11):1324-6.

19. Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. Am J Clin Dermatol. 2014;15(6):467-78.

20. Chan AC, Carter PJ. Therapeutic antibodies for autoimmunity and inflammation. Nat Rev Immunol. 2010;10(5):301-16.

21. Rencz F, Kemeny L, Gajdacsi JZ, Owczarek W, Arenberger P, Tiplica GS, et al. Use of biologics for psoriasis in Central and Eastern European countries. J Eur Acad Dermatol Venereol. 2015;29(11):2222-30.

22. Isaacs JD, Cutolo M, Keystone EC, Park W, Braun J. Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody. J Intern Med. 2016;279(1):41-59.

23. Nast A, Rosumeck S, Seidenschnur K. Biosimilars: a systematic review of published and ongoing clinical trials of antipsoriatics in chronic inflammatory diseases. J Dtsch Dermatol Ges. 2015;13(4):294-300.

24. Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. J Invest Dermatol. 2015;135(11):2641-8.

25. Xu Z, Davis HM, Zhou H. Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety. J Clin Pharmacol. 2015;55 Suppl 3:S60-74.

26. Gadina M. Janus kinases: an ideal target for the treatment of autoimmune diseases. J Investig Dermatol Symp Proc. 2013;16(1):S70-2.

27. Yiu ZZ, Warren RB. Efficacy and safety of emerging immunotherapies in psoriasis. Immunotherapy. 2015;7(2):119-33.

28. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.

29. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov. 2010;9(4):325-38.

30. Lecluse LL, de Groot M, Bos JD, Spuls PI. Experience with biologics for psoriasis in daily practice: switching is worth a try. Br J Dermatol. 2009;161(4):948-51.

31. Moots RJ, Mays R, Stephens J, Tarallo M. Burden of dose escalation with tumour necrosis factor inhibitors in rheumatoid arthritis: a systematic review of frequency and costs. Clin Exp Rheumatol. 2015;33(5):737-45.

32. Brezinski EA, Armstrong AW. Off-label biologic regimens in psoriasis: a systematic review of efficacy and safety of dose escalation, reduction, and interrupted biologic therapy. PLoS One. 2012;7(4):e33486.

33. Vogelzang EH, Pouw MF, Nurmohamed M, Kneepkens EL, Rispens T, Wolbink GJ, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. Ann Rheum Dis. 2015;74(2):474-5.

34. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71(11):1914-5.

35. van Vugt LJ, van den Reek J, Hannink G, Coenen MJH, de Jong E. Association of HLA-C*06:02 Status With Differential Response to Ustekinumab in Patients With Psoriasis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019;155(6):708-15.

36. Wang YC, Wang J, Hon YY, Zhou L, Fang L, Ahn HY. Evaluating and Reporting the Immunogenicity Impacts for Biological Products-a Clinical Pharmacology Perspective. AAPS J. 2015.

37. Menting SP, Coussens E, Pouw MF, van den Reek JM, Temmerman L, Boonen H, et al. Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis: A Step Toward Personalized Treatment. JAMA Dermatol. 2015;151(6):616-22.

38. Dannepond C, Maruani A, Machet L, Ternant D, Paintaud G, Samimi M. Serum infliximab concentrations in psoriatic patients treated with infliximab: a systematic review. Acta Derm Venereol. 2015;95(4):401-6.

39. Hsu L, Armstrong AW. Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response. Expert Rev Clin Immunol. 2013;9(10):949-58.

40. Salomon J, Szepietowski JC, Proniewicz A. Psoriatic nails: a prospective clinical study. J Cutan Med Surg. 2003;7(4):317-21.

41. van der Velden HM, Klaassen KM, van de Kerkhof PC, Pasch MC. The impact of fingernail psoriasis on patients' health-related and disease-specific quality of life. Dermatology. 2014;229(2):76-82.

42. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail psoriasis: a questionnaire-based survey. Br J Dermatol. 2013;169(2):314-9.

43. de Vries AC, Bogaards NA, Hooft L, Velema M, Pasch M, Lebwohl M, et al. Interventions for nail psoriasis. The Cochrane database of systematic reviews. 2013(1):Cd007633.

44. Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. J Am Acad Dermatol. 2007;57(1):1-27.

45. Gutierrez-Manjarrez J, Gutierrez M, Bertolazzi C, Afaro-Rodriguez A, Pineda C. Ultrasound as a useful tool to integrate the clinical assessment of nail involvement in psoriatic arthritis. Reumatologia. 2018;56(1):42-4.

46. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49(2):206-12.

47. Callis Duffin K, Merola JF, Christensen R, Latella J, Garg A, Gottlieb AB, et al. Identifying a Core Domain Set to Assess Psoriasis in Clinical Trials. JAMA Dermatol. 2018;154(10):1137-44.

48. Leung YY, Ogdie A, Orbai AM, Tillett W, Coates LC, Strand V, et al. Classification and Outcome Measures for Psoriatic Arthritis. Front Med (Lausanne). 2018;5:246.

PART I

Treating psoriasis with combinational therapies

CHAPTER 2

Combined use of systemic agents for psoriasis

A systematic review

CIM Busard, J Zweegers, J Limpens, M Langendam, PI Spuls

JAMA Dermatol 2014 Nov;150(11):1213-20

Abstract

Importance: Combined use of systemic agents may be necessary to achieve disease control in therapy-resistant patients. However, to our knowledge, an overview of evidence, including quality assessments, is not yet available, and no guidance on monitoring, contraindications, and interactions exists.

Objective: To summarize and critically appraise the evidence on efficacy and safety of combination therapy with systemic agents in plaque-type psoriasis.

Evidence review: Through March 2013, an electronic search limited to randomized clinical trials was performed in MEDLINE, EMBASE, The Cochrane Library, and ongoing trial registers. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach.

Findings: The initial search retrieved 2583 records, of which 17 met the inclusion criteria. Most studies favoured combination therapy, albeit with low significance and low quality of evidence. Etanercept plus methotrexate was the only combination therapy investigated with an adequate sample size (n = 478). In the short term, this combination had superior efficacy with a moderate quality of evidence compared with etanercept monotherapy (Psoriasis Area and Severity Index, 75; relative risk, 1.28; 95% CI, 1.14-1.45). Although this finding coincided with an increase in adverse events (relative risk, 1.25; 95% CI, 1.10-1.42), the overall safety profile remained acceptable.

Conclusions and Relevance: This systematic review provides a comprehensive overview on the validity of different systemic combination therapies. For most combinations, insufficient evidence is available. Initial results indicate that combined therapy with etanercept plus methotrexate may be beneficial in patients that are therapy resistant under intensive follow-up. Dose reductions should be taken into account to minimize adverse effects.

Introduction

Combination therapy with systemic agents is used in clinical practice because it may enhance efficacy, accelerate the onset of remission, and reduce adverse effects (AEs) by permitting dose reductions. However, it may also induce more, unknown, and other AEs, and no guidance is available on monitoring, contraindications, and interactions. Although several systematic reviews[1-3] provide a summary of studies that report on combination therapy with systemic agents, no risk-of-bias assessments of the individual studies were provided. The National Clinical Guideline Centre performed quality assessments on combination therapy with retinoids and phototherapy, but no other combination therapies with systemic agents were analyzed.[4] Recommendations in clinical guidelines on combination therapy, if any, are frequently based on few randomized clinical trials (RCTs) or observational studies, case reports, and expert opinion.[5-8] We conducted a systematic review of RCTs on the efficacy and safety of combination therapy with systemic agents for plaque-type psoriasis. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[9]

Methods

Search method

A medical librarian (J.L.) performed a literature search to identify RCTs of combination therapy with systemic agents in plaque-type psoriasis. Through March 2013, MEDLINE (OVID, from 1948), EMBASE (OVID, from 1980), Cochrane Central Register of Controlled Trials (CENTRAL, from inception), PubMed (the publisher subset fraction, which contains publications ahead of print that are not yet included in OVID MEDLINE), and ongoing trial registers (http://clinicaltrials.gov/) were searched with no language restrictions. The latest update was March 2013. Animal studies were safely excluded by using double negation. The search strategies consisted of searching for the keywords psoriasis and combination therapy in Medical Subject Headings and titles and abstracts. In MEDLINE and EMBASE, the topic search was combined with a methodologic filter adapted from the Cochrane Central Register of Controlled Trials to identify RCTs and clinical controlled trials (eFigure in the Supplement details the entire MEDLINE search).[10,11] The search included an iterative process for each database to refine the search strategy through incorporation of new search terms as new relevant citations were identified (ie, by checking reference lists and citing articles using ISI Web of Science

[Thomson Reuters]). Reference Manager software, version 12.0 (Thomson Reuters), was used to deduplicate, store, and analyse the search results.

Selection criteria

The RCTs (N>10) that reported on the efficacy and safety of combination therapy with systemic agents compared with systemic monotherapy or another systemic combination therapy in plaque-type psoriasis were included. Studies that reported on other types of psoriasis, sequential or rotational therapies, and unclear (i.e., Chinese herbal) combination therapies and studies that reported on alefacept and efalizumab were excluded because these treatment modalities are no longer available. Furthermore, studies that report on phototherapy plus acitretin were excluded because, for this type of combination therapy, an overview of RCT evidence according to the GRADE approach already exists[4].

Study selection

Titles and abstracts from the electronic searches were screened, and full articles of all citations that met the predefined selection criteria were obtained. Subsequently, full articles were examined for inclusion or exclusion. Two reviewers (C.B. and J.Z.) independently performed the selection. Any disagreements were resolved by consensus or arbitration of a third reviewer (P.I.S.).

Data extraction

Information on study reference, year of publication, study design, number of patients, baseline disease severity, treatment regimen, duration of combination therapy, and follow-up were extracted. Critical and important outcomes were selected to assess the quality of evidence. Critical outcomes were defined as the proportion of patients who attained a Psoriasis Area and Severity Index (PASI) of 75, a PASI of 90, and a Physician Global Assessment (PGA) of clear or almost clear; withdrawal because of AEs; proportion of patients who experienced serious adverse events (SAEs); and mean change in Dermatology Life Quality Index (DLQI). Important outcomes were defined as number of withdrawals because of lack of efficacy, proportion of patients with AEs, mean change in PASI (0-72, 0-16, and 0-18), mean time to clearance, and mean time to relapse. Only results from intent-to-treat analysis were used if both intent-to-treat and per-protocol data were available. Efficacy outcomes were divided into 2 groups based on duration of combination therapy: 12 weeks or less or more than 12 weeks. The number of events and total number of participants in each group were used for extracting dichotomous variables. Means (SDs) were used for extracting continuous variables.

Assessment and Evaluation of the Quality of Evidence

The risk of bias in the individual studies was assessed in duplicate (C.B. and J.Z.) using the Cochrane Risk of Bias tool.[10] Accordingly, we graded sequence generation, allocation concealment, masking of caregivers and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias as low, unclear, or high risk of bias. Subsequently, an overall assessment for each RCT was conducted using the same three criteria. The quality of evidence for each outcome (body of evidence) was assessed according to the GRADE approach[9] by using the GRADE profiler software, version 3.2.2.[12]

Statistical Analysis

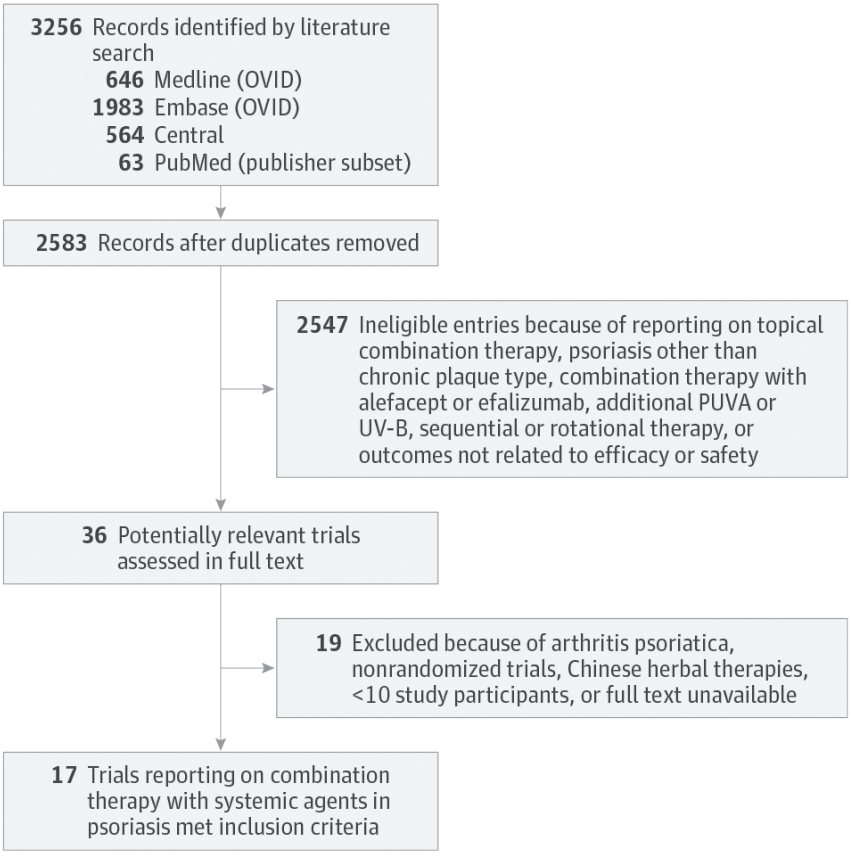
The threshold for statistical significance was set at P <0.05 for effect sizes. Mean difference and 95% CIs were calculated for continuous variables. An imputed correlation coefficient of0.70 was used to calculate the change-from-baseline SDs. The value of the correlation coefficient could not be imputed from another study and was therefore hypothesized.10 Relative risk or risk ratio (RR) with a 95% CI was used to calculate the effects for dichotomous outcomes. The optimal information size was calculated using an RR of 25% and assuming an α of .05 and a β of .2 if consideration of 95% CIs alone suggested a robust effect, but the total sample size and the number of events were small.[13] Meta-analysis to calculate a weighted treatment effect across trials and a funnel plot to detect publication and other reporting biases by plotting could not be performed because of a lack of more than one trial of the same comparison or absence of similar treatment regimens.

Results

Trial Characteristics

The initial search identified 2583 references to RCTs that investigated combination therapy with systemic agents for psoriasis. Thirty-six references were selected for full-text examination, and 17 RCTs with a total of 1071 participants (median, 71 participants; range, 10-478 participants) were included (Figure). The characteristics of the included studies and outcome measures used for analysis are listed in the Table.

Figure. Search Strategy and Retrieved Articles



Search and selection process for randomized clinical trials on the combined use of systemic agents for psoriasis. PUVA indicates psoralen–UV-A.

Table. Characteristics of included studies

Source, y	Study Design	No. of Patients	Baseline disease severity	Intervention	Control Group	Study Length, wk	Follow up, wk	Outcome Measures Used in Study Analysis Efficacy	Safety	Other
Phototherapy in Combination With Traditional Systemic Agents[a]										
Mahajan et al,[17] 2007	RCT, single-blind, ITT analysis	40	>10% of body surface involvement	UV-B, 3 times weekly and methtrexate, 0.5 mg/kg	Placebo and UV-B, 3 times weekly	24	12	PASI of 75, withdrawal because of lack of efficacy	Percentage of patients with AEs	Mean time to clearance or relapse
Asawanonda and Nateetongrungsak,[14] 2006	RCT, doble -blind, ITT analysis	24	>20% of body surface involvement	UV-B, 3 times weekly and methtrexate, 15 mg/wk	Placebo and UV-B, 3 times weekly	24	24	PASI of 90, mean change in PASI	Percentage of patients with AEs, withdrawal because of AEs	Median time to clearance or relapse, mean change in DLQI
Shehzad et al,[2] 2004	RCT, open-label, per protocol analysis	60	PASI > 10	PUVA, 4 treatments per week and methtrexate, 10 mg/wk	PUVA, 4 treatments per week and methotrexate, 10 mg/wk	32	NR	Mean change in PASI	NR	Mean time to clearance
Prystowsky et al,[23] 1996	RCT, patient-masked, per-protocol analysis	19	>20% of body surface involvement	UV-B, 4 treatments weekly and calcitriol, 0.5-2.0 µg/d	UV-B, 4 treatments weekly and placebo	5	NR	Mean change in PASI (scale, 0-16)	NR	NR

Table. Characteristics of included studies (continued)

Source, y	Study Design	No. of Patients	Baseline disease severity	Intervention	Control Group	Study Length, wk	Follow up, wk	Outcome Measures Used in Study Analysis		
								Efficacy	Safety	Other
Gupta et al,[24] 1989	RCT, double-blind, per-protocol analysis	20	10 – 50% of body surface involvement	UV-B, twice per week and 10 capsules of eicosapentaenoic acid daily	UV-B, twice per week and 10 capsules olive oil daily	8	NR	Mean change in PASI (scale, 0-18)	NR	NR
Phototherapy in Combination With Biologics										
Lynde et al,15 2012	RCT, investigator-masked, ITT-analysis	75	PASI > 10	UV-B, 3 times weekly and etanercept, 50 mg/wk	Etanercept, 50 mg/wk	12	NR	PASI of 75, PASI of 90, PGA of clear or almost clear, withdrawal because of lack of efficacy	Percentage of patients with SAEs	Mean change in DLQI
Park et al,[25] 2012	RCT, Open label, ITT-analysis	30	PASI > 10 and >10% of body surface involvement	UV-B, 3 times weekly and etanercept, 50 mg/wk	Etanercept, 50 mg/wk	12	NR	PASI of 75, PASI of 90, PGA of clear or almost clear, mean change in PASI	NR	NR
Wolf et al, [26] 2011	RCT, left-right, open-label, per-protocol analysis	10	PASI > 10	UV-B, 3 times weekly and ustekinumab, 45 or 90 mg at week 0 and 4	Ustekinumab, 45 or 90 mg once every 3 weeks	6	NR	PASI of 75, mean change in PASI	Percentage of patients with AEs, withdrawal because of AEs	NR

Table. Characteristics of included studies (continued)

Source, y	Study Design	No. of Patients	Baseline disease severity	Intervention	Control Group	Study Length, wk	Follow up, wk	Outcome Measures Used in Study Analysis		
								Efficacy	Safety	Other
Biologics in combination with traditional systemic agents										
Gottlieb et al,[16] 2012	RCT, double-blind, ITT-analysis	478	PASI > 10 and >10% of body surface involvement	Etanercept, 50 mg/wk and methtrexate, 7.5-15.0 mg/wk	Etanercept, 50 mg/wk and placebo	12	NR	PASI of 75, PASI of 90, PGA of clear or almost clear, withdrawal because of lack of efficacy	Percentage of patients with AEs and SAEs, withdrawal because of AEs	NR
Zachariae et al,[18] 2008	RCT, open label, ITT-analysis	60	PASI > 8 and >10% of body surface involvement	Etanercept, 50 mg twice weekly for 12 weeks, then 50 mg/wk and methtrexate, >7.5 mg/wk	Etanercept, 50 mg twice weekly for 12 weeks, then 50 mg/wk and methotrexate treatment discontinued at week 4	24	NR	PASI of 75, PASI of 90, PGA of clear or almost clear, mean change in PASI, withdrawal because of lack of efficacy	Percentage of patients with AEs and SAEs, withdrawal because of AEs	Mean change in DLQI
Gisondi et al,[19] 2008	RCT, investigator-masked, ITT-analysis	60	Clinicaly stable moderate to severe plaque-type psoriasis	Etanercept, 50 mg wk and acitretin, 0.4 mg kg daily	Etanercept, 50 mg/wk and acitretin, 0.4 mg/kg daily	24	NR	PASI of 75, withdrawal because of lack of efficacy	Percentage of patients with AEs	NR

Table. Characteristics of included studies (continued)

Source, y	Study Design	No. of Patients	Baseline disease severity	Intervention	Control Group	Study Length, wk	Follow up, wk	Outcome Measures Used in Study Analysis		
								Efficacy	Safety	Other
Combination of traditional systemic agents										
El-Mofty et al,[27] 2011b	RCT, unclear masking, ITT-analysis	16	>25% of body surface involvement	Sulfasalazine, 2 g/d and pentoxfylline, 1200 mg/d	Methotrexate, 25 mg/wk	8	NR	Mean change in PASI, withdrawal because of lack of efficacy	Percentage of patients with AEs	NR
Mittal et al,[20] 2009	RCT, doble-blind, ITT-analysis	41	>20% of body surface involvement	Acitretin, 25 mg/d and piogl-itazone hydrchloride, 15 mg/d	Acitretin, 25 mg/d and placebo	12	NR	PASI of 75, PGA of clear or almost clear, mean change in PASI, withdrawal because of lack of efficacy	Percentage of patients with AEs and SAEs, withdrawal because of AEs	NR
Gupta and Gupta,[28] 2007[c]	RCT, open label, per-protocol analysis	24	PASI > 10 and >10% of body surface involvement	Methtrexate, 15 mg/ wk and betameth-asone, 3mg/wk	Methotrexate, 15 mg/wk	NR	NR	NR	NR	Mean time to clearance, mean time to relapse
Ezquerra et al,[29] 2007	RCT, umasked, per-protocol analysis	40	PASI > 15 and < 40	Acitretin, 25 mg/d and calcitriol, 0.25 µg/d	Acitretin, 25 mg/d	12	NR	Mean change in PASI	Percentage of patients with AEs	NR
Reitamo et al,[21] 2001[b]	RCT, double-blind, ITT-analysis	33	PASI > 12	Sirolimus, 3.0 mg/d and cyclosporine, 1.25 mg/ kg daily	Sirolimus, 5 mg/kg daily	8	4	PASI of 75, mean change in PASI	Withdrawal because of AEs	NR

Table. Characteristics of included studies (continued)

Source, y	Study Design	No. of Patients	Baseline disease severity	Intervention	Control Group	Study Length, wk	Follow up, wk	Outcome Measures Used in Study Analysis		
								Efficacy	Safety	Other
Danno and Sugie,[30] 1998	RCT, unmasked, ITT analysis	40	Moderately involved, chronic plaque-type psoriasis	Etretinate, 20 mg/d and eicosapentaenoic acid, 1800 mg/d	Etretinate, 20 mg/d	12	NR	PASI of 75 (scale, 0-12)	Percentage of patients with AEs	Mean time to clearance

[a] Concomitant treatment with phototherapy and acitretin was excluded because, for this type of combination therapy, an overview of RCT evidence according to the GRADE approach already exists.
[b] Only the most clinically relevant comparisons are reported (sulfasalazine plus pentoxifylline vsmethotrexate monotherapy and sirolimus 3.0mg/m daily and cyclosporine, 1.25mg/kg daily vs sirolimus, 5mg/kg daily).
[c] Efficacy in terms of PASI outcomes were based on nonrandomized patients.

Quality of Evidence of the Included studies

Assessment of the risk of bias of the individual studies resulted in low risk for 3 trials [14-16] intermediate risk for 5 trials[17-21] and high risk for 9 trials[22-30]. Methodologic limitations were unclear allocation concealment (14 of 14 trials), inadequate or partial masking (14 of 14 trials), unclear baseline comparability (8 of 14 trials), unclear random sequence generation (5 of 14 trials), and per-protocol analysis (5 of 14 trials). The overall quality of evidence at outcome level ranged from moderate to very low because of risk of bias, insufficient sample size, small number of events, and wide 95% CIs (eTables 1-16 in the Supplement).

Effects of interventions

Duration of Systemic Combined Therapy 12 Weeks or Less

PASI of 75 | Nine trials[15,16,18-21,25,26,30] assessed the proportion of patients who attained a PASI of 75. Two of these trials[16,18] found statistically significant differences in favour of etanercept plus methotrexate with moderate quality of evidence (eTable 6 in the Supplement). Zachariae et al[18] found that 54.8% of patients in the etanercept plus methotrexate group attained a PASI of 75 compared with 25.0% in the etanercept plus methotrexate tapering group (methotrexate therapy discontinued at week 4) (RR, 2.19; 95% CI, 1.07-4.49). Gottlieb et al[16] found that 77.4% of patients in the etanercept plus methotrexate group attained a PASI of 75 compared with 60.3% in the etanercept plus placebo group (RR, 1.28; 95% CI, 1.14-1.45). A trial by Wolf et al[26] found statistically significant differences in favor of ustekinumab plus UV-B with very low quality of evidence. In patients treated with ustekinumab, 77.8% attained a PASI of 75 on UV-B–irradiated body halves compared with 11.1% on unirradiated body halves (RR, 7.0; 95% CI, 1.07-45.9) (eTable 5 in the Supplement).

PASI of 90 | Four trials[15,16,18,25] assessed the proportion of patients who attained a PASI of 90 or higher. The trial by Gottlieb et al[16] found a statistically significant difference, with 52.3% of patients in the etanercept plus methotrexate group attaining a PASI of 90 compared with 33.1% of patients in the etanercept plus placebo group (RR, 1.58; 95% CI, 1.27-1.97) (eTable 6 in the Supplement). Quality of evidence was moderate.

PGA of Clear or Almost Clear | Five trials[15,16,18,20,25] assessed the proportion of patients who attained a PGA of clear or almost clear. Two trials[16,18] found a statistically significant difference between treatment groups with moderate quality of evidence

in favor of etanercept plus methotrexate (eTable 6 in the Supplement). Gottlieb et al[16] found that 72.0% in the etanercept plus methotrexate group attained a PGA of clear or almost clear compared with 54.4% in the etanercept plus placebo group (RR, 1.32; 95% CI, 1.15-1.52), and Zachariae et al[18] found that 71.0% of patients in the etanercept plus methotrexate group attained a PGA of clear or almost clear compared with 39.3% in the etanercept plus methotrexate tapering group (RR, 1.81; 95% CI, 1.08-3.02).

Mean change in PASI | Nine trials[18,20,21,23-27,29] assessed the mean change in PASI from baseline. Three trials[26,27,29] had a statistically significant difference between treatment groups with very low quality of evidence. Wolf et al[26] found a mean change in PASI of 4.1 in favour of UV-B–irradiated body halves compared with UV-B–unirradiated body halves in patients treated with ustekinumab (eTable 5 in the Supplement), and Ezquerra et al[29] found a mean change in PASI of 4.6 in favor of acitretin plus calcitriol compared with acitretin monotherapy (eTable 13 in the Supplement). El-Mofty et al[27] found a mean change in PASI of 9.04 in favor of methotrexate monotherapy compared with sulfasalazine plus pentoxifylline (eTable 11 in the Supplement).

Time to Clearance | Two trials[24,30] assessed the mean time to clearance. Danno and Sugie[30] found a statistically significant difference of 2.5 weeks in favour of etretinate plus eicosapentaenoic acid (fish oil) compared with etretinate monotherapy (eTable 15 in the Supplement). Quality of evidence was very low.

Withdrawal Because of Lack of Efficacy | Four trials[15,16,20,27] assessed the proportion of patients who were withdrawn because of lack of efficacy. No statistically significant differences among treatment groups could be found, and quality of evidence was very low.

Mean Change in DLQI | A trial by Lynde et al[15] assessed the mean change in DLQI from baseline. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Duration of Systemic Combined Therapy Longer Than 12 Weeks

PASI 75 | Three trials[17-19] assessed the proportion of patients who attained a PASI of 75. Two trials found a statistically significant difference between treatment groups. Mahajan et al[17] found that 95% in the UV-B plus methotrexate group attained a PASI of 75 compared with 70% in the UV-B plus placebo group (RR, 1.36; 95% CI, 1.00-

1.84), with very low quality of evidence (eTable 1 in the Supplement). Zachariae et al[18] found that 71.0% of patients in the etanercept plus methotrexate group attained a PASI of 75 compared with 35.7% in the etanercept plus methotrexate tapering group (RR, 1.99; 95% CI, 1.15- 3.43), with moderate quality of evidence (eTable 6 in the Supplement).

PASI 90 | Two trials[14,18] 3 assessed the proportion of patients who attained a PASI of 90. A trial by Asawanonda and Nateetongrungsak[14] found a statistically significant difference between treatment groups, with 90.9% of patients in the UV-B plus methotrexate group attaining a PASI of 90 compared with 38.5% in the UV-B plus placebo group (RR, 2.36; 95% CI, 1.16-4.82) (eTable 1 in the Supplement). Quality of evidence was very low.

PGA of Clear or Almost Clear | A trial by Zachariae et al[18] 3 assessed the proportion of patients who attained a PGA of clear or almost clear and had a statistically significant difference, with 67.7% of patients in the etanercept plus methotrexate group compared with 35.7% in the etanercept plus methotrexate tapering group attaining a PGA of clear or almost clear (RR, 1.90; 95% CI, 1.09-3.30) (eTable 6 in the Supplement). Quality of evidence was very low.

Mean change in PASI | Three trials[14,17,18] assessed the mean change in PASI from baseline. Two trials found a statistically significant difference with very low quality of evidence. Zachariae et al[18] found a mean change in the PASI of 5.1 in favour of methotrexate plus etanercept compared with etanercept plus methotrexate tapering (eTable 6 in the Supplement), and Asawanonda and Nateetongrungsak[14] found a mean change in the PASI of 7.75 in favour of UV-B plus methotrexate compared with UV-B plus placebo (eTable 1 in the Supplement).

Time to Clearance | Four trials[14,17,22,28] assessed the mean or median time to clearance and found statistically significant differences between treatment groups, with very low quality of evidence. Gupta and Gupta[28] found a difference in time to clearance of 9.3 days in favor of methotrexate plus betamethasone compared with methotrexatemonotherapy (eTable 12 in the Supplement). Shehzad et al[22] found a difference in time to clearance in favor of psoralen–UV-A (PUVA) plus methotrexate of 3 weeks compared with PUVA monotherapy of 5.5 weeks compared with methotrexate monotherapy (eTables 2 and 3 in the Supplement). Asawanonda and Nateetongrungsak[14] found a time to clearance of 4 weeks for UV-B plus methotrexate compared with more than 24weeks for UV-B plus placebo, and Mahajan et al[17] found a difference in mean time of clearance of 6 weeks in

favour of UV-B plus methotrexate compared with UV-B plus placebo (eTable 1 in the Supplement).

Time to Relapse | Three trials[14,17,28] assessed the time to relapse. Gupta and Gupta[28] found a statistically significant difference of 53.24 days in favour of methotrexate plus betamethasone compared with methotrexate monotherapy, with very low quality of evidence (eTable 12 in the Supplement).

Withdrawal Because of Lack of Efficacy | Four trials[15,16,20,27] assessed the proportion of patients who were withdrawn because of lack of efficacy. No statistically significant differences among treatment groups could be found, and quality of evidence was very low.

Mean Change in DLQI | A trial by Lynde et al[15] assessed the mean change in DLQI from baseline. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Duration of Systemic Combined Therapy Longer Than 12 Weeks

PASI 75 | Three trials[17-19] assessed the proportion of patients who attained a PASI of 75. Two trials found a statistically significant difference between treatment groups. Mahajan et al[17] found that 95% in the UV-B plus methotrexate group attained a PASI of 75 compared with 70% in the UV-B plus placebo group (RR, 1.36; 95% CI, 1.00-1.84), with very low quality of evidence (eTable 1 in the Supplement). Zachariae et al[18] found that 71.0% of patients in the etanercept plus methotrexate group attained a PASI of 75 compared with 35.7% in the etanercept plus methotrexate tapering group (RR, 1.99; 95% CI, 1.15- 3.43), with moderate quality of evidence (eTable 6 in the Supplement).

PASI 90 | Two trials[14,18] 3 assessed the proportion of patients who attained a PASI of 90. A trial by Asawanonda and Nateetongrungsak[14] found a statistically significant difference between treatment groups, with 90.9% of patients in the UV-B plus methotrexate group attaining a PASI of 90 compared with 38.5% in the UV-B plus placebo group (RR, 2.36; 95% CI, 1.16-4.82) (eTable 1 in the Supplement). Quality of evidence was very low.

PGA of Clear or Almost Clear | A trial by Zachariae et al[18] 3 assessed the proportion of patients who attained a PGA of clear or almost clear and had a statistically significant difference, with 67.7% of patients in the etanercept plus methotrexate

group compared with 35.7% in the etanercept plus methotrexate tapering group attaining a PGA of clear or almost clear (RR, 1.90; 95% CI, 1.09-3.30) (eTable 6 in the Supplement). Quality of evidence was very low.

Mean change in PASI | Three trials[14,17,18] assessed the mean change in PASI from baseline. Two trials found a statistically significant difference with very low quality of evidence. Zachariae et al[18] found a mean change in the PASI of 5.1 in favour of methotrexate plus etanercept compared with etanercept plus methotrexate tapering (eTable 6 in the Supplement), and Asawanonda and Nateetongrungsak[14] found a mean change in the PASI of 7.75 in favour of UV-B plus methotrexate compared with UV-B plus placebo (eTable 1 in the Supplement).

Time to Clearance | Four trials[14,17,22,28] assessed the mean or median time to clearance and found statistically significant differences between treatment groups, with very low quality of evidence. Gupta and Gupta[28] found a difference in time to clearance of 9.3 days in favour of methotrexate plus betamethasone compared with methotrexate monotherapy (eTable 12 in the Supplement). Shehzad et al[22] found a difference in time to clearance in favour of psoralen–UV-A (PUVA) plus methotrexate of 3 weeks compared with PUVA monotherapy of 5.5 weeks compared with methotrexate monotherapy (eTables 2 and 3 in the Supplement). Asawanonda and Nateetongrungsak[14] found a time to clearance of 4 weeks for UV-B plus methotrexate compared with more than 24weeks for UV-B plus placebo, and Mahajan et al[17] found a difference in mean time of clearance of 6 weeks in favour of UV-B plus methotrexate compared with UV-B plus placebo (eTable 1 in the Supplement).

Time to Relapse | Three trials[14,17,28] assessed the time to relapse. Gupta and Gupta[28] found a statistically significant difference of 53.24 days in favour of methotrexate plus betamethasone compared with methotrexate monotherapy, with very low quality of evidence (eTable 12 in the Supplement).

Withdrawal Because of Lack of Efficacy | Three trials[17-19] assessed the proportion of patients who were withdrawn because of lack of efficacy. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Mean Change in DLQI | Two trials[14,18] assessed the mean change in DLQI from baseline. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Overall Summary Across Studies

Phototherapy in Combination with Traditional Systemic Agents
Small statistically significant differences in favour of UV-B plus methotrexate[14,17] and PUVA plus methotrexate[22] were found. For UV-B plus fish oil[24] and UV-B plus calcitriol[23] 7 no significant superiority was found. No major differences in safety profiles between treatment groups were found, and no SAEs were reported. Quality of evidence was very low for all outcomes in this section.

Phototherapy in Combination with Biologics
Small statistically significant differences in favour of UV-B plus ustekinumab were found. [26] For UV-B plus etanercept, no significant superiority was found.[15,25] No major differences in safety profiles between treatment groups were found. No SAEs were reported in the combination therapy groups compared with 3 SAEs in the monotherapy groups; all were considered to be unrelated to study treatment. Quality of evidence was very low for all outcomes in this section.

Biologics in combination with traditional systemic agents
Statistically significant differences in terms of efficacy in favour of etanercept plus methotrexate were found, with moderate quality of evidence.[16,18] However, this effect coincided with a statistically significant increase in AEs. In the etanercept plus methotrexate group, 74.9% of patients experienced AEs compared with 59.8% of patients in the etanercept plus placebo group (RR, 1.25; 95% CI, 1.10- 1.42). For infectious AEs, a statistically significant higher incidence was found in the combination therapy group compared with the group treated with etanercept plus placebo (34.7% vs 25.9%; RR, 1.34; 95% CI, 1.02-1.76)[16].

Most AEs were considered mild to moderate. Five SAEs were reported in the etanercept plus methotrexate groups compared with 8 SAEs in the control groups (etanercept plus placebo and etanercept plus methotrexate tapering).
Seven SAEs were considered to be related to study medication: 2 in the combination therapy groups (infection and vomiting) and 5 in the control groups (infections, pustular psoriasis, heart insufficiency, and atrial fibrillation).Quality of evidence for safety outcomes ranged from moderate (AEs) to very low (SAEs) (eTable 6 in the Supplement).

For etanercept plus acitretin compared with etanercept monotherapy, dose reductions without loss of efficacy were found with very low quality of evidence.[19] No major differences in safety profiles between these treatment groups were found, and no SAEs were reported.

Combination of traditional systemic agents
Small statistically significant differences in favour of acitretin plus calcitriol,[29] etretinate plus eicosapentaenoic acid,[30] and betamethasone plus methotrexate[28] were found. For acitretin plus pioglitazone hydrochloride[20] and sirolimus plus cyclosporine,[21] no significant superiority was found, although dose reductions were possible for sirolimus plus cyclosporine. Equal efficacy for sirolimus plus low dose cyclosporine (1.25 mg/kg) compared with cyclosporine monotherapy (5.0 mg/kg) was found.[21] Statistically significant lower efficacy was found for sulfasalazine plus pentoxifylline compared with methotrexate monotherapy.[27]
No major differences in safety profiles between treatment groups were found. One SAE was reported in the monotherapy groups [20] compared with no SAEs in the combination therapy groups. Quality of evidence was very low for all outcomes in this section.

Discussion

Several RCTs have been conducted in the field of combination therapy with systemic agents, but only one large-scale, methodologically well-designed clinical trial exists.[16] All combination therapies evaluated in this study had either superior or similar efficacy compared with control groups except for one study that had lower efficacy for sulfasalazine plus pentoxifylline compared with methotrexatemonotherapy.[27] The RCT conducted by Gottlieb et al[16] (moderate quality of evidence) contributes to the evidence of the superior efficacy of etanercept plus methotrexate over etanercept monotherapy in the short term, although this increased efficacy was accompanied by a higher incidence of AEs and, specifically, significantly more infectious AEs. The AEs were mild to moderate, and the incidence of SAEs was low and comparable in the treatment groups. For 6 other combination therapies with systemic agents, statistically significant superiority for some outcomes was found (very low quality of evidence mainly because of insufficient sample sizes). Some of these combination therapies could be valuable in high need patients, but more high-quality research is needed before recommendations for clinical practice can be made.

When comparing baseline characteristics of patients enrolled in RCTs of combination therapies [17-30] with baseline characteristics of patients enrolled in large-scale RCTs of single agents,[31-37] no to minor differences in disease severity, disease duration, or prior systemic therapies were found for most comparisons. However, in 5 combination therapy trials (PUVA plus methotrexate,[22] UV-B plus fish oil,[24] sulfasalazine plus pentoxifylline,[27] acitretin plus calcitriol,[29] and sirolimus plus cyclosporine[21]) patients with more severe and relatively more difficult-to-treat

psoriasis were included compared with patients included in large-scale, systemic single-agent RCTs.[31-37]

Overall safety profiles for combination therapy with systemic agents seem tolerable in the short term, and the incidence of SAEs was very low. Long-term data are missing. Real-life data from observational registries may additionally inform us in the future and will be needed to monitor the long-term safety profile of combination therapy with systemic agents.

Potential biases and limitations in this study are as follows. There was significant heterogeneity in clinical outcome measures and treatment duration among trials included in this study, which may influence the precision of overall effect sizes and make it impossible to combine results in a meta-analysis. To obtain a complete overview on the efficacy and safety of systemic combination therapy, it would be of interest to add data from high-quality observational studies. Small controlled studies might not provide substantial greater evidence compared with open observational trials.

Conclusions

Implications for Practice

The available clinical evidence on the efficacy and safety of combination therapy with systemic agents reveals that most evidence currently exists for the superior efficacy of etanercept plus methotrexate in the short term. This combination therapy may be beneficial in the treatment of therapy-resistant patients. However, treatment should be well monitored, and dose reductions of either agent should be taken into consideration to minimize AEs. Unfortunately, all other combination therapies included had very low quality of evidence for all outcomes selected for this review. The lack of good data for these combination therapies does not mean that these combinations are not valuable but only that they did not have enough power to provide evidence-based recommendations. In severe therapy resistant patients, the introduction of these systemic combination therapies with well-monitored follow-up could be considered.

Implications for Research

Long-term, methodologically well-designed studies with adequate sample size achieved by performing a priori power and sample size calculations that compare the different combination therapies with monotherapy and other combination therapies are needed. To improve the comparability of data, clinical homogeneity should be reached by clear descriptions of the populations (e.g., isolated plaque-

type psoriasis or involvement of joints [arthritis psoriatica], disease severity, duration of treatment, outcome measurements, and time points of assessments). Future studies should include assessments of quality of life. Furthermore, future trials must be performed with sufficient duration to report the efficacy of the intervention (preferably >24 weeks), and follow-up must be long enough to be able to detect AEs and relapse rates after *treatment discontinuation*.

Supplemental content
Please find the supplementary material (GRADE summary of findings eTables 1-16 and electronic search) in the electronic version of this thesis.

References

1. Jensen P, Skov L, Zachariae C. Systemic combination treatment for psoriasis: a review. *Acta Derm Venereol*. 2010;90(4):341-9
2. Gustafson CJ, Watkins C, Hix E et al. Combination therapy in psoriasis: an evidence-based review. *Am J Clin Dermatol*. 2013;14(1):9-25.
3. Bailey EE, Ference EH, Alikhan A, et al. Combination treatments for psoriasis: a systematic review and meta-analysis. *Arch Dermatol*. 2012;148(4):511-22.
4. http://guidance.nice.org.uk/. Accessed October 2012.
5. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol*. doi:10.1111/j.2010.1468
6. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol*. 2009;161(5):987-1019.
7. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65(1):137-74.
8. Nast A, Boehncke WH, Mrowietz U, et al. S3-guidelines on the treatment of psoriasis vulgaris. Update. *J Dtsch Dermatol Ges*. doi:10.1111/j.2012.1610.
9. Guyatt GH, Oxman AD, Vist G, et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J*. 2008;336(7650):924-926.
10. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
11. Glanville JM, Lefebvre C, Miles JN, Camsosso-Stefinovic J. How to indentify randomized controlled trials in MEDLINE: ten years on. *J Med Libr Assoc*. 2006;94(2):130-6.
12. GRADEpro. http://ims.cochrane.org/gradepro. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008.
13. Guyatt GH, Oxman AP, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *J Clin Epidemiol*. 2011;64(12):1283-1293.
14. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. *J Am Acad Dermatol*. 2006;54(6):1013–1018.

15. Lynde CW, Gupta AK, Guenther L, et al. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. *J Dermatolog Treat*. 2012;23(4):261-7.

16. Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167(3):649-57.

17. Mahajan R, Kaur I, Kanwar AJ. Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis: a randomized single-blinded placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2010;24(5): 595-600.

18. Zachariae C, Mork NJ, Reunala T, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol*. 2008;88(5):495–501.

19. Gisondi P, Del Giglio M, Cotena C, et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. *Br J Dermatol*. 2008;158(6):1345–1349.

20. Mittal R, Malhotra S, Pandhi P, et al. Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol*. 2009;145(4): 387–393.

21. Reitamo S, Spuls P, Sassolas B, et al. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol*. 2001;145(3):438–445.

22. Shehzad T, Dar NR, Zakria M. Efficacy of concomitant use of PUVA and methotrexate in disease clearance time in plaque type psoriasis. *J Pak Med Assoc*. 2004;54(9):453–455.

23. Prystowsky JH, Knobler EH, Muzio PJ. Oral calcitriol (1,25-dihydroxyvitamin D3) does not augment UVB phototherapy for plaque psoriasis. *J Am Acad Dermatol*. 1996;35(2Pt1):272-4.

24. Gupta AK, Ellis CN, Tellner DC, et al. Double-blind, placebo-controlled study to evaluate the efficacy of fish oil and low-dose UVB in the treatment of psoriasis. *Br J Dermatol*. 1989;120(6):801-7.

25. Park KK, Wu JJ, Koo J. A randomized, 'head-to-head' pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients. *J Eur Acad Dermatol Venereol*. 2012;27(7):899-906.

26. Wolf, P., Weger, W., Legat, et al. Treatment with 311-nm ultraviolet B enhanced response of psoriatic lesions in ustekinumab-treated patients: a randomized intra-individual trial. *Br J Dermatol*. 2012;166(1):147–153.

27. El-Mofty M, el-Darouti M, Rasheed H et al. Sulfasalazine and pentoxifylline in psoriasis: a possible safe alternative. *J Dermatolog Treat*. 2011;22(1):31-7.

28. Gupta R, Gupta S. Methotrexate-betamethasone weekly oral pulse in psoriasis. *J Dermatolog Treat*. 2007;18(5):291–294.

29. Ezquerra GM, Regana MS, Millet PU. Combination of acitretin and oral calcitriol for treatment of plaque-type psoriasis. *Acta Derm Venereol*. 2007;87(5):449–450.

30. Danno K, Sugie N. Combination therapy with low-dose etretinate and eicosapentaenoic acid for psoriasis vulgaris. *The Journal of Dermatology*. 1998;25(11):703–705.

31. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol*. 2003;139(12):1627-32.

32. Papp KA, Tyring S, Lahfa M, et al. Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304-12.

33. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349(21):2014-22.

34. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med*. 2003;14;349(7):658-65.

35. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med*. 2011;365(17):1586-96.

36. Kleinpenning MM, Smits T, Boezeman J, van de Kerkhof PC, Evers AW, Gerritsen MJ. Narrowband ultraviolet B therapy in psoriasis: randomized double-blind comparison of high-dose and low-dose irradiation regimens. *Br J Dermatol*. 2009;161(6):1351-6.

37. Kirke SM, Lowder S, Lloyd JJ, Diffey BL, Matthews JN, Farr PM. A randomized comparison of selective broadband UVB and narrowband UVB in the treatment of psoriasis. *J Invest*

CHAPTER 3

Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis

Real-life data from PSONET registries

CIM Busard, AD Cohen, P Wolf, S Gkalpakiotis, S Cazzaniga, RS Stern, BA Hutten, I Feldhamer, F Quehenberger, R Lichem, M Kojanova, E Adenubiova, A Addis, L Naldi, PI Spuls

J Eur Acad Dermatol Venereol 2018;32(2):245-253

Abstract

Background: Biologics have greatly improved psoriasis management. However, primary and secondary non-response to treatment requires innovative strategies to optimize outcomes.

Objective: To describe the use of combined treatment of biologics with conventional systemic agents or phototherapy in daily clinical practice.

Methods: We collected data on frequency of use, demographics, treatment characteristics and drug survival of biologics combined with conventional systemic agents or phototherapy in five PSONET registries.

Results: Of 9922 biologic treatment cycles, 982 (9.9%) were identified as combination treatment. 72.9% of treatment cycles concerned concomitant use of methotrexate, 25.3% concerned concomitant UVB therapy, acitretin or cyclosporin and 1.8% concerned combined treatment with PUVA, fumaric acids or a second biologic. Substantial variation was detected in type and frequency of combination treatments prescribed across registries. Patients initiated on combined treatment had generally severe disease and were affected with psoriasis for many years. The extent to which patients had been priory treated with biologic monotherapy and the proportion of patients affected with psoriatic arthritis differed between registries. Survival rates for etanercept, adalimumab, infliximab and ustekinumab with methotrexate ranged between 43 and 92%, 28 and 83%, 65 and 87% and 53 and 77%, respectively, across registries after one year with no consistent superior survival for a particular biologic. Longest survival on a biologic combined with methotrexate, acitretin or cyclosporin was 103, 78 and 34 months, respectively.

Conclusion: Methotrexate was the most commonly used concomitant treatment for patients on a biologic. Wide geographical variations in treatment selection and persistence of combination treatment exist. Data derived from ongoing studies may help to determine whether combined treatment is superior to biologic monotherapy.

Introduction

Possible approaches for patients that develop loss of response to a biologic agent include dose-intensification or switch to another therapy.[1-3] The addition of a conventional systemic agent or phototherapy is an alternative option. Combined treatment may enhance efficacy, accelerate onset of disease remission and enable dose reductions of individual agents which potentially reduces costs and toxicity.[4]

For biologics combined with methotrexate (MTX) there is substantial experience in other inflammatory diseases including rheumatoid arthritis (RA) and inflammatory bowel disease.[5-11] Evidence exists for synergistic interactions between anti- TNFα agents (adalimumab, infliximab and etanercept) and MTX. The combination of anti- TNFα agents and MTX demonstrated a decrease in immunogenicity and clearance of the biologic and an increase in serum drug concentrations. Subsequently, serum drug concentrations are more likely to remain within the therapeutic range with a positive effect on drug survival and a decrease in primary (lack of improvement of clinical signs and symptoms with induction therapy) and secondary (loss of response during treatment) non-response.[11-13] Whether this applies to psoriasis populations and to biologics that do not exert their mechanisms of action through inactivation of anti-TNFα (e.g. ustekinumab) remains uncertain as there is a gap of evidence on biologic combination treatment in psoriasis literature. Therapeutic benefits of other combination treatments may rely upon the additive immunosuppressive effects of combined treatment. As such, combined use of these treatments may optimize treatment response in patients that do not reach desired treatment goals on monotherapy.

Although combination of biologics and conventional systemic agents or phototherapy is used in clinical practice for psoriasis patients, available evidence and recommendations in clinical guidelines are limited.[14, 15] In psoriasis, most evidence exists for etanercept combined with MTX which demonstrated superior efficacy compared to etanercept monotherapy in two separate randomized controlled trials (RCT) among approximately 600 patients.[16, 17] Small RCTs and observational studies investigating etanercept combined with acitretin and etanercept, adalimumab or ustekinumab combined with phototherapy demonstrated slightly superior response rates for combination therapy with acceptable short-term safety profiles.[14, 18, 19] Concomitant treatment with fumaric acids, cyclosporin or a second biologic has only been reported in case studies.[20-22]

PSONET, an international collaboration of psoriasis registries, provides a scientific platform to explore the use of systemic treatment in clinical practice.[23, 24] With this multinational population based paper we aim to enhance the current knowledge on the combined use of biologics and conventional systemic agents or phototherapy with assessment of frequency of use, demographics, treatment characteristics and drug survival in a real-life population in five countries.

Materials and methods

Data sources and data collection

For the purpose of this study we collected data from five PSONET registries: Clalit Health Services (Israel) [25], Psocare (Italy) [26], PsoRA (Austria) [27], BioREP (Czech Republic) and the AMC (the Netherlands) [28].

Patients with chronic plaque psoriasis aged ⩾18 were included in the analysis if they received treatment with a biologic in combination with a conventional systemic agent or phototherapy at any time between registry enrollment and May 2015 and if at least one follow-up visit had been conducted. To avoid reporting on bridging therapy, a treatment cycle was defined as the period a patient receives a certain combination treatment (e.g. etanercept and MTX) for at least one 1 month. Patients treated with alefacept and efalizumab were excluded as these agents are no longer available.

Registry characteristics (year of registry establishment, design, geographical area, number of biologic treatment cycles, schedule of visits, period available for analysis, funding and data collection modality) and frequency of use of combination treatment were extractedAdditional data on demographics (age, gender, body mass index (BMI), disease duration, psoriatic arthritis (PsA), disease severity (Psoriasis Area and Severity Index (PASI)), prior conventional systemic therapy, prior biologic therapy), treatment characteristics (reasons to initiate or discontinue combination therapy, timing of initiation, dosing and interval) and data on drug survival were extracted if the number of treatment cycles on a particular combination exceeded 10 within a registry.

Statistical analysis

Demographics and treatment characteristics extracted from the registries were combined by calculating weighted averages. If for a particular variable <50% of the patients and/or less than 10 treatment cycles were available, data from this registry were not incorporated in the calculation. Drug survival was explored by constructing Kaplan-Meier survival curves and defined as the time from initiation until discontinuation of combination therapy. Discontinuation of therapy was defined as any gap in treatment for more than 3 months.[29] Data were censored when therapy was continued till last available follow-up date.

Results

Registry characteristics are summarized in Table 1. Registries differ in size, that is the number of reference centres per registry ranges from 1 to 155 and the number of biologic treatment cycles per registry ranged from 266 to 5768. The period available for analysis differed between Psocare (2005 - 2009) and the other registries (2004/2007 - 2015). Schedule of visits was every 3 months in the majority of registries. However, Psocare and BioREP apply different follow-up schedules.

Table 1. Registry characteristics

	Clalit (Israel)	Psocare (Italy)	PsoRA (Austria)	BioREP (Czech Republic)	AMC (The Netherlands)
Year established	2007	2005	2004	2005	2005
Geographical area	14 centres	155 centres	16 centres	2 centres	1 centre
Number of biologic treatment cycles	1723	5768	1736	266	429
Schedule of visits	Every 3 months	8, 16, 32, 52, 78, 104, 208 weeks from entry	Every 3 months	0, 3, 6 months, every 6 months thereafter	Every 3 months
Period for analysis	2007-2015	2005-2009	2004-2015	2005-2015	2005-2015
Modality of data collection	Clalit Health Services database	Electronic form, web based	Electronic form, web based	Electronic form, web based	Electronic form, web based

Frequency of use of combination treatment

Of 9922 biologic treatment cycles in total, 982 (9.9%) treatment cycles (912 patients) were identified as combination treatment (Table 2). Biologics and MTX accounted for 72.9% of combinations (n = 716). Concurrent treatment with MTX was used in all registries. However, frequency of use varied substantially across registries (3.5% to 17.9% of biologic treatment cycles). Exposure to other biologic combination treatments accounted for 27.1% of all combinations identified (n = 266), of which 25.3% concerned combinations with UVB, acitretin or cyclosporin and 1.8% concerned combinations with PUVA, a second biologic or fumaric acids. Combinations with UVB were used in all registries except the Italian registry (Psocare) (accounting for 0.99% of all biologic treatment cycles). Combinations with acitretin were used in all registries (accounting for 0.9% of all biologic treatment cycles) and combinations with cyclosporin were only used in Israel (Clalit) and Italy (Psocare) (accounting for 0.61% of all biologic treatment cycles). Combinations with UVB were most commonly used in Israel (Clalit) and Austria (PsoRA) and combinations with acitretin were most commonly used in Israel (Clalit). Biologics

were rarely combined with PUVA, fumaric acids or a second biologic (accounting for <0.1% of all biologic treatment cycles).

Table 2. Frequency of us of combination treatment

	Clalit*	Psocare*	PsoRA*	BioREP*	AMC*	Total †
Biologic + MTX	191 (11.1%)	199 (3.5%)	203 (11.7%)	47 (17.9%)	76 (17.7%)	N = 716 (7.2%)
Biologic + UVB	38 (2.2%)		53 (3.1%)	5 (1.91%)	2 (0.47%)	N = 98 (0.99%)
Biologic + Acitretin	50 (2.9%)	16 (0.4%)	17 (0.98%)	5 (1.9%)	1 (0.23%)	N = 89 (0.9%)
Biologic + Cyclosporin	11 (0.64%)	50 (0.87%)				N = 61 (0.61%)
Biologic + PUVA	2 (0.12%)	1 (0.02%)	6 (0.35%)			N = 9 (0.09%)
Biologic + Biologic	1 (0.06%)	6 (0.1%)				N = 7 (0.07%)
Biologic + Fumaric acid			1 (0.06%)		1 (0.23%)	N = 2 (0.02%)

* Number of combination treatment cycles as a proportion of total amount of biologic treatment cycles registered in the registry
† Number of combination treatment cycles as a proportion of total amount of biologic treatment cycles registered in all registries

Demographics, treatment characteristics and drug survival

The number of combination treatment cycles was sufficient (n ⩾ 10) to extract data on demographics, treatment characteristics and drug survival for: biologics (etanercept, adalimumab, ustekinumab, infliximab) with MTX (all registries), biologics (etanercept and adalimumab) with UVB (Clalit and PsoRA), biologics (etanercept and adalimumab) with acitretin (Clalit, Psocare and PsoRA) and etanercept with cyclosporin (Clalit and Psocare). Average numbers of respondents for each variable and each registry are presented in Supplementary file (Table 1).

Demographics

Table 3 presents demographic characteristics. Males were more frequently treated with combination therapy compared to females. Patients had generally extensive disease, a high BMI and been affected with the psoriasis for many years (disease duration >15 years; PASI >17; BMI ⩾26.0) at initiation of combination treatment. Mean age ranged from 43.6 to 53.2 years for different combinations, with lower age in patients concomitantly treated with cyclosporin and higher age in patients concomitantly treated with acitretin. Overall, 56.5% of patients on combination treatment were diagnosed with psoriatic arthritis (PsA). Patients with PsA were most commonly concomitantly treated with MTX (62.5% of patients on MTX was affected with PsA). Prior to combination therapy 93.9% of patients (range 73.0 to 97.3% for different combinations) had been treated with conventional systemic monotherapy42.7% of patients (range 13.4 to 60.2% for different combinations) had

been treated with biologic monotherapy and 14.9% of patients (range 4.9 to 26.8% for different combinations) had been exposed to two or more biologic monotherapies.

Most baseline characteristics (age, gender, BMI, disease duration, disease severity) did not vary substantially across registries. However, profound differences were detected in the proportion of patients affected with PsA and the extent to which patients had been treated with biologic monotherapy prior to combination therapy. The proportion of patients with PsA was > 60% in Italy (Psocare), Austria (PsoRA) and Czech Republic (BioREP) while in the Netherlands (AMC) and Israel (Clalit) the majority of patients was not affected with PsA (37.3% and 45.9% of patients were affected with PsA in AMC and Clalit, respectively). The number of patients priory treated with biologic monotherapy was > 45% in Israel (Clalit), Asutria (PsoRA), Czech Republic (BioREP) and the Netherlands (AMC) (56.9%, 45.5%, 86.7% and 52.2%, respectively) but substantially lower in Italy (Psocare) (14%) (Table S2).

Table 3. Demographics by drug exposure

	Biologic† + MTX		Biologic‡ + UVB		Biologic‡ + Acitretin		Etanercept + Cyclosporin
Number of treatment cycles	716		98		89		61
Age in years (mean-range*)	49.1	(48-50.3)	46.6	(47.1-54.3)	53.2	(52.5-52.8)	43.6
Female (%-range*)	41.8	(37.6-58.1)	38.4	(40.4-47.2)	19.9	(16.7-20.0)	39.3
BMI (mean-range*)	28.4	(28.3-28.9)	29.5	(26.2-31.9)	28.3	(22.3-30.2)	26.2
Disease duration in years (mean-range*)	20.5	(16.6-21.5)	20.5	(20.2-20.7)	16.8	(16.9-16.9)	15.2
Diagnosis of PsA (%-range*)	62.5	(56.2-60.7)	43.4	(49.2-51.6)	34.1	(28.2-29.2)	39.4
PASI (mean-range*)	17.2	(13.2-20.0)	-	-	18.1	(18.1-18.1)	19.7
Prior conventional therapy (%-range*)	94.8	(90.3-96.7)	97.3	(86.1-94.2)	93.9	(92.3-95.8)	73.0
Prior biologic therapy (%-range*)	44.1	(41.0-74.2)	60.2	(57.7-72.3)	32.6	(36.7-45.8)	13.4
Prior biologic therapy n ≥2 (%-range*)	14.9	(10.5-54.8)	26.8	(19.4-21.2)	8.5	(4.2-10.2)	4.9

* Relates to different biologics
†·Etanercept, adalimumab, ustekinumab, infliximab
‡ Etanercept and adalimumab

Treatment characteristics

Most frequently reported reasons to initiate combination treatment included insufficient efficacy on monotherapy or diagnosis of PsA. Other, occasionally

reported reasons, included prevention of antibody formation and localization of lesions in critical areas (e.g. hands, feet, face). Initiation of combination treatment to permit dose reductions of individual agents was uncommon.

In 52.5% of patients (range 39.0 to 62.8% for different combinations) concomitant therapy started prior to or at initiation of biologic therapy. In the remaining patients concomitant therapy was added to biologic therapy after several months to years (Table S3).

Data extraction on dosing was limited. For biologics standard dosing and interval regimens were generally applied. Biologic dose or interval reductions were uncommon. Concomitant MTX was prescribed in an average dosage of 12.3mg and cyclosporin and acitretin were prescribed in a dosage of ⩽3mg/kg/day and ⩽20mg/day in the majority of cases, respectively (Table S4).

Drug survival

In total, 1133 patient-years of follow up (mean 1.7; range 0.2-8.5) were available for drug survival analysis. 992 patient-years relate to biologics and MTX, during which 291 treatment cycles were discontinued and 141 patient-years relate to biologics and acitretin or cyclosporin, during which 59 treatment cycles were discontinued.

Survival rates for etanercept, adalimumab, infliximab and ustekinumab combined with MTX ranged from 43 to 92%, 28 to 83%, 65 to 87% and 53 to 77% across registries, respectively, after one year. Although most registries show survival rates > 70% after one year, the Italian registry (Psocare) demonstrated substantial lower first year survival rates (range 28-65% for different biologics). Survival rates for biologics with MTX after the second, third and fourth year varied between 0 and 77%, 0 and 72% and 0 and 67% across registries, respectively. The longest survival on a biologic combined with MTX was 103 months. None of the biologics demonstrated consistently superior survival rates across registries (Fig 1).

Survival rates for biologics and acitretin were comparable to survival rates of biologics and MTX in Israel (Clalit; 78% after one year), but substantially lower in Italy (Psocare; 15% after one year) and Austria (PsoRA; 40% after one year). Survival rates for biologics with cyclosporin were 100% (Clalit) and 35% (Psocare) after one year, but <23% after two years. The longest survival on a biologic combined with acitretin or cyclosporin was 78 months and 34 months respectively. Detailed data on drug survival for biologics combined with UVB were not available but treatment continuation was estimated to be similar to UVB monotherapy (i.e. 3 to 6 months) (Table 4).

Discontinuation of combination treatment due to lack of effectiveness or adverse events was generally low (19% discontinued due to lack of efficacy, 8.2%

discontinued due to adverse events; Table S5). Other factors identified as reasons to discontinue combined treatment included remission or partial remission, non-adherence, patients' preference and pregnancy.

Table 4. Median drug survival and survival rates by years 1-4

	Etanercept + MTX Clalit n=75 Psocare n=87 PsoRA n=69 BioREP n=11 AMC n=37	**Adalimumab + MTX** Clalit n=62 Psocare n=16 PsoRA n=83 BioREP n=26 AMC n=19	**Infliximab + MTX** Clalit n=44 Psocare n=62 PsoRA n=35 AMC n=11	**Ustekinumab + MTX** Clalit n=10 PsoRA n=16	**Biologic † + acitretin** Clalit n=50 Psocare n=13 PsoRA n=11	**Etanercept + cyclosporin** Clalit n=11 Psocare n=43
Clalit						
Median (in months)	*	36	29	13	38	15
Year 1	92%	81%	87%	53%	78%	100%
Year 2	78%	57%	62%	13%	70%	0%
Year 3	67%	33%	49%	-	70%	-
Year 4	67%	17%	49%		35%	-
Psocare						
Median (in months)	10	6	16		6	5
Year 1	43%	28%	65%		15%	35%
Year 2	25%	0%	34%		15%	23%
Year 3	-	0%	29%		-	-
Year 4	-	0%	-		-	-
PsoRA						
Median (in months)	31	*	44	*	10	
Year 1	71%	83%	72%	77%	40%	
Year 2	55%	77%	62%	77%	40%	
Year 3	41%	63%	50%	77%	40%	
Year 4	30%	57%	43%	77%	27%	

Table 4. Median drug survival and survival rates by years 1-4 (continued)

	Etanercept + MTX Clalit n=75 Psocare n=87 PsoRA n=69 BioREP n=11 AMC n=37	**Adalimumab + MTX** Clalit n=62 Psocare n=16 PsoRA n=83 BioREP n=26 AMC n=19	**Infliximab + MTX** Clalit n=44 Psocare n=62 PsoRA n=35 AMC n=11	**Ustekinumab + MTX** Clalit n=10 PsoRA n=16	**Biologic † + acitretin** Clalit n=50 Psocare n=13 PsoRA n=11	**Etanercept + cyclosporin** Clalit n=11 Psocare n=43
BioREP						
Median (in months)	50	21				
Year 1	72%	68%				
Year 2	72%	47%				
Year 3	61%	47%				
Year 4	61%	38%				
AMC						
Median (in months)	18	19	52			
Year 1	70%	63%	72%			
Year 2	45%	41%	72%			
Year 3	17%	41%	72%			
Year 4	6%	33%	36%			

* Median survival not estimable as cumulative survival is > 0.5
†Etanercept and adalimumab

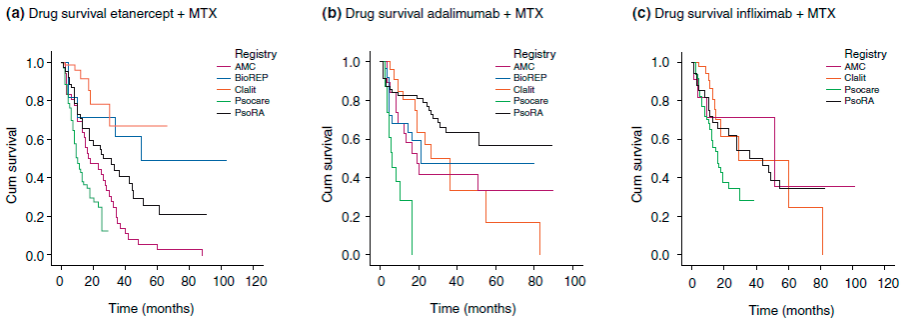


Figure 1. Drug survival of the most frequently prescribed combinations in our study population; etanercept (a), adalimumab (b) and infliximab (c) combined with MTX

Discussion

This analysis represents the largest multinational, observational, real-life cohort that assesses combined use of biologics and other immunosuppressive therapies in psoriasis to date. Results demonstrate that 9.9% of biologic treatments were combined with conventional systemic agents or phototherapy. In a recently performed study by Iskandar et al.[30], this proportion was much higher; 749 of 2980 patients (25.1%) enrolled in the BADBIR registry used conventional systemic agents concomitantly with a biologic. Inclusion of patients on bridging therapy (21.4% of patients) in the BADBIR analysis might partly explain for this difference.

Combinations of biologics and MTX were most commonly reported in our study population. Combinations of biologics and UVB, acitretin or cyclosporin were infrequently used in most registries and combined treatment with PUVA, fumaric acids or a second biologic was rare. In the report published by BADBIR frequency of concomitant use of MTX or acitretin is comparable with our results. However, much more biologic treatments were combined with cyclosporin (29.2% compared to 6.2% in our study) or fumaric acids (4.9% compared to 0.2% in our study).[30]

Our results indicate that there seems to be limited uniformity in prescription of biologic combination treatment. It is unknown which factors contribute to these differences in treatment prescription. Limited guidance on indications for prescribing combination treatment[31], availability of different drugs and different behavior in (the order of) prescribing drugs[32] (e.g. in Italy cyclosporin is more frequently used compared to the other countries) may play a role.

Patients selected for biologic combination treatment had generally been affected with severe psoriasis for many years. Although in most registries the

majority of patients had been treated with at least one biologic monotherapy prior to combination treatment, in Italy (Psocare) 86% of patients that initiated on combination treatment were biologic-naive. Diagnosis of PsA was one of the reasons to start combined treatment. However, many patients with only plaque psoriasis were also selected for combination treatment.

Antibody formation may occur as early as in the first few weeks on a biologic agent.[33] To enable MTX to exert a full effect on biologic pharmacokinetics concomitant treatment can be initiated prior to or simultaneously with biologic treatment.[6] In our cohort, this was the case in about 50% of biologic and MTX treatment cycles, while in the study reported by Iskandar et al.[30], the proportion of patients that initiated concomitant MTX prior to or simultaneously with a biologic was much higher (79.7%). Emerging evidence indicates that the addition of MTX during maintenance treatment with anti-TNFα monotherapy may still be effective to eliminate anti-drug antibodies and restore clinical response.[34]

Dosing of concomitant MTX was on average 12.3mg. A dose-dependent effect of MTX on biologic pharmacokinetics has been demonstrated for RA with a dose of 5mg MTX that seems sufficient to maintain serum concentrations within the therapeutic range.[35] In psoriasis, no studies have yet explored the minimally effective dose of MTX during combination treatment. Although a RCT performed in psoriasis has demonstrated the potential for dose reductions with combination treatment[36], dose reductions of combined agents were uncommonly applied in our cohort.

The majority of registries demonstrated survival rates > 70% for biologics combined with MTX after the first year and survival rates that varied between 0 and 77%, 0 and 72% and 0 and 67% across registries after the second, third and fourth year respectively. These survival rates seem comparable to survival rates for biologic monotherapy.[37] However, in a study investigating predictors of biologic discontinuation, concomitant prescription of MTX (and cyclosporin) were detected as predictors of biologic discontinuation. To determine whether drug survival of biologic combination treatment is superior to biologic monotherapy future research with direct comparison is needed.[38] Survival rates of biologics with acitretin and biologics with cyclosporin should be interpreted with caution due to small sample sizes (< 75).

Treatment termination due to safety issues was infrequently reported in our study population. However, cautious interpretation of these results is needed as we did not extract in-depth data on type and severity of adverse events.

The combination of (anti-TNFα) biologics and MTX has been investigated in 2 RCTs enrolling 550 psoriasis patients and in 80 RCTs enrolling 24521 rheumatological patients.[14, 39] In these studies combination therapy was generally well-tolerated with no major differences in safety profile for combination versus monotherapy. However, the risk for tuberculosis reactivation seems higher when (anti-TNFα) biologics are

combined with MTX (24/4241 versus 2/5769).[40] For combinations with acitretin, UVB and cyclosporin extensive safety data are lacking.

Strengths and limitations

Major strengths of this study include the prospective real-life design, the sample size, and the participation of registries from different geographical areas. However, some limitations apply. As PSONET is a collaborative network of psoriasis registries, potential differences in patient selection and the way data are captured may influence outcomes. Data were extracted in each registry separately instead of central collection of data from a data entry platform. Although the study was observational, we did not adjust drug survival for potential clinically relevant covariables. Finally, sample sizes of combination treatment categories varied, which might influence the accuracy of outcomes for small treatment groups.

Conclusion

We provide a multinational population-based description on the combined use of biologics and conventional systemic agents or phototherapy during the last decade. Concomitant use of MTX is most common and has the most extensive and supportive scientific base. However, future research in psoriasis populations is needed to adequately examine potential benefits and harms and to determine the position of combined therapy in the management of psoriasis. When combination treatment is prescribed, gaps of evidence should be discussed with the patient and potential benefits should be balanced against their possible harms taking into account factors such as comorbidity, prior systemic therapy and patients' needs and preferences.

Supplemental content

Please find the supplementary material (Table S1-5) in the electronic version of this thesis.

Acknowledgements

PSONET (www.psonet.eu) represents an international collaboration and is dependent on contributions from many members and participants of national registries who are gratefully acknowledged for their contribution. The authors would like to acknowledge the vital support of many individuals who contribute to Psocare, Clalit Health Services, PsoRA, BioREP and AMC psoriasis registry; Petr Arenberger, Petra Gkalpakioti, Martin Inzinger, Wolfgang Salmhofer, Wolfgang Weger, Franz Legat, Angelika Hofer, Alexandra Gruber-Wackernagel, Katharina Wippel-Slupetzky, Christine Bangert, Georg Stingl, Leo Richter, Klemens Rappersberger, Alexander Mlynek, Georg Klein, Barbara Gruber-Fleischanderl, Werner Saxinger, Christine Scheurecker, Martina Schütz-Bergmayr, Josef Auböck, Nicolaus Sandor, Claudia Kölli, Robert Müllegger, Daniela Mairhofer-Muri, Johanna Eder, Martin Mosleh, Franz Trautinger, Paul Sator, Andreas Steiner, Sabine Moser-Oberthaler, Gudrun Ratzinger, Norbert Reider, Matthias Schmuth, Nina Häring, Lukas Kraus, Golnaz Delir, Robert Strohal, Petra Viznerova, Adrian Tanew, Elisabeth Riedl, Clemens Painsi, Michael Patscheider, Bernhard Lange-Asschenfeldt, Peter Ponholzer, Beatrix Volc-Platzer, Rafaella Tatarski, Sylvia Selhofer, Wilhelm Brenner, Marleen Bonnerjee and all members of the Italian Psocare Centers (please see appendix).

References

1. Lecluse LL, de Groot M, Bos JD, Spuls PI. Experience with biologics for psoriasis in daily practice: switching is worth a try. Br J Dermatol. 2009;161(4):948-51.
2. Moots RJ, Mays R, Stephens J, Tarallo M. Burden of dose escalation with tumour necrosis factor inhibitors in rheumatoid arthritis: a systematic review of frequency and costs. Clin Exp Rheumatol. 2015;33(5):737-45.
3. Brezinski EA, Armstrong AW. Off-label biologic regimens in psoriasis: a systematic review of efficacy and safety of dose escalation, reduction, and interrupted biologic therapy. PLoS One. 2012;7(4):e33486.
4. Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. Am J Clin Dermatol. 2014;15(6):467-78.
5. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011;305(14):1460-8.
6. Zhuang Y, Xu Z, Frederick B, de Vries DE, Ford JA, Keen M, et al. Golimumab pharmacokinetics after repeated subcutaneous and intravenous administrations in patients with rheumatoid arthritis and the effect of concomitant methotrexate: an open-label, randomized study. Clin Ther. 2012;34(1):77-90.
7. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003;25(6):1700-21.
8. Ungar B, Chowers Y, Yavzori M, Picard O, Fudim E, Har-Noy O, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut. 2014;63(8):1258-64.
9. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007;56(9):1226-31.
10. Mok CC, Tsai WC, Chen DY, Wei JC. Immunogenicity of anti-TNF biologic agents in the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2016;16(2):201-11.
11. Ternant D, Ducourau E, Perdriger A, Corondan A, Le Goff B, Devauchelle-Pensec V, et al. Relationship between inflammation and infliximab pharmacokinetics in rheumatoid arthritis. Br J Clin Pharmacol. 2014;78(1):118-28.

12. Vogelzang EH, Pouw MF, Nurmohamed M, Kneepkens EL, Rispens T, Wolbink GJ, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. Ann Rheum Dis. 2015;74(2):474-5.

13. Xu Z, Davis HM, Zhou H. Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety. J Clin Pharmacol. 2015;55 Suppl 3:S60-74.

14. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. JAMA Dermatol. 2014;150(11):1213-20.

15. Armstrong AW, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation. JAMA Dermatol. 2015;151(4):432-8.

16. Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2012;167(3):649-57.

17. Zachariae C, Mork NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88(5):495-501.

18. Gambichler T, Tigges C, Scola N, Weber J, Skrygan M, Bechara FG, et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. Br J Dermatol. 2011;164(6):1383-6.

19. Takeshita J, Wang S, Shin DB, Callis Duffin K, Krueger GG, Kalb RE, et al. Comparative effectiveness of less commonly used systemic monotherapies and common combination therapies for moderate to severe psoriasis in the clinical setting. J Am Acad Dermatol. 2014;71(6):1167-75.

20. Cohen Barak E, Kerner M, Rozenman D, Ziv M. Combination therapy of cyclosporine and anti-tumor necrosis factor alpha in psoriasis: a case series of 10 patients. Dermatol Ther. 2015;28(3):126-30.

21. Wilsmann-Theis D, Frambach Y, Philipp S, Weyergraf AJ, Jacobi A, Mossner R, et al. Systemic antipsoriatic combination therapy with fumaric acid esters for plaque-type psoriasis: report on 17 cases. Dermatology. 2015;230(2):119-27.

22. Gniadecki R, Bang B, Sand C. Combination of antitumour necrosis factor-alpha and anti-interleukin-12/23 antibodies in refractory psoriasis and psoriatic arthritis: a long-term case-series observational study. Br J Dermatol. 2016;174(5):1145-6.

23. Lecluse LL, Naldi L, Stern RS, Spuls PI. National registries of systemic treatment for psoriasis and the European 'Psonet' initiative. Dermatology. 2009;218(4):347-56.

24. Garcia-Doval I, Rustenbach SJ, Stern R, Dam TN, Cohen AD, Baker C, et al. Systemic psoriasis therapy shows high between-country variation: a sign of unwarranted variation? Cross-sectional analysis of baseline data from the PSONET registries. Br J Dermatol. 2013;169(3):710-4.

25. Shalom G, Zisman D, Harman-Boehm I, Biterman H, Greenberg-Dotan S, Polishchuk I, et al. Factors associated with drug survival of methotrexate and acitretin in patients with psoriasis. Acta Derm Venereol. 2015;95(8):973-7.

26. Gisondi P, Cazzaniga S, Chimenti S, Maccarone M, Picardo M, Girolomoni G, et al. Latent tuberculosis infection in patients with chronic plaque psoriasis: evidence from the Italian Psocare Registry. Br J Dermatol. 2015;172(6):1613-20.

27. Inzinger M, Wippel-Slupetzky K, Weger W, Richter L, Mlynek A, Fleischander B, et al. Survival and Effectiveness of Tumour Necrosis Factor-alpha Inhibitors in the Treatment of Plaque Psoriasis under Daily Life Conditions: Report from the Psoriasis Registry Austria. Acta Derm Venereol. 2016;96(2):207-12.

28. Menting SP, Sitaram AS, Bonnerjee-van der Stok HM, de Rie MA, Hooft L, Spuls PI. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. Br J Dermatol. 2014;171(4):875-83.

29. van den Reek JM, Kievit W, Gniadecki R, Goeman JJ, Zweegers J, van de Kerkhof PC, et al. Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls. J Invest Dermatol. 2015;135(7):e34.

30. Iskandar IYK, Ashcroft DM, Warren RB, Evans I, McElhone K, Owen CM, et al. Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017;176(5):1297-307.

31. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-94.

32. Hwang ST, Nijsten T, Elder JT. Recent Highlights in Psoriasis Research. J Invest Dermatol. 2017;137(3):550-6.

33. Hsu L, Armstrong AW. Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response. Expert Rev Clin Immunol. 2013;9(10):949-58.

34. Ben-Horin S, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(4):444-7.

35. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis. 2015;74(6):1037-44.

36. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol. 2008;158(6):1345-9.

37. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.

38. Busard C, Menting S, van Bezooijen SJ, van den Reek J, Hutten B, Prens E, et al. Optimizing adalimumab treatment in psoriasis with concomitant methotrexate (OPTIMAP): study protocol for a pragmatic, single-blinded, investigator-initiated randomized controlled trial. Trials. 2017;18(1):52.

39. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ. 2016;353:i1777.

40. Lorenzetti R, Zullo A, Ridola L, Diamanti AP, Lagana B, Gatta L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. Ann Med. 2014;46(7):547-54.

CHAPTER 4

Optimizing adalimumab treatment in psoriasis with concomitant methotrexate (OPTIMAP)

Study protocol for a pragmatic, single-blinded, investigator-initiated randomized controlled trial

CIM Busard, SP Menting, JS van Bezooijen, JM van den Reek, BA Hutten, EP Prens, EM de Jong, MB van Doorn, PI Spuls

Trials 2017 Mar;18(1):113

Abstract

Background: The introduction of anti-tumour necrosis factor medications has revolutionized the treatment of psoriasis with achievement of treatment goals (Psoriasis Area and Severity Index score 75, remission) that are not usually met with conventional systemics. Nevertheless, some patients continue to experience persistent disease activity or treatment failure over time. Strategies to optimize treatment outcomes include the use of concomitant methotrexate, which has demonstrated beneficial effects on pharmacokinetics and treatment efficacy in psoriasis and other inflammatory diseases.

Methods: This is an investigator-initiated, multicenter randomized controlled trial (RCT) designed to compare the combination treatment of adalimumab and methotrexate with adalimumab monotherapy in patients with psoriasis. The primary outcome is adalimumab drug survival at week 49. Other outcomes include improvement in disease severity and quality of life, tolerability, and safety. Moreover, anti-adalimumab antibodies and adalimumab serum concentrations will be measured and correlations between genotypes and clinical outcomes will be assessed. Patient recruitment started in March 2014. Up to now, 36 patients have been randomized. Many more patients have been (pre)screened. A total of 93 patients is desired to meet an adequate sample size. In our experience, the main limitation for recruitment is prior adalimumab therapy and intolerability or toxicity for methotrexate in the past.

Discussion: OPTIMAP is the first RCT to examine combination therapy with adalimumab and methotrexate in a psoriasis population. With data derived from this study we expect to provide valuable clinical data on long-term treatment outcomes. These data will be supported by assessment of the impact of concomitant methotrexate on adalimumab pharmacokinetics. Furthermore, the influence of several single nucleotide polymorphisms on adalimumab response will be analysed in order to support the development of a more personalized approach for this targeted therapy.

Background

Adalimumab has been shown to be highly valued by patients with psoriasis due to its profound improvements in disease severity and its favorable safety profile.[1,2] Although its introduction (together with other anti-tumour necrosis factor (TNF) medications) has majorly advanced psoriasis care, some patients experience persistent disease activity (primary non-responders), treatment failure over time (secondary non-responders), or side effects.[3-5] Several factors have been identified to play a role in primary and secondary non-response to anti-TNFs, including pharmacokinetic factors such as the formation of antidrug antibodies (immunogenicity) and inter-individual variation in serum drug concentrations as well as pharmacogenetic factors such as the absence or presence of certain single nucleotide polymorphisms (SNPs) affecting drug metabolization.[6,7]

When anti-drug antibodies are formed in patients treated with an anti-TNFα, clearance of the biologic can, to a certain extent, be accelerated depending on the concentration of the anti-drug antibodies.[8] Moreover, anti-drug antibodies can be functionally neutralizing, thereby directly affecting treatment efficacy.[9] Multiple studies observed an association between the formation of anti-adalimumab antibodies, reduced serum levels, and diminished clinical response in psoriasis and other chronic inflammatory diseases.[3, 10–13] In rheumatoid arthritis (RA) and Crohn's disease, concomitant use of methotrexate (MTX) during treatment with certain TNFα inhibitors (adalimumab, infliximab, and golimumab) has been demonstrated to decrease immunogenicity and significantly reduce clearance, resulting in higher systemic exposure and enhanced clinical efficacy.[11,14-18]

Therefore, the use of combination therapy may be beneficial for successful long-term adalimumab treatment. In addition, combination therapy may enable dose reductions of individual agents, thereby decreasing toxicity and improving tolerability and compliance.[19] By targeting unregulated increased cytokine levels associated with inflammatory comorbid conditions, it is hypothesized that combination therapy may also provide a broader benefit to the patient by reducing the risk of, for example, cardiovascular events.[20] On the other hand, combination therapy may theoretically convey an increased risk for serious infections and malignancies.

Currently available evidence on anti-TNFα therapy with MTX in psoriasis is limited to two randomized controlled trials (RCTs) on etanercept with MTX[19, 21, 22] and a few observational studies and case series on other different anti-TNFα agents with MTX[23-25]. The two RCTs on etanercept and MTX provided promising results with superior efficacy of etanercept with MTX compared to etanercept monotherapy. RCTs investigating combined treatment with adalimumab and MTX are lacking.[19, 26] In order to investigate whether adalimumab treatment can be

optimized by using concomitant MTX, long-term clinical and pharmacokinetic data on the use of adalimumab in combination with MTX are desired. Additionally, as several polymorphisms have been identified as potential predictors for anti-TNF therapy in psoriasis (e.g., TNFR1B, TNFAIP3, IL12B/IL23R)[6, 27] and other chronic inflammatory diseases (e.g., FcGR and ATG16L1),[28, 29] it will be valuable to detect genetic factors associated with response to adalimumab in order to support personalized care.

Aims and objectives

The aims and objectives of this trial are:

- To gain long-term RCT data on the efficacy and safety of adalimumab combined with MTX compared to adalimumab monotherapy
- To assess the impact of concomitant MTX on adalimumab immunogenicity and serum concentrations
- To test appropriate candidate genes and correlate genotypes with trial outcomes

Methods

This is a multicentre RCT reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Table 1 (SPIRIT table) and Additional file 1 (SPIRIT checklist)). The trial was granted ethics approval by the Academic Medical Center research ethics committee (METC 2013_346). The trial is registered at The Netherlands National Trial Register (trial number: NTR4499) and in the European Clinical Trials Database (EudraCT number: 2013-004918-18). All participants will sign informed consent before participation. The study is being conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other relevant guidelines, regulations, and acts.

Table 1. Timeline of the study according to the SPIRIT guidelines

Time	Screening	Week -2	Week -1	Week 0	Week 3	Week 5	Every 12 weeks from week 13 up to week 145	Early Temination
Enrollment								
Informed consent	X							
Demography, medical history	X							
Vital signs and full physical examination	X			X		X	X	X
Psoriasis Area and Severity Index (PASI)	X			X		X	X	X
Eligibility criteria	X							
Laboratory assessments	X		X	X	X	X	X	X
Chest X-ray, Mantoux test, and interferon-gamma release assay (IGRA)	X							
Randomization	X							
Intervention								
Adalimumab (Humira) + MTX		X (MTX)	X (MTX)	X (Humira + MTX)				
Humira monotherapy				X (Humira)				
Assessments								
Laboratory assessments	X		X	X	X	X	X	X
PASI	X			X		X	X	X
Physician global assessment	X			X		X	X	X
Patient global assessment	X			X		X	X	X

Table 1. Timeline of the study according to the SPIRIT guidelines (continued)

Time	Screening	Week -2	Week -1	Week 0	Week 3	Week 5	Every 12 weeks from week 13 up to week 145	Early Temination
Impact on quality of life (Skindex 29 and Dermatology Life Quality Index (DLQI))	X			X		X	X	X
Prior or concomitant therapy	X			X		X	X	X
Adverse events	X			X		X	X	X
Drug adherence				X		X	X	X

Participants

Patients will be recruited from the outpatient clinics of the Departments of Dermatology of the Academic Medical Center (AMC) Amsterdam, Erasmus University Medical Center (EMC) Rotterdam, and the Radboud University Medical Center (RUMC) Nijmegen. Moreover, other dermatologists will be contacted to recruit and refer eligible patients to the participating centers. Participants must meet the inclusion criteria and none of the exclusion criteria (Table 2) in order to participate.These will be assessed at the screening visit. Potential participants who are deemed ineligible at screening will be allowed a second screening visit if the reason for ineligibility is a temporary status (e.g. latent tuberculosis).

These criteria will be assessed at the screening visit. Potential participants who are deemed ineligible at screening will be allowed a second screening visit if the reason for ineligibility is a temporary status (e.g., latent tuberculosis).

Table 2. Eligibility criteria

Inclusion	Exclusion
⩾18 years	History of significant MTX toxicity, in-
Diagnosis of moderate to severe	tolerability or contraindication
plaque psoriasis (PASI ⩾8)	Known liver or kidney malfunction
Adalimumab naïve	Alcohol abuse
Candidate for biologic therapy	Bone marrow hypoplasia, leukocytopenia,
Willing and able to use adequate con-	thrombocytopenia or significant anaemia
traceptives during the study	Known severe or chronic infec-
	tions like tuberculosis or HIV
	Ulcers in the oral cavity or known
	active ulcers in digestive tract
	Pregnant or nursing women
	Need for live vaccinations
	Use of other immunosuppressive medication
	(e.g., prednisone, mycophenolate mofetil
	(Cellcept), cyclosporine (Neoral), sirolimus
	(Rapamune), systemic tacrolimus (Prograft))

Interventions

All patients receive adalimumab 40 mg subcutaneously every other week starting 1 week after a loading dose of 80 mg and will be randomized 1:1 to receive either oral MTX 10 mg weekly (combination group) or no addition of MTX (monotherapy group). MTX therapy will be initiated 2 weeks prior to adalimumab therapy, and administration will be followed by folic acid 5 mg 24 hours after MTX intake (see Table 1). In case of MTX toxicity (e.g., liver toxicity or leukopenia) or intolerability, dosing can be paused (for a maximum of 2 weeks up to four times during the entire

study), or the dose can be adjusted to 7.5 mg. Moreover, patients are allowed to switch from oral to subcutaneous administration. In case of adalimumab toxicity or intolerability, dosing can be paused (for a maximum of 2 weeks up to four times during the entire study). Throughout the study, no systemic anti-psoriatic drugs are allowed for treatment other than the study medication (Table 3). If medically necessary (i.e., to control intolerable psoriasis activity), rescue treatment with topical corticosteroids, vitamin D derivates (calcipotriol/betamethasone or calcitriol), or calcineurin inhibitors may be provided to study patients at the discretion of the investigator after baseline and through week 145 (end of study) (Table 4).

Table 3. Wash out-periods

Therapy	Wash-out period
Topical therapy	2 weeks
Phototherapy	2 weeks
Conventional systemic therapy /etanercept	4 weeks
Infliximab/ustekinumab	6 weeks

Table 4. Allowed escape medication

Scalp/palms/soles	Low or high potency corticosteroids, calcitriol/ calcipotriol, or a combination
Face and body	Low potency corticosteroids, calcitriol/ calcipotriol, or topical tacrolimus 0.1% or 0.03%
Inverse psoriasis	Topical tacrolimus 0.1% or 0.03%

Randomization and blinding

Consecutive patients will be prospectively enrolled and randomly assigned if eligible to either the intervention (adalimumab with MTX) or control (adalimumab monotherapy) group after obtaining informed consent. Each consecutive patient will be assigned a randomization number according to a computer-generated randomization list (ALEA) using random block sizes of 2, 4, 6, and 8 to ensure allocation concealment. Randomization is stratified for TNFα-blocker exposure status to achieve balance with regard to prior TNFα-blocker exposure in the study population.

This is an observer-blinded study. The observer (outcome assessor) will perform clinical outcome assessments of disease severity (Psoriasis Area and Severity Index (PASI) and investigator global assessment (IGA)) at each study visit. The clinician performs all other study procedures and is not blinded. Both clinician and participant know the treatment allocation; as such, no special measures are required to allow for breaking of treatment codes. However, treatment allocation

will not be revealed to the recruiting physician until participants' details and key stratification variables have been irrevocably entered onto the web-based randomization site.

Endpoints

The primary outcome is adalimumab drug survival (number of patients still on adalimumab treatment) at week 49.

Secondary outcomes are the following:

- Proportion of patients who reach treatment goals at week 13, week 25, week 49, and week 145
- Proportion of patients achieving PASI 75 at weeks 49 and 145
- Proportion of patients achieving IGA clear or almost clear at weeks 49 and 145
- Mean improvement in PASI at weeks 49 and 145
- Proportion of patients with PGA clear or almost clear at weeks 49 and 145
- Mean improvement in Dermatology Life Quality Index (DLQI) and Skindex at weeks 49 and 145
- Proportion of patients with (serious) adverse events at weeks 49 and 145
- Proportion of patients with changes in laboratory assessments at weeks 49 and 145
- Proportion of patients with (no, low, or high) levels of antibodies at weeks 49 and 145
- Median adalimumab trough concentrations (mg/L) at weeks 49 and 145
- Correlation between genetic polymorphisms and adalimumab response

Procedures and Assessments

Patients will visit the outpatient clinic at screening, baseline, week 5, week 13, and every 12 weeks thereafter until study completion (weeks 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145) (Table 1).

A variety of parameters will be collected during each visit to assess efficacy, including physician- (PASI/IGA (static; scale 0–4 [30])) and patient-reported (patient-reported global assessment (PGA static; scale 0–4)) outcomes. Quality of life assessment will be performed using Skindex and DLQI questionnaires. Safety will be assessed by evaluating the incidence of (serious) adverse events, obtaining a detailed medical history, thorough physical examination, vital signs, clinical laboratory testing, and urinalysis (including pregnancy tests for females of childbearing potential at screening). Concomitant medication and medical procedures will be collected from obtainment of informed consent up to end of study. Patients will receive a diary in which they will register the administration dates of

adalimumab (and MTX in the combination group), any changes in their health status, and/or changes in concomitant medication used. The local investigator reviews the diary to determine drug adherence and the incidence and type of adverse events. An independent Data Safety Monitoring Board (DSMB) has been established to review efficacy and safety data periodically in an unblinded fashion.

Laboratory testing

Blood samples will be collected at each visit (serum samples are collected just before administration of adalimumab (3-day window) to ensure accurate determination of serum through levels) to monitor drug safety, to determine immunogenicity against adalimumab, and to measure adalimumab serum through levels. Samples for serum preparation are kept at room temperature for 1–2 hours for coagulation, followed by centrifugation at 3000 RPM for 15 minutes at room temperature. Supernatant is collected, aliquoted, and stored at –20 °C until further use. Adalimumab serum through levels will be determined using a non-commercial enzyme-linked immunosorbent assay (ELISA, Sanquin, Amsterdam, The Netherlands). Detection of anti-adalimumab antibodies will be performed through a radioimmunoassay (Sanquin). The antibody test will be considered positive when the antibody concentration exceeds 12 AU/mL. Concentrations between 12 and 100 AU/mL will be considered low antibody titers; those above 100 AU/mL will be considered high antibody titers.[3] Additionally, a single blood sample will be collected at screening from which DNA will be collected and stored at −80 °C. As scientific interest in this field is currently increasing, DNA analysis will be performed based upon accumulating data acquired from (ongoing) pharmacogenetic studies.

Justification of sample size

A total of 84 patients (randomized 1:1 to concomitant MTX or no MTX) will give the study at least 80% power at a 0.05 two-sided significance level using a two-sample chi-squared test to detect a difference of 28% in drug survival at week 49. We aim to enroll 93 patients to allow for an approximate 10% loss to follow-up. These calculations were performed using Nquery 6.0.2. Due to the lack of data in a psoriasis population, the expected clinically relevant difference in drug survival between both treatment groups was hypothesized based on studies performed in patients with RA. The prevalence of (clinically relevant) anti-drug antibody formation is estimated to be 45% in patients on adalimumab monotherapy (a similar percentage is found in patients with psoriasis[30] and around 17% in patients on adalimumab with low-dose (5–10 mg) MTX after 49 weeks[31]. A clear correlation between antibody formation and treatment failure (with subsequent treatment

discontinuation) in patients on adalimumab has been demonstrated.[32] Based on these data, drug survival is estimated to be 83% (100 minus 17) for the experimental group and 55% (100 minus 45) for the control group after 49 weeks of follow-up.

Statistical analysis

The primary analysis will be conducted on the intention-to-treat population, including all randomized participants in the groups to which they were randomized. A per-protocol population (excluding major protocol violations) will be used to check the robustness of the primary analyses. The safety population will consist of all patients receiving at least one dose of the study drug. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event classification. The overall incidence of (serious) adverse events and number and proportion of patients reporting such events will be summarized by treatment group. Differences in dichotomous outcomes among the two study groups will be analysed using the chisquared test or Fisher's exact test when the expected cell frequencies fall below five. We will express differences in drug survival as absolute differences and relative risks, with associated 95% confidence intervals, with the group on adalimumab monotherapy as the reference. In case patients are lost to follow-up during the study period, we will analyse these data by means of survival analysis. We will construct cumulative survival curves (Kaplan-Meier method) for the treatment groups, and these curves will be compared using the log-rank test. One-way analysis-of-variance statistics will be calculated to compare continuous outcome measures between groups. There are no formal planned interim analyses, but progress reports on all data issues are presented to the DSMB.

Trial status

Patient recruitment started in March 2014 and is currently ongoing. Based on our experience so far, recruitment is limited by two main factors: prior use of adalimumab and intolerability or toxicity for MTX in the past. Moreover, disease activity in patients who are transitioned from another biologic is often suppressed (< PASI 8). To enlarge the geographical area in which patients can participate in the study and to enhance patient recruitment, three additional hospitals have been activated for patient recruitment: Amphia Hospital (Breda) and Bravis Hospital (Bergen op Zoom) in The Netherlands and Ghent University Hospital in Belgium.

Discussion

Although combination treatment with anti-TNFs and MTX is being prescribed for psoriasis in clinical practice, available evidence and guidance on the use of combination treatment is limited. No consensus about certain treatment aspects such as timing of initiation of MTX (prior to anti-TNF or during anti-TNF therapy) and MTX dosing exists. Therefore, besides the rationale for our primary endpoints, we would like to emphasize the choice of dosing and initiation of comedication for the current RCT.

Primary endpoint

In this study, drug survival after 49 weeks of treatment is chosen as the primary endpoint. Based on currently available evidence, response rates to anti-TNFs in patients with and without concomitant MTX may remain similar; however, drug survival is often superior in patients receiving comedication compared to monotherapy, and this difference tends to be more prominent than differences in response rates.[33–36] Moreover, by categorizing reasons for treatment discontinuation (lack of efficacy, safety concerns), several important treatment aspects are being combined.

Initiation of MTX prior to adalimumab therapy

Concomitant use of MTX has been demonstrated to significantly reduce the clearance of adalimumab, resulting in higher adalimumab trough levels in patients with RA.[14, 37] However, it takes time for MTX to exert a full effect on the pharmacokinetics of adalimumab.[37] The slow onset of drug action of MTX can be attributed to an intracellular accumulation process.[38, 39] After MTX uptake into cells, it is converted to MTX polyglutamates, active metabolites which are believed to exert the anti-inflammatory actions of MTX. The current product label for adalimumab indicates that MTX decreases the apparent clearance of adalimumab after single and multiple doses by 29% and 44%, respectively.[37] In order to ensure maximal potential for MTX to exert a beneficial effect on adalimumab pharmacokinetics from the start on, MTX therapy is initiated 2 weeks before administration of adalimumab in the intervention group.

Choice of MTX dosing

The dose of MTX as monotherapy can range from 7.5 to 25 mg/week, depending on national guidelines and patient/physician's preference. A systematic literature review of MTX monotherapy has recommended initial treatment with 10–15 mg orally with dose increases to 20 mg/week if needed and tolerated.[40] Available evidence

suggests that MTX toxicity is dose-dependent and low-dose MTX monotherapy treatment can be effective. However, no RCTs have explored the minimally effective dose of MTX in a group of patients when used in combination with a TNFα inhibitor. This dose may differ from minimally effective monotherapy doses.

MTX tends to reduce immunogenicity and increase adalimumab serum levels in a dose-dependent manner in patients with RA. Results indicate a (non-significant) increase in adalimumab serum concentrations with higher doses of MTX (10–20 mg) compared to low-dose MTX. However, a dose of 5–10 mg of concomitant MTX seems already sufficient to substantially decrease immunogenicity against adalimumab and maintain serum concentrations within the therapeutic range.[32, 41] In the treatment of psoriasis, MTX 10 mg per week is an accepted dose for treating psoriasis according to (inter)national guidelines.[40] In order to avoid an increased risk of side effects like hepatotoxicity, a dosage of 10 mg MTX/week is chosen in our RCT over a higher dose. With this RCT we aim to improve the body of evidence on efficacy and safety of adalimumab and MTX combination treatment in order to investigate whether MTX can optimize adalimumab treatment. Moreover, with the analysis of pharmacogenetic data, we hope to support personalized medicine and more accurate prediction of treatment response.

Study strengths and limitations

This study represents the first RCT on combined treatment with adalimumab and methotrexate. Data will be extracted and analysed independent of industry. It is an observer-blinded study with concealment of allocation. Clinical as well as pharmacokinetic and pharmacogenetic outcomes will be assessed in the short and long term. However, some limitations apply. Due to the pragmatic study design, the trial is not conducted as double-blind. Moreover, the sample size limits assessment of the predictive performance of genetic polymorphisms on clinical and pharmacokinetic outcomes. Optimal dosing and timing of MTX comedication are not evaluated in this study and will have to be investigated in future research.

Endnotes

[1]Treatment goals will be achieved if patients reach PASI ⩾ 75 or PASI ⩾ 50 in combination with DLQI ⩽ 5. Treatment goals will not be achieved if PASI < 50 or PASI ⩾50 < 75 in combination with DLQI ⩾ 5.[42]

Acknowledgements

We would like to thank Jo Lambert (UZ Gent (Belgium)), Wim de Kort (Amphia Hospital Breda (Netherlands)), Milan Tijoe (Bravis Hospital Bergen op Zoom (Netherlands)), and their team members for their enthusiasm and commitment in participating in the study as recruiting centers.

References

1. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.
2. van den Reek JM, van Luumig PP, Otero ME, Zweegers J, van de Kerkhof PC, Ossenkoppele PM, et al. Satisfaction of treatment with biologics is high in psoriasis: results from the Bio-CAPTURE network. Br J Dermatol. 2014;170(5):1158-65.
3. Menting SP, van Lumig PP, de Vries AC, van den Reek JM, van der Kleij D, de Jong EM, et al. Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up. JAMA Dermatol. 2014;150(2):130-6.
4. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.
5. Bito T, Nishikawa R, Hatakeyama M, Kikusawa A, Kanki H, Nagai H, et al. Influence of neutralizing antibodies to adalimumab and infliximab on the treatment of psoriasis. Br J Dermatol. 2014;170(4):922-9.
6. Prieto-Perez R, Cabaleiro T, Dauden E, Abad-Santos F. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. Pharmacogenomics J. 2013;13(4):297-305.
7. Coto-Segura P, Batalla A, Gonzalez-Fernandez D, Gomez J, Santos-Juanes J, Queiro R, et al. CDKAL1 gene variants affect the anti-TNF response among Psoriasis patients. Int Immunopharmacol. 2015;29(2):947-9.
8. Xu Z, Davis HM, Zhou H. Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety. J Clin Pharmacol. 2015;55 Suppl 3:S60-74.
9. van Schouwenburg PA, van de Stadt LA, de Jong RN, van Buren EE, Kruithof S, de Groot E, et al. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. Ann Rheum Dis. 2013;72(1):104-9.
10. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011;305(14):1460-8.

11. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007;66(7):921-6.

12. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis. 2009;68(11):1739-45.

13. West RL, Zelinkova Z, Wolbink GJ, Kuipers EJ, Stokkers PC, van der Woude CJ. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. Aliment Pharmacol Ther. 2008;28(9):1122-6.

14. Zhuang Y, Xu Z, Frederick B, de Vries DE, Ford JA, Keen M, et al. Golimumab pharmacokinetics after repeated subcutaneous and intravenous administrations in patients with rheumatoid arthritis and the effect of concomitant methotrexate: an open-label, randomized study. Clin Ther. 2012;34(1):77-90.

15. Baert F, Noman M, Vermeire S, Van Assche G, G DH, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348(7):601-8.

16. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispens T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis. 2015;74(3):513-8.

17. Kuriya B, Arkema EV, Bykerk VP, Keystone EC. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010;69(7):1298-304.

18. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003;25(6):1700-21.

19. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. JAMA Dermatol. 2014;150(11):1213-20.

20. Hugh J, Van Voorhees AS, Nijhawan RI, Bagel J, Lebwohl M, Blauvelt A, et al. From the Medical Board of the National Psoriasis Foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol. 2014;70(1):168-77.

21. Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2012;167(3):649-57.

22. Zachariae C, Mork NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88(5):495-501.

23. Dalaker M, Bonesronning JH. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with methotrexate or azathioprine in a retrospective cohort. J Eur Acad Dermatol Venereol. 2009;23(3):277–82.

24. van den Reek JM, van Lumig PP, Kievit W, Zweegers J, van de Kerkhof PC, Seyger MM, et al. Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice. J Dermatolog Treat. 2013;24(5):361–8.

25. Driessen RJ, van de Kerkhof PC, de Jong EM. Etanercept combined with methotrexate for high-need psoriasis.

26. van Bezooijen JS, Prens EP, Pradeepti MS, Atiqi R, Schreurs MW, Koch BC, et al. Combining biologics with methotrexate in psoriasis: a systematic review. Br J Dermatol. 2015;172(6):1676-80.

27. Gallo E, Cabaleiro T, Roman M, Solano-Lopez G, Abad-Santos F, Garcia-Diez A, et al. The relationship between tumour necrosis factor (TNF)-alpha promoter and IL12B/IL-23R genes polymorphisms and the efficacy of anti-TNF-alpha therapy in psoriasis: a case-control study. Br J Dermatol. 2013;169(4):819-29.

28. Koder S, Repnik K, Ferkolj I, Pernat C, Skok P, Weersma RK, et al. Genetic polymorphism in ATG16L1 gene influences the response to adalimumab in Crohn's disease patients. Pharmacogenomics. 2015;16(3):191-204.

29. Davila-Fajardo CL, van der Straaten T, Baak-Pablo R, Medarde Caballero C, Cabeza Barrera J, Huizinga TW, et al. FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis. Pharmacogenomics. 2015;16(4):373-81.

30. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26(1):23-31.

31. Menting SP, van den Reek JM, Baerveldt EM, de Jong EM, Prens EP, Lecluse LL, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. Br J Dermatol. 2015;173(3):855-7.

32. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71(11):1914-5.

33. Zhang J, Xie F, Delzell E, Yun H, Lewis JD, Haynes K, et al. Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. Arthritis Care Res. 2015;67(5):624–32. 34.

34. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis. 2014;73(1):132–7. 35.

35. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008;59(2):234–40. 36.

36. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis. 2008;67(3):364–9.

37. Inc AV. Humira US Prescribing Information. 2013. http://www.accessdata.fda. gov/drugsatfda_docs/label/2013/125057s327lbl.pdf. Accessed 23 Dec 2015.

38. Nielsen OH, Bjerrum JT, Herfarth H, Rogler G. Recent advances using immunomodulators for inflammatory bowel disease. J Clin Pharmacol. 2013;53(6):575-88.

39. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. Clin Pharmacokinet. 1978;3(1):1-13.

40. Menting SP, Dekker PM, Limpens J, Hooft L, Spuls PI. Methotrexate Dosing Regimen for Plaque-type Psoriasis: A Systematic Review of the Use of Test-dose, Start-dose, Dosing Scheme, Dose Adjustments, Maximum Dose and Folic Acid Supplementation. Acta Derm Venereol. 2015.

41. Vogelzang EH, Pouw MF, Nurmohamed M, Kneepkens EL, Rispens T, Wolbink GJ, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. Ann Rheum Dis. 2015;74(2):474–5.

42. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.

CHAPTER 5

Adalimumab with methotrexate versus adalimumab monotherapy in psoriasis

First-year results of a randomized controlled trial

CIM Busard and GE van der Kraaij, J van den Reek, SP Menting, AH Musters, BA Hutten, MA de Rie, JS van Bezooijen, E Prens, T Rispens, A de Vries, EMGJ de Jong, W de Kort, J Lambert, MBA van Doorn and PI Spuls

Submitted to the Journal of Investigative Dermatology

Abstract

Adalimumab is normally prescribed with methotrexate (MTX) in rheumatoid arthritis given the enhanced treatment effect and reduced antidrug antibody (ADA) formation compared to adalimumab monotherapy. In psoriasis the long-term treatment effects and pharmacokinetic profile have not been investigated extensively.

We conducted a randomized controlled trial to assess the efficacy, safety, pharmacokinetics and immunogenicity of adalimumab combined with MTX (ADL-MTX group) compared to adalimumab monotherapy (ADL group) in chronic plaque psoriasis.

Thirty-one patients in the ADL-MTX group and 30 in the ADL group were analysed. After one year, a (non-significant) better drug survival was found in the ADL-MTX group (74.2% vs 58.6%, respectively; p=0.15). Significantly more patients in the ADL-MTX group achieved a 75% improvement of the Psoriasis Area and Severity Index (58.1% vs. 31.0%; p=0.04). No serious adverse events (SAEs) occurred. Patients in the ADL-MTX group had higher median (IQR) trough concentrations (6.7 (3.9-9.5) vs. 3.9 (0.8-7.4) mg/L; p=0.03) and fewer patients showed ADA during the first year (22.6% vs. 60.0%; p<0.01).

Adalimumab seems more effective when combined with MTX, with less patients showing ADA. No SAEs occurred during the first year of treatment. Combination therapy with MTX can be considered when starting adalimumab treatment in patients with chronic plaque psoriasis.

Introduction

Adalimumab is a tumor necrosis alpha (TNF-α) inhibitor, which is frequently used in psoriasis patients. However, immunogenicity (i.e. the formation of antidrug antibodies (ADA)) is an important factor that contributes to adalimumab treatment failure, although the reported incidence varies widely (0-51%).[1] These neutralizing ADA bind to the circulating adalimumab, thereby preventing the drug to bind TNF.[2,3] Moreover, this binding results in immune complexes, which may lead to enhanced clearance of the drug.[3-5] Both mechanisms can result in low serum adalimumab concentrations which is associated with loss of clinical response and treatment discontinuation.[1,6,7]

Adding low dose methotrexate (MTX) to adalimumab has shown to enhance the clinical response, reduce antibody formation and promote higher serum drug concentrations in patients with rheumatoid arthritis (RA) and is therefore common clinical practice.[8-11] It is hypothesized that MTX induces anergy, a state in which T cells and B cells are unresponsive to specific antigens, thereby preventing plasma cell conversion and antibody formation.[12] This effect is supplementary to the anti-inflammatory effects of MTX.

Evidence supporting the use of combination therapy of biologics with immunomodulatory agents in psoriasis is limited.[13] Data from randomized controlled trials support superior efficacy of etanercept with MTX compared to etanercept monotherapy, although ADA formation does not play a major role in etanercept as antibodies are non-neutralizing.[14-16] Combination treatment of adalimumab or infliximab with MTX has been evaluated in a small number of observational studies and has shown promising results.[17-20]

Combination therapy of adalimumab and MTX has not been prospectively studied in psoriasis. Therefore we conducted this randomized controlled trial (RCT) to compare combination of adalimumab and low dose MTX with adalimumab monotherapy regarding the one-year drug survival, efficacy, safety, pharmacokinetics (PK) and immunogenicity in patients with chronic plaque psoriasis.

Materials & Methods

Study design and trial population

This single-blinded, randomized controlled trial was performed in four academic centers (Amsterdam UMC, Radboud UMC Nijmegen, Erasmus MC Rotterdam, UZ Ghent) and one non-academic hospital (Amphia Hospital, Breda) in The Netherlands and Belgium. The study was registered in The Netherlands National Trial Register (number: NTR4499) and the protocol has previously been published.[21] Adalimumab-naive patients, ≥18 years of age, with moderate to severe plaque type psoriasis (PASI ≥8) were eligible. Exclusion criteria were a history of significant MTX toxicity or intolerability and a contraindication for adalimumab or MTX according to the national guideline.[22]

There was a wash-out period of two weeks for topical therapy and phototherapy, four weeks for conventional systemic therapy, apremilast and etanercept and six weeks for all other biologics. During the treatment-phase, patients were allowed to use class II (face and body) or class III (scalp, palms and soles) topical corticosteroids, vitamin D derivatives or calcineurin inhibitors if needed. Concomitant use of immunosuppressive drugs other than MTX was not allowed throughout the study.

Randomization, treatment regimens and trial procedures

Eligible patients were randomized by the treating physician 1:1 to receive adalimumab (Humira) with MTX or adalimumab (Humira) monotherapy. Randomization was performed by a centralised online randomization service (ALEA), in blocks of 8 and stratified by biologic naivety.

Adalimumab was dosed according to label, i.e. 80mg at baseline, followed by 40mg at week 1 and every 2 weeks thereafter. MTX was introduced 2 weeks before adalimumab in the ADL-MTX group, in a weekly dose of 10mg, followed by 5mg of folic acid 24 hours later. We chose 10mg MTX as the lowest effective dose, (despite the dose depended effect on immunogenicity in RA patients[9], to minimize the risk of side effects, especially hepatotoxicity which is increased in patients with severe psoriasis.

Treatment adherence was evaluated by patient diaries. In case of MTX toxicity or intolerability, the dose could be decreased to 7.5mg. For both adalimumab and MTX, treatment could be temporary interrupted (for a maximum of two weeks up to four times during the entire study).

Clinical efficacy, safety, PK and immunogenicity assessments were performed at baseline and at weeks 5, 13, 25, 37, and 49 (or early termination). The study is still ongoing; three-year follow-up data with study assessments every 12 weeks

will be reported when available. Disease severity (PASI and IGA) was measured by a blinded outcome assessor at each study visit. The physicians performed all other study procedures and were not blinded. Patients were also not blinded and filled out questionnaires on the quality of life (DLQI) and SKINDEX-29) and disease severity (PGA).

Blood samples for safety, PK and immunogenicity were collected at each visit just before adalimumab administration (3-day window). To assess liver enzyme concentrations a 45mg/ml and 50mg/ml cut-off value represents the upper limit of normal for AST and ALT, respectively.

The serum trough concentration and ADA titers were assessed by Sanquin laboratory Amsterdam using a validated enzyme-linked immunosorbent assay (ELISA) and a validated radioimmunoassay, respectively. ADA titers <12 AU/mL were defined as no antibodies, 12-100 AU/mL were classified as low ADA titers and ≥100 AU/mL as high ADA titers.[6]

Endpoints

The primary endpoint was adalimumab drug survival at the final first-year study visit (week 49).

Secondary clinical endpoints were the mean change in PASI, proportion of patients achieving PASI 75 and PASI 90, proportion of patients achieving IGA 0/1, mean change in DLQI and Skindex-29 (all assessed in week 49).

Furthermore the proportion of patients achieving treatment goals[23], defined as achievement of PASI≥75 or PASI ≥50<75 and DLQI≤5was assessed (weeks 13, 25, 49) and the proportion of patients with (serious) AEs and/or changes in liver enzyme concentrations throughout the study.

Secondary pharmacokinetic and immunogenicity endpoints were the median adalimumab trough concentrations (week 49) and the proportion of patients achieving drug concentrations within the therapeutic range (defined as 3.2-7mg/L)[24] the proportion of patients with (no, low or high) ADA titers (week 49) and the correlation between ADA titers, serum trough concentrations and clinical response (defined as good responders (PASI≥75), moderate responders (PASI≥50<75) and nonresponders (PASI<50).

Sample size calculation and statistical analysis

In RA, clinically relevant antidrug antibodies (ADA) were found in 17% of patients treated with adalimumab and MTX and in 45% of patients treated with adalimumab monotherapy.[9] The latter is comparable with the prevalence of ADA in psoriasis patients treated with adalimumab monotherapy.[6] Given the clear correlation between antibody formation and treatment failure (with subsequent

discontinuation) we estimated a difference in drug survival of 28%, which was considered clinically relevant. A sample size of 42 patients per group with a two-sided level of significance of 0.05, would have 80% power to detect a difference of 28% in drug survival between the groups. Considering a 10% drop out rate, we aimed to enroll 93 patients.

Cumulative survival curves (Kaplan-Meier) were constructed to evaluate the difference in adalimumab drug survival between the ADL-MTX group and ADL group. The event was defined as discontinuation of adalimumab therapy and patients were censored when lost to follow-up or in case of protocol deviations. Differences between the groups were assessed using a log-rank test.

Analysis for the secondary clinical endpoints were performed on the intention-to-treat population, consisting of all patients that had received at least one dose of adalimumab. Analysis for the secondary immunogenicity endpoints were performed on the per protocol population. Missing data were imputed using last observation carried forward in both analyses.

Secondary outcomes were analyzed using Chi-square test, Fisher's exact test, Independent t-test or Mann-Whitney U test as appropriate. Correlations between ADA titers, serum trough concentrations and clinical response were analyzed using the Spearman rank test.

In case of a large clinically relevant difference in a baseline characteristic, that is also associated with the outcome (i.e. potential confounder) we considered to adjust for this variable in a regression analyses.

A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 25.

Results

Study population

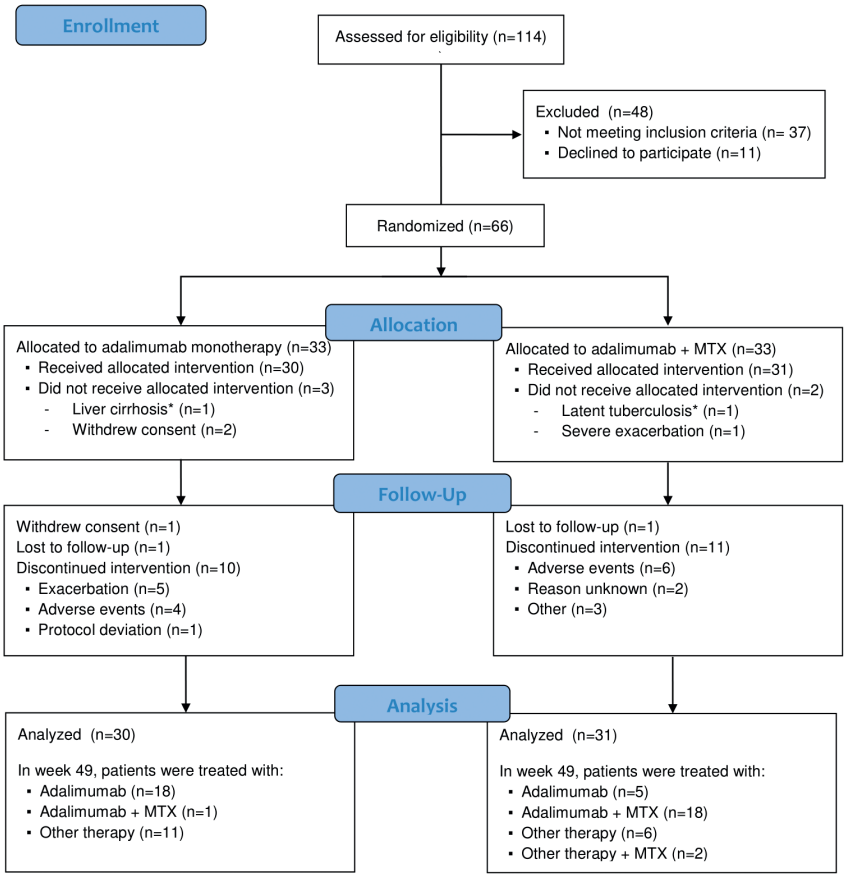
Of the 114 patients screened between March 2014 and November 2017, 66 patients were randomized; 33 to adalimumab with MTX (ADL-MTX group) and 33 to adalimumab monotherapy (ADL group); see flowchart Fig. 1. Patient demographics and baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

		ADL-MTX group (n = 31)	**ADL group (n = 30)**
Male gender		25 (80.6)	19 (63.3)
Age at baseline (years)		47.3 ± 13.9	48.3 ± 13.2
Disease duration (years)		14.8 (10.8 - 29.7)	22.8 (12.7 - 34.8)
Diagnosed with PsA		7 (22.6)	5 (17.2)
Weight (kg)		79.0 (63.7-94.3)	84.0 (75.0-93.0)
BMI (kg/m^2)		25.0 (22.7 – 28.1)	28.4 (24.1 – 31.5)
Current smoker		17 (54.8)	9 (32.1)
Current alcohol use		19 (61.3)	21 (75)
Biologic naïve		22 (71.0)	22 (73.3)
Previous MTX used		23 (74.2)	22 (73.3)
PASI score		14.0 ± 6.5	13.6 ± 6.0
IGA	Clear	0 (0)	0 (0)
	Almost clear	0 (0)	0 (0)
	Mild	5 (16.1)	1 (3.4)
	Moderate	14 (45.1)	14 (48.3)
	Severe	12 (38.7)	14 (48.3)
PGA	Clear	0 (0)	0 (0)
	Almost clear	1 (3.3)	0 (0)
	Mild	4 (13.3)	3 (10.3)
	Moderate	10 (30.0)	12 (41.4)
	Severe	15 (50.5)	14 (48.3)
DLQI		12.55 ± 6.6	11.59 ± 7.3
Skindex-29		50.0 ± 23.0	45.2 ± 24.2

Data displayed as n (percentage), mean ± SD or median (IQR). ADL-MTX group = adalimumab and methotrexate group, ADL-group = adalimumab group, PsA = Psoriatic arthritis, BMI = Body Mass Index, PASI = Psoriasis Area and Severity Index, IGA = Investigator Global Assessment, PGA = Patient Global Assessment, DLQI = Dermatology Life Quality Index

Figure 1. Flowchart of the study



*screen failures, patients were erroneously randomized.
n= number, MTX = methotrexate

Reasons for treatment discontinuation

In the ADL-MTX group (n=31), 30 patients completed the 49-week study-period. Eighteen patients remained on their allocated treatment, 11 patients discontinued study medication prematurely, one patient never started MTX (reason unknown) and one patient was lost to follow-up. In the ADL-MTX group adverse events were the most frequent reason for discontinuation of the allocated treatment (n=6; adalimumab and MTX (n=2), adalimumab (n=2), MTX (n=2)). Three patients discontinued MTX prematurely for other reasons than adverse events (AEs) (suspected interaction with pre-existent B cell lymphocytosis, reason unknown, fear of side effects) while continuing adalimumab. One patient discontinued

MTX (fear of side effects) and eventually also discontinued adalimumab due to psoriasis exacerbation.

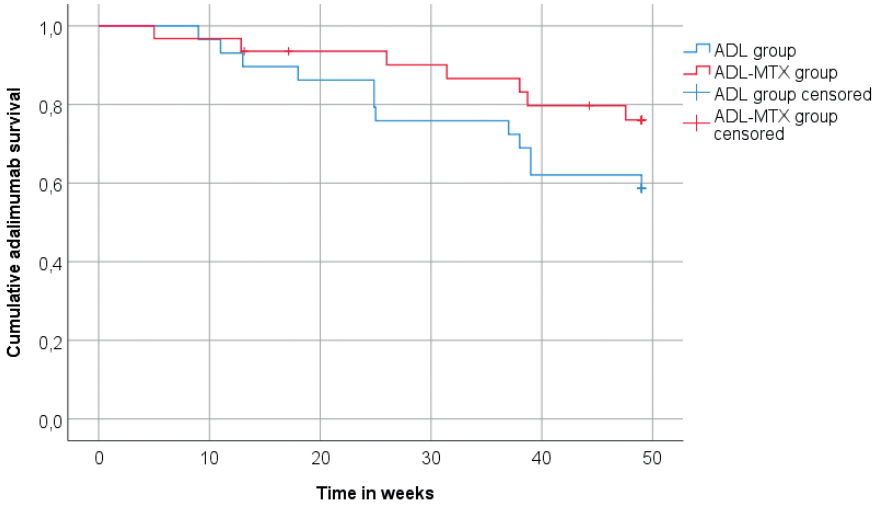
In the ADL group (n=30), 28 patients completed the 49-week study-period. Eighteen patients remained on their allocated treatment and 12 patients did not. One patient received MTX co-medication, and in 11 patients adalimumab treatment was discontinued due to psoriasis exacerbation (n=5), AEs (n=4) or protocol deviation (n=1, elective surgery).

Efficacy

Adalimumab drug survival

The adalimumab survival curves for both groups are presented in Figure 2. The curves overlap up to week 13, but after this time point more patients continue adalimumab therapy in the ADL-MTX group with a cumulative survival of 74.2% in the ADL-MTX group and 58.6% in the ADL group (p=0.15).

Figure 2. Kaplan-Meier curves of adalimumab drug survival in the ADL-MTX group and ADL group during the first year.



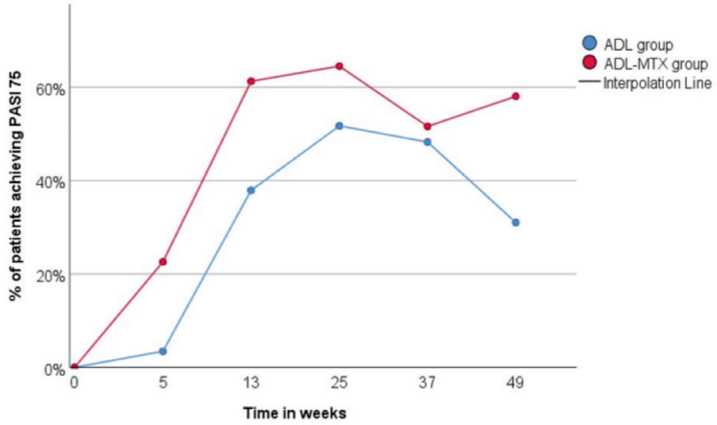
At week 49 the cumulative survival was 74.2% in the ADL-MTX group and 58.6% in the ADL group (p=0.15). ADL-MTX group = adalimumab and methotrexate group, ADL-group = adalimumab group.

PASI score and global assessment

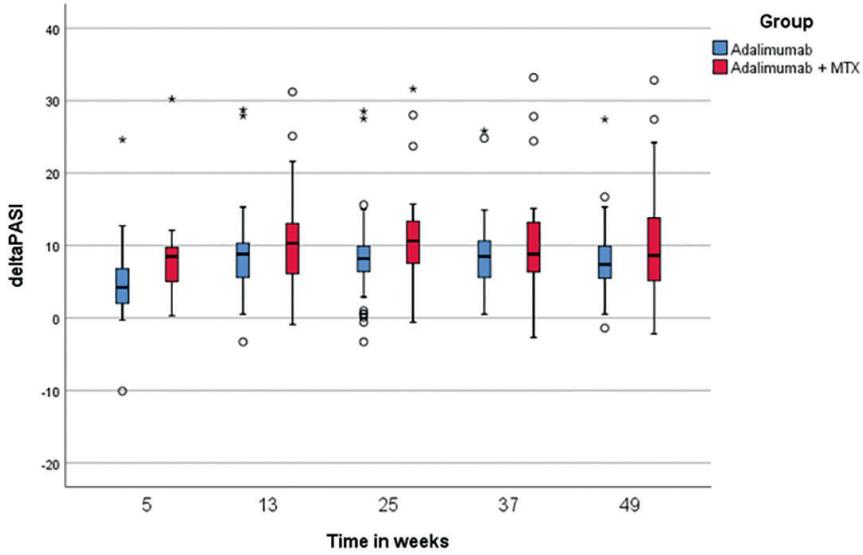
Significantly more patients achieved PASI 75 in the ADL-MTX group compared to the ADL group at week 5 (22.6% vs 3.4%; p=0.03) and week 49 (58.1% vs. 31.0%; p=0.04), but the difference was not statistically significant at weeks 13, 25 or 37 (Fig. 3a). In addition, more patients achieved PASI 90 at week 49 in the ADL-MTX versus ADL group (25.8% vs. 13.8%; p=0.34), but this difference was not statistically significant. The improvement of median (IQR) ΔPASI was significantly greater in the ADL-MTX group at week 5 (4.2 (1.6-6.9) vs. 8.5 (6.1-10.9); p<0.01), but no significant differences were found for the other time points. At week 49 the median ΔPASI was 8.6 (4.6-13.8) vs. 7.4 (5.3-10.1); p=0.31) for the ADL-MTX and ADL group respectively (Fig. 3b). Significantly more patients achieved Investigator Global Assessment (IGA) 0/1 (clear or almost clear) in the ADL-MTX group compared to the ADL group at week 49 (61.3% vs 30.0%, p=0.02) and all other time points except for week 37.

Patients reported substantial improvement in disease severity measured with Patient Global Assessment (PGA), with no significant difference between the groups during the study. In week 49, PGA 0/1 was achieved by 70.9% of patients in the ADL-MTX group and 63.3% in the ADL group (p=0.59).

Figure 3. Efficacy in the first year of treatment



3a: Proportion of patients who achieve PASI 75 in ADL-MTX group and ADL group per time point.



3b: Median ΔPASI in ADL-MTX group and ADL group per time point.
The top and bottom borders of the box indicate the interquartile, the horizontal bar within the box indicates the median, and the I bars indicate the range of observations. ° represent outliers. * represent far outliers. ADL-MTX group = adalimumab and methotrexate group, ADL-group = adalimumab group.

Quality of life

Improvement in mean Δ Dermatology Life Quality Index (DLQI) at week 49 was 8.77 (95% CI 6.1; 11.5) in the ADL-MTX group and 9.01 (95% CI 6.4; 11.7; p=0.87) in the ADL group. Improvement in ΔSkindex-29 at week 49 was 28.3 (95% CI 19.8; 36.8) in the ADL-MTX group and 26.6 (95% CI 33.8; 19.5; p=0.76) in the ADL group.

Proportion of patients reaching treatment goals

In week 13, significantly more patients in the ADL-MTX group (83.9% vs. 58.6%; p=0.045) achieved the treatment goals (defined as PASI ⩾75 or PASI ⩾50<75 and DLQI⩽5).[23] However, in weeks 25 and 49 there was no significant difference between the ADL-MTX group and ADL group (77.4% vs. 68.9%; p=0.56 and 64.5% vs. 62.1%; p=1.00 respectively).

Safety

An overview of treatment emergent AEs is presented in Table 2. No serious adverse events occurred. Among all patients, ⩾1 AE was reported by 85.2%, with no major

differences between groups. Gastrointestinal tract disorders and feelings of fatigue appeared to occur more frequently in the ADL-MTX group. Infections and headache were slightly more common in the ADL group. One opportunistic infection was reported; herpes zoster in a patient on adalimumab monotherapy.

Over 49 weeks, two patients in the ADL group and three patients in the ADL-MTX group experienced AEs that led to an adjustment (MTX lowered to 7.5mg) or interruption (administration of adalimumab with an interval of three instead of two weeks was performed once) of study medication. Ten patients discontinued treatment due to AEs. Six patients in the ADL-MTX group discontinued treatment at weeks 5, 25, 37 or 48 due to nausea, gastro-intestinal complaints, flu-like symptoms or headache respectively. Four patients in the ADL group discontinued treatment at weeks 5, 13, 37 or 42 due to fatigue, injection site reactions, lymphopenia or persistent flu-like symptoms respectively.

In the ADL-MTX group 54.8% of patients showed liver enzyme elevations at a certain time point during the study versus 46.7% of patients in the ADL group. In 26.9% of these patients, mild elevation of liver enzymes was already present at screening and in 38.5% of patients elevated concentrations were transient during the study period.

Elevated liver enzyme concentrations ranged from 52-177 U/L for alanine aminotransferase concentrations (ALT) and from 47-130 U/L for aspartate aminotransferase (AST).

Table 2. Patients with adverse events

	ADL + MTX group (n=31)	**ADL group (n=30)**
⩾1 AE reported	26 (83.9)	26 (86.7)
Discontinuation of study drug(s) due to AE	6 (19.4)	4 (13.3)
AE at least possibly related to study drug(s)	93/127 (73.2)	74/121 (61.2)
Gastro-intestinal complaints	10 (32.3)	3 (10)
Headache	3 (9.7)	5 (16.7)
Tiredness	6 (19.4)	4 (13.3)
Infection	9 (29.0)	11 (36.7)
Opportunistic infection	0 (0.0)	1 (3.3)
SAE	0 (0.0)	0 (0.0)
Malignancies (excluding non-melanoma skin cancer)*	0 (0.0)	0 (0.0)
Liver enzyme concentrations >ULN	14 (45.2)	12 (40.0)
Liver enzyme concentrations >2x ULN	3 (9.7)	2 (6.7)

Data displayed as n (%). ADL-MTX group = adalimumab and methotrexate group, ADL-group = adalimumab group, AE = Adverse event, SAE = Serious adverse event, ULN = Upper limit of normal
* Basal cell carcinoma was reported in one patient in the ADL-MTX group.

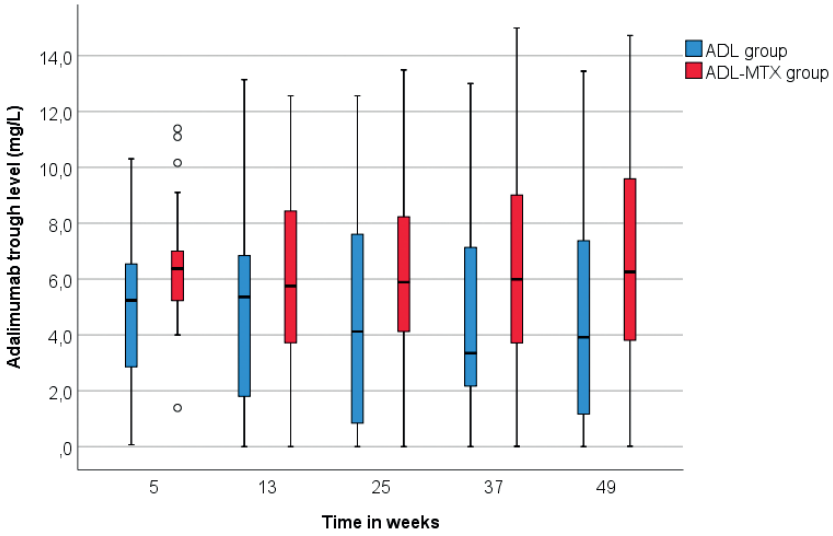
Pharmacokinetic endpoints

Adalimumab serum trough concentrations

The median (IQR) adalimumab trough concentrations were significantly higher in the ADL-MTX group compared to the ADL group at all time points except for week 13 (week 49; 6.7 (3.9-9.5) mg/L and 3.9 (0.8-7.4) mg/L; p=0.03; Fig. 4). Significantly more patients in the ADL group failed to reach adalimumab serum concentrations above 3.2mg/L (the lower bound of the therapeutic range[24] during the first year (week 5: 29.6% vs. 3.3%; p=0.01; week 49: 46.7% vs. 16.1%; p=0.01).

Good responders (PASI ⩾75) had higher serum adalimumab trough concentrations than non- or moderate responders at week 49 (5.8 (3.3-8.3) vs 2.9 (0.5-7.8); p=0.09) in the ADL-group and (7.9 (5.4-10.5) vs 4.4 (2.2-6.6); p<0.01) in the ADL-MTX group. In the ADL-group a significant correlation was found between median ΔPASI and serum through concentrations at all time points (week 49: Spearman's rho 0.57; p=0.001). In the ADL-MTX group, a significant correlation was only found at week 49 (Spearman's rho 0.48; p<0.01) but not at any of the other time points.

Figure 4. Boxplots representing adalimumab trough levels per time point



The top and bottom borders of the box indicate the interquartile, the horizontal bar within the box indicates the median, and the I bars indicate the range of observations. ° represent outliers. The adalimumab trough concentration was significantly higher in the ADL-MTX group at all time points, except in week 13 (p=0.15). ADL-MTX group = adalimumab and methotrexate group, ADL-group = adalimumab group.

Adalimumab antidrug antibodies

During the study 25 patients (41.0%) showed ADA at a certain time point. Eighteen were treated in the ADL group (60.0%) and 7 patients (22.6%) in the ADL-MTX group (p<0.01). In 14 of 25 patients ADA were persistent (n=10 ADL and n=4 ADL-MTX group), in 5 patients ADA were transient and in 6 patients persistence of ADA was unknown (missing data (n=4) and treatment discontinuation (n=2)). ADA formation appeared faster and significantly more often in the ADL group compared to the ADL-MTX group (week 5: 25.9% vs. 0%; p<0.01, week 49: 46.7% vs. 16.1%; p<0.01).

High (>100 AU/mL), low (12-100 AU/mL) or no (<12 AU/mL) ADA were associated with significantly lower adalimumab serum trough concentrations in week 49 in the ADL group (Spearman's rho -0.68; p=0.001) and the ADL-MTX group (Spearman's rho -0.40; p=0.03; Fig. S1).

In the ADL group high ADA titers correlated with a lower treatment response. In patients with no ADA the median ΔPASI in week 49 was 9.0 (7.1-10.9), for low ADA 6.6 (3.2-10.0) and for high ADA 2.8 (-1.3-6.9); Spearman's rho -0.56 (p=0.001).

In the ADL-MTX group ADA titers did show a significant correlation with treatment response in week 49 but not in any of the other weeks. In patients with no ADA the median Δ PASI at week 49 was 11.4 (7.4-15.4), for low ADA (only 3 patients) it was 2.5 (-1.6-12.2) and only two patients showed high ADA with ΔPASI of 0.3 and 4.6. (Spearman's rho −0.37, p=0.04).

Effect of bodyweight

Despite randomization we found a clinically relevant difference in bodyweight between the groups. Therefore, adjustments were made in a post-hoc linear regression model, which showed a change in association between treatment group and trough levels at week 49 when weight was added to the model (B 0.27, p=0.03 towards B 0.19, p=0.14).

The associations between treatment group and ΔPASI or number of patients with ADA at week 49 did not change when weight was added to the model.

Discussion

The results of this randomized controlled trial demonstrate that significantly more patients achieved PASI 75 and IGA clear or almost clear in the ADL-MTX group compared to the ADL group after one year of treatment. Patient reported outcomes on disease severity and quality of life improved significantly in both groups compared to baseline, with no major differences between the groups.

One-year drug survival seemed higher in the ADL-MTX group, although this was not statistically significant. The adalimumab survival rate in our study is comparable with real life drug survival data.[25] The tendency towards a prolonged drug survival in the ADL-MTX group is in line with data from an Israeli database, where in a small number of patients it was shown that MTX co-medication during biologic treatment resulted in a significant lower hazard ratio for treatment discontinuation compared to monotherapy.[19]

Significantly higher serum trough concentrations were found in the ADL-MTX group, with less patients showing drug concentrations below the therapeutic range of 3.2mg/L. However, the clinical relevance of this difference in serum trough levels needs to be explored in future studies as a correlation between drug concentrations and clinical response was not convincingly observed in the combination group.

In the ADL group high ADA titers correlated with low treatment response, but in the ADL-MTX group no correlation was found at most time points probably because very few patients showed antibodies in this group. The relatively good clinical response in some patients despite high ADA titers might be explained by the anti-inflammatory effect of MTX in these patients.

Post-hoc analysis showed an association between weight and adalimumab trough concentrations, which is a known and previously reported factor.[26] The lower bodyweight in the ADL-MTX group might have contributed to the enhanced treatment effect and higher trough levels, although weight did not influence the clinical response or the number of patients that showed ADA in the first year of treatment.

Evidence for the required dose of MTX co-medication as well as timing of introduction during adalimumab treatment was limited when the study started in 2014. We chose 10mg MTX/week, which reduces immunogenicity in RA patients, two weeks prior to the start of adalimumab. More recent studies in RA show a dose depended increase in adalimumab serum concentrations with MTX weekly doses of 2.5 to 10mg.[27] Higher doses might further enhance the clinical response, but do not add to the impact on ADA formation or adalimumab serum concentrations in RA.[27,28]

Pharmacokinetic studies (in RA patients) report that, at the same dose level, bioavailability of MTX may vary between individuals.[29] Although this variability is more pronounced in medium-to-high dosages (i.e., >15 mg/week) of MTX,

differences in serum concentrations of MTX might have contributed to the extent of efficacy in patients on combination therapy.

Overall, a tolerable safety profile for both treatment regimens was observed with no occurrence of serious adverse events. Slightly more patients discontinued treatment due to side effects in the ADL-MTX group compared to the ADL group. Changes in liver enzyme concentrations were small with no notable differences between treatment groups. Safety data of larger patient groups are needed as well as more long-term data. It should be taken into account that the prevalence of risk factors for MTX-related fibrosis (obesity, diabetes mellitus and alcohol intake) is higher in psoriasis compared with other inflammatory chronic diseases like RA.[30] More data will become available when the three-year follow up of this study is completed.

Strengths and limitations

Due to the pragmatic trial design we expect that our findings can be extrapolated directly to daily clinical practice and support guidance on the use of adalimumab combination therapy with MTX. Other study strengths include the blinded assessment of efficacy outcomes limiting detection bias and the standardized visit schedule allowing us to collect homogenous PK and immunogenicity data.

Not reaching the calculated sample size and a relative high drop-out rate before baseline are limitations of this study since it might limit the power to detect clinically relevant differences between the groups. The availability of different biologics, patients' previous exposure to adalimumab, their resistance to (re)introduce MTX and to meet the washout period hampered patient recruitment. This selection might also have biased the tolerability of MTX in our study, since 73.8% of participants had previously used MTX (without significant toxicity or intolerability).

Clinical implication and future perspectives

Despite the fact that new therapeutic agents are regularly introduced, long-term efficacy of available therapies remains important in the treatment of chronic diseases like psoriasis. Adalimumab has been a corner stone treatment in psoriasis due to its well-known beneficial treatment profile and the recent decrease in costs (as a result of the introduction of biosimilars) might retain its attractiveness. The enhanced effect obtained by addition of low dose MTX supports successful long-term treatment and might enable prolongation of dosing interval preferably under monitoring of trough concentrations in the future. This way the risk of side effects and treatment costs can be further reduced. Long-term (up to three years) follow-up data of this study might show a significant better drug survival in the ADL-MTX group, since the cumulative survival curves seem to diverge from week 13 onwards. Combination therapy with low dose MTX might reduce immunogenicity in other

biologics with neutralizing antibodies, such as infliximab, but more research in psoriasis patients is needed.[32]

Conclusion

Combination therapy of adalimumab and low dose MTX seems to improve the clinical efficacy, reduces ADA formation and increases adalimumab trough concentrations after one year of treatment compared to adalimumab monotherapy. It shows a tendency towards a prolonged drug survival. Adverse events were low, balanced between the groups, and did not result in significant treatment discontinuation. We believe combination therapy with low dose MTX should be considered when initiating adalimumab treatment in patients with plaque psoriasis.

Supplemental content
Please find the supplementary material (Fig. S1) in the electronic version of this thesis.

Acknowledgements

We thank S. Atalay, M. van Burken, N. Maes, R. Soenen, L. Prens, M. Tjong Joe Wai, F.M. Vermeulen, L. van Vugt for support in data collection, G.A. Appel, M. Kooijman-Otero, N. Pouw, H.M. van der Stok for monitoring this study, B. van Montfrans, S.W. Tas, A.H. Zwinderman for participating in data safety monitoring board.

References

1. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2017.
2. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. J Invest Dermatol. 2015;135(1):31-8.
3. Schouwenburg PA, Stadt LA, Jong RN, Buren EE, Kruithof S, Groot EJARD. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. 2013;72.
4. Berends SE, Strik AS, Van Selm JC, Lowenberg M, Ponsioen CY, D'Haens GR, et al. Explaining Interpatient Variability in Adalimumab Pharmacokinetics in Patients With Crohn's Disease. Therapeutic drug monitoring. 2018;40(2):202-11.
5. Xu Z, Davis HM, Zhou HJJCP. Clinical impact of concomitant immunomodulators on biologic therapy: pharmacokinetics, immunogenicity, efficacy and safety. 2015;55.
6. Menting SP, van Lumig PP, de Vries AC, van den Reek JM, van der Kleij D, de Jong EM, et al. Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up. JAMA Dermatol. 2014;150(2):130-6.
7. Menting SP, Coussens E, Pouw MF, van den Reek JM, Temmerman L, Boonen H, et al. Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis: A Step Toward Personalized Treatment. JAMA Dermatol. 2015;151(6):616-22.
8. Fagerli KM, Lie E, Heijde D, Heiberg MS, Lexberg AS, Rodevand EJARD. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. 2014;73.
9. Krieckaert CL, Nurmohamed MT, Wolbink GJJARD. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis 2012;71(11):1914-5.
10. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-77.

11. Zhang J, Xie F, Delzell E, Yun H, Lewis JD, Haynes KJACR. Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. 2015;67.

12. Farhangian ME, Feldman SR. Immunogenicity of biologic treatments for psoriasis: therapeutic consequences and the potential value of concomitant methotrexate. American journal of clinical dermatology. 2015;16(4):285-94.

13. Busard CI, Cohen AD, Wolf P, Gkalpakiotis S, Cazzaniga S, Stern RS, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. J Eur Acad Dermatol Venereol. 2018;32(2):245-53.

14. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. JAMA Dermatol. 2014;150(11):1213-20.

15. Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer KJBJD. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. 2012;167.

16. Zachariae C, Mork NJ, Reunala T, Lorentzen H, Falk E, Karvonen SLJADV. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. 2008;88.

17. Dalaker M, Bonesronning JHJJEADV. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with methotrexate or azathioprine in a retrospective cohort. 2009;23.

18. Driessen RJ, Kerkhof PC, Jong EMJBJD. Etanercept combined with methotrexate for high-need psoriasis. 2008;159.

19. Shalom G, Cohen AD, Ziv M, Eran CB, Feldhamer I, Freud T, et al. Biologic drug survival in Israeli psoriasis patients. J Am Acad Dermatol. 2017;76(4):662-9 e1.

20. Van den Reek JMPA, van Lümig PPM, Kievit W, Zweegers J, van de Kerkhof PCM, Seyger MMB, et al. Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice. Journal of Dermatological Treatment 2013;24(5):361-8.

21. Busard CIM, SP Menting, JS van Bezooijen, JM van den Reek, BA Hutten, EP Prens, EM de Jong, MB van Doorn, Ph I Spuls. Optimizing adalimumab treatment in psoriasis with concomitant methotrexate (OPTIMAP): study protocol for a pragmatic, single-blinded, investigator-initiated randomized controlled trial. Trials. 2017;18(1).

22. van der Kraaij GE, Balak DMW, Busard CI, van Cranenburgh OD, Chung Y, Driessen RJB, et al. Highlights of the updated Dutch evidence- and consensus-based guideline on psoriasis 2017. Br J Dermatol. 2019;180(1):31-42.

23. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.

24. Wilkinson N, Tsakok T, Dand N, Bloem K, Duckworth M, Baudry D, et al. Defining the Therapeutic Range for Adalimumab and Predicting Response in Psoriasis: A Multicenter Prospective Observational Cohort Study. J Invest Dermatol. 2019;139(1):115-23.

25. Egeberg AA-O, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178(2):509-19.

26. Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2017;31(3):490-7.

27. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis 2015;74(6):1037-44.

28. Nakashima Y, Miyahara H, Kondo M, Fukuda T, Harada H, Haraguchi A, et al. Impact of methotrexate dose on efficacy of adalimumab in Japanese patients with rheumatoid arthritis: Results from registered data analyses. Mod Rheumatol 2017;27(1):15-21.

29. Bianchi G, Caporali R, Todoerti M, Mattana P. Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration. Advances in therapy 2016;33(3):369-78.

30. Barker J, Horn EJ, Lebwohl M, Warren RB, Nast A, Rosenberg W, et al. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol 2011;25(7):758-64.

31. Strik AS, van den Brink GR, Ponsioen C, Mathot R, Löwenberg M, D'Haens GR. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2017;45(8):1128-34.

PART II

Pharmacodynamics, pharmacogenetics and immunogenicity of Ustekinumab

CHAPTER 6

Clinical consequences of antibody formation, serum concentrations, and HLA-Cw6 Status in psoriasis patients on ustekinumab

CIM Busard and E de Keyser, S Lanssens, L Meuleman, BA Hutten, A Costanzo, JM van den Reek, J Zweegers, J Lambert, PI Spuls

Ther Drug Monit 2019 Oct;41(5):634-639

Abstract

Background: Ustekinumab for the treatment of psoriasis is currently administered in a standard dosing regimen. However, some patients tend to benefit from alternative dosing regimens, a step towards personalized medicine.

Objective: To investigate the role of ustekinumab serum concentrations, anti-ustekinumab antibodies [AUA] and HLA-Cw6 status as tools for optimizing ustekinumab treatment.

Methods: A multicenter, prospective cohort study was conducted at an academic hospital with affiliated non-academic hospitals in Belgium (cohort 1) and two academic hospitals in the Netherlands (cohort 2 and 3). Patients with plaque-type psoriasis were eligible if treated with ustekinumab for ⩾16 weeks. Serum samples and Psoriasis Area and Severity Index [PASI] scores were obtained at baseline, week 16, 28, 40, 52 and/or ⩾ 64 of ustekinumab treatment.

Results: A total of 137 patients with 229 observations for serum concentrations and AUA and 61 observations for HLA-Cw6 status were included. Presence of AUA (prevalence of 8.7%) was significantly associated with a diminished clinical response (P=0.032). The median ustekinumab trough concentration was 0.3 µg/ml (<0.02-3.80). No differences in serum concentrations were observed between moderate to good responders and non-responders (P=0.948). Serum trough concentrations were not affected by methotrexate comedication. Prevalence of HLA-Cw6 positivity was 41% with no statistically significant difference in clinical response between HLA-Cw6 positive and negative patients (P=0.164).

Conclusion: The presence of AUA was associated with treatment failure in this patient population, measurement of AUA may therefore be a candidate marker for personalized pharmacotherapy. The clinical utility of ustekinumab serum trough concentrations or HLA-Cw6 status determination remains less clear. Further exploration on the potential of measuring ustekinumab serum concentrations and other biomarkers in predicting therapy outcomes should be encouraged.

Introduction

Improved knowledge of the underlying molecular mechanisms involved in the pathogenesis of immune-mediated inflammatory diseases resulted in novel targeted biologic therapies, which greatly advanced psoriasis care over the last decade. Currently registered biologics for psoriasis include the tumor necrosis factor (TNF) inhibitors adalimumab, infliximab and etanercept, the interleukin (IL)-17 inhibitors secukinumab, ixekizumab and brodalumab, the IL-12/ IL-23 inhibitor ustekinumab and p19/IL23-inhibitor guselkumab. Although they all inhibit pro-inflammatory cytokines, they differ in composition, efficacy and their pharmacokinetic and pharmacodynamic behavior. For more than a decade now, physicians have used standard recommended dosing regimens to treat psoriasis patients resulting in remarkable improvements in psoriasis treatment outcomes.[1-3] However, some patients fail to achieve desired outcomes or fail to maintain improvement over time.[4] Various theories have been investigated elaborately to address this problem, including immunogenicity.[5-7] Available evidence demonstrates that anti-adalimumab and anti-infliximab antibodies are associated with a decreased treatment response. However, the significance of anti-ustekinumab antibodies is less clear.[8,9]

Other factors that might contribute to loss of response include patient or disease factors (such as extent and severity or body weight) that lead to variable serum concentrations among patients over time.[10] Recently, we have proposed a therapeutic range for adalimumab, based on a significant association between clinical response (Psoriasis Area and Severity Index [PASI]) and serum trough concentrations.[11] The defined therapeutic range suggested that a third of the patients were actually over treated, which may lead to unnecessary higher costs and increased risk of adverse events.[12,13]

Ustekinumab is generally administered in a standard weight-dependent treatment regimen at week 0, 4 and every 12 weeks thereafter. Currently, limited evidence on therapeutic drug monitoring is available. With this study, we aim to determine whether ustekinumab serum trough concentrations, anti-ustekinumab antibodies (AUA) and HLA-Cw6 status are associated with clinical response in order to identify potential tools for ustekinumab drug monitoring.

Materials & Methods

Participants

Patients were eligible if they were ⩾18 years of age, suffering from plaque-type psoriasis, and treated with subcutaneous ustekinumab for a minimum of 16 weeks. Ustekinumab dosing and interval were generally administered in a standard weight-dependent treatment regimen (dose of 45mg for patients < 100 kg and 90mg for patients ⩾100kg) every 12 weeks. However, dosing and interval could be adjusted in case of treatment failure (based on clinical response, not on pharmacokinetic outcomes) according to daily clinical practice. Patients were recruited from different centers: The Ghent University Hospital and non-academic affiliated hospitals in Belgium (cohort 1) and the Academic Medical Center and Radboud University Medical Center in the Netherlands (cohort 2 and 3). Patient recruitment started in January 2011 and ended in August 2015. Patient demographics (age, sex, body mass index [BMI], disease duration, diagnosis of psoriatic arthritis, prior biologic treatment, disease severity at initiation of ustekinumab therapy [PASI baseline]) and treatment characteristics (ustekinumab dosing and concomitant use of methotrexate [MTX]) were collected at study entry.

Serum trough concentrations, AUA, HLA-Cw6 status and determination of clinical response

At baseline, week 16, week 28, week 40, week 52 and/or ⩾ week 64, serum samples were collected to determine ustekinumab trough concentrations, AUA and HLA-Cw6 status and PASI assessment was performed to determine clinical response.

The serum samples, obtained within 3 days before ustekinumab administration, were each centrifuged for 10 minutes at 1500g. Serum samples from cohort 1 and 3 were stored at −80°, whereas samples of cohort 2 were kept at −20°, until they were sent batchwise to the Laboratory for Monoclonal Therapeutics, Sanquin Diagnostic Services, Amsterdam, the Netherlands. Ustekinumab trough concentrations were determined using an enzyme-linked immunosorbent assay (ELISA). This assay is based on the principle that ustekinumab is captured through its ability to bind IL-12 and rabbit anti-ustekinumab for the detection of ustekinumab.[14,15] Results were reported in micrograms per milliliter (mcg/mL). Detection of AUA was performed trough a radioimmunoassay, which measures specific high avidity IgG antibodies against ustekinumab by an antigen-binding-test. These results were converted into arbitrary units (AU) per milliliter, with a cut-off value for positivity set at 12 AU/ml. [16,17]

Serum samples to determine ustekinumab trough concentrations and the presence of AUA were collected from all study patients. In cohort 1, HLA-Cw6 status was determined additionally. Samples for HLA-Cw6 allele genotyping were

stored at -80°C and DNA was extracted from leukocytes with the Promega Kit (ReliaPrep Large Volume HT gDNA Isolation System, Madison, Wisconsin, USA). PCR was performed with allele-specific primers: 5'-TACTACAACCAGAGCGAGGA-3'; 5'-GGTCGAGCCATACATCCA-3'. Results were interpreted as either positive or negative. All methods were performed according to the manufacturer's instructions.

To assess clinical response, PASI and mean change in PASI (ΔPASI) were obtained and patients were classified as non-responder (ΔPASI <50.00%), moderate responder (ΔPASI 50.00-74.99%) or good responder (ΔPASI 75.00-100.00%).

Statistical analysis

SPSS Statistics 22.0 (IBM, Armonk, NY, USA) was used for the statistical analysis of all data. To compare baseline characteristics between the three cohorts and between subgroups of patients, a Fisher exact test was used for categorical variables and Mann-Whitney U or Kruskal-Wallis tests were used for continuous variables. The associations between serum trough concentrations, AUA and clinical response were evaluated using a linear mixed model. To ensure results would not be influenced by transitioning from another biologic or concomitant use of MTX, these factors were accounted for. A Fisher exact test was used to compare clinical response between HLA-Cw6 positive and HLA-Cw6 negative patients. For each test, a p-value <0.05 was considered statistically significant.

Ethics

Approval for this multicenter cohort study was obtained from the medical ethics committees of all participating hospitals and all patients gave their written informed consent before participation. The study is being conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other relevant guidelines, regulations and acts.

Results

Study population

Of 141 eligible patients, two patients refused participation and two patients were excluded as these patients had isolated nail psoriasis. Consequently, 137 patients were included in the cohort (respectively 62, 48 and 27 patients in cohort 1, 2 and 3). Table 1 demonstrates demographic characteristics, which were comparable between cohorts. Patients (69.1% male) had a high body mass index (BMI of 28.9 [± 6.1] kg/m^2), a mean disease duration of 23.6 ± 12.9 years and a mean PASI of 14.2 ± 7.6 at initiation of ustekinumab treatment. Thirty patients (21.9%) were diagnosed with psoriatic arthritis and most patients (76.8%) received other biologic treatment(s) prior to ustekinumab. Twenty-five of 137 patients (18.2%) did not receive the standard ustekinumab dosing and schedule. In these patients dosing was adjusted based on clinical response. Seven patients with a body weight of 93-99 kg received 90 mg and 6 patients with a body weight of 101-105 kg received 45 mg. Twelve patients received ustekinumab every 10 weeks instead of every 12 (due to insufficient response).

In total, forty-three patients (31.2%) were treated with ustekinumab 90 mg and 15 patients (10.9%) used MTX comedication.

Data on serum trough concentrations, AUA and clinical response were collected in all study patients. Data were collected at a single time point in 77 patients and at repeated time points in 60 patients (in 28 patients at two time points and in 32 patients at three time points). Data were collected in 75 patients at week 16, in 64 patients at week 28, in 10 patients at week 40, in 42 patients at week 52 and in 38 patients after ⩾ 64 weeks. Subsequently, during this study, 229 observations for serum trough concentrations, AUA and clinical response were obtained. At week 16, week 28, week 40-52 and ⩾ 64, 34.7%, 32.8%, 48.1% and 65.8% of patients achieved PASI 75, respectively.

Table 1. Patient demographics

Age in yr, mean (SD)	50.0 (± 12.6)
Male sex, No (%)	96 (70.1)
BMI in kg/m^2, mean (SD)	28.9 (± 6.1)
Psoriasis disease duration in yr, mean (SD)	23.6 (± 12.8)
Diagnosis of PsA, No (%)	30 (21.9)
Concomitant methotrexate, No (%)	15 (10.9)
Prior biologic treatment, No (%)	105 (76.6)
PASI baseline, mean (SD)	14.1 (± 7.4)

BMI, body mass index, PsA, psoriasis arthritis.

Ustekinumab serum trough concentrations

The median (range) serum trough concentration was 0.3 µg/ml (<0.02-3.80). Four patients had undetectable serum trough concentrations (<0.02) at week 16. At week 28, 40, 52 and ≥64 no undetectable serum trough concentrations were observed. No statistically significant difference in trough concentrations was observed for patients receiving 45mg versus 90mg, with median (range) values of 0.30 µg/ml (<0.02-3.60) and 0.40 (<0.02-3.80) µg/ml respectively (P=0.14). Patients that used MTX comedication (n=15, 10.9% of study population; 26 observations) demonstrated ustekinumab trough concentrations similar to patients on ustekinumab monotherapy; 0.30 µg/ml (<0.02-3.60) and 0.30 µg/ml (<0.02-3.80), respectively (P=0.95).

No statistically significant difference was found in serum trough concentrations between moderate to good responders and non-responders [median (range); 0.3 (<0.02-3.80), 0.3 (<0.02-3.60) and (<0.02-1.96) respectively, P=0.948; fig 1].Additionally, no significant correlation was found between ustekinumab trough levels and Δ PASI (P=0.302).

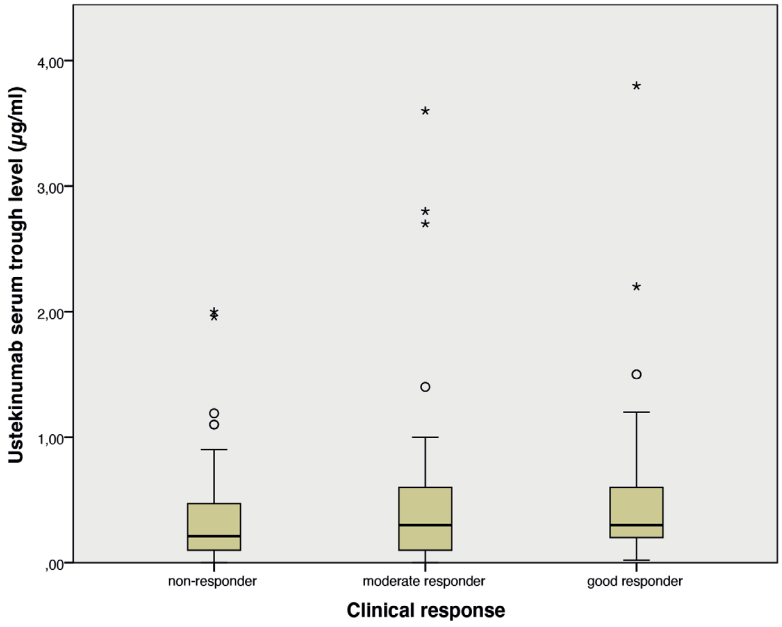


Figure 1. Box-and-whisker plot showing Ustekinumab trough concentrations across response groups. No statistically significant difference in serum trough concentrations was found between nonresponders, moderate responders, and good responders (P = 0.948). The limits of the boxes represent the interquartile (IQ) range. The line in the boxes is the median. The whiskers extend from the upper and lower edge of the box to the highest and lowest values, which are no greater than 1.5 times the IQ range. The circles and asterisks indicate outliers (values between 1.5 and 3 times the IQ range) and extreme outliers (values more than 3 times the IQ range), respectively.

Development of AUA

AUA were detected in 12 of 137 patients (8.7%). In 3 of these patients AUA were cleared during the study. Two of these patients remained non-responders and 1 patient achieved a good clinical response when AUA were cleared. In the other patients AUA persisted during the study (n=5) or the evolution of AUA-status remained unknown (n=4), out of which AUA-status was only collected at a single time point (n=3) or AUA were only detected at the final study observation (n=1).

AUA were detected in 6 of 75 observations (8.0%) at week 16, in 7 of 64 observations (10.9%) at week 28, in 1 of 10 observations (10%) at week 40, in 4 of 42 observations (9.5%) at week 52 and in 0 of 38 observations (0.0%) after ≥ 64 weeks. The AUA titer in AUA positive patients ranged from 22 - 320 AU/ml. Median (range) serum trough concentrations were significantly lower in antibody-positive patients compared to antibody-negative patients; 0.02 µg/ml (<0.02-0.20) versus 0.30 µg/ml (<0.02-3.80) µg/respectively (P<0.001). A good response was significantly more frequently achieved in AUA-negative patients compared to AUA-positive patients (44.1% vs. 22.2%, P=0.032), Figure 2.

In patients on MTX comedication, 1 of 15 patients (6.7%) developed AUA compared to 11 of 122 patients (9.0%) on ustekinumab monotherapy, with no statistically significant differences between groups (P=0.77).

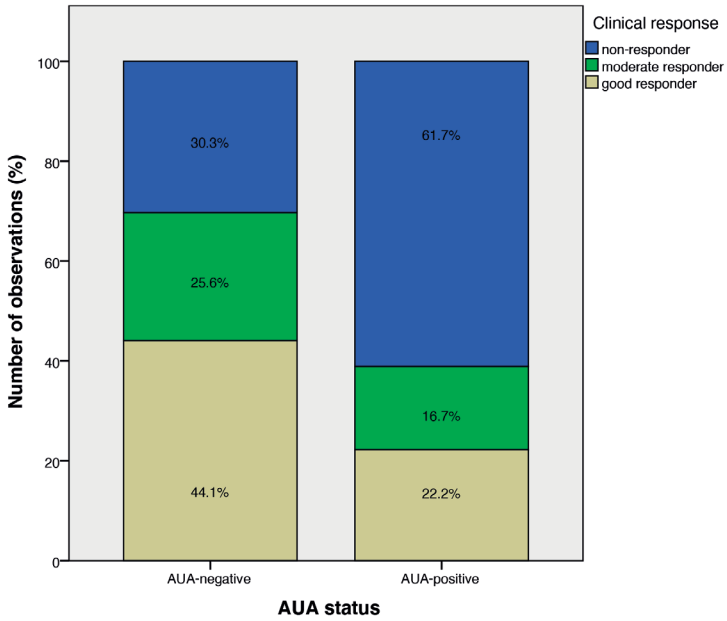


Figure 2. Clinical response according to AUA status. A good response was significantly more frequent achieved in AUA-negative patients compared with AUA-positive patients (44.1% versus 22.2%, P = 0.032).

HLA-Cw6 genotyping

HLA-Cw6 status was determined in 61 of 137 patients (44.5% of study population). Prevalence of HLA-Cw6 positivity was 41%. Most of the demographic characteristics were comparable between HLA-Cw6 positive and negative patients, except for age at onset of psoriasis and prevalence of psoriatic arthritis. HLA-Cw6 positive patients developed psoriasis at an earlier age (21.4 versus 31.6 years, p=0.012) and the prevalence of psoriatic arthritis was higher (though not significant) in HLA-Cw6 negative patients (28.6 vs. 8.3%, P=0.098). No statistically significant difference in clinical response (assessed ⩾ 16 weeks) between Cw6-positive and Cw6-negative patients could be demonstrated (P=0.164), although on average slightly better response rates in Cw6-positive patients were observed (Fig. 3).

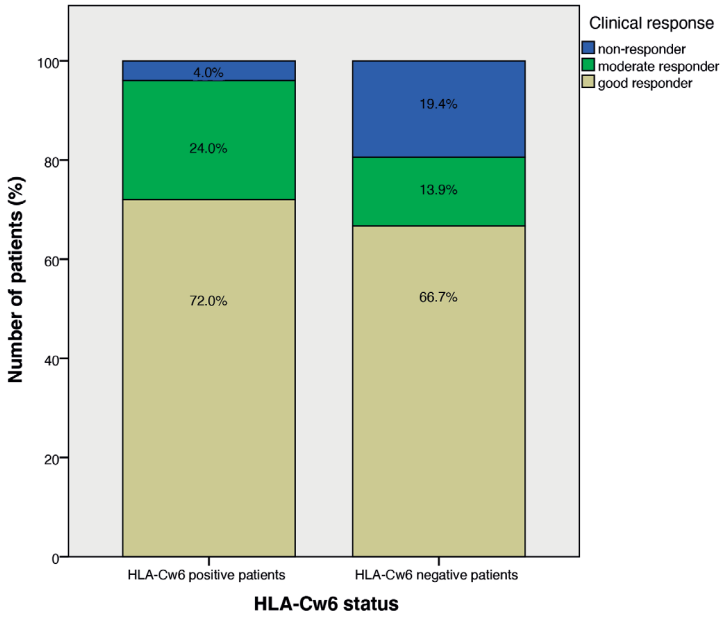


Figure 3. Clinical response according to HLACw6 status. There was no statistically significant difference in response between HLA-Cw6–positive and HLA-Cw6–negative patients (P = 0.164).

Discussion

The prevalence of AUA development was 8.7% which is comparable to the prevalence rates reported in the current literature (1 – 11 %),[9,18-20] but much lower than observed for other biologics such as adalimumab and infliximab. AUA-positivity significantly reduced serum trough concentrations and impaired clinical response. These data are supported by previously reported findings suggesting a trend towards decreased treatment response with the formation of AUA.[18,21,22]

In this cohort, AUA did develop during the first 52 weeks of ustekinumab treatment. However, the number of observations obtained in the first year of ustekinumab treatment (n=191) was higher compared to the number of observations obtained in patients > 1 year on ustekinumab treatment (n=38) which might underestimate the prevalence of AUA formation after long-term ustekinumab treatment.

We did not find a significant association between ustekinumab serum trough concentrations and clinical response. This observation is in line with the findings of Menting et al.[19] An optimal ustekinumab threshold trough concentration as suggested in other inflammatory diseases can therefore not yet be recommended. In a cohort study by Toro-Montecinos et al., maintenance trough concentrations of ustekinumab in Crohn's disease above 4.5 µg/mL at 26 weeks or later was identified to correspond to an optimal clinical effect.[23]

In a small number of patients (1.7%) in our cohort, undetectable ustekinumab serum trough concentrations were measured. This could be partly explained by the presence of anti-drug antibodies. Other factors that could have contributed to this include patient's non-adherence, total clearance of ustekinumab at the time of serum sample collection or inadequate detection of serum trough concentrations in patients with severe and active psoriasis in which all ustekinumab is bound to IL-12 and IL-23.

For anti-TNF inhibitors a significant association between immunomodulatory comedication (e.g. MTX) and serum trough concentrations has been demonstrated in several studies.[24-26] In our study, MTX comedication did not significantly impact ustekinumab serum concentrations, which might be partly due to the low incidence of anti-ustekinumab antibodies. However, results should be interpreted with caution due to the small number of patients on MTX comedication. The therapeutic impact of MTX in patients on ustekinumab needs to be confirmed by future studies with sufficient power.

In this cohort, we included patients treated with ustekinumab for a minimum of 16 weeks. More and more data arise showing that early pharmacokinetic drug measurements, i.e. during induction phase, might be predictive for drug concentrations and clinical response on maintenance treatment. Recently, Wilkinson et al. reported

on a large adalimumab cohort of 544 psoriasis patients and demonstrated that early drug concentration measurements (obtained between 1 and 12 weeks) were predictive for clinical response at 6 months.[27] Whether measurement of ustekinumab early in treatment will help to make strategic treatment decisions is currently unknown and will be a valuable topic for future research.

With regard to pharmacogenetic markers, HLA-Cw6 has been suggested to potentially predict clinical response in psoriasis patients on ustekinumab.[28-31] We observed a slight increase in response to ustekinumab in HLA-Cw6 positive patients compared to HLA-Cw6 negative patients, but the differences were small and not statistically significant. Several studies have elaborated on single nucleotide polymorphisms other than HLA-Cw6 and detected an association between some of these polymorphisms and response to ustekinumab treatment.[31,32] These results will have to be further explored to assess whether pharmacogenetic markers can play a role in the prediction of response to ustekinumab.

Our study has some limitations. First, it is still not an extensive patient population, especially to draw conclusions on whether HLA-Cw6 status can predict clinical response. Second, not all possible factors that might influence treatment response to ustekinumab (e.g. topical therapy and adherence) were considered. Third, the data were collected at different time points and serial measurements were collected only in part of the patients (43.8%) which might impact the detection of e.g. AUA formation.

Conclusion

Based on available evidence and our study results, we conclude that there is currently overall insufficient evidence to support the use of serum trough concentrations or HLA-Cw6 status to guide treatment decisions in ustekinumab patients. Measurement of AUA in ustekinumab patients should be considered if treatment response is unsatisfactory.

Future research is needed to gain a better understanding on ustekinumab pharmacokinetics and pharmacodynamics and to identify additional tools for therapeutic drug monitoring in psoriasis patients on ustekinumab treatment.

References

1. Grine L, Dejager L, Libert C, et al. An inflammatory triangle in psoriasis: TNF, type I IFNs and IL-17. Cytokine Growth Factor Rev. 2015;26(1):25-33.
2. Benson JM, Sachs CW, Treacy G, et al. Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. Nat Biotechnol. 2011;29(7):615-24.
3. Wang YM, Wang J, Hon YY, et al. Evaluating and reporting the immunogenicity impacts for biological products-a clinical pharmacology perspective. AAPS J. 2016;18(2):395-403.
4. Warren RB, Smith CH, Yiu ZZN, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.
5. de la Brassinne M, Ghislain PD, Lambert JL, et al. Recommendations for managing a suboptimal response to biologics for moderate-to-severe psoriasis: A Belgian perspective. J Dermatolog Treat. 2016;27(2):128-33.
6. Lambert J, Nast A, Nestle FO, et al. Practical guidance on immunogenicity to biologic agents used in the treatment of psoriasis: What can be learnt from other diseases? J Dermatolog Treat. 2015;26(6):520-7.
7. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72(2):165-78
8. Bito T, Nishikawa R, Hatakeyama M, et al. Influence of neutralizing antibodies to adalimumab and infliximab on the treatment of psoriasis. Br J Dermatol. 2014;170(4):922-9.
9. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: a systematic review. *Br J Dermatol*. 2014;170(2):261-73.
10. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. *J Invest Dermatol*. 2015;135(1):31-8.
11. Menting SP, Coussens E, Pouw MF, et al. developing a therapeutic range of adalimumab serum concentrations in management of psoriasis*:* a step toward personalized treatment. *JAMA Dermatol*. 2015;151(6):616-22.
12. Krieckaert CL, Nair SC, Nurmohamed MT, et al. Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Ann Rheum Dis*. 2015;74(2):361-8

13. Lebwohl M, Yeilding N, Szapary P, et al. Impact of weight on the efficacy and safety of ustekinumab in patients with moderate to severe psoriasis: rationale for dosing recommendations. *J Am Acad Dermatol*. 2010;63(4):571-9.

14. van Schouwenburg PA, Bartelds GM, Hart MH, et al. A novel method for the detection of antibodies to adalimumab in the presence of drug reveals "hidden" immunogenicity in rheumatoid arthritis patients. *J Immunol Methods*. 2010;362(1-2):82-8.

15. Rispens T, Leeuwen Av, Vennegoor A et al. Measurement of serum levels of natalizumab, an immunoglobulin G4 therapeutic monoclonal antibody. *Anal Biochem*. 2011;411(2):271-6.

16. Rispens T, de Vrieze H, de Groot E et al. Antibodies to constant domains of therapeutic monoclonal antibodies: anti-hinge antibodies in immunogenicity testing. *J Immunol Metho*ds. 2012;375(1-2):93-9.

17. Wolbink GJ, Vis M, Lems W, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum*. 2006;54(3):711-5.

18. Chiu HY, Chu TW, Cheng YP, et al. The association between clinical response to Ustekinumab and immunogenicity to Ustekinumab and prior Adalimumab. *PLoS One*. 2015;10(11):e0142930.

19. Menting SP, van den Reek JM, Baerveldt EM, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. *Br J Dermatol*. 2015;173(3):855-7.

20. Strand V, Balsa A, Al-Saleh J, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. *BioDrugs*. 2017;31:299-316.

21. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci*. 2011;63(3):154-63.

22. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371(9625):1675-84.

23. Toro-Montecinos M, Ballesca F, Ferrandiz A, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2017;15(9):1427-34.

24. Ternant D, Ducourau E, Perdriger A, et al. Relationship between inflammation and infliximab pharmacokinetics in rheumatoid arthritis. *Br J Clin Pharmacol*. 2014;78(1):118-28.

25. Vogelzang EH, Pouw MF, Nurmohamed M, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2015;74(2):474-5.

26. Xu Z, Davis HM, Zhou H. Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety. *J Clin Pharmacol*. 2015;55 Suppl 3:S60-74.

27. Wilkinson N, Tsakok T, Dand N, et al. Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study. *J Invest Dermatol*. 2019;139(1):115-123.

28. Talamonti M, Galluzzo M, van den Reek JM, et al. Role of the HLA-C*06 allele in clinical response to ustekinumab: evidence from real life in a large cohort of European patients. *Br J Dermatol*. 2017;177(2):489-496.

29. Talamonti M, Galluzo M, Chimenti S, et al. HLA-C*06 and response to ustekinumab in Caucasian patients with psoriasis: Outcome and long-term follow-up. *J Am Acad Dermatol*. 2016;74(2):374-5.

30. Chiu HY, Wang TS, Chan CC, et al. Human leucocyte antigen-Cw6 as a predictor for clinical response to ustekinumab, an interleukin-12/23 blocker, in Chinese patients with psoriasis: a retrospective analysis. *Br J Dermatol*. 2014;171(5):1181-8.

31. Talamonti M, Botti E, Galluzzo M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol*. 2013;169(2):458-63.

32. Prieto-Perez R, Llamas-Velasco M, et al. Pharmacogenetics of ustekinumab in patients with moderate-to-severe plaque psoriasis. *Pharmacogenomics*. 2017;18(2):157-164.

33. Prieto-Perez R, Solano-Lopez G, Cabaleiro T, et al. New polymorphisms associated with response to anti-TNF drugs in patients with moderate-to-severe plaque psoriasis. *Pharmacogenomics J*. 2018;18(1):70-75.

PART III

(Gaps in) the management of patients with nail psoriasis

CHAPTER 7

Reporting of outcomes in randomized controlled trials on nail psoriasis

A systematic review

CIM Busard, JYC Nolte, MC Pasch, PI Spuls

Br J Dermatol 2018 Mar;178(3):640-649

Summary

Background: Harmonization of outcome measures is needed to increase the value of clinical trials on nail psoriasis.

Objectives: To provide the first step in core outcome set (COS) development for nail psoriasis.

Methods: A systematic review was performed to identify outcome instruments and corresponding outcome domains used in (ongoing) randomized controlled trials.

Results: Identified outcome domains included clinical signs, quality of life, symptoms and delivery of care. The Nail Psoriasis Severity Index (NAPSI) was the most commonly used measure to assess clinical signs (74% of studies). Other outcome instruments used included the Nail Area Severity score, composite fingernail score, a Physician's Global Assessment, individual nail features or a combination of these. Heterogeneity in type and reporting (e.g. NAPSI 50, NAPSI 75) of outcome instruments was high and characteristics were often insufficiently reported. In total 43% of studies assessed quality of life, with 3% of studies using a nail psoriasis-specific tool. Assessment of symptoms an d delivery of care was limited.

Conclusions: Heterogeneity in the type and reporting of nail psoriasis outcome instruments needs to be addressed in the process towards COS development. Sufficient reporting of instrument characteristics should be encouraged. As nail psoriasis is generally assessed secondarily to psoriasis of the skin or joints, collaboration between different research groups in COS development is needed.

Introduction

Nail psoriasis is estimated to be present in 50 to 80% of patients with plaque psoriasis and can be associated with substantial restrictions in daily life activities.[1] Treatment can be challenging due to limited penetration through the nail plate and slow regeneration of the nail.[2] Moreover, patients with nail psoriasis are often undertreated.[3] Fortunately, scientific interest in the field of nail psoriasis has increased over the last couple of years and important new data on nail psoriasis interventions have emerged. In 2013 de Vries *et al.* published a Cochrane systematic review on nail psoriasis interventions, which is currently being updated.[4] Although a comprehensive overview of available nail psoriasis treatment options could be provided, data synthesis was severely limited due to substantial heterogeneity in outcome measurement instruments (further referred to as outcome instruments).

Generally, assessment of nail psoriasis severity is based on the presence or absence of diverse morphological changes resulting from inflammation at the nail matrix or nail bed. Based on the anatomical structure of the nail, nail features can be categorized into features of the nail matrix (e.g. pitting, red spots in the lunula, leukonychia, crumbling, Beau's lines, longitudinal ridges and onychomadesis) and nail bed (e.g. onycholysis, splinter hemorrhages, salmon patches, oil drop discoloration and subungual hyperkeratosis).

Over the last two decades multiple outcomes instruments have been developed.5 Each of these tools scores the absence or presence of nail features, but they differ in selection and methods used to assess included nail features. The Psoriasis Nail Severity Score was introduced in 19946, followed by the Nail Area Severity (NAS) score[7], the Baran scoring system8, the Nail Psoriasis Severity Index (NAPSI)[9, 10], the modified NAPSI[11, 12,] the Nijmegen-Nail psoriasis Activity Index tool[5], the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) and the Brigham Scalp Nail Inverse Palmoplantar Psoriasis Composite Index.[13] Moreover, quite recently, the first nail psoriasis-specific quality-of-life instruments (Nail Psoriasis Quality 10, NPQ10; and Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life, NAPPA-QoL) have been introduced.[14, 15]

In the era of evidence-based medicine, scientific interest in outcome research and the development of core outcome sets (COSs) has increased substantially. A COS is defined as an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. In dermatology, the Harmonising Outcome Measures for Eczema (HOME)[16] initiative provides general and methodological guidance for the selection process and implementation of a COS among other initiatives that have been developed to guide and monitor the process towards harmonization of outcome measures.[17-21] The development of

a COS is ongoing for conditions including atopic eczema and vitiligo.[22-25] For nail psoriasis, harmonization of outcome instruments is urgently needed to increase the comparability of clinical trials, enable meta-analyses and ensure that only valid and reliable tools are used. Currently, the Outcome Measures in Rheumatology (OMERACT) working group is developing a COS for psoriatic arthritis in which nail psoriasis as a component of psoriatic skin disease is selected for the inner core set [which should be measured in all randomized controlled trials (RCTs) and longitudinal observational studies].[26, 27] Similarly, the International Dermatology Outcome Measures (IDEOM) psoriasis working group is in the process of developing a COS for psoriasis, which might include assessment of psoriatic nails.[28] However, currently, no comprehensive overview of nail psoriasis outcome instruments is available.

With this systematic review we aim to (i) identify all outcome instruments previously and currently used in RCTs on nail psoriasis and (ii) categorize identified outcome instrumentsin corresponding outcome domains.

Methods

This systematic review has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[29] The study has been registered at Cochrane Skin Group Core Outcomes Set Initiative (COUSIN) and at the COMET database.

Eligibility criteria

RCTs on any type of intervention in patients with nail psoriasis as main clinical feature or in patients with psoriasis of the skin or joints and involvement of the nails were eligible for inclusion. RCTs reporting on pustular psoriasis of the nails, acropustulosis keratotica and acrodermatitis continua of Hallopeau were excluded.

Literature search

We searched the following databases up to 23 November 2015: Cochrane Skin Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974) and LILACS (Latin American and Caribbean Health Science Information database, from 1982) (Table S1; see Supporting Information). Additionally, the following trial registers were searched on 1 December 2015 using the terms ‘nail’ and ‘psoriasis’: (i) the metaRegister of Controlled Trials (http://www.isrctn.com); (ii) the U.S. National Institutes of Health ongoing trials register (www.clinicaltrials.gov); (iii) the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); (iv) the World

Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch); and (v) the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The reference lists of identified RCTs and key review articles were checked for further references of relevant trials. No language restrictions were applied.

Study selection

Two review authors (C.I.M.B. and M.C.P.) independently checked the titles and abstracts identified from the searches, taking into account inclusion and exclusion criteria. If assessment of nail psoriasis was not mentioned in the title and/or abstract, full texts of the initially selected studies were independently checked by the same two reviewers to determine whether they met the predefined eligibility criteria. Differences in selection were discussed with a third review author (P.I.S.).

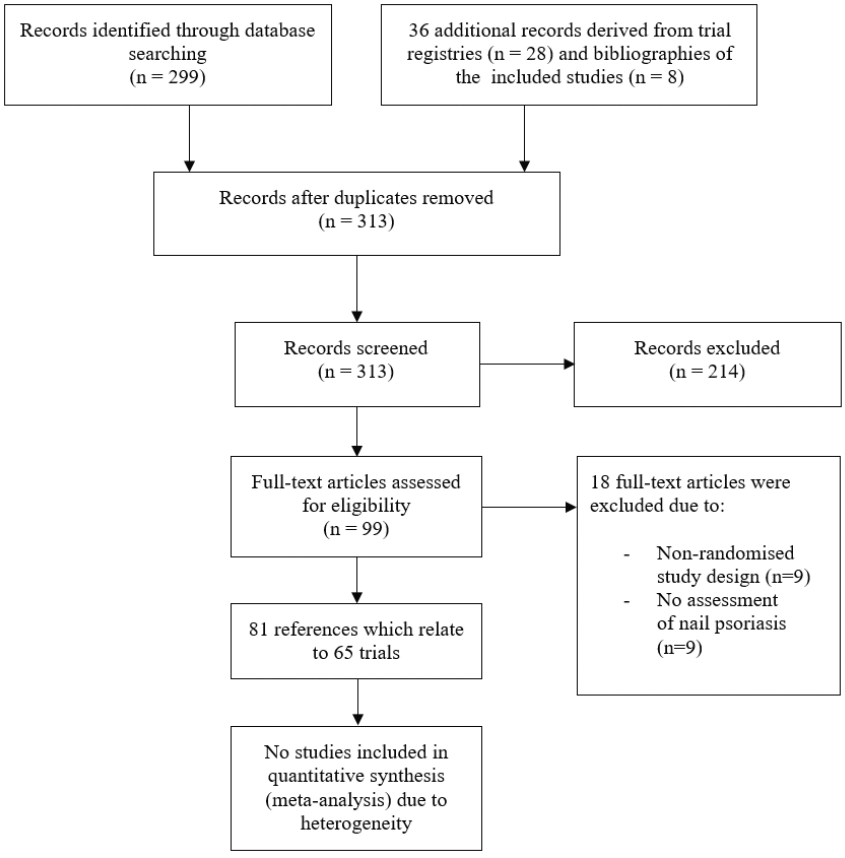
Data extraction

Two reviewers (C.I.M.B. and J.Y.C.N.) independently extracted the data. For each included study, the author and year of publication (or trial register number and year of conduction or completion for trials that have not yet been published) and type of intervention were extracted. All outcome instruments used in each RCT were included, except for outcomes related to safety. Outcome instruments that measure different outcomes were defined as composite outcome instruments (e.g. NAPSI), and outcome instruments that measure a single outcome were defined as stand-alone outcome instruments (e.g. subungual hyperkeratosis). Subsequently, outcome instruments were categorized into corresponding outcome domains. Numbers of studies using the same outcome instrument were summarized quantitatively.

Results

The search identified 335 references. Ninety-nine references were selected for full-text examination, and 65 RCTs (37 published, 28 awaiting publication or ongoing) were included (Fig. 1). The trial characteristics are provided in Table S2 (see Supporting Information). Four outcome domains were identified: clinical signs, quality of life, symptoms and delivery of care. 'Clinical signs' corresponds to outcome instruments that measure morphological changes of nail psoriasis disease (e.g. onycholysis); 'quality of life' corresponds to outcome instruments that measure the impact of nail psoriasis disease on daily life activities; 'symptoms' corresponds to outcome instruments that assess an appearance or feeling that is noticed by the patient, indicating the presence of disease or abnormality (e.g. pain); and 'delivery of care' corresponds to outcome instruments that measure factors associated with delivery of health care (e.g. patient satisfaction).

Fig 1. Study flow diagram



Clinical signs

Composite outcome instruments

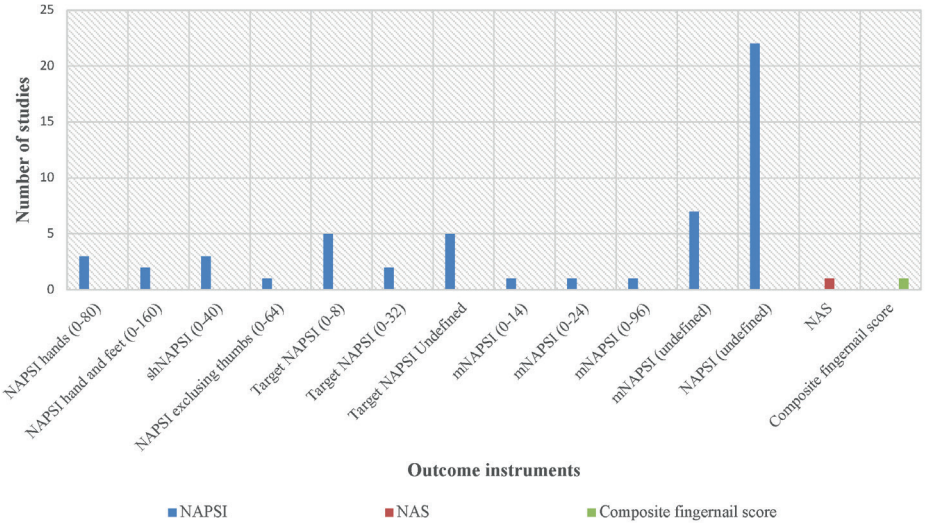
Nail Psoriasis Severity Index assessment. NAPSI can be categorized into three primary subtypes: NAPSI with assessment of nail matrix and nail bed features, generally applied to four quadrants of all 10 fingernails and/or toenails;[9] the target NAPSI with assessment of nail matrix and nail bed features in the most severely affected nail;[9] and the modified NAPSI with addition of a degree of severity (0-3) for each nail matrix and nail bed feature in the most severely affected nail.[11, 12]

Overall, 74% of studies assessed one or more types of NAPSI. A target NAPSI was most commonly used, with assessment in 27% of studies on a scale of 0-8.[30-42] A modified NAPSI was used in 22% of studies with assessment on scales of 0-24 (degree of severity for nail matrix and nail bed features),[43] 0-96 (degree of severity for each nail matrix and bed feature assessed separately in each quadrant),[44] 0-14 (degree of severity for crumbling, onycholysis and pitting only)[45] or on a scale that was not defined.[37, 46-51] A NAPSI of multiple nails was used in 20% of studies, with assessment of all finger and/or toenails[42, 52-54], a single-hand[43, 46, 47] or all fingernails excluding the thumbnails[32]. The majority of (mostly ongoing) studies (46%) did not adequately report the characteristics of NAPSI (to be) used. (Fig. 2, Table S3; see Supporting Information).[42, 48, 50, 55-72]

The way NAPSI was analyzed and reported varied widely between RCTs. [32, 38, 44, 48, 50, 64] Examples are proportion of patients who achieved ≥50% (NAPSI 50), ≥75% (NAPSI 75), ≥90% (NAPSI 90) or 100% improvement (NAPSI 100), mean improvement in NAPSI over time and NAPSI ≤4.

NAS and composite fingernail score. Two other composite outcome instruments were used to assess clinical signs: the NAS with assessment of the extent of the nail pitting area, the number of nail pits, subungual keratosis, onycholysis and oil spots in a target nail of each hand;[7] and the composite fingernail score with assessment of all fingernails.[73] It remained unclear which nail features were assessed using this outcome instrument.

Fig 2. Clinical signs – composite outcome instruments



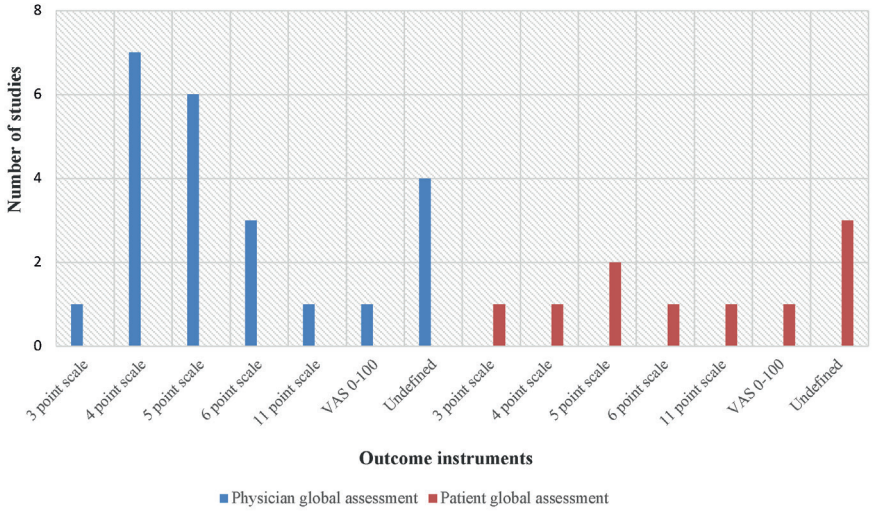
NAPSI, Nail Psoriasis Severity Index; mNAPSI, modified nail psoriasis severity index; shNAPSI, single hand nail psoriasis severity index; NAS, nail area severity

Stand-alone outcome instruments

Global assessment by a physician or patient. In total 38% of studies reported on global assessment to assess clinical signs. (Fig. 3, Table S4; see Supporting Information). The majority (23 studies) reported on global assessment by a physician. Ten studies reported on global assessment by the patient. A fourpoint[43, 74-79] or five-point scale[7, 33, 35, 36, 75, 80, 81] were most commonly used. Other studies assessed global assessment on a three-point,[37, 82] six-point,[46, 79, 83] 11-point,[84] 100-point,[32] or undefined scale.[50, 72, 85, 86,67, 83] Generally, it remained unclear whether and which nail features or characteristics were taken into account and whether global assessment concerned all or part of the nails.

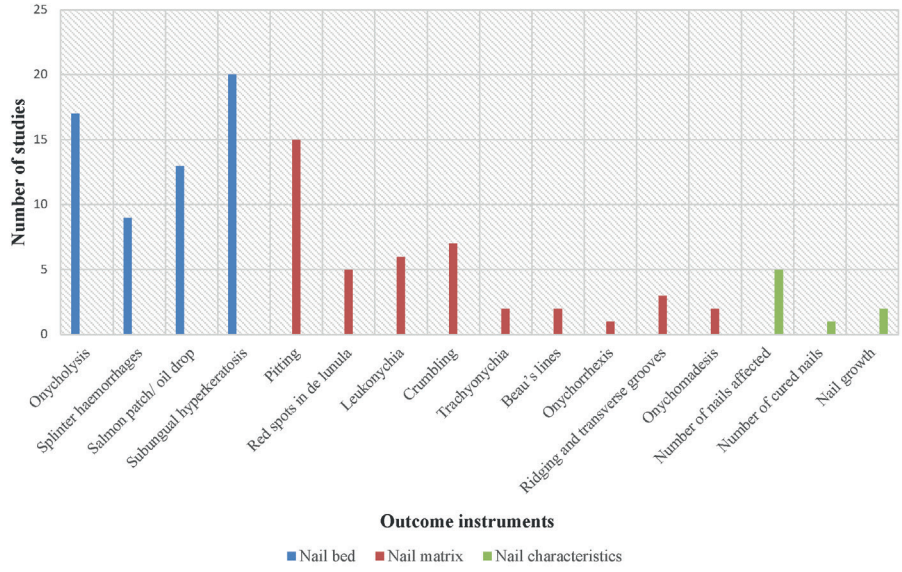
Individual nail features and characteristics. Overall, 35% of studies reported on individual nail features or characteristics to assess clinical signs (Fig. 4, Table S5; see Supporting Information). Nineteen studies[7,33,34,43,47,53,61,75-77,80,81,87-93] reported on individual nail features, of which subungual hyperkeratosis, onycholysis and pitting were most commonly assessed (in 19, 17 and 15 studies, respectively). Other nail characteristics assessed included nail growth, number of cured nails and change in number of affected nails.[33,34,39,43,49,65,87,90] The majority of studies combined assessment of individual nail features or characteristics with NAPSI or global assessment.

Fig 3. Clinical signs – stand-alone outcome instruments (global assessment)



VAS, Visual Analogue Scale

Fig 4. Clinical signs - stand-alone outcome instruments (nail features and characteristics)



Quality of life, symptoms and delivery of care

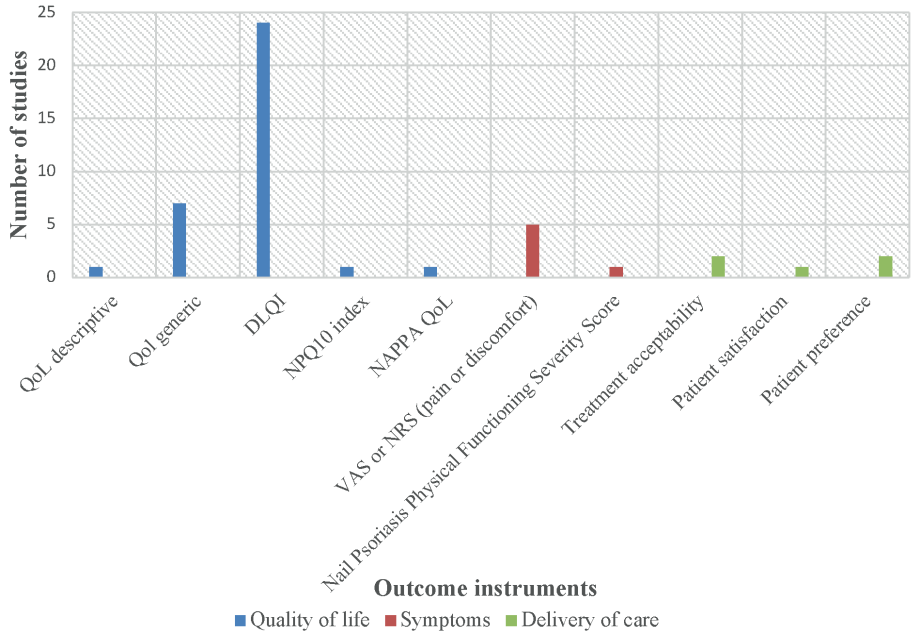
Quality of life was assessed in 43% of studies (Fig. 5, Table S6; see Supporting Information). The majority of studies used a generic or dermatology-specific

instrument (e.g. Dermatology Life Quality Index).[30, 32, 35, 36, 38, 39, 41, 42, 55-62, 64, 67, 69-72, 85] Recently introduced nail psoriasis-specific quality-of-life questionnaires were incorporated in two study protocols of ongoing studies (NPQ10[15] and NAPPA-QoL[14]). A Nail Psoriasis Physical Functioning Severity Score was assessed in one study.[50] It remained unclear which items were assessed by using this instrument.

Symptoms (limited to pain and discomfort) were assessed in only 8% of studies, using a visual analogue scale or numerical rating scale (Fig. 5, Table S6). In two studies[52, 91] symptoms were scored to assess tolerability of treatment. In the remaining studies[50, 60, 72] symptoms were scored to detect a change in pain or discomfort under treatment with the investigational drug.

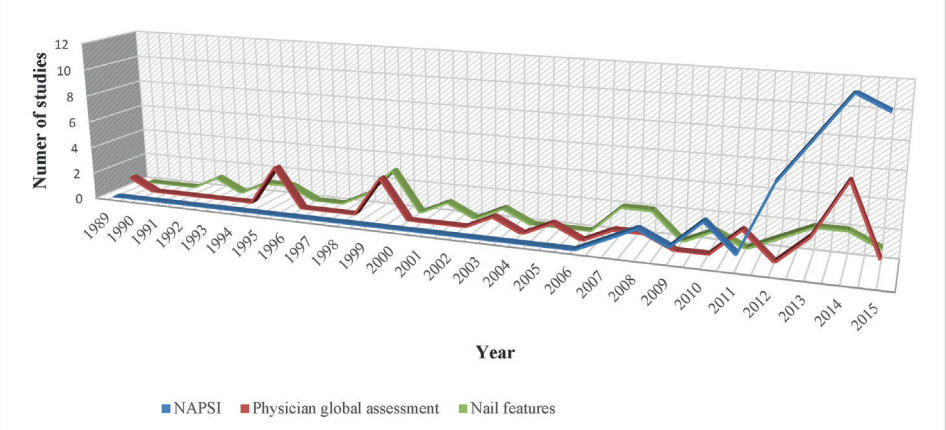
Delivery of care (acceptability of treatment, treatment satisfaction and patient preference) was assessed in 8% of studies (Fig. 5, Table S6) using point scales or a single question (e.g. which of two treatment options is preferred?).[44, 90,64,46, 47]

Fig 5. Quality of life, symptoms and delivery of care



QoL, Quality of life; DLQI, Dermatology Life Quality Index; NPQ10, Nail psoriasis quality 10, NAPPA QoL, Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; NPPFSS, Nail Psoriasis Physical Functioning Severity Score

Fig 6. Historical use of common outcome instruments to assess clinical signs



NAPSI, Nail Psoriasis Severity Index

Discussion

Previous research has evaluated outcome instruments used in the field of nail psoriasis to a certain extent. Based on these results, important issues have been raised. The majority of tools to assess nail psoriasis disease severity are not validated,[93] with only a few studies that address validation of outcome instruments, although some studies have explored the correlation between different outcome instruments.[5, 94] Moreover, the number of nails that need to be assessed for a representative reflection of nail psoriasis, the sensitivity to reflect meaningful clinical responsiveness with assessment of commonly used outcome instruments such as NAPSI, and the threshold for diagnosis of nail psoriasis have been questioned.[95]

In the current overview, a wide variety in outcome instruments used in clinical trials has been identified, although heterogeneity detected within outcome instruments might be even more prominent. The majority of studies reported on clinical signs by assessment of a NAPSI, a global assessment, individual nail features or a combination of these. Historically, NAPSI is the most commonly reported outcome instrument and its use has increased over the last couple of years (Fig. 6). However, eight different subtypes of NAPSI assessment were identified. Similar variations were identified for global assessment, with the use of six different outcome scales. Besides NAPSI or global assessment, reporting on nail features individually was common. Prevalent nail features, pitting, subungual hyperkeratosis and onycholysis, were most commonly assessed.

Our results demonstrate that issues regarding outcome assessment in nail psoriasis are not limited to heterogeneity in type of outcome instruments used. Insufficient reporting on characteristics of outcome instruments (e.g. subtype, scale) and wide varieties in the way outcomes are analysed and reported (e.g. NAPSI 50, mean NAPSI improvement, (NAPSI ⩽ 4) contribute substantially and need to be addressed (e.g. by reaching consensus on cut-off values for NAPSI assessment) in the process towards COS development.

Besides clinical signs, outcome instruments corresponding to quality of life, symptoms and delivery of care have been identified. Two recently introduced questionnaires, NPQ10[15] and NAPPA-QoL[14] may be promising tools to enable evaluation and monitoring of condition-specific quality-of-life impact, although their use in RCTs is currently limited. Assessment of symptoms was scarce which is striking as nail psoriasis lesions can be painful and impair the use of the hands; this can seriously affect emotional, social, or working life.[96]

As nail psoriasis is often assessed secondarily to psoriasis of the skin or joints, feasibility of outcome assessment should be highly valued in the process towards COS development. Moreover, consensus on the use of nail psoriasis outcome instruments should preferably be reached among different disciplines by active collaboration between research groups (e.g. OMERACT, COUSIN and IDEOM).

A major strength of this systematic review concerns the comprehensive electronic search that was performed to identify outcome instruments used in both published and ongoing RCTs on nail psoriasis. Moreover, in-depth data extraction has been conducted, emphasizing different aspect of nail psoriasis outcome reporting.

Regarding unpublished trials, data extraction was based on trial protocols published in trial registers. This might have limited in-depth data extraction for some of these trials, contributing to the number of outcome instruments for which several aspects (e.g. type, scale) remain unclear. Another study limitation concerns data extraction of outcome instruments used in RCTs only. Most outcome instruments identified will overlap outcome instruments used in non-RCTs. In case a validated outcome instrument has solely been used in non-RCTs, it will be detected in the process towards COS development at the stage of assessment of measurement properties.

In conclusion, harmonization of outcome instruments is needed to increase the value of clinical trials investigating nail psoriasis interventions, certainly as the number of trials investigating nail psoriasis interventions doubled over the last 3 years. Increased applicability of emerging data and emphasizing the importance of patient-reported outcomes will

strengthen clinical decision making. The current comprehensive overview on nail psoriasis outcome instruments can contribute to increased awareness among researchers about the

substantial variation (with)in the use of outcome instruments for nail psoriasis, encouraging sufficient reporting on characteristics of outcome instruments. It provides the first step

towards COS development for nail psoriasis. Formation of a nail psoriasis consensus group to define the applicability of the COS for nail psoriasis and to reach consensus on the core outcome domain(s) to be selected for the COS will be the next step.

Supplemental content

Please find the supplementary material (Table S1-6) in the electronic version of this thesis.

References

1. Salomon J, Szepietowski JC, Proniewicz A. Psoriatic nails: a prospective clinical study. J Cutan Med Surg. 2003;7(4):317-21.
2. van der Velden HM, Klaassen KM, van de Kerkhof PC, Pasch MC. The impact of fingernail psoriasis on patients' health-related and disease-specific quality of life. Dermatology. 2014;229(2):76-82.
3. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail psoriasis: a questionnaire-based survey. The British journal of dermatology. 2013;169(2):314-9.
4. de Vries AC, Bogaards NA, Hooft L, Velema M, Pasch M, Lebwohl M, et al. Interventions for nail psoriasis. The Cochrane database of systematic reviews. 2013(1):Cd007633.
5. Klaassen KMG, van de Kerkhof PCM, Bastiaens MT, Plusjé LGJM, Baran RL, Pasch MC. Scoring nail psoriasis. Journal of the American Academy of Dermatology. 2014;70(6):1061-6.
6. Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G, McHugh NJ. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. Br J Rheumatol. 1994;33(9):834-9.
7. de Jong EM, Menke HE, van Praag MC, van De Kerkhof PC. Dystrophic psoriatic fingernails treated with 1% 5-fluorouracil in a nail penetration-enhancing vehicle: a double-blind study. Dermatology. 1999;199(4):313-8.
8. Baran RL. A nail psoriasis severity index. The British journal of dermatology. 2004;150(3):568-9.
9. Rich P, Scher RK. Nail psoriasis severity index: a useful tool for evaluation of nail psoriasis. Journal of the American Academy of Dermatology. 2003;49(2):206-12.
10. Aktan S, Ilknur T, Akin C, Ozkan S. Interobserver reliability of the Nail Psoriasis Severity Index. Clinical and experimental dermatology. 2007;32(2):141-4.
11. Parrish CA, Sobera JO, Elewski BE. Modification of the nail psoriasis severity index. Journal of the American Academy of Dermatology. 2005;53(4):745-6.
12. Cassell SE, Bieber JD, Rich P, Tutuncu ZN, Lee SJ, Kalunian KC, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. The Journal of rheumatology. 2007;34(1):123-9.
13. Patel M, Liu SW, Qureshi A, Merola JF. The Brigham Scalp Nail Inverse Palmoplantar Psoriasis Composite Index (B-SNIPI): a novel index to measure all non-plaque psoriasis subsets. The Journal of rheumatology. 2014;41(6):1230-2.
14. Augustin M, Blome C, Costanzo A, Dauden E, Ferrandiz C, Girolomoni G, et al. Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA): development and validation of a tool for assessment of nail psoriasis outcomes. The British journal of dermatology. 2014;170(3):591-8.

15. Ortonne JP, Baran R, Corvest M, Schmitt C, Voisard JJ, Taieb C. Development and validation of nail psoriasis quality of life scale (NPQ10). Journal of the European Academy of Dermatology and Venereology. 2010;24(1):22-7.

16. Schmitt J, Apfelbacher C, Spuls PI, Thomas KS, Simpson EL, Furue M, et al. The Harmonizing Outcome Measures for Eczema (HOME) Roadmap: A Methodological Framework to Develop Core Sets of Outcome Measurements in Dermatology. Journal of Investigative Dermatology. 2015;135(1):24-30.

17. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res. 2010;19(4):539-49.

18. Gargon E, Williamson PR, Altman DG, Blazeby JM, Clarke M. The COMET initiative database: progress and activities update (2014). Trials. 2015;16(1):1-5.

19. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. The Journal of rheumatology. 1997;24(4):799-802.

20. Schmitt J, Deckert S, Alam M, Apfelbacher C, Barbaric J, Bauer A, et al. Report from the kick-off meeting of the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN). British Journal of Dermatology. 2016;174(2):287-95.

21. Prinsen CA, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. Trials. 2016;17(1):449.

22. Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). The British journal of dermatology. 2016;175(1):69-79.

23. Eleftheriadou V, Thomas K, van Geel N, Hamzavi I, Lim H, Suzuki T, et al. Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. Pigment Cell Melanoma Res. 2015;28(3):363-9.

24. Gerbens LA, Chalmers JR, Rogers NK, Nankervis H, Spuls PI, Harmonising Outcome Measures for Eczema i. Reporting of symptoms in randomized controlled trials of atopic eczema treatments: a systematic review. The British journal of dermatology. 2016;175(4):678-86.

25. Eleftheriadou V, Thomas KS, Whitton ME, Batchelor JM, Ravenscroft JC. Which outcomes should we measure in vitiligo? Results of a systematic review and a survey among patients and clinicians on outcomes in vitiligo trials. The British journal of dermatology. 2012;167(4):804-14.

26. Ogdie A, de Wit M, Callis Duffin K, Campbell W, Chau J, Coates LC, et al. Defining Outcome Measures for Psoriatic Arthritis: A Report from the GRAPPA-OMERACT Working Group. The Journal of rheumatology. 2017;44(5):697-700.

27. Orbai AM, de Wit M, Mease P, Shea JA, Gossec L, Leung YY, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis. 2016.

28. Callis Duffin K, Gottlieb AB, Merola JF, Latella J, Garg A, Armstrong AW. Defining Outcome Measures for Psoriasis: The IDEOM Report from the GRAPPA 2016 Annual Meeting. The Journal of rheumatology. 2017;44(5):701-2.

29. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

30. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study Group. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. Journal of Dermatology. 2012;39(3):242-52.

31. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Annals of the rheumatic diseases. 2014;73(9):1689-94.

32. Ortonne JP, Paul C, Berardesca E, Marino V, Gallo G, Brault Y, et al. A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. British journal of dermatology. 2013;168(5):1080-7.

33. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: Results from PHOENIX 1. British journal of dermatology. 2014;170(2):398-407.

34. Rich P, Griffiths CE, Reich K, Nestle FO, Scher RK, Li S, et al. Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year. Journal of the American Academy of Dermatology. 2008;58(2):224-31.

35. NCT02207244. A Study of Guselkumab in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis With Randomized Withdrawal and Retreatment (VOYAGE 2). wwwclinicaltrialsgov/show/NCT02207244. 2014.

36. NCT02207231. A Study of Guselkumab in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis (VOYAGE 1). wwwclinicaltrialsgov/show/NCT02207231. 2014.

37. Nakamura R C, Abreu L d, Duque-Estrada B, Tamler C, Leverone A P. Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. Anais brasileiros de dermatologia. 2012;87(2):203-11.

38. Poulin Y, Crowley J J, Langley R G, Unnebrink K, Goldblum O M, Valdecantos W C. Efficacy of adalimumab across subgroups of patients with moderate-to-severe chronic plaque psoriasis of the hands and/or feet: Post hoc analysis of REACH. Journal of the European Academy of Dermatology and Venereology : JEADV. 2014;28(7):882-90.

39. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. Journal of dermatological science. 2010;59(1):40-9.

40. Tzung TY, Chen CY, Yang CY, Lo PY, Chen YH. Calcipotriol used as monotherapy or combination therapy with betamethasone dipropionate in the treatment of nail psoriasis. Acta dermato-venereologica [Internet]. 2008; 88(3):[279-80 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/513/CN-00648513/frame.html.

41. 2012-005750-27. A Phase IIa, Multicentre, Randomised, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Safety, Tolerability and Clinical Efficacy of MT-1303 in Subjects with Moderate to Severe Chronic Plaque Psoriasis. https://wwwclinicaltrialsregistereu/ctr-search/trial/2012-005750-27/EE. 2014.

42. 2008-007492-24. An independent prospective randomised controlled trial comparing the efficacy and cost effectiveness of infliximab and etanercept in 'high need' patients with moderate to severe chronic plaque type psoriasis. https://wwwclinicaltrialsregistereu/ctr-search/trial/2008-007492-24/NL. 2010.

43. Simone C, Maiorino A, Tassone F, D'Agostino M, Caldarola G. Tacrolimus 0.1% ointment in nail psoriasis: A randomized controlled open-label study. Journal of the European Academy of Dermatology and Venereology : JEADV. 2013;27(8):1003-6.

44. Cantoresi F, Caserini M, Bidoli A, Maggio F, Marino R, Carnevale C, et al. Randomized controlled trial of a water-soluble nail lacquer based on hydroxypropyl-chitosan (HPCH), in the management of nail psoriasis. Clinical, cosmetic and investigational dermatology. 2014;7:185-90.

45. Mease P J, Fleischmann R, Deodhar A A, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Annals of the rheumatic diseases. 2014;73(1):48-55.

46. Lin Y K, See L C, Huang Y H, Chang Y C, Tsou T C, Lin T Y, et al. Efficacy and safety of Indigo naturalis extract in oil (Lindioil) in treating nail psoriasis: A randomized, observer-blind, vehicle-controlled trial. Phytomedicine. 2014;21(7):1015-20.

47. Lin YK, Chang YC, Hui RC, See LC, Chang CJ, Yang CH, et al. A Chinese Herb, Indigo Naturalis, Extracted in Oil (Lindioil) Used Topically to Treat Psoriatic Nails: A Randomized Clinical Trial. JAMA dermatology. 2015;151(6):672-4.

48. Ozmen I, Erbil A H, Koc E, Tunca M. Treatment of nail psoriasis with tumor necrosis factor-alpha blocker agents: an open-label, unblinded, comparative study. Journal of Dermatology. 2013;40(9):755-6.

49. NCT00666354. Dose response and safety study of topical methotrexate for the treatment of fingernail psoriasis. wwwclinicaltrialsgov/show/NCT00666354. 2007.

50. NCT02016482. A Study to Evaluate the Safety and Efficacy of Adalimumab in Subjects With Chronic Plaque Psoriasis and Nail Psoriasis. wwwclinicaltrialsgov/show/NCT02016482. 2014.

51. NCT02168933. 308nm Excimer Laser for Treatment of Fingernail Psoriasis (NAPSI). wwwclinicaltrialsgov/show/NCT02168933. 2014.

52. Goldust M, Raghifar R. Clinical Trial Study in the Treatment of Nail Psoriasis with Pulsed Dye Laser. Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology. 2013.

53. NCT01807520. Study of Safety, Tolerability, and Efficacy of Secukinumab in Subjects With Moderate to Severe Nail Psoriasis (TRANSFIGURE). wwwclinicaltrialsgov/show/NCT01807520.

54. Langley RG, Rich P, Menter A, Krueger G, Goldblum O, Dutronc Y, et al. Improvement of scalp and nail lesions with ixekizumab in a phase 2 trial in patients with chronic plaque psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV. 2015;29(9):1763-70.

55. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Journal of the American Academy of Dermatology. 2015;73(1):37-49.

56. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. The British journal of dermatology. 2015;173(4):949-61.

57. 2012-002716-10. An international prospective, double-blind, placebo-controlled phase III RCT in which patients with moderate to severe psoriasis vulgaris are treated with s.c. methotrexate using an optimized treatment schedule. https://wwwclinicaltrialsregistereu/ctr-search/trial/2012-002716-10/GB. 2012.

58. 2012-005685-35. A randomised, double blind, double dummy, active comparator and placebo controlled confirmative non-inferiority trial of FP187 compared to Fumaderm in moderate to severe plaque psoriasis. https://wwwclinicaltrialsregistereu/ctr-search/trial/2012-005685-35/DE. 2013.

59. 2013-001368-46. A phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of tofacitinib (CP-690,550) in subjects with active psoriatic arthritis and an inadequate response to at least one TNH inhibitor. https://wwwclinicaltrialsregistereu/ctr-search/trial/2013-001368-46/ES. 2013.

60. EUCTR2010-019706-16-IT. A randomized, double blind, placebo controlled, parallel groups, pilot study to assess the effects of two new nail lacquers, cyclosporine 5% and calcipotriol 0.005%, in the treatment of nail psoriasis - ND. wwwclinicaltrialsregistereu/ctr-search/search?query=EUCTR2010-019706-16-IT. 2010.

61. ISRCTN18043449. A study of pre-clinical joint disease in psoriasis and the imaging response to ustekinumab. http://wwwisrctncom/ISRCTN18043449. 2012.

62. NCT00570986. A Study Comparing the Safety and Efficacy of Two Dosing Regimens of ABT-874 to Placebo in Subjects With Moderate to Severe Chronic Plaque Psoriasis. wwwclinicaltrialsgov/show/NCT00570986. 2013.

63. NCT01245140. Efficacy of Alitretinoin Treatment in Patients With Pustular Form of Psoriasis. https://wwwclinicaltrialsgov/ct2/show/NCT01245140. 2015.

64. NCT01309737. A One-Year Study To Evaluate The Efficacy And Safety Of CP-690,550 For Patients With Moderate To Severe Chronic Plaque Psoriasis. wwwclinicaltrialsgov/show/NCT01309737. 2014.

65. NCT01703325. Comparison of Efficacy of Intralesional Triamcinolone Injection and Clobetasol Propionate Ointment for Psoriatic Nails. wwwclinicaltrialsgov/show/NCT01703325. 2012.

66. NCT01765985. Treatment of Palmoplantar Psoriasis With Low Doses Interferential Current. wwwclinicaltrialsgov/show/NCT01765985. 2013.

67. NCT02129777. Efficacy and Safety of Namilumab (MT203) for Plaque Psoriasis. wwwclinicaltrialsgov/show/NCT02129777. 2014.

68. NCT02235480. Efficacy and Safety of Tazarotene Gel in Nail Psoriasis. wwwclinicaltrialsgov/show/NCT02235480. 2015.

69. NCT02325219. An Efficacy and Safety of CNTO 1959 (Guselkumab) in Participants With Moderate to Severe Plaque-type Psoriasis. wwwclinicaltrialsgov/show/NCT02325219. 2015.

70. NCT02513550. A Study Comparing Different Dosing Regimens of Ixekizumab (LY2439821) in Participants With Moderate to Severe Plaque Psoriasis (IXORA-P). clinicaltrialsgov/show/NCT02513550. 2015.

71. NCT02561806. A Study of Ixekizumab (LY2439821) in Participants With Moderate-to-Severe Plaque Psoriasis (IXORA-S). clinicaltrialsgov/show/NCT02561806. 2015.

72. NCT02606760. Study to Evaluate the Efficacy and Safety of P-3073 Nail Solution in the Treatment of Nails Affected by Psoriasis. clinicaltrialsgov/show/NCT02606760. 2015.

73. Paul C, Reich K, Gottlieb A B, Mrowietz U, Philipp S, Nakayama J, et al. Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. Journal of the European Academy of Dermatology & Venereology. 2014;28(12):1670-5.

74. Baran R, Tosti A. Topical treatment of nail psoriasis with a new corticoid-containing nail lacquer formulation. Journal of Dermatological Treatment. 1999;10(3):201-4.

75. Cannavo SP, Guarneri F, Vaccaro M, Borgia F, Guarneri B. Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study. Dermatology. 2003;206(2):153-6.

76. Kole L, Cantrell W, Elewski B. A randomized, double-blinded trial evaluating the efficacy and tolerability of vectical ointment (calcitriol 3 mcg/g ointment) when compared to betamethasone diproprionate ointment (64 mg/g) in patients with nail psoriasis. Journal of Drugs in Dermatology: JDD. 2014;13(8):912-5.

77. Lindelof B. Psoriasis of the nails treated with grenz rays: a double-blind bilateral trial. Acta Dermato-Venereologica. 1989;69(1):80-2.

78. Mahrle G, Schulze HJ, Farber L, Weidinger G, Steigleder GK. Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail, and joint involvement. Journal of the American Academy of Dermatology. 1995;32(1):78-88.

79. Tzung TY, Chen CY, Yang CY, Lo PY, Chen YH. Calcipotriol used as monotherapy or combination therapy with betamethasone dipropionate in the treatment of nail psoriasis. Acta Dermato-Venereologica. 2008;88(3):279-80.

80. Kwang TY, Nee TS, Seng KT. A therapeutic study of nail psoriasis using electron beams. Acta Dermato-Venereologica. 1995;75(1):90-.

81. Kavanaugh A Mclnnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis & Rheumatism. 2009;60(4):976-86.

82. Levell NJ, Shuster S, Munro CS, Friedmann PS. Remission of ordinary psoriasis following a short clearance course of cyclosporin. Acta Derm Venereol. 1995;75(1):65-9.

83. EUCTR2004-004825-87-HU. Efficacy and safety of 0,1%, 0,5% and 1% TAZAROTENE nail lacquer formulation versus vehicle in nail psoriasis. International, multicenter, double-blind, randomized study of four parallel groups. - Dose ranging for Tazarotene nail lacquer. http://appswhoint/trialsearch/Trial2aspx?TrialID=EUCTR2004-004825-87-HU. 2005.

84. Gumusel M, Ozdemir M, Mevlitoglu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. Journal of the European Academy of Dermatology & Venereology. 2011;25(9):1080-4.

85. 2007-007160-19. A double blind, randomized, placebo controlled, multicenter, dose finding study of oral AEB071 assessing Psoriasis Area and Severity Index (PASI) response as a function of dose and treatment duration (primary outcome) in patients with plaque psoriasis. https://wwwclinicaltrialsregistereu/ctr-search/trial/2007-007160-19/IT. 2011.

86. EUCTR2006-006569-18-FR. Efficacy and safety of 8% clobetasol nail lacquer formulation versus vehicle in nail psoriasis. wwwclinicaltrialsregistereu/ctr-search/search?query=EUCTR2006-006569-18-FR. 2007.

87. Flori ML, Rubegni P, Micheli S, Andreassi L. Treatment of psoriasic onychodystrophy with a hyaluronic acid product and chondroitinsulphates. Giornale Italiano di Dermatologia e Venereologia. 1994;129(3):129-33.

88. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. Acta Dermato-Venereologica. 2007;87(2):167-8.

89. Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. Cutis. 2001;68(5):355-8.

90. Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. British Journal of Dermatology. 1998;139(4):655-9.

91. Treewittayapoom C, Singvahanont P, Chanprapaph K, Haneke E. The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. Journal of the American Academy of Dermatology. 2012;66(5):807-12.

92. Yu RC, King CM. A double-blind study of superficial radiotherapy in psoriatic nail dystrophy. Acta Dermato-Venereologica. 1992;72(2):134-6.

93. Augustin M, Ogilvie A. Methods of outcomes measurement in nail psoriasis. Dermatology. 2010;221 Suppl 1:23-8.

94. Kyriakou A, Patsatsi A, Sotiriadis D. The agreement among the different ways of measuring NAPSI and their correlation with DLQI. J Dtsch Dermatol Ges. 2014;12(11):1051-3.

95. Korver JE, van de Kerkhof PC, Pasch MC. Alefacept treatment of psoriatic nail disease: how severe should nail psoriasis be? J Am Acad Dermatol. 2006;54(4):742-3.

96. Blome C, Costanzo A, Dauden E, Ferrandiz C, Girolomoni G, Gniadecki R, et al. Patient-relevant needs and treatment goals in nail psoriasis. Qual Life Res. 2016;25(5):1179-88.

CHAPTER 8

Interventions for nail psoriasis

A systematic review

CIM Busard, M Pasch, E Schuit, L Hooft, PI Spuls

Submitted

This is summary; full version can be found in the electronic version of this thesis

Summary

Background: Nails are affected in a large number of psoriasis patients which requires effective management and treatment strategies.

Objectives: To update Cochrane Review (Jan 2013) on the efficacy and safety of nail psoriasis interventions.

Methods: We searched CENTRAL, MEDLINE, Embase, LILACS and ongoing trials registers (June 2019) for randomized controlled trials and included all randomised controlled trials investigating nail psoriasis interventions. Outcomes of interest were nail disease severity, quality of life, symptoms, treatment satisfaction and adverse events. Induction (<24 weeks) and maintenance phase (≥24 weeks) data were assessed separately.

Results: Thirty-six new trials were added in this update making a total of 54 trials, comprising 7467 patients. Heterogeneity in e.g. outcome measurement instruments was high across trials. Local therapy has been investigated on small scale with variable results. Improvements of approximately 50% in nail disease severity after 12-24 weeks compared to baseline have been reported for corticosteroids (e.g. clobetasol nail lacquer), vitamin-D-derivates, tazarotene nail lacquer and cyclosporine oil with no substantial differences between active comparators, however some studies report no difference compared to vehicle. Tacrolimus ointment has also shown beneficial results. Oral methotrexate (MTX) and cyclosporine seemed equally effective. All investigated small molecules and biologics showed statistically significant improvement (ranging from 20-45%) in NAPSI during induction treatment compared to placebo except for ustekinumab and namilumab. Significant faster improvement was shown on etanercept compared to apremilast and ixekizumab compared to etanercept are reported. Efficacy is enhanced during maintenance treatment with up to 76% and 84% improvement in NAPSI on small molecules and biologics respectively.

Conclusions: Randomised controlled trials investigating nail psoriasis interventions have rapidly expanded over the last few years. The most robust body of evidence exists for small molecules and biologics, although several local interventions and conventional systemic agents have also shown to be beneficial. The comprehensive overview on nail psoriasis data presented in this review can provide guidance on treatment selection tailored to patients' preferences and needs and to manage patient expectations regarding clinical efficacy. Large

heterogeneity in reported outcomes emphasizes the importance of current initiatives of core outcome set development for nail psoriasis to improve future data synthesis of nail psoriasis interventions.

Introduction

Nail psoriasis is estimated to be present in 50 to 80% of patients with plaque psoriasis.[1, 2] There tends to be a higher prevalence of nail psoriasis in patients with psoriatic arthritis, genital psoriasis, inverse psoriasis and psoriasis capitis.[1, 3] Men and women are equally affected and fingernails are more commonly affected than toenails.[1]

Nail psoriasis can affect different anatomical structures of the nail including the nail matrix and nail bed. Depending on the anatomical structure that is affected different morphological changes can be observed: nail bed psoriasis shows onycholysis, oil-drop dyschromia, splinter hemorrhages and subungual hyperkeratosis and nail matrix psoriasis shows pitting, leukonychia, red spots in the lunula and nail plate crumbling.[4, 5] Several nail psoriasis scoring systems have been developed that include assessment of some or all of these morphological changes of which Nail Psoriasis Area and Severity assessment (NAPSI) is most known and widely used. Since 2010 two patient reported scoring instruments (nail psoriasis-specific quality-of-life questionnaires (NPQ10 and NAPPA-QoL) have been added which allow the assessment of treatment benefit by the patient.[6, 7]

Although about 50% of patients experience pain and restrictions in daily life activities and more than 90% of patients experience cosmetic problems,[8] only a minority of patients with nail psoriasis receives treatment. For example, Klaassen et al.[1] reported that 16.4% of patients indicated that they had received treatment for their nail psoriasis although 46.7% of patients stated that they would like to receive treatment for their nail disorder.

When response to treatment is achieved, there is generally no permanent nail plate damage. However, treatment response may be slow, the result is sometimes disappointing, and relapse is common.[9]

The aim of this systematic review was to update efficacy and safety data of all nail psoriasis interventions to determine the most effective treatment strategies.

Materials and methods

This updated systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.[10] The content of the full updated review including a comprehensive report on materials and methods is provided in Appendix S1 (see Supporting Information).

Search strategies
We searched CENTRAL (in The Cochrane Library), MEDLINE, Embase and LILACS up to 13 June 2019 (see Appendix S1). Furthermore, C.B. and P.S. searched trials registers on 11 December 2019 with the terms 'nail' and 'psoriasis'.

Inclusion criteria
Randomized controlled trials (RCTs) examining interventions in patients with nail psoriasis as the main clinical feature as well as studies where nail psoriasis was just one of several components in patients with psoriatic arthritis or plaque type psoriasis were included.

Outcome measures
Our primary outcome was improvement in nail disease severity. We extracted data on all outcome instruments to measure nail disease severity as reported in the original studies to generate a comprehensive overview on available data on nail psoriasis interventions and to detect variance in the use of outcome definitions and instruments across nail psoriasis studies.

A complete overview of all outcome data can be found in Appendix S1. Here we present the most commonly reported outcomes in the following order to enable (indirect) comparison between trials:

1. "Target NAPSI": any type of instrument that assessed the (modified) NAPSI on one (most affected) nail only[11]
2. "Overall NAPSI": any type of instrument that assessed the (modified) NAPSI on all finger (or toe) nails[12]
3. If no target or overall NAPSI was reported: any other type of NAPSI (e.g. NAPSI single hand, NAPSI 50)
4. If no NAPSI was reported: NAS, composite fingernail score, physician global assessment or individual nail features

Outcomes on nail disease severity were reported for induction (<24 weeks) and maintenance (≥24 weeks) treatment (if available) separately.

Secondary outcomes were improvement in patient global assessment, quality of life, symptoms, treatment satisfaction, and incidence/type of adverse events.

Data extraction and risk-of-bias assessment

Data on trial methods (e.g. sample size, date and setting of study, method of analysis) patient characteristics (e.g. study population, in and exclusion criteria, baseline disease severity), interventions/comparisons (e.g. type and dosage, treatment duration), outcomes (type/scale of outcome instrument) and risk of bias (using the Cochrane Collaboration's domain-based assessment tool) were extracted for included studies. Moreover, characteristics of ongoing studies and studies awaiting classification (completed, but not (yet) published) were extracted.

Statistical analysis

We calculated risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes and their associated 95% confidence interval (CI). In case of missing measures of variance, we described the data narratively. We did not perform a meta-analysis due to heterogeneity in outcome measures reported. All analyses were undertaken using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

We retrieved 611 references through databases and trial registers searching and by going through bibliographies of included studies. Based on title and abstract, 113 full-text articles were screened. Seventy references relate to our 54 included studies with a total of 7467 patients, of which 36 studies were newly added in this review. (see Table 1)

Quality of evidence

The quality (certainty) of evidence for local interventions and conventional systemic agents was generally low. Limitations include small sample sizes contributing to imprecision of results, lack of comparison data contributing to indirectness of results, limitations in study reporting (e.g. baseline characteristics, statistical analysis,) limitations in study design and the use of uncommon and unvalidated outcome instruments.

The most robust body of evidence exists for small molecules and biologics, although some limitations apply. Besides limitations in study design and outcome instruments used (major heterogeneity and limited use of Patient Reported

Outcomes (PRO's), part of the data (e.g. safety) is not specified for the nail psoriasis population which introduces indirectness of evidence. Due to focus on plaque psoriasis or arthritis psoriatica, results on nail psoriasis were often based on a single (secondary) outcome.

Intervention/ comparison[a]	N[b]	Main outcome[c,d]	Population[e]	Duration[f] (wk)
Local interventions				
Clobetasol nail lacquer vs base-coat nail lacquer	90 (4 studies)	NAPSI, PGA	NP	10-24
Calcipotriol/calcitriol vs class 3 corticosteroids	108 (3 studies)	PGA, nail thickness	NP	12-20
Triamcinolone intralesional/ iontophoresis vs. class 3 corticosteroids	32 (2 studies)	(Target) NAPSI	NP	24
Tazarotene vs clobetasol and placebo	282 (3 studies)	Individual nail features	NP	12-24
Cyclosporine vs maize oil	16	PGA	NP	12
Cyclosporine and calcipotriol nail lacquers vs placebo	80	NAPSI	NP	24
Tacrolimus vs. no treatment	21	NAPSI	NP	12
Systemic interventions (placebo-controlled trials)				
Alitretinoin	18	NAPSI	PP	24
Methotrexate	79	Target NAPSI	PS	52
Tofacitinib	1018 (2 studies)	NAPSI	PS	16
Apremilast	996 (3 studies)	Target NAPSI, NAPSI	PS	104
Ustekinumab	647 (2 studies)	Target NAPSI, mNAPSI	PS	52-64
Etanercept	951 (2 studies)	(Target) NAPSI	PS	16
Infliximab	348 (2 studies)	Target NAPSI	PS, PsA	46
Adalimumab	1027 (4 studies)	Target NAPSI, NAPSI 50	PP, PS, PsA	16-52
Ixekizumab[g]	1358 (4 studies)	NAPSI	PS, PsA	52-72
Secukinumab	502 (2 studies)	NAPSI, Composite fingernail score	PS	12-80
Certolizumab pegol[g]	197	mNAPSI	PsA	96
Golimumab[g]	287	Target NAPSI	PsA	256
Guselkumab	610 (2 studies)	Target NAPSI	PS	16-52

Intervention/ comparison[a]	N[b]	Main outcome[c,d]	Population[e]	Duration[f] (wk)
Namulimab	122	NAPSI	PS	52
Systemic interventions (head-to-head trials)				
Methotrexate vs cyclosporin	37	NAPSI	NP	24
Ciclosporin vs etretinate	137	PGA	PS	22
Apremilast vs etanercept	142	NAPSI	PS	16
Etanercept once vs biweekly	72	NAPSI	NP	24
Adalimumab vs etanercept vs infliximab	28	NAPSI	NP	48
Ixekizumab vs adalimumab	289	NAPSI	PsA	16
Ixekizumab vs etanercept	809	NAPSI	PS	12
Guselkumab vs adalimumab	484	Target NAPSI	PS	16

[a] Dosing according to label unless otherwise reported; [b] N= number of patients with nail psoriasis on each intervention90; [c] NAPSI = assessment of all fingernails unless otherwise reported; [d] NAPSI and physician global assessment were reported using different numerical scales (please see supplementary material for details on outcome reporting); [e] NP = nail psoriasis involvement in all randomized patients; PS = plaque-type psoriasis with nail psoriasis involvement in a part of the randomized patients; PsA = psoriatic arthritis with nail psoriasis involvement in a part of the randomized patients; PP = psoriasis palmoplantaris with nail psoriasis involvement in all randomized patients; [f] Placebo-controlled study phase lasted up to maximum 26 weeks, afterwards patients were crossed-over to active systemic treatment, [g] In part of patients treated with this intervention MTX was used as comedication.

1. Local interventions

Local interventions included topical therapy (20 trials; n=552 participants), radiotherapy (3 trials; n=44 participants) and laser therapy (2 trials; n=60 participants).

Efficacy

Corticosteroids (Clobetasol nail lacquer)
Trials reporting on clobetasol nail lacquer were all intra-individual and compared treatment on affected fingernails of one hand with treatment on the affected fingernails of the other hand. One study (n=15) reported (non-statistically significant) improvements of 52.9%, 49.2% and 52.3% in target NAPSI for clobetasol nail lacquer 0.05%, 1% and 8% respectively.[13] Another publication reporting on two studies (n=27 and 18)[14] demonstrated improvement (global assessment) in 16 and 5 hands treated with clobetasol 8% nail lacquer compared to 2 and 3 hands treated with base coat lacquer respectively. A study registered in a trial register (n=30)[15] (unpublished data) reported no difference in treatment efficacy between clobetasol 8% nail lacquer compared to vehicle nail lacquer.

Corticosteroids (Triamcinolone intralestional/iontophoresis)
One study (n=16; intra-individual study) investigated intralesional triamcinolone (injected at baseline and 2 months) compared to clobetasol ointment [16] and reported statistically significant improvement of 24.2% and 45.5% in target NAPSI for intralesional triamcinolone at 2 months and 4 months respectively but not at end of study (21.3% at 6 months). Intralesional triamcinolone was significantly superior compared to control fingernails and clobetasol ointment at 4 months, but not at 6 months (improvement with clobetasol of 16.1%, 17.7% and 12.4% at 2, 4 and 6 months respectively). Triamcinolone iontophoresis was also investigated on small scale (n=16; intra-individual study).[17] Statistically significant improvement in NAPSI of 69.5% for triamcinolone iontophoresis versus 55.5% for calcipotriol/betamethasone dipropionate ointment was reported with no significant differences between groups.

Vitamin D derivates
Calcipotriol and calcitriol were actively compared with class 3 corticosteroids in three studies reporting moderate improvement for both interventions with no significant differences between groups. One study[18] (n=32) reported moderate and marked (global) improvement in 47% and 6% of patients on calcipotriol monotherapy

respectively compared to 20% and 33% on calcipotriol and betamethasone dipropionate combination treatment. Tosti et al (n=58)[19] reported improvement in nail thickness of 26.5% with calcipotriol and 30.4% with betamethasone treatment. Another study[20] (n=10) compared calcitriol with betamethasone and reported mean (global) improvement of 50% for the calcitriol group versus 7.4% for the betamethasone group.

Retinoids

Tazarotene nail lacquer was compared with vehicle lacquer or clobetasol lacquer in three studies with conflicting results. One study[21] (n=31) reported statistically significant superior improvement in pitting (33.3%) and onycholysis (30.0%) for tazarotene 0.1% compared to vehicle. These findings were not confirmed in a study registered in a trial register[22] (unpublished data) (n=205) in which different concentrations of tazarotene nail lacquer treatment were found to be comparable to vehicle nail lacquer. Another study that actively compared tazarotene with clobetasol reported statistically significant improvement in pitting, onycholysis, subungual hyperkeratosis and salmon patches ranging from 58-85% for both interventions.[23]

Calcineurin inhibitors

Tacrolimus ointment 0.1% was investigated intra-individually in 21 patients and demonstrated statistically significant improvement of 65.1% in target NAPSI compared to 0.8% improvement in control hands.[24] Data on topical ciclosporin are conflicting, with one small trial (n=16)[25] reporting significant (global) improvement of 77% on maize-oil dissolved ciclosporin treatment compared to 11% improvement on maize oil only. Another trial (n=80)[26] reported (unpublished) data in a trial register and demonstrated a decrease in overall NAPSI of 6.87, 2.42 and 1.11 (no baseline NAPSI reported) for calcipotriol, ciclosporin and placebo treated patients respectively, with no significant differences between active treatment and placebo.

Patient global assessment, quality of life, symptoms and treatment satisfaction

Equal (global) improvement as assessed by the patient was reported for calcipotriol with betamethasone compared to calcipotriol monotherapy (53%)[18] and for clobetasol[27] and tazarotene[28] nail laquers compared to placebo. Increased improvement was reported for oil dissolved ciclosporin compared to maize oil only (88% versus 0% reported good to excellent improvement).[25]

More improvement on quality of life was reported for topical ciclosporin (assessed with NPQ-10) and calcipotriol (assessed descriptively) compared to

placebo[25, 26], although changes in experienced pain of the nails were small.[26] Other trials investigating local treatment did not assess quality of life or symptoms.

Treatment satisfaction was reported descriptively. Forty-four percent of patients rated treatment satisfaction with calcipotriol as good and 16% of patients as excellent and 58% of patients rated betamethasone treatment as good and 19% as excellent.[19] Moderate to excellent treatment satisfaction was reported in patients on clobetasol nail lacquer in 60% of patients.[13] Patients on calcipotriol or ciclosporin rated treatment satisfaction as very good or good in 81% and 67% respectively.[26] No difference in treatment satisfaction was reported between triamcinolon iontophoresis and calcipotriol/betamethasone ointment.[17]

Adverse events

Adverse events in patients on treatment with topical corticosteroids, vitamin D derivates or calcineurin inhibitors were infrequent and generally mild in severity. Transient local skin reactions such as erythema, desquamation and periungual irritation were reported in a small portion of patients. One patient on clobetasol experienced blue coloration of all treated nails.[15] In patients treated with tazarotene gel or cream a substantial proportion of patients experienced infections, peeling, irritation and burning sensations of the skin periungual.[21-23]

Other local interventions

Several experimental local interventions that are not (widely) available (yet) for clinical practice have been investigated on small scale. Topical interventions such as hyaluronic acid and chondroitin sulphate[29], dithranol with salicylic acid and UVB [30], Belanyx lotion (with or without 1% 5-fluorouracil)[31], Lindioil [32, 33] and hydroxypropyl chitosan nail lacquer [34] have been investigated in individual RCTs and demonstrated some (statistically significant) improvements in nail disease severity. Pulsed-dye laser treatment with different pulse durations has been evaluated with some beneficial effects. However, petechiae and hyperpigmentation were commonly reported adverse events and some patients experienced pain during treatment.[35, 36] Radiotherapy has been investigated on small scale with limited efficacy and relative high incidence of (permanent) post-radiation changes of the skin (e.g. darkening, scarring).[37-39]

2. Systemic interventions

Systemic interventions included conventional systemic therapy (5 trials; n=300), small molecules (5 trials; n=1984), and biologics (19 trials; n=4527).

Efficacy

Improvement in nail disease severity assessed with (any type of) NAPSI during treatment induction (10-16 weeks) was significantly superior compared to placebo for MTX[40], small molecules (apremilast (in 2 out of 3 studies[41, 42]), tofacitinib[43]), TNF-α inhibitors (infliximab[44, 45], etanercept[41, 46], adalimumab[47-51], golimumab[52], certolizumab[53]) and interleukin-inhibitors (ixekizumab[46, 50, 54, 55], guselkumab[47, 56]). Mean improvement in NAPSI ranged from 20% to 45.3%. (Fig. 1)

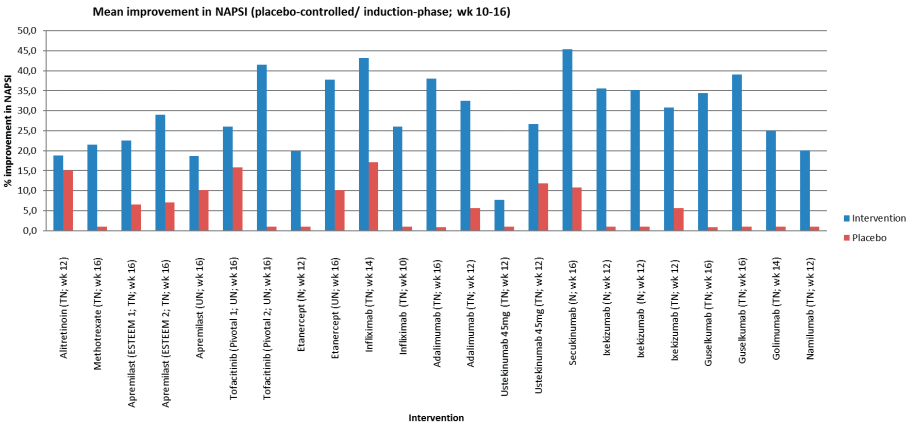
For alitretinoin, ustekinumab and namilumab improvement in nail disease severity with (any type of) NAPSI (ranging from 7.7% to 29%) assessed during treatment induction (10-16 weeks) was not significantly superior to placebo.[57-60]

In the trials on ixekizumab[50, 54], golimumab[52] and certolizumab[53] part of the patients used other systemic agents (including MTX) concomitantly during the trial but results on nail disease were not corrected for concomitant use of other systemic agents.

For ciclosporin only active comparison data versus MTX, etretinate and dithranol combined with UVB are available. Mean improvement in NAPSI of 37.2% (significant in nail bed score but not in nail matrix score) was reported by Gumusel et al.[61], reduction of 17.5% in global assessment was reported by Mahrle et al.[62] and improvement of 17.5% (outcome not further specified) was reported by Levell et al.[30] No difference in efficacy was demonstrated compared to MTX[61], etretinate[62] or dithranol combined with UVB [30].

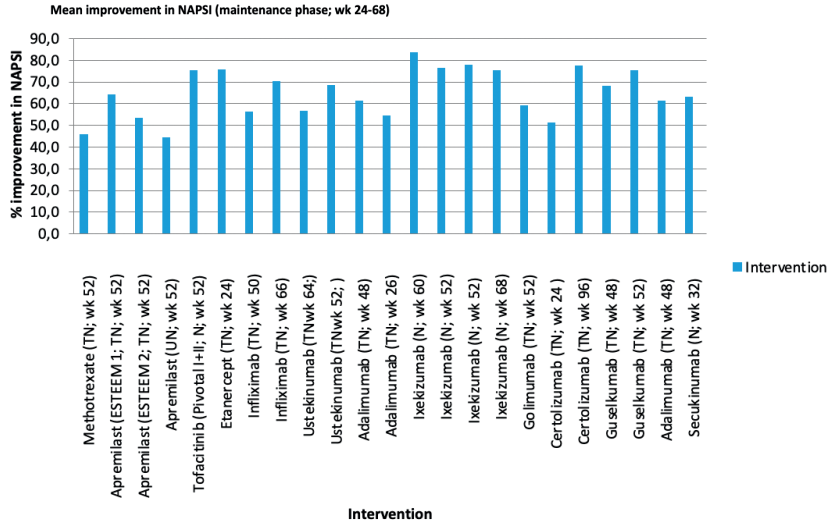
Efficacy of systemic nail psoriasis interventions is enhanced during maintenance treatment on MTX, small molecules and biologics with up to 46%, 76% (range 45-76%) and 84% (range 51-84%) improvement in (any type of) NAPSI after 24-68 weeks respectively.

Figure 1. Improvement in NAPSI during induction treatment in placebo-controlled studies on systemic interventions



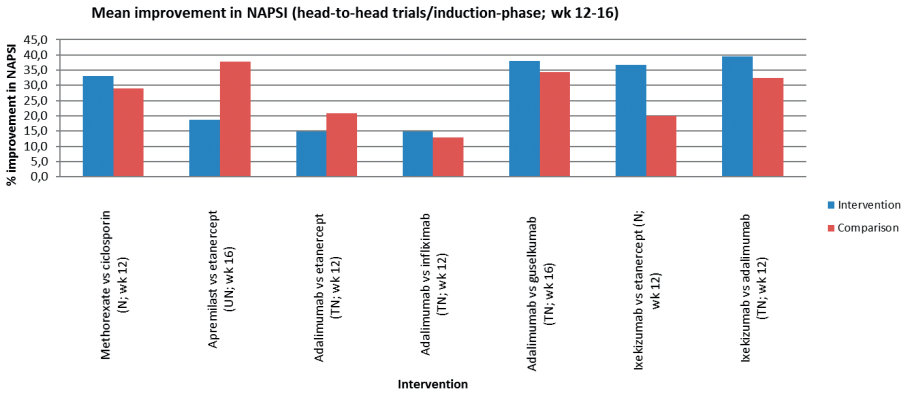
*Certolizumab was statistically significant superior to placebo at week 24 (no induction-phase data available; see data in figure 2). Data on secukinumab reported by Paul et al. show significant improvement of 19,1% in composite fingernail score compared to -14.4% on placebo at week 12 (no data on NAPSI; therefore not included in this figure). TN= (modified) target NAPSI; N= NAPSI (all types of NAPSI that assess multiple toe or fingernails); UN= undefined NAPSI.

Figure 2. Improvement in NAPSI during maintenance treatment in long-term extension studies on systemic interventions



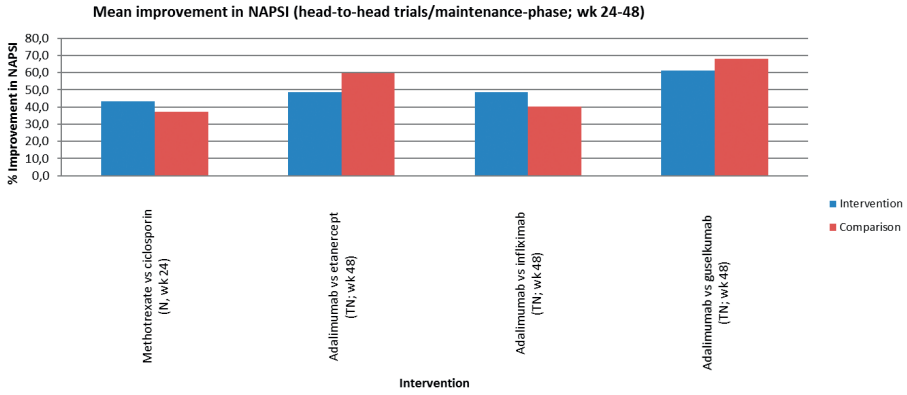
TN= (modified) target NAPSI; N= NAPSI (all types of NAPSI that assess multiple toe or fingernails); UN= undefined NAPSI.

Figure 3. Improvement in NAPSI during induction treatment in head-to-head trials



TN= (modified) target NAPSI; N= NAPSI (all types of NAPSI that assess multiple toe or fingernails); UN= undefined NAPSI.

Figure 4. Improvement in NAPSI during maintenance treatment in head-to-head trials



TN= (modified) target NAPSI; N= NAPSI (all types of NAPSI that assess multiple toe or fingernails)

Head-to-head studies investigating biologics and small molecules demonstrated statistically significant better efficacy during induction treatment with etanercept compared to apremilast and with ixekizumab compared to etanercept.[41,46] Whether this superiority in treatment effect is maintained during maintenance treatment is unclear as comparison data are only available up to week 16. Other interventions (etanercept versus adalimumab and infliximab[63], ixzumab versus adalimumab[50] and adalimumab versus guselkumab[47]) did not substantially differ in clinical efficacy during either induction or maintenance treatment.

Patient global assessment, quality of life, symptoms and treatment satisfaction
Global assessment of disease severity by the patient was assessed in three trials. No (statistically significant) differences in patient evaluation of nail psoriasis were reported between MTX and ciclosporin (moderate improvement in 41% of patients in both groups), between etanercept once and biweekly (62% vs 69%). More improvement in patient global assessment was reported for secukinumab 300 and 150mg (90% and 86%) compared to placebo (6%).

One trial reported on improvement in quality of life associated with nail psoriasis treatment and two trials reported on symptoms. Elewski et al. (n=217) reported a statistically significant greater improvement in Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life (NAPPA-QoL) for adalimumab compared to placebo (39.5% versus 11.7%).[48] The same study assessed the Nail Psoriasis Physical Functioning and Severity Score (67.6% versus 9.9%) and Numeric Rating Scale (NRS) pain (68.9% versus 18.0%) which improved statistically significant more in patients on adalimumab compared to placebo.[48] Poulin et al. (n=36) reported a greater reduction in pain Visual Analogue Scale (VAS) score in responders (patients that achieved NAPSI 50) versus non-responders on adalimumab (86.1% versus 1.4% reduction in pain score).[51]

Adverse events
In most trials investigating systemic interventions safety data was reported for the entire study population including patients with only chronic plaque type psoriasis or psoriatic arthritis and not specified for patients with nail psoriasis.

Nausea was commonly experienced on MTX[40, 61] and hypercholesterolemia, headache and hirsutism was reported in patients on ciclosporin [30, 61, 62]. Infections, headache and injection site reactions were commonly reported in patients on small molecules and biologics. For more details on the proportion and type of adverse events for each intervention see supplementary material.

Discussion

Since 2012 the number of RCTs investigating nail psoriasis interventions tripled. Nearly 90% of patients studied have been treated with small molecules or biologics (leading to most robust body of evidence) and only a relative small number of patients received conventional systemic agents or local therapy.

Based on available data we conclude that local interventions (low quality of evidence) can be beneficial in the treatment of nail psoriasis. Class 3 corticosteroids and vitamin D derivates have been most commonly studied, are generally well-tolerated and seem to moderately improve nail psoriasis disease with no major differences in treatment efficacy between interventions.[13-15, 18-20, 23] Intralesional triamciolone also improved nail disease severity but did not perform better than clobetasol ointment at end of follow-up.[16] Tacrolimus ointment has been studied on small scale in one study and demonstrated substantial improvement in nail disease severity with a tolerable safety profile and can therefore be considered for clinical practice.[24] Data on topical ciclosporin are conflicting [25, 26], pharmaceutical instability has been reported and discolouring of the nails is common [64]. Therefore the use of topical ciclosporin in clinical practice cannot be advised.

All other investigated local interventions such as Lindioil or laser therapy are not suggested for use in clinical practice (yet) due to either safety concerns or lack of evidence.

Theoretically, occlusion might enhance treatment efficacy of local interventions. However, evidence to support this hypothesis is lacking, only one RCT examined an occluded nail versus an unoccluded nail and found no difference in treatment efficacy.[23]

Availability of topical treatments differs between geographical areas and can limit their applicability. In general, potent topical corticosteroids, vitamin-D derivates and calcineurin inhibitors (tacrolimus 0.1%) are widely available, although not in all investigated formulations (e.g. nail lacquer). It is questionable if a compound in a nail lacquer is able to penetrate the psoriatic nail in therapeutic amounts to the relevant area (nail bed and nail matrix).[65, 66]

Based on the performance of systemic agents, systemic therapy seems superior to local treatment, although RCT evidence with active comparison of local and systemic agents is lacking. Mean improvement in (target) NAPSI with systemic treatment ranged from 20% to 45% during induction treatment and from 45% to 84% during maintenance treatment. The improved efficacy during maintenance, supports the need for long-term treatment to allow for the full potential of (systemic) treatment. Studies reporting on ustekinumab did not find statistical significant superiority compared to placebo during induction treatment. During

maintenance treatment efficacy improved comparable with TNF-α inhibitors and other interleukin-inhibitors.[58, 59] Alitretinoin, etretinate and namilumab did not substantially improve nail psoriasis (up to now only induction-phase data are available for these interventions).[57, 60, 62] No RCT evidence exists for fumaric acids, although one trial is ongoing.[67]

In some trials, biologics (ixekizumab[50, 54], golimumab[52] and certolizumab[53]) were combined with MTX in part of the patients part of the patients. Unfortunately, it remains unclear whether combined systemic treatment is beneficial in the treatment of nail psoriasis as results on nail disease were not corrected for concomitant use of MTX.

A small number of head-to-head trials comparing systemic interventions have been performed in the field of nail psoriasis, although head-to-head trials comparing systemic agents to local interventions or conventional systemics to small molecules and biologics are lacking. Oral ciclosporin and MTX seemed to perform comparable with moderate improvement in nail psoriasis although no placebo-controlled data are available to support the efficacy of ciclosporin.[61] A significant quicker response to treatment was reported for etanercept compared to apremilast and for ixekizumab compared to etanercept.[41, 46] Other small molecules and biologics did not seem to differ substantially in clinical efficacy during induction or maintenance treatment.

A small retrospective study in 84 nail psoriasis patients found no significant difference in effectiveness between conventional agents (MTX, ciclosporin, acitretine, UV-therapy) and TNF-α inhibiters.[68]

To assess whether a patient desires local or systemic therapy, an expert consensus group recommended to define nail psoriasis severity using NAPSI and the number of affected nails (mild disease ⩽3 affected nails, NAPSI<20).[69] In deciding which treatment is initiated, shared decision making with acknowledgement of patient preferences should be valued in order to direct treatment strategies towards achieving improvements in both disease activity and general well-being.

Prior to initiation of a nail psoriasis intervention it is important to rule out factors that can complicate treatment. Onychomycosis is more prevalent in nail psoriasis patients and its presence can complicate diagnosis and treatment, therefore it is important to examine the nail for fungal infections and, when suspected, to prescribe antifungal treatment along with nail psoriasis treatment. Avoidance of drugs and of activities that might exacerbate nail psoriasis by koebnerization should be discussed, and cutting the oncolytic part of the nail plate should be promoted.[69]

Once treatment in initiated, it is recommended to provide instructions on skin and nail care and to discuss expectations on treatment efficacy (time of onset with

an estimate of treatment success) and safety to manage patient expectations and promote compliance. Predefined treatment goals could be helpful to achieve this.

To follow-up on nail psoriasis, assessment of patient reported outcomes should be encouraged, certainly since it is questioned whether NAPSI adequately reflects the severity of nail psoriasis and has the sensitivity to detect clinically relevant changes in severity. Until now, assessment of symptoms and other patient reported outcomes are underexposed in clinical trials. The process towards development of a core outcome set for nail psoriasis trials is ongoing and aims to enable better comparison between trials and to promote the universal use of (patient) relevant outcome measures.[70]

Conclusion

The thirty-six newly added RCTs in this update substantially improve the body of evidence for nail psoriasis interventions. Especially, the body of evidence for small molecules and biologics has exponential increased. In the last couple of years data on nail psoriasis efficacy became available to support the use of the small molecules tofacitinib and apremilast and of all currently registered biologics. MTX and ciclosporin seem equally effective however data on ciclosporin are not placebo-controlled. Trials on local interventions support the use of local corticosteroids and vitamin D derivates and the first RCT data were added on tacrolimus ointment and intralesional triamcinolone. Severe heterogeneity was detected in outcome measurement instruments reported in RCTs which limited outcome comparability between trials. Future standardization of outcome reporting including assessment of PROs is pivotal to improve data synthesis and to ensure that only reliable and relevant outcomes are reported.

Supplemental content
Please find the full version of this systematic review in the electronic version of this thesis.

References

1. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail psoriasis: a questionnaire-based survey. Br J Dermatol. 2013;169(2):314-9.
2. Salomon J, Szepietowski JC, Proniewicz A. Psoriatic nails: a prospective clinical study. J Cutan Med Surg. 2003;7(4):317-21.
3. Sadek HA, Abdel-Nasser AM, El-Amawy TA, Hassan SZ. Rheumatic manifestations of psoriasis. Clin Rheumatol. 2007;26(4):488-98.
4. van der Velden HM, Klaassen KM, van de Kerkhof PC, Pasch MC. Fingernail psoriasis reconsidered: a case-control study. J Am Acad Dermatol. 2013;69(2):245-52.
5. Kaur I, Saraswat A, Kumar B. Nail changes in psoriasis: a study of 167 patients. Int J Dermatol. 2001;40(9):601-3.
6. Ortonne JP, Baran R, Corvest M, Schmitt C, Voisard JJ, Taieb C. Development and validation of nail psoriasis quality of life scale (NPQ10). J Eur Acad Dermatol Venereol. 2010;24(1):22-7.
7. Augustin M, Blome C, Costanzo A, Dauden E, Ferrandiz C, Girolomoni G, et al. Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA): development and validation of a tool for assessment of nail psoriasis outcomes. Br J Dermatol. 2014;170(3):591-8.
8. Kyriakou A, Patsatsi A, Sotiriadis D. Quality of life and severity of skin and nail involvement in patients with plaque psoriasis. Eur J Dermatol. 2014;24(5):623-5.
9. de Vries AC, Bogaards NA, Hooft L, Velema M, Pasch M, Lebwohl M, et al. Interventions for nail psoriasis. Cochrane Database Syst Rev. 2013(1):CD007633.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.
11. Cassell SE, Bieber JD, Rich P, Tutuncu ZN, Lee SJ, Kalunian KC, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol. 2007;34(1):123-9.
12. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49(2):206-12.
13. Nakamura RC, Abreu L, Duque-Estrada B, Tamler C, Leverone AP. Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. An Bras Dermatol. 2012;87(2):203-11.

14. Baran R TA. Topical treatment of nail psoriasis with a new corticoid-containing nail lacquer formulation. Journal of Dermatological Treatment. 2009;10(3):201-4.

15. Efficacy and safety of 8% clobetasol nail lacquer formulation versus vehicle in nail psoriasis [Internet]. 2016.

16. Boontaveeyuwat E, Silpa-Archa N, Danchaivijitr N, Wongpraparut C. A randomized comparison of efficacy and safety of intralesional triamcinolone injection and clobetasol propionate ointment for psoriatic nails. J Dermatolog Treat. 2019;30(2):117-22.

17. Saki N, Hosseinpoor S, Heiran A, Mohammadi A, Zeraatpishe M. Comparing the Efficacy of Triamcinolone Acetonide Iontophoresis versus Topical Calcipotriol/ Betamethasone Dipropionate in Treating Nail Psoriasis: A Bilateral Controlled Clinical Trial. Dermatol Res Pract. 2018;2018:2637691.

18. Tzung TY, Chen CY, Yang CY, Lo PY, Chen YH. Calcipotriol used as monotherapy or combination therapy with betamethasone dipropionate in the treatment of nail psoriasis. Acta Derm Venereol. 2008;88(3):279-80.

19. Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol. 1998;139(4):655-9.

20. Kole L, Cantrell W, Elewski B. A randomized, double-blinded trial evaluating the efficacy and tolerability of vectical ointment (calcitriol 3 mcg/g ointment) when compared to betamethasone diproprionate ointment (64 mg/g) in patients with nail psoriasis. J Drugs Dermatol. 2014;13(8):912-5.

21. Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. Cutis. 2001;68(5):355-8.

22. Efficacy and safety of 0,1%, 0,5% and 1% tazarotene nail lacquer formulation versus vehicle in nail psoriasis; international, multicenter, double-blind, randomized study of four parallel groups [Internet]. 2016.

23. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. Acta Derm Venereol. 2007;87(2):167-8.

24. De Simone C, Maiorino A, Tassone F, D'Agostino M, Caldarola G. Tacrolimus 0.1% ointment in nail psoriasis: a randomized controlled open-label study. J Eur Acad Dermatol Venereol. 2013;27(8):1003-6.

25. Cannavo SP, Guarneri F, Vaccaro M, Borgia F, Guarneri B. Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study. Dermatology. 2003;206(2):153-6.

26. A randomized, double blind, placebo controlled, parallel groups, pilot study to assess the effects of two new nail lacquers, cyclosporine 5% and calcipotriol 0.005%, in the treatment of nail psoriasis [Internet]. 2010.

27. Efficacy and safety of 8% clobetasol nail lacquer formulation versus vehicle in nail psoriasis. EUCTR2006-006569-18-FR: www.clinicaltrialsregister.eu; Accessed February 2017.

28. Efficacy and safety of 0,1%, 0,5% and 1% tazarotene nail lacquer formulation versus vehicle in nail psoriasis. EUCTR2004-004825-87-HU: www.clinicaltrialsregister.eu; Accessed February 2017.

29. Flori ML RP, Micheli S, Andreassi L Treatment of psoriasic onychodystrophy with a hyaluronic acid product and chondroitinsulphates. Giornale Italiano di Dermatologia e Venereologia. 1994;129(3):129-33.

30. Levell NJ, Shuster S, Munro CS, Friedmann PS. Remission of ordinary psoriasis following a short clearance course of cyclosporin. Acta Derm Venereol. 1995;75(1):65-9.

31. de Jong EM, Menke HE, van Praag MC, van De Kerkhof PC. Dystrophic psoriatic fingernails treated with 1% 5-fluorouracil in a nail penetration-enhancing vehicle: a double-blind study. Dermatology. 1999;199(4):313-8.

32. Lin YK, Chang YC, Hui RC, See LC, Chang CJ, Yang CH, et al. A Chinese Herb, Indigo Naturalis, Extracted in Oil (Lindioil) Used Topically to Treat Psoriatic Nails: A Randomized Clinical Trial. JAMA Dermatol. 2015;151(6):672-4.

33. Lin YK, See LC, Huang YH, Chang YC, Tsou TC, Lin TY, et al. Efficacy and safety of Indigo naturalis extract in oil (Lindioil) in treating nail psoriasis: a randomized, observer-blind, vehicle-controlled trial. Phytomedicine. 2014;21(7):1015-20.

34. Cantoresi F, Caserini M, Bidoli A, Maggio F, Marino R, Carnevale C, et al. Randomized controlled trial of a water-soluble nail lacquer based on hydroxypropyl-chitosan (HPCH), in the management of nail psoriasis. Clin Cosmet Investig Dermatol. 2014;7:185-90.

35. Goldust M, Raghifar R. Clinical Trial Study in the Treatment of Nail Psoriasis with Pulsed Dye Laser. J Cosmet Laser Ther. 2013.

36. Treewittayapoom C, Singvahanont P, Chanprapaph K, Haneke E. The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. J Am Acad Dermatol. 2012;66(5):807-12.

37. Lindelof B. Psoriasis of the nails treated with grenz rays: a double-blind bilateral trial. Acta Derm Venereol. 1989;69(1):80-2.

38. Yu RC, King CM. A double-blind study of superficial radiotherapy in psoriatic nail dystrophy. Acta Derm Venereol. 1992;72(2):134-6.

39. Kwang TY, Nee TS, Seng KT. A therapeutic study of nail psoriasis using electron beams. Acta Derm Venereol. 1995;75(1):90.

40. Warren RB, Mrowietz U, von Kiedrowski R, Niesmann J, Wilsmann-Theis D, Ghoreschi K, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10068):528-37.

41. Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-17.

42. Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol. 2016;74(1):134-42.

43. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015;173(4):949-61.

44. Rich P, Griffiths CE, Reich K, Nestle FO, Scher RK, Li S, et al. Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year. J Am Acad Dermatol. 2008;58(2):224-31.

45. Torii H, Nakagawa H, Japanese Infliximab Study i. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010;59(1):40-9.

46. van de Kerkhof P, Guenther L, Gottlieb AB, Sebastian M, Wu JJ, Foley P, et al. Ixekizumab treatment improves fingernail psoriasis in patients with moderate-to-severe psoriasis: results from the randomized, controlled and open-label phases of UNCOVER-3. J Eur Acad Dermatol Venereol. 2017;31(3):477-82.

47. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17.

48. Elewski BE, Okun MM, Papp K, Baker CS, Crowley JJ, Guillet G, et al. Adalimumab for nail psoriasis: Efficacy and safety from the first 26 weeks of a phase 3, randomized, placebo-controlled trial. J Am Acad Dermatol. 2018;78(1):90-9 e1.

49. Leonardi C, Langley RG, Papp K, Tyring SK, Wasel N, Vender R, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. Arch Dermatol. 2011;147(4):429-36.

50. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.

51. Poulin Y, Crowley JJ, Langley RG, Unnebrink K, Goldblum OM, Valdecantos WC. Efficacy of adalimumab across subgroups of patients with moderate-to-severe chronic plaque psoriasis of the hands and/or feet: post hoc analysis of REACH. J Eur Acad Dermatol Venereol. 2014;28(7):882-90.

52. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-86.

53. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.

54. Genovese MC, Combe B, Kremer JM, Tsai TF, Behrens F, Adams DH, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. Rheumatology (Oxford). 2018;57(11):2001-11.

55. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190-9.

56. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. J Dermatol. 2018;45(9):1053-62.

57. Reich K, Graff O, Mehta N. Oral alitretinoin treatment in patients with palmoplantar pustulosis inadequately responding to standard topical treatment: a randomized phase II study. Br J Dermatol. 2016;174(6):1277-81.

58. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study G. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012;39(3):242-52.

59. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol. 2014;170(2):398-407.

60. Papp KA, Gooderham M, Jenkins R, Vender R, Szepietowski JC, Wagner T, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) as a therapeutic target in psoriasis: randomized, controlled investigation using namilumab, a specific human anti-GM-CSF monoclonal antibody. Br J Dermatol. 2019;180(6):1352-60.

61. Gumusel M, Ozdemir M, Mevlitoglu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. J Eur Acad Dermatol Venereol. 2011;25(9):1080-4.

62. Mahrle G, Schulze HJ, Farber L, Weidinger G, Steigleder GK. Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail, and joint involvement. J Am Acad Dermatol. 1995;32(1):78-88.

63. Ozmen I, Erbil AH, Koc E, Tunca M. Treatment of nail psoriasis with tumor necrosis factor-alpha blocker agents: an open-label, unblinded, comparative study. J Dermatol. 2013;40(9):755-6.

64. Prins AM, Vos K, Franssen EJ. Instability of topical ciclosporin emulsion for nail psoriasis. Dermatology. 2007;215(4):362-3.

65. Gomez EC, Anguiano Igea S, Gomez Amoza JL, Otero Espinar FJ. Evaluation of the promoting effect of soluble cyclodextrins in drug nail penetration. Eur J Pharm Sci. 2018;117:270-8.

66. Valdes BSG, Serro AP, Marto J, Santos RGD, Gomez EC, Otero-Espinar FJ, et al. Polyurethanes as New Excipients in Nail Therapeutics. Pharmaceutics. 2018;10(4).

67. 2012-005685-35. A randomised, double blind, double dummy, active comparator and placebo controlled confirmative non-inferiority trial of FP187 compared to Fumaderm in moderate to severe plaque psoriasis. www.clinicaltrialsregister.eu.

68. Sanchez-Regana M, Sola-Ortigosa J, Alsina-Gibert M, Vidal-Fernandez M, Umbert-Millet P. Nail psoriasis: a retrospective study on the effectiveness of systemic treatments (classical and biological therapy). J Eur Acad Dermatol Venereol. 2011;25(5):579-86.

69. Rigopoulos D, Baran R, Chiheb S, Daniel CR, 3rd, Di Chiacchio N, Gregoriou S, et al. Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis: A dermatologist and nail expert group consensus. J Am Acad Dermatol. 2019;81(1):228-40.

70. Busard CI, Nolte JYC, Pasch MC, Spuls PI. Reporting of outcomes in randomized controlled trials on nail psoriasis: a systematic review. Br J Dermatol. 2018;178(3):640-9.

CHAPTER 9

Discussion and future perspectives

Part I: Treating psoriasis with a combination of therapies

In **Chapter 2** we systematically identified and evaluated all randomized controlled trials (RCTs) that have been performed investigating efficacy and safety of systemic combination treatments in patients with plaque-psoriasis. Results demonstrate a significant decrease in psoriasis lesions for several combinations such as ustekinumab or methotrexate combined with phototherapy and etanercept combined with methotrexate. Etanercept in a single weekly dose combined with acitretin was equally effective compared to etanercept in a double weekly dose. Most evidence exists for etanercept combined with methotrexate (MTX) as this intervention has been investigated in two medium to large scale RCTs. Quality of evidence for the outcomes related to other combined interventions was low, mainly due to risk of bias and small sample sizes. Results on (short-term) safety assessments did not seem to differ between combination and monotherapy for most interventions, although more patients on combination treatment with etanercept and MTX experienced (mostly infectious) adverse events.[1] This is consistent with previous randomized trials with etanercept and methotrexate in rheumatoid arthritis.[2, 3] A higher risk of tuberculosis reactivation has been reported when tumour necrosis factor alpha (TNFα) inhibitors (infliximab adalimumab and certolizumab) were combined with MTX, but patients on etanercept were not included in this analysis.[4]

In several international guidelines, the evidence on combination treatments was summarized and (weak) recommendations for the use of several combination treatments (e.g. combinations with biologics, ultraviolet B (UVB), MTX, acitretin and more recently apremilast) were suggested.[5-7]

Although only combinations with the biologics etanercept and ustekinumab has been investigated using a randomized controlled design, several biologics are being combined with other systemic agents or phototherapy in daily clinical practice. In **Chapter 3** we examined the use and extent to which patients are treated with these combinations in collaboration with five PSONET registries. PSONET represents a European surveillance network consisting of independent registries to monitor the long-term effectiveness and safety of systemic agents in the treatment of psoriasis.[8]

Among participating registries (originating from Italy, Israel, Austria, Czech Republic and The Netherlands) on average 10% of biologic treatments were combined with a systemic agent or phototherapy. Higher rates of patients on combination treatment have been published in the British Association of Dermatologists Biologic Interventions Register (BADBIR); however, most included

patients in this registry were on bridging therapy, which might partly explain for this difference.[9]

The vast majority of treatments concerned a biologic combined with MTX, a combination that was prescribed in all countries. Combinations with (UVB) phototherapy, cyclosporine and acitretin were also prescribed with some regularity. Biologics were rarely combined with psoralen and ultraviolet A (PUVA), fumaric acids or a second biologic. Patients with psoriasis who started on a combination regimen had generally extensive disease, a high body mass index (BMI) and been affected with the psoriasis for many years. More than half of patients were diagnosed with psoriatic arthritis (PsA). In an observational registry study by Bonomo et al., descriptive characteristics of combination therapy groups were compared with biologic monotherapy. While combination therapy patients were more likely to have PsA, no major differences were seen in disease morphology, duration or baseline disease severity indicating that combination treatment is not solely prescribed in therapy resistant patients.[10] Treatment termination due to safety issues was infrequently reported in our study population, but in-depth data on type and severity of adverse events could not be extracted.

Our results highlight that there is substantial variation in timing of initiation and persistence on combination treatment across patients in different participating countries. There seems to be limited uniformity in patient selection and prescription of combination treatments. Factors that might contribute to differences in treatment prescription of these combinations include limited guidance in (inter) national guidelines, differences in the availability of treatments and differences in (the order of) prescribing drugs.[11]

As we identified no RCTs in **Chapter 4** on one of the most commonly used combination treatments in daily clinical practice (adalimumab with MTX; **Chapter 3**), we conducted an investigator-initiated, multicenter RCT to compare combination of adalimumab and MTX with adalimumab monotherapy in patients with plaque-psoriasis. RCTs in the field of rheumatology has shown that concomitant MTX augments the efficacy of adalimumab in rheumatoid arthritis, while its therapeutic benefit in patients with psoriatic arthritis was not demonstrated.[12] The goal of this study was to examine whether concomitant MTX impacts therapeutic outcomes in adalimumab treated patients with psoriasis. The methods and objectives of this trial were presented in **Chapter 4**. Patients received adalimumab according to the product label, were randomized 1:1 to receive 10mg MTX weekly or no additional treatment and were followed up for three years.

Guidance regarding treatment aspects such as timing of introduction and dosing of MTX when given concomitant with biologic therapy is limited in current psoriasis literature. Some data suggest that addition of MTX may still reverse

immunogenicity and regain response to biologic therapy when antibodies have already been detected.[13] However, besides decreased immunogenicity other mechanisms may play a role in the reduced clearance of (anti-TNFα) biologics that has been observed in the presence of concomitant MTX.[14] To exert a full effect on adalimumab pharmacokinetics, introduction of MTX at induction of adalimumab treatment might therefore be most favorable. As it takes time for MTX to convert to MTX polyglutamates, we choose to introduce MTX two weeks prior to adalimumab treatment.

Concerning dosing of concomitant MTX, evidence is limited to data in rheumatoid arthritis. MTX tends to reduce immunogenicity and increase adalimumab serum levels in a dose-dependent manner, although a dose of 5–10 mg of MTX seems already sufficient to substantially decrease immunogenicity against adalimumab and maintain serum concentrations within the therapeutic range.[15, 16] To avoid a high rate of discontinuation due to side effects, patients in our trial were treated with 10mg MTX weekly.

The results of this RCT with assessment of one-year efficacy, safety, pharmacokinetic and immunogenicity data of adalimumab combined with MTX compared to adalimumab monotherapy in patients with moderate to severe psoriasis were presented in **Chapter 5**.

A (non-significant) better drug survival and significant decrease in disease severity (PASI 75) was found in the combination group as compared to the monotherapy group. The tendency towards a prolonged drug survival with this combined treatment is in line with data derived from observational plaque-psoriasis studies.[17] Patient reported outcomes improved in both groups, with no major differences between interventions. A lower proportion of patients in the combination group showed anti-adalimumab antibodies and patients in the combination group had higher circulating adalimumab concentrations with less patients showing drug concentrations below the therapeutic range compared to patients on monotherapy. However, the clinical relevance of this difference in serum trough levels remains uncertain as a correlation between adalimumab concentrations and clinical response was not convincingly observed and an association between weight and adalimumab concentrations was found which might have contributed to the increase in adalimumab concentrations.[18]

An acceptable safety profile for both treatment regimens was observed with no occurrence of serious adverse events. Slightly more patients discontinued treatment due to side effects (nausea, gastro-intestinal complaints, flu-like symptoms and headache) in the combination group. Changes in liver enzyme concentrations were small with no notable differences between treatment groups.

In conclusion, there has been increasing interest in the utility of combination therapies, especially concerning anti-TNFα biologics and MTX. Promising data on characteristics of use, clinical efficacy, immunogenicity and pharmacokinetics were presented in this first part of the thesis. Although no major safety concerns were raised in psoriasis populations, tolerability of combination treatment warrants further investigation as the power to detect clinically relevant differences in adverse events was limited. As risk factors (e.g. obesity, diabetes mellitus, and alcohol intake) differ in psoriasis patients from populations with other inflammatory chronic diseases, safety data cannot be directly extrapolated from fields with more clinical and scientific experience with combination treatments.[19]

Part II: Pharmacokinetics, pharmacogenetics and immunogenicity of ustekinumab

In **Chapter 6** we investigated the role of ustekinumab serum concentrations, anti-ustekinumab antibodies and HLA-Cw6 status as potential tools to help tailor individualised treatment algorithms by performing a multicenter, prospective cohort study.

Formation of anti-ustekinumab antibodies was detected in 9% of patients, comparable to the prevalence rates reported in the current literature.[20] Patients with antibodies had lower circulating ustekinumab concentrations and a greater risk for treatment failure compared to patients with no antibodies, which is supported by previously reported findings.[21] Although anti-ustekinumab antibodies can lead to inefficacy, its contribution to treatment failure is probably limited when compared to other biologics such as adalimumab and infliximab.[20]

We did not find an association between circulating ustekinumab trough levels and treatment response. This is in line with previous reports, although studies performed in other inflammatory diseases (e.g. Crohn's disease) do suggest that ustekinumab trough levels within a certain range is associated with an optimal clinical effect.[22]

Besides the measurement of trough levels and anti-drug-antibodies, pharmacogenetic markers have been suggested as possible biomarkers for ustekinumab treatment. One of these markers is HLA-Cw6 status. Several publications reported on the possible advantage in the selection of patients for successful treatment by using HLA-Cw6 status.[23, 24] One possible explanation might be that HLA-Cw6 identifies a molecularly different subtype of psoriasis that is highly dependent on interleukin (IL)-12/23 signaling for its maintenance and auto-amplification and therefore is more sensitive to the selective blockade of this

signaling pathway.[25] In our patient population we observed a slight increase in response to ustekinumab in HLA-Cw6 positive patients compared to HLA-Cw6 negative patients, but the differences were small and not statistically significant.

In conclusion, measurement of anti-ustekinumab antibodies may be considered if treatment response is unsatisfactory. Therapeutic drug monitoring by measurement of trough levels and the usefulness of HLA-Cw6 as a pharmacogenetic marker remain under debate.

Several other single nucleotide polymorphisms are being investigated.[26] Immune profiling has also been increasingly researched and correlations between certain serum cytokines and treatment effect have been demonstrated on small scale.[25] Identification of useful biomarkers will help to optimize individualized therapy and to guide treatment decisions in psoriasis patients.

Part III: (Gaps in) the management of patients with nail psoriasis

The decision for a specific systemic (combination) treatment might be adjusted based on the presence of nail psoriasis. In this third part, we provide an up-to-date comprehensive overview of available evidence on nail psoriasis interventions and we perform the first step towards harmonization of outcome measurement instruments used in clinical trials on nail psoriasis, as this is a key requirement to improve trial reporting and facilitate data synthesis.

In **Chapter 7** we identified all outcome instruments outcome instruments (previously) used in nail psoriasis clinical trials. Identified outcome instruments were categorized in four outcome domains: clinical signs, quality of life, symptoms and delivery of care (e.g. patient satisfaction with received treatment).

Severe heterogeneity was identified in assessment of clinical signs (morphological features of nail psoriasis disease (e.g. onycholysis)). Both composite (Nail Psoriasis Severity Index (NAPSI), Nail Area Severity (NAS) and the composite fingernail score) and stand-alone outcome instruments (global assessment, nail features (e.g. subungual hyperkeratosis) or characteristics (e.g. number of cured nails, nail growth)) were used and in most clinical trials multiple outcome instruments were reported. NAPSI was the most commonly reported outcome instrument with assessment in 74% of all RCTs. Global assessment and nail features or characteristics assessed individually were reported in 38% and 35% of trials respectively.

Besides variety in type of outcome instruments, substantial diversity was detected in the way the most commonly assessed outcome instruments were handled. NAPSI, which was originally applied to four quadrants of all fingernails

and/or toenails was adjusted to assessment of a single-hand or all fingernails excluding the thumbnails in some studies and modified NAPSI (applied to the most severely affected nail with addition of a degree of severity for each nail feature) was reported in several variations assessing different nail features. Another subtype includes the target NAPSI (applied to the most severely affected nail with addition of a degree of severity), which was most commonly reported.[27, 28] Global assessment was reported on six different outcome scales. Insufficient reporting of outcome instrument characteristics (e.g. scale or subtype) and diversity in the way outcome instruments are analyzed (e.g. NAPSI 50, mean improvement in NAPSI) were other identified factors contributing to limited comparability of data between clinical trials.

Patient reported outcomes on clinical signs, symptoms and delivery of care were infrequently examined which is striking considering interventions for nail psoriasis intend to diminish complaints (e.g. pain) which can be best determined by the patient. Quality of life was assessed in half of the trials, however, mostly using a dermatology generic tool, which does not provide a clear impression of the impact of nail psoriasis on quality of life in specific. Two tools that enable evaluation of nail psoriasis on patients quality of life have been developed, which may be preferred above the dermatology generic tools that were used up to now if validated for the different measurement properties.[29, 30]

The majority of tools to assess clinical signs are not validated,[31] although some studies have explored the correlation between different outcome instruments.[32, 33] Moreover, the number of nails that need to be assessed for a representative reflection of nail psoriasis, the sensitivity to reflect meaningful clinical responsiveness with assessment of commonly used outcome instruments such as NAPSI, and the threshold for diagnosis of nail psoriasis have been questioned.[34]

As discussed in the introduction, an up-to-date overview of evidence covering nail psoriasis interventions is desirable for clinical decision making, especially since the number of trials investigating nail psoriasis interventions tripled in the last few years. We performed an update of the Cochrane systematic review and presented the results in **Chapter 8**.

Results indicate that nearly 90% of study patients have been treated with new generation systemic agents (biologics or small molecules) and only a relative small number of patients received conventional systemic interventions or local therapy.

Significant improvements in nail disease severity up to 45% during induction treatment were reported for biologics (except for ustekinumab and namilumab), small molecules and methotrexate compared to placebo. Efficacy improved up to 84% during maintenance treatment, which supports the need for long-term treatment. Etanercept performed better during induction therapy compared to

apremilast and ixekizumab performed better during induction therapy compared to etanercept.[35, 36] Other biologics and small molecules did not seem to differ substantially in clinical efficacy during induction or maintenance treatment, however indirect comparison is limited due to heterogeneity in outcome measures. Cyclosporine and methotrexate performed comparably although no placebo-controlled data are available to support the efficacy of ciclosporin.[37] No RCT evidence exists for fumaric acids, although one trial is ongoing.[38] Randomized clinical trials comparing conventional systemic agents with new generation interventions are lacking. A small (retrospective) study compared the effectiveness of different systemic agents in clinical practice and found no differences between conventional agents and anti-TNF-α biologics.[39]

In the trials on ixekizumab, golimumab and certolizumab part of the patients used other systemic agents (including methotrexate) concomitantly during the trial. Unfortunately, results on nail disease were not corrected for concomitant use of other systemic agents. As such it remains unclear whether combined systemic treatment is beneficial in the treatment of nail psoriasis.

If patients do not qualify for systemic therapy, local intervention can be indicated. Several local interventions demonstrated a beneficial effect. Class 3 corticosteroids and vitamin D derivates have been most commonly studied, are generally well-tolerated and seem to moderately improve nail psoriasis disease with no major differences in treatment efficacy between interventions.[40-46] Intralesional triamcinolone also improved nail disease severity but did not perform better than clobatesol ointment.[47] Tacrolimus ointment has been studied on small scale and demonstrated beneficial results.[48]

In conclusion, scientific interest in the field of nail psoriasis has increased and the body of evidence for new generation systemic agents has expanded over the last couple of years. The presence of nail psoriasis impacts may affect decision-making and should be acknowledged by the physician. Future research is needed to critically appraise the validation data of the identified instruments to examine whether these identified instruments are appropriate to use as a core instrument in nail psoriasis trials. Improved outcome reporting will reduce waste of research and ensure research is relevant to patients.

References

1. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. JAMA Dermatol. 2014;150(11):1213-20.
2. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372(9636):375-82.
3. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54(4):1063-74.
4. Lorenzetti R, Zullo A, Ridola L, Diamanti AP, Lagana B, Gatta L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. Ann Med. 2014;46(7):547-54.
5. AbuHilal M, Walsh S, Shear N. Use of Apremilast in Combination With Other Therapies for Treatment of Chronic Plaque Psoriasis: A Retrospective Study. J Cutan Med Surg. 2016;20(4):313-6.
6. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-72.
7. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-94.
8. Lecluse LL, Naldi L, Stern RS, Spuls PI. National registries of systemic treatment for psoriasis and the European 'Psonet' initiative. Dermatology. 2009;218(4):347-56.
9. Iskandar IYK, Ashcroft DM, Warren RB, Evans I, McElhone K, Owen CM, et al. Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017;176(5):1297-307.
10. Bonomo L, Abittan BJ, Hashim PW, Karki C, Mason M, Lebwohl M. Combination Use of Systemic Therapies in Psoriasis: Baseline Characteristics from the Corrona Psoriasis Registry. J Drugs Dermatol. 2019;18(8):731-40.

11. Busard CI, Cohen AD, Wolf P, Gkalpakiotis S, Cazzaniga S, Stern RS, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. J Eur Acad Dermatol Venereol. 2018;32(2):245-53.

12. Behrens F, Koehm M, Schwaneck EC, Schmalzing M, Wittig BM, Gnann H, et al. Addition or removal of concomitant methotrexate alters adalimumab effectiveness in rheumatoid arthritis but not psoriatic arthritis. Scand J Rheumatol. 2019;48(5):375-82.

13. Ungar B, Kopylov U, Engel T, Yavzori M, Fudim E, Picard O, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment Pharmacol Ther. 2017;45(2):276-82.

14. Xu Z, Davis HM, Zhou H. Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety. J Clin Pharmacol. 2015;55 Suppl 3:S60-74.

15. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71(11):1914-5.

16. Vogelzang EH, Pouw MF, Nurmohamed M, Kneepkens EL, Rispens T, Wolbink GJ, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. Ann Rheum Dis. 2015;74(2):474-5.

17. Shalom G, Cohen AD, Ziv M, Eran CB, Feldhamer I, Freud T, et al. Biologic drug survival in Israeli psoriasis patients. J Am Acad Dermatol. 2017;76(4):662-9 e1.

18. Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2017;31(3):490-7.

19. Barker J, Horn EJ, Lebwohl M, Warren RB, Nast A, Rosenberg W, et al. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol. 2011;25(7):758-64.

20. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: a systematic review. Br J Dermatol. 2014;170(2):261-73.

21. Chiu HY, Chu TW, Cheng YP, Tsai TF. The Association between Clinical Response to Ustekinumab and Immunogenicity to Ustekinumab and Prior Adalimumab. PLoS One. 2015;10(11):e0142930.

22. Battat R, Kopylov U, Bessissow T, Bitton A, Cohen A, Jain A, et al. Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2017;15(9):1427-34 e2.

23. Talamonti M, Botti E, Galluzzo M, Teoli M, Spallone G, Bavetta M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. Br J Dermatol. 2013;169(2):458-63.

24. Talamonti M, Galluzzo M, van den Reek JM, de Jong EM, Lambert JLW, Malagoli P, et al. Role of the HLA-C*06 allele in clinical response to ustekinumab: evidence from real life in a large cohort of European patients. Br J Dermatol. 2017;177(2):489-96.

25. Litman T. Personalized medicine-concepts, technologies, and applications in inflammatory skin diseases. APMIS. 2019;127(5):386-424.

26. Prieto-Perez R, Llamas-Velasco M, Cabaleiro T, Solano-Lopez G, Marquez B, Roman M, et al. Pharmacogenetics of ustekinumab in patients with moderate-to-severe plaque psoriasis. Pharmacogenomics. 2017;18(2):157-64.

27. Parrish CA, Sobera JO, Elewski BE. Modification of the nail psoriasis severity index. Journal of the American Academy of Dermatology. 2005;53(4):745-6.

28. Cassell SE, Bieber JD, Rich P, Tutuncu ZN, Lee SJ, Kalunian KC, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. The Journal of rheumatology. 2007;34(1):123-9.

29. Ortonne JP, Baran R, Corvest M, Schmitt C, Voisard JJ, Taieb C. Development and validation of nail psoriasis quality of life scale (NPQ10). Journal of the European Academy of Dermatology and Venereology. 2010;24(1):22-7.

30. Augustin M, Blome C, Costanzo A, Dauden E, Ferrandiz C, Girolomoni G, et al. Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA): development and validation of a tool for assessment of nail psoriasis outcomes. The British journal of dermatology. 2014;170(3):591-8.

31. Augustin M, Ogilvie A. Methods of outcomes measurement in nail psoriasis. Dermatology. 2010;221 Suppl 1:23-8.

32. Kyriakou A, Patsatsi A, Sotiriadis D. The agreement among the different ways of measuring NAPSI and their correlation with DLQI. J Dtsch Dermatol Ges. 2014;12(11):1051-3.

33. Klaassen KMG, van de Kerkhof PCM, Bastiaens MT, Plusjé LGJM, Baran RL, Pasch MC. Scoring nail psoriasis. Journal of the American Academy of Dermatology. 2014;70(6):1061-6.

34. Korver JE, van de Kerkhof PC, Pasch MC. Alefacept treatment of psoriatic nail disease: how severe should nail psoriasis be? J Am Acad Dermatol. 2006;54(4):742-3.

35. Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-17.

36. van de Kerkhof P, Guenther L, Gottlieb AB, Sebastian M, Wu JJ, Foley P, et al. Ixekizumab treatment improves fingernail psoriasis in patients with moderate-to-severe psoriasis: results from the randomized, controlled and open-label phases of UNCOVER-3. J Eur Acad Dermatol Venereol. 2017;31(3):477-82.

37. Gumusel M, Ozdemir M, Mevlitoglu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. J Eur Acad Dermatol Venereol. 2011;25(9):1080-4.

38. 2012-005685-35. A randomised, double blind, double dummy, active comparator and placebo controlled confirmative non-inferiority trial of FP187 compared to Fumaderm in moderate to severe plaque psoriasis. www.clinicaltrialsregister.eu.

39. Sanchez-Regana M, Sola-Ortigosa J, Alsina-Gibert M, Vidal-Fernandez M, Umbert-Millet P. Nail psoriasis: a retrospective study on the effectiveness of systemic treatments (classical and biological therapy). J Eur Acad Dermatol Venereol. 2011;25(5):579-86.

40. Efficacy and safety of 8% clobetasol nail lacquer formulation versus vehicle in nail psoriasis [Internet]. 2016.

41. Nakamura RC, Abreu L, Duque-Estrada B, Tamler C, Leverone AP. Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. An Bras Dermatol. 2012;87(2):203-11.

42. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. Acta Derm Venereol. 2007;87(2):167-8.

43. Baran R TA. Topical treatment of nail psoriasis with a new corticoid-containing nail lacquer formulation. Journal of Dermatological Treatment. 2009;10(3):201-4.

44. Kole L, Cantrell W, Elewski B. A randomized, double-blinded trial evaluating the efficacy and tolerability of vectical ointment (calcitriol 3 mcg/g ointment) when compared to betamethasone diproprionate ointment (64 mg/g) in patients with nail psoriasis. J Drugs Dermatol. 2014;13(8):912-5.

45. Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol. 1998;139(4):655-9.

46. Tzung TY, Chen CY, Yang CY, Lo PY, Chen YH. Calcipotriol used as monotherapy or combination therapy with betamethasone dipropionate in the treatment of nail psoriasis. Acta Derm Venereol. 2008;88(3):279-80.

47. Boontaveeyuwat E, Silpa-Archa N, Danchaivijitr N, Wongpraparut C. A randomized comparison of efficacy and safety of intralesional triamcinolone injection and clobetasol propionate ointment for psoriatic nails. J Dermatolog Treat. 2019;30(2):117-22.

48. De Simone C, Maiorino A, Tassone F, D'Agostino M, Caldarola G. Tacrolimus 0.1% ointment in nail psoriasis: a randomized controlled open-label study. J Eur Acad Dermatol Venereol. 2013;27(8):1003-6.

CHAPTER 10

Summary and conclusion
Samenvatting en conclusie

Summary

Psoriasis is a chronic inflammatory disease, which can lead to a significant burden on quality of life. Many patients experience physical complaints and restrictions in daily life activities.

The prevalence is around 1.3-2.2% in the world population, with variations according to geographic region, being more common in countries more distant from the equator.

There is no cure yet, but the availability of biologics therapies targeting selective key immune pathways has radically transformed the treatment for moderate-to-severe psoriasis. Ever since the first biologic for treating psoriasis was approved in 2005, research has shown that these drugs can effectively and safely treat the disease. With the introduction of many new generation systemic agents, it became possible to combine different systemic treatments and to tailor therapy to different manifestations such as psoriasis arthropathica and nail psoriasis.

More knowledge about the use, monitoring and long-term effects of biologic (combination) treatment is needed to offer patients optimal therapy.

The studies described in this thesis aimed at improving the outcome of psoriasis patients by concentrating on three domains: evaluation of the potential benefits and harms of systemic combination treatment (**Part I**), examination of biomarkers to support personalized treatment with ustekinumab (**Part II**), and assessment of efficacy and safety of nail psoriasis interventions with a first step towards the development of a core outcome set (**Part III**).

Part I: Treating psoriasis with a combination of therapies

Combination of two systemic agents is suggested to be beneficial due to enhanced efficacy, acceleration of onset of disease remission and the potential to reduce the dose of individual agents, thereby decreasing toxicity and improving tolerability and compliance. There are reasons to believe that specific combinations, the addition of methotrexate (MTX) to a biological, can reduce immunogenicity and promote increased drug concentrations with subsequent maintained improvements in clinical response over time.

In **Chapter 2** we summarized and critically appraised the RCT evidence on efficacy and safety of combination therapy with systemic agents in plaque-type psoriasis. Etanercept with MTX was the only combination therapy investigated with an adequate sample size and results demonstrated superior efficacy compared to etanercept monotherapy. Although this finding coincided with an increase in

adverse events, the overall safety profile remained acceptable. For combination of other biologics with MTX, no RCT evidence exists. Most other studies (e.g. biologics with phototherapy or oral retinoids) favored combination therapy, albeit with low quality of evidence.

In **Chapter 3** we examined the use of biologic combination treatment in clinical practice across different geographical regions by collecting data from different prospective patient registries. Of 9922 biologic treatment cycles, 982 (9.9%) were identified as combination treatment. The vast majority (72.9%) concerned concomitant use of MTX, 25.3% concerned concomitant UVB therapy, acitretin or cyclosporin and 1.8% concerned combined treatment with PUVA, fumaric acids or a second biologic. Substantial variation was detected in type and frequency of combination treatment prescribed across registries, the extent to which patients had been priory treated with biologic monotherapy and the proportion of patients affected with psoriatic arthritis. No consistent superior drug survival for a particular biologic combination was demonstrated and longest survival on a biologic combined with methotrexate, acitretin or cyclosporin was 103, 78 and 34 months, respectively.

In **Chapter 4** we presented the study protocol of the first RCT to investigate combination therapy with adalimumab and MTX in a psoriasis population. Patients received adalimumab according to the product label and were randomized to receive 10mg MTX weekly or no additional treatment. In this chapter we discuss the methods and objectives of this trial and we emphasize on dosing and timing of initiation of MTX as the impact of these factors on successful combination therapy are not yet known.

As it is not clear whether addition of MTX may still reverse immunogenicity when introduced during maintenance treatment and whether the potential beneficial effects of concomitant MTX are dose-dependent, we choose to initiate MTX two weeks prior to adalimumab treatment in a dose of 10mg. This dose seems already sufficient to substantially decrease immunogenicity against adalimumab and maintain serum concentrations within the therapeutic range.

In **Chapter 5** the first-year results of the RCT with assessment of efficacy, safety, pharmacokinetic and immunogenicity data were presented. A total of 61 patients were analyzed (31 on combined treatment and 30 on adalimumab monotherapy). After one year, a (non-significant) better drug survival was found in the combination group (74.2% vs 58.6%) and significantly more patients in the combination group achieved a 75% improvement of the Psoriasis Area and Severity Index (PASI; 58.1% vs. 31.0%) compared to monotherapy. A lower proportion of patients in the combination group showed anti-adalimumab antibodies and patients in the combination group had higher circulating adalimumab concentrations with less

patients showing drug concentrations below the therapeutic range compared to patients on monotherapy. The safety profile was acceptable for both treatment regimens with no occurrence of serious adverse events and no major differences between groups.

Promising data on characteristics of use, clinical efficacy, immunogenicity and pharmacokinetics were presented in this first part of the thesis. Although no major safety concerns were raised in psoriasis populations, tolerability of combination treatment warrants further investigation as the power to detect clinically relevant differences in adverse events was limited. Future research is needed to evaluate which patients benefit most of combination therapy.

Part II: Pharmacokinetics, pharmacogenetics and immunogenicity of ustekinumab

Ustekinumab for the treatment of psoriasis is currently administered in a standard dosing regimen. However, some patients tend to benefit from alternative dosing regimens, a step towards personalized medicine. In **Chapter 6** we investigated the role of ustekinumab serum concentrations, anti-ustekinumab antibodies and HLA-Cw6 status (a pharmacogenetic marker) as potential tools to help tailor treatment algorithms by performing a multicenter, prospective cohort study. A total of 137 patients were included and repeated measurements on efficacy and serum trough levels were obtained during the first year of ustekinumab treatment. Formation of anti-ustekinumab antibodies was detected in 9% of patients and was significantly associated with lower circulating ustekinumab concentrations and diminished clinical response. No differences in serum concentrations were observed between moderate to good responders and non-responders and serum concentrations were not affected by MTX co-medication. The prevalence of HLA-Cw6 positivity was 41% with no statistically significant difference in clinical response between HLA-Cw6 positive and negative patients.

Measurement of anti-ustekinumab antibodies may be considered if treatment response is unsatisfactory. Although anti-ustekinumab antibodies can lead to inefficacy, its contribution to treatment failure is probably limited when compared to other biologics such as adalimumab and infliximab. Therapeutic drug monitoring by measurement of trough levels and the usefulness of HLA-Cw6 as a pharmacogenetic marker remain under debate. Concomitant use of MTX did not impact circulating ustekinumab concentrations, but due to the small number of patients on MTX comedication, the therapeutic impact of MTX in patients on ustekinumab needs to be confirmed by future studies with sufficient power.

In the quest for biomarkers to personalize psoriasis care, ongoing research on pharmacogenetic markers and immune profiling is promising. Identification of useful biomarkers will help to optimize individualized therapy and to guide treatment decisions in psoriasis patients.

Part III: (Gaps in) the management of patients with nail psoriasis

As the decision for a specific systemic (combination) treatment might be adjusted based on the presence of nail psoriasis a comprehensive overview of evidence on available interventions is desirable. In 2013, a Cochrane systematic review on nail psoriasis interventions was published. Although a comprehensive overview of available nail psoriasis treatment options could be provided, data synthesis was limited due to substantial heterogeneity in outcome measurement instruments.

In **Chapter 7** we performed the first step towards standardization of outcome reporting by identification of outcome instruments and corresponding outcome domains used in (ongoing) RCTs. Identified outcome domains included clinical signs, quality of life, symptoms and delivery of care. Severe heterogeneity was identified in assessment of clinical signs. Both composite and stand-alone outcome instruments were used and in most clinical trials multiple outcome instruments were reported. NAPSI was the most commonly reported outcome instrument with assessment in 74% of all RCTs. Besides variety in type of outcome instruments, substantial diversity was detected in the way the most commonly assessed outcome instruments were handled (different scales were used and variations were detected in application of use (e.g. NAPSI of a single-hand instead of both hands)). Insufficient reporting of outcome instrument characteristics (e.g. scale or subtype) and diversity in the way outcome instruments are analyzed (e.g. proportion of patients that achieve 50% improvement in NAPSI (NAPSI 50)) were other factors contributing to limited comparability of data between clinical trials. Patient reported outcomes were infrequently examined which is striking considering interventions for nail psoriasis intend to diminish complaints (e.g. pain) which can be best determined by the patient.

In **Chapter 8** we systematically identified evidence on the efficacy and safety of nail psoriasis interventions. Nearly 90% of study patients (n=6511) have been treated with new generation systemic agents (biologics or small molecules) and only limited RCTs are available with a relative small number of patients received conventional systemic interventions or local therapy. Improvements in nail disease severity up to 45% during induction treatment (significant compared to placebo) were reported for biologics (except for ustekinumab and namilumab), small

molecules and methotrexate. Efficacy improved up to 84% during maintenance treatment, which supports the need for long-term treatment. Etanercept performed better during induction therapy compared to apremilast and ixekizumab performed better during induction therapy compared to etanercept. Cyclosporin and methotrexate performed comparably although no placebo-controlled data are available to support the efficacy of cyclosporin. Up to now, no RCT has been performed to evaluate fumaric acids as intervention for nail psoriasis, although one trial is ongoing. Unfortunately, results on nail disease were not corrected for concomitant use of MTX which was the case in four of the fifty-four trials. As such it remains unclear whether combined systemic treatment is beneficial in the treatment of nail psoriasis. Several local interventions demonstrated a beneficial effect compared to baseline and can be indicated if patients do not qualify for systemic therapy.

Scientific interest in the field of nail psoriasis has increased over the last couple of years. Standardization of outcome domains and the use of outcome measurement instruments is paramount to facilitate data synthesis and to ensure that only valid, reliable and relevant outcome measurement instruments are used. Future research is needed to critically appraise the validation data of the identified instruments to examine whether these identified instruments are appropriate to use as a core instrument in the core outcome set for nail psoriasis trials.

Samenvatting

Psoriasis is een chronische ontstekingsziekte die de kwaliteit van leven aanzienlijk kan beïnvloeden. Veel patiënten ervaren fysieke klachten en beperkingen in het dagelijks leven. De prevalentie van psoriasis wordt geschat tussen de 1,3% en 2,2% van de wereldbevolking. Genezing is nog niet mogelijk, echter is de behandeling sinds de introductie van biologische medicijnen die zich richten op specifieke afweercellen of boodschapper-eiwitten in het immuunsysteem (biologicals) wel revolutionair verbeterd voor patiënten met matig tot ernstige psoriasis. De eerste biological voor de behandeling van psoriasis werd in 2005 geregistreerd, sindsdien is er veel onderzoek verricht naar de effectiviteit en veiligheid van deze behandelingen. Met de introductie van deze medicijnen werd het mogelijk om systemische behandelingen met elkaar te combineren en bij de keuze voor behandeling factoren zoals de aanwezigheid van psoriasis arthropathica en nagelpsoriasis mee te wegen.

Meer kennis over het gebruik, de monitoring en de lange termijn effecten van (combinatie behandeling met) biologicals is gewenst om patiënten een optimale therapie te kunnen bieden.

De studies beschreven in dit proefschrift richten zich op het optimaliseren van de behandeling van psoriasis patiënten. Het proefschrift is opgedeeld in drie delen: de evaluatie van potentiele voordelen en mogelijke bezwaren van systemische combinatie behandeling (**Deel I**), het in kaart brengen van de waarde van biomarkers ter ondersteuning van gepersonaliseerde behandeling met ustekinumab (**Deel II**) en de beoordeling van effectiviteit en veiligheid van interventies voor nagel psoriasis met een eerste stap richting het harmoniseren van meetinstrumenten (**Deel III**).

Deel I: Combinatie therapie voor patiënten met psoriasis

Een combinatie van twee systemische middelen zou zinvol kunnen zijn vanwege een potentiele verbetering in effectiviteit en snellere werkzaamheid. Een andere reden om twee behandelingen te combineren zou kunnen zijn om de dosis van afzonderlijke middelen te kunnen verlagen, waardoor de kans op bijwerkingen af kan nemen en therapietrouw bevordert kan worden. Uit studies onder patiënten met reumatoïde artritis blijkt dat specifieke combinaties, zoals het toevoegen van methotrexaat (MTX) aan een biological, de immunogeniciteit (het maken van antistoffen tegen het medicijn) kan verminderen en de concentratie geneesmiddel in het bloed kan verhogen, met een verbeterde klinische respons tot gevolg.

In **Hoofdstuk 2A** verrichtten we een literatuuronderzoek naar de werkzaamheid en veiligheid van systemische combinatiebehandelingen op basis van gerandomiseerde gecontroleerde onderzoeken (RCTs). De combinatie etanercept met MTX werd het meest uitvoerig onderzocht en de resultaten tonen een significant grotere afname van ernst en oppervlak van de aangedane huid met combinatie behandeling in vergelijking met etanercept als monotherapie. Er werden meer bijwerkingen gerapporteerd in de combinatietherapie groep, onder andere het aantal patiënten met maag-darm klachten en leverenzymstoornissen was hoger in deze groep. Dit waren echter geen ernstige bijwerkingen en de incidentie was laag. Voor combinatie van andere biologicals met MTX in vergelijking met monotherapie waren er (nog) geen RCTs verricht. Onderzoeken naar het effect van andere combinatie behandelingen (onder andere combinaties van biologicals met lichttherapie of orale retinoïden) toonden enige toename van effect (afname van ernst en oppervlak aangedane huid) voor combinatiebehandeling ten opzichte van monotherapie, zij het met lage kwaliteit van bewijs.

In **Hoofdstuk 2B** werd het gebruik van combinatiebehandelingen in de klinische praktijk onderzocht. Data verzameld in prospectieve patiënt registers uit verschillende geografische regio's in Europa werden gezamenlijk geanalyseerd. Van de 9922 behandelcycli met biologicals betrof 982 (9,9%) een combinatiebehandeling. In de overgrote meerderheid (72,9%) was er sprake van combinatie met MTX, in 25,3% was er sprake van combinatie met lichttherapie, acitretine of ciclosporine en in 1,8% was er sprake van een gecombineerde behandeling met PUVA, fumaarzuur of een tweede biological. Er werd substantiële variatie waargenomen in type en frequentie van voorgeschreven combinatiebehandelingen tussen de verschillende landen. Tevens was er sprake van variatie in patiënt gerelateerde factoren zoals eerdere behandeling met een biological als monotherapie en het aantal patiënten met de diagnose artritis psoriatica. De maximale drug survival (de duur dat patiënten een geneesmiddel gebruiken) van biological therapie in combinatie met MTX, acitretine of ciclosporine was respectievelijk 103, 78 en 34 maanden.

In **Hoofdstuk 2C** presenteren we het studieprotocol van een onderzoeker geïnitieerde RCT waarin combinatietherapie met adalimumab en MTX werd vergeleken met adalimumab monotherapie bij patiënten met matig tot ernstige psoriasis. Patiënten werden behandeld met adalimumab en werden gerandomiseerd naar wel of geen combinatietherapie met wekelijks 10 mg MTX. In dit hoofdstuk bespraken we de methode en doelstellingen van deze studie. Er werd extra ingegaan op de protocol keuzes omtrent dosering en het moment van introduceren van MTX, aangezien hier geen consensus over bestaat en deze factoren mogelijk van invloed kunnen zijn op het slagen van behandeling. Het is vooralsnog onduidelijk of het toevoegen van MTX het falen van behandeling nog kan tegengaan op het moment

dat er reeds antistoffen zijn gevormd. Ook is onbekend of de potentieel gunstige effecten van MTX indien gecombineerd met adalimumab dosisafhankelijk zijn. Voor deze RCT kozen wij ervoor om MTX twee weken voorafgaand aan adalimumab te starten in een dosering van 10 mg/week. Deze dosering lijkt op basis van studies verricht in patiënten met reumatoïde artritis voldoende om de immunogeniciteit tegen adalimumab te verlagen en de adalimumab concentraties in het bloed binnen de therapeutische range (waardes waarbinnen een goed effect van behandeling aannemelijk wordt geacht) te houden.

In **Hoofdstuk 2D** presenteren we de resultaten van de RCT die beschreven is in hoofdstuk 2C ten aanzien van de uitkomsten drug survival, effectiviteit, veiligheid, farmacokinetiek en immunogeniciteit na 1 jaar follow-up. In totaal werden 61 patiënten geanalyseerd (31 op combinatie behandeling en 30 op monotherapie met adalimumab). Na een jaar werd een (niet-significante) betere drug survival gevonden in de combinatiegroep en significant meer patiënten in de combinatiegroep bereikten een verbetering van 75% van de Psoriasis Area and Severity Index (PASI) vergeleken met monotherapie. Een kleiner aantal patiënten in de combinatiegroep vormde anti-adalimumab-antilichamen en patiënten in de combinatiegroep hadden hogere circulerende adalimumab-concentraties in het bloed in vergelijking met patiënten op monotherapie. Het veiligheidsprofiel was acceptabel voor beide behandelgroepen, er traden geen ernstige bijwerkingen op.

In dit eerste deel van het proefschrift werden data op het gebied van systemische combinatiebehandelingen gepresenteerd. Naar de effectiviteit en veiligheid van combinatiebehandeling is nader onderzoek gerechtvaardigd. Toekomstig onderzoek zal moeten uitwijzen welke patiënten het meest baat hebben bij welke combinatie behandeling en welke plaats combinatie behandeling inneemt in het behandelalgoritme van psoriasis.

Deel II: Farmacokinetiek, farmacogenetica en immunogeniciteit van ustekinumab

Ustekinumab wordt voor de behandeling van psoriasis in het algemeen toegediend in een standaard doseringsschema van een keer per 12 weken na een opstartdosis. Sommige patiënten zouden echter baat kunnen hebben van een aangepast behandelinterval, een stap in de richting van gepersonaliseerde geneeskunde. In **Hoofdstuk 3** voerden we een multicenter, prospectief cohortonderzoek met 137 geïncludeerde patiënten uit om de rol van ustekinumab serumconcentraties, anti-ustekinumab-antilichamen en HLA-Cw6-status (een farmacogenetische marker) in relatie tot de effectiviteit van de behandeling te onderzoeken.

Vorming van anti-ustekinumab-antilichamen werd gedetecteerd bij 9% van de patiënten en ging gepaard met een lagere ustekinumab serum concentratie en een verminderd klinisch effect. Er werd geen verschil in ustekinumab serum concentratie waargenomen tussen patiënten met een matig tot goed effect op behandeling en patiënten met een slecht behandel effect (non-responders). Ook werd er geen verschil in ustekinumab serum concentratie vastgesteld tussen patiënten met en zonder MTX als comedicatie.

De prevalentie van HLA-Cw6-positiviteit was 41%. Er werd geen verschil in effectiviteit (afname ernst en oppervlak van de aangedane huid) waargenomen tussen HLA-Cw6-positieve en negatieve patiënten.

Het meten van anti-ustekinumab-antilichamen kan worden overwogen als het effect op behandeling onvoldoende is. Hoewel de vorming van anti-ustekinumab-antilichamen tot therapie falen kan leiden, speelt immunogeniciteit een kleinere rol dan bij andere biologicals zoals adalimumab en infliximab. Aanvullend onderzoek is nodig naar de relevantie van het monitoren van behandeling op basis van ustekinumab serum concentraties, het nut van HLA-Cw6 als farmacogenetische marker en het gelijktijdig gebruik van MTX. Onderzoek naar farmacogenetische en immunologische markers zou in de toekomst tot bruikbare biomarkers kunnen leiden en kunnen bijdragen aan gepersonaliseerde behandeling van psoriasispatiënten.

Deel III: (Hiaten in) de behandeling van patiënten met nagelpsoriasis

Nagel psoriasis is een van de factoren die wordt meegewogen bij de beslissing voor een specifieke systemische (combinatie) behandeling. Een overzicht van de effecten van beschikbare interventies voor nagelpsoriasis is daarom waardevol. In 2013 werd een systematisch literatuuronderzoek naar de interventies van nagelpsoriasis gepubliceerd door onze onderzoeksgroep in de Cochrane library. Hoewel een overzicht van beschikbare behandelingsopties voor nagelpsoriasis kon worden gegeven, was de vergelijking van verschillende interventies beperkt door het relatief lage aantal RCTs en door aanzienlijke heterogeniteit in gerapporteerde meetinstrumenten in de geïncludeerde studies.

In **Hoofdstuk 4A** hebben we de eerste stap gezet naar harmonisatie van meetinstrumenten die gebruikt worden in (lopende) RCTs naar interventies voor nagel psoriasis door een overzicht te genereren van alle gebruikte meetinstrumenten tot nu toe.

Om een behandeleffect (verbetering van nagelafwijkingen) te meten werden zowel samengestelde als enkelvoudige meetinstrumenten gebruikt en in de

meeste RCTs werd een combinatie van meetinstrumenten gebruikt. De Nail Area and Severity Index (NAPSI) werd gebruikt in 74% van de RCTs en was daarmee het meest frequent gebruikte meetinstrument. NAPSI is onder te verdelen in target NAPSI (beoordeling van de meest ernstige beschadigde nagel), modified NAPSI (beoordeling van de meest ernstige beschadigde nagel met een maat voor de ernst van beschadiging), en de originele NAPSI (beoordeling van alle nagels). Binnen deze indeling werd er echter ook grote diversiteit geconstateerd in de manier waarop NAPSI werd geanalyseerd. Een ander veelgebruikt meetinstrument was de 'Physician Global Assessment' die ook op diverse manieren werd geanalyseerd. Naast heterogeniteit in gebruikte meetinstrumenten was er ook sprake van beperkte vermelding van kenmerken behorend bij het gebruik van de meetinstrumenten (bijv. de schaal). Patiënt gerapporteerde meetinstrumenten waren schaars en werden ook zeer beperkt gemeten in RCTs. Dit is opvallend aangezien belangrijke indicatoren voor een succesvolle behandeling (bijv. afname van pijn) het beste door de patiënt kunnen worden vastgesteld.

In **Hoofdstuk 4B** bespraken we de update van de systematische literatuurstudie die we verrichtten naar de effectiviteit en veiligheid van nagelpsoriasis interventies. Bijna 90% van de onderzoekspatiënten (n=6511) werd behandeld met een biological of een small molecule geneesmiddel en slechts een relatief klein aantal patiënten werd behandeld met conventionele systemische interventies (zoals MTX) of lokale therapie. Verbetering in de ernst en uitgebreidheid van nagelpsoriasis tot 45% ten opzichte van baseline (significant in vergelijking met placebo) werd bereikt tijdens inductiebehandeling met alle onderzochte biologicals (behalve ustekinumab en namilumab), small molecules en MTX. De effectiviteit nam toe tot 84% verbetering ten opzichte van baseline tijdens onderhoudsbehandeling (≥24 weken), wat de behoefte aan langdurige behandeling onderstreept. Ciclosporine lijkt qua effectiviteit vergelijkbaar met MTX. Naar ciclosporine is in tegenstelling tot MTX echter geen placebo-gecontroleerd onderzoek verricht. Voor fumaarzuur, een van de andere veel gebruikte conventionele systemische behandelingen, wordt momenteel een RCT verricht naar het effect op nagel psoriasis.

In enkele studies werden meerdere systemische interventies onderzocht en met elkaar vergeleken. Op basis van deze data bleek etanercept effectiever dan apremilast en ixekizumab effectiever dan etanercept tijdens inductie therapie. Lange termijn data waarbij interventies direct (op eenzelfde studie populatie) met elkaar worden vergeleken zijn niet beschikbaar.

In vier van de 54 studies werd een deel van de studie populatie behandeld met een combinatie van een biological en MTX. De data werden echter niet gecorrigeerd voor het effect op nagel psoriasis waardoor niet vast te stellen valt of het combineren van systemische behandelingen van toegevoegde waarde

kan zijn voor patiënten met nagel psoriasis. Diverse lokale interventies zoals corticosteroïden, vitamine D preparaten en calcineurine remmers lieten tevens een gunstig effect zien op nagelafwijkingen en kunnen worden ingezet bij patiënten met milde klachten.

In de afgelopen jaren zijn er meerdere nieuwe systemische behandelopties beschikbaar gekomen voor psoriasis van de huid, de gewrichten en voor nagelpsoriasis. Heterogeniteit in het gebruik van meetinstrumenten beperkt de interpretatie van studieresultaten en harmonisatie van meetinstrumenten is daarom van cruciaal belang om ervoor te zorgen dat studieresultaten een waardevolle basis vormen voor de hedendaagse patiëntenzorg.

10

ADDENDUM

List of abbreviations

ADA	Adalimumab anti-Drug Antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AU	Arbitrary Units
AUA	Anti-Ustekinumab Antibodies
BMI	Body Mass Index
CI	Confidence Interval
COS	Core Outcome Set
COUSIN	Cochrane Skin Group Core Outcomes Set Initiative
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EADV	European Academy of Dermatology and Venereology
ELISA	Enzyme-Linked Immunosorbent Assays
EQ-5D	European Quality of Life-5 Dimensions
5-FU	5-Fluorouracil
IGA	Investigator Global Assessment
LTFU	Lost To Follow Up
PGA	Patient or Physician Global Assessment
PK	Pharmacokinetic
PUVA	Psoralen–UV-A
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDEOM	International Dermatology Outcome Measures
IL	Interleukin
ITT	Intention To Treat
MTX	Methotrexate
MCS	Mental Component Score
MD	Mean Difference
mNAPSI	Modified Nail Psoriasis Severity Index
NAPPA-QoL	Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life
NAPSI	Nail Psoriasis Severity Index
NAS	Nail Area Severity
NPQ10	Nail Psoriasis Quality 10
NRS	Numerical Rating Scale

OMERACT	Outcome Measures in Rheumatology
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Score
PNSS	Psoriasis Nail Severity Score
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	Psoriatic Arthritis
PSSM	Patient Satisfaction with Study Medication questionnaire
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RR	Risk Ratio
SAE	Serious Adverse Event
ShNAPSI	Single hand Nail Psoriasis Severity Index
SF36	Short Form-36
SNP	Single Nucleotide Polymorphism
TNFα	Tumor Necrosis Factor alfa
TMSQ	Treatment Medication Satisfaction Questionnaire
ULN	Upper Limit of Normal
UVB	Ultraviolet B
VAS	Visual Analogue Scale
QoL	Quality of Life

List of contributing authors

E. Adenubiova, MD
Department of Dermatovenereology, Third Faculty of Medicine, Charles University and University Hospital of Kralovske Vinohrady, Prague, Czech Republic

A. Addis, MsC, PhD
Department of Epidemiology, Servizio Sanitario Regionale, Regione Lazio, Italy

J.S. van Bezooijen, MD, PhD
Department of Dermatology, Erasmus Medical Centre, Erasmus University Rotterdam, Rotterdam, the Netherlands

S. Cazzaniga, MsC, PhD
Centro Studi GISED, Fondazione per la Ricerca, Ospedale Maggiore, Bergamo, Italy

A.D. Cohen, MD, PhD
Department of Quality measurements and research, Clalit Health Services, Tel-Aviv, Israel

A. Costanzo, MD, PhD
Department of Dermatology, Sapienza University, Rome, Italy

M.B.A. van Doorn, MD, PhD
Department of Dermatology, Erasmus Medical Centre, Erasmus University Rotterdam, Rotterdam, the Netherlands

I. Feldhamer, MsC, PhD
Department of Quality measurements and research, Clalit Health Services, Tel-Aviv, Israel

S. Gkalpakiotis, MD, PhD
Department of Dermatovenereology, Third Faculty of Medicine, Charles University and University Hospital of Kralovske Vinohrady, Prague, Czech Republic

L. Hooft, MsC, PhD
Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

B.A. Hutten, MsC, PhD
Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, the Netherlands

E.M.G.J. de Jong, MD, PhD (Professor)
Department of Dermatology, Radboud university medical center, Nijmegen, The Netherlands

M. Kojanova, MD
Department of Dermatovenereology, Charles University, First Faculty of Medicine and General University Hospital, Prague, Czech Republic

E. De Keyser, MD
Department of Dermatology, Ghent University Hospital, Ghent, Belgium

W. de Kort, MD, PhD
Amphia hospital, Department of Dermatology, Breda, The Netherlands

G.E. van der Kraaij, MD
Amsterdam UMC, University of Amsterdam, Department of Dermatology, Amsterdam, The Netherlands

J. Lambert, MD, PhD (Professor)
Department of Dermatology, Ghent University Hospital, Ghent, Belgium

S. Lanssens, MD
Department of Dermatology, Ghent University Hospital, Ghent, Belgium

R. Lichem, MD, PhD
Department of Dermatology, Medical University of Graz, Graz, Austria

J. Limpens, PhD
Medical Library, Amsterdam UMC, Amsterdam, The Netherlands

S.P. Menting, MD, PhD
Department of Dermatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

L. Meuleman, MD
Private dermatology practice, Lede, Belgium

A.H. Musters, MD
Department of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

L. Naldi, MD, PhD (Professor)
Centro Studi GISED, Fondazione per la Ricerca, Ospedale Maggiore, Bergamo, Italy

J.Y.C. Nolte, MD
Department of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

M.C. Pasch, MD, PhD
Department of Dermatology, Radboud university medical center, Nijmegen, The Netherlands

E. Prens, MD, PhD (Professor)
Department of Dermatology, Erasmus Medical Centre, Erasmus University Rotterdam, Rotterdam, the Netherlands

P. Wolf, MD, PhD (Professor)
Department of Dermatology, Medical University of Graz, Graz, Austria

F. Quehenberger, MsC, PhD
Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

J. van den Reek, MD, PhD
Radboud UMC, Radboud University, Department of Dermatology, Nijmegen, The Netherlands

M.A. de Rie, MD, PhD (Professor)
Amsterdam UMC, University of Amsterdam, Department of Dermatology, Amsterdam, The Netherlands

T. Rispens, MsC, PhD
Sanquin Research and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Department of Blood Cell Research, Amsterdam, Netherlands

E. Schuit, MsC, PhD
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands

P.I. Spuls, MD, PhD (Professor)
Amsterdam UMC, University of Amsterdam, Department of Dermatology, Amsterdam, The Netherlands

R.S. Stern, MD, PhD (Professor)
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass., USA

A. de Vries, MsC, PhD
Sanquin Diagnostic Services, Sanquin, Amsterdam, the Netherlands

J. Zweegers, MD, PhD
Radboud UMC, Radboud University, Department of Dermatology, Nijmegen, The Netherlands

List of publications

C.I.M. Busard, M.C. Pasch, E. Schuit, L. Hooft, P.I. Spuls. Interventions for nail psoriasis. *Submitted for publication in British Journal of Dermatology.*

C.I.M. Busard and G.E. van der Kraaij, J. van den Reek, S.P. Menting, A.H. Musters, B.A. Hutten, M.A. de Rie, J.S. van Bezooijen, E. Prens, T. Rispens, A. de Vries, M.G.J. de Jong, W. de Kort, J. Lambert, M.B.A. van Doorn, P.I. Spuls. Adalimumab with methotrexate versus adalimumab monotherapy in psoriasis: First-year results of a single-blind randomized controlled trial. *Submitted for publication in the Journal of Investigative Dermatology.*

C.I.M. Busard, E. de Keyser, S. Lanssens, L. Meuleman, B.A. Hutten, A. Constanzo, J. van den Reek, J. Zweegers, J. Lambert, P.I. Spuls. Clinical Consequences of Antibody Formation, Serum Concentrations, and HLA-Cw6 Status in Psoriasis Patients on Ustekinumab. *Therapeutic Drug Monitoring. 2019; 41(5):634-639.*

C.I.M. Busard. Interventies voor nagelpsoriasis. *Nederlands Tijdschrift voor Dermatologie en Venereologie. 2019; 29(3):20-22.*

G.E. van der Kraaij, D.M.W. Balak, **C.I.M. Busard**, O.D. van Cranenburgh, Y. Chung, R.J.B. Driessen, M. de Groot, E.M.G.J de Jong, P.M.J.H. Kemperman, W.J.A. de Kort, S.A. Karsch, A. Lamberts, L.L.A. Lecluse, P.P.M. van Lümig, S.P. Menting, E.P. Prens, J.M.P.A. van den Reek, M.M.B. Seyger, H.B. Thio, W.R. Veldkamp, M. Wakkee, A. Nast, A. Jacobs, S. Rosumeck, P.I. Spuls. Highlights of the Updated Dutch Evidence- And Consensus-Based Guideline on Psoriasis 2017. *British Journal of Dermatology. 2019; 180(1):31-42.*

C.I.M. Busard, AD Cohen, P Wolf, S. Gkalpakiotis, S. Cazzaniga, R.S. Stern, B.A. Hutten, I. Feldhamer, F. Quehenberger, R. Lichem, M. Kojanova, E. Adenubiova, A. Addis, L. Naldi, P.I. Spuls. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. *Journal of the European Academy of Dermatology and Venereology. 2018; 32(2):245-253.*

C.I.M. Busard, J.Y.C. Nolte, M.C. Pasch, P.I. Spuls. Reporting of outcomes in randomized controlled trials on nail psoriasis: a systematic review. *British Journal of Dermatology. 2018; 178(3):640-649.*

C.I.M. Busard, S. Menting, S.J. van Bezooijen, J. van den Reek, B.A. Hutten, E. Prens, E.M.G.J de Jong, M. van Doorn, P.I. Spuls. Optimizing adalimumab treatment

in psoriasis with concomitant methotrexate (OPTIMAP): study protocol for a pragmatic, single-blinded, investigator-initiated randomized controlled trial. *Trials. 2017; 18(1):113.*

J. Kottner, L. Jacobi, E. Hahnel, M. Alam, K. Balzer, D. Beeckman, **C.I.M. Busard**, J. Chalmers, S. Deckert, V. Eleftheriadou, K. Furlan, S.E.R. Horbach, J. Kirkham, A. Nast, P.I. Spuls, D. Thiboutot, L. Thorlacius, K. Weller, H.C. Williams and J. Schmitt, on behalf of the International Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN) group. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. *British Journal of Dermatology. 2018 Apr;178(4):e279-e285.*

C.I.M. Busard, P.I. Spuls. Combinatiebehandelingen voor psoriasis. *Nederlands Tijdschrift voor Dermatologie en Venereologie. 2016; 26(5):246-250.*

S.P. Menting, **C.I.M. Busard**, L.L.A. Lecluse, P.I. Spuls. Serumspiegel- en antistofbepaling bij biologicals voor psoriasis in de dermatologische dagelijkse praktijk. *Nederlands Tijdschrift voor Dermatologie en Venereologie. 2016; 26(5):238-241.*

Ph. I. Spuls, **C.I.M. Busard**. Fumaarzuur bij psoriasis: effectief, maar vaak bijwerkingen.
Nederlands Tijdschrift voor Geneeskunde. 2015; 159:A9625

C.I.M. Busard, J. Zweegers, J. Limpens, M. Langendam, P.I. Spuls. Combined use of systemic agents for psoriasis: a systematic review. *JAMA Dermatology. 2014; 150(11):1213-20.*

PhD Portfolio

PhD student: C.I.M. Busard
PhD period: 01-03-2014 till 01-06-2020
Promotor: prof. dr. P.I. Spuls
Co-promotor: dr. B.A. Hutten

1. PhD training	Year	Workload (ECTS)
General courses		
Good Clinical Practice (BARQA)	2013	0.3
GRADE workshop	2013	0.3
Endnote	2014	0.1
Evidence based searching	2014	0.2
AMC World of Science	2014	0.7
Basic Course Legislation and Organization (BROK)	2014	1.0
Practical biostatistics	2015	1.1
Oral presentations at (inter)national conferences		
Systematic review on combined use of systemic agents for psoriasis. European Academy of Dermatology and Venereology (EADV), Istanbul,Turkey	2013	0.6
A multinational, observational, real-life cohort that assesses combined use of biologics and other immunosuppressive therapies. Scientific PSONET meeting, Bergamo, Italy	2014	0.6
Systematic review on interventions for nail psoriasis. European Society for Dermatological Research (ESDR), Rotterdam, the Netherlands	2014	0.5
Systematic review on interventions for nail psoriasis. European Academy of Dermatology and Venereology (EADV), Copenhagen, Denmark	2015	0.5
Presentation of PhD projects on combined treatment for psoriasis. Psoriasis International Network (PIN), Paris, France	2016	0.6
Presentation of PhD projects. Refereeravond Amsterdam UMC, Amsterdam, the Netherlands	2016	0.9

Presentation of PhD projects on combination treatment for psoriasis. Clinical scientific meeting, Department of Dermatology Amsterdam UMC, location AMC, Amsterdam, the Netherlands	2016	0.2
Combinatiebehandelingen voor psoriasis. Wetenschappelijke vergadering Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV), Amsterdam, the Netherlands *De behandeling van nagel psoriasis.* Dermatologendagen 2019, Utrecht, the Netherlands	2016 2019	0.2 0.5

Poster presentations at (inter)national conferences

Systematic review on combined use of systemic agents for psoriasis. European Academy of Dermatology and Venereology (EADV), Istanbul,Turkey	2013	0.4
Systematic review on interventions for nail psoriasis. European Society for Dermatological Research (ESDR), Rotterdam, the Netherlands	2015	0.4
Systematic review on interventions for nail psoriasis. Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren (the Netherlands).	2016	0.4
Therapeutic drug monitoring of ustekinumab in psoriatic patients: sense or nonsense? Psoriasis International Network (PIN), Paris, France	2016	0.4
Adalimumab and methotrexate versus adalimumab for moderate to severe psoriasis: first year results of a Randomized Controlled Trial. Psoriasis International Network (PIN), Paris, France	2019	0.4

International conferences

European Academy of Dermatology and Venereology (EADV), Istanbul, Turkey	2013	0.9
Scientific PSONET meeting, Bergamo, Italy	2014	0.9
European Academy of Dermatology and Venereology (EADV), Amsterdam, the Netherlands Scientific PSONET meeting, Madrid, Spain	2015	0.7
European Society for Dermatological Research (ESDR), Rotterdam, the Netherlands	2015	0.6
European Academy of Dermatology and Venereology (EADV), Copenhagen, Denmark	2015	0.9
Psoriasis International Network (PIN), Paris, France	2016	0.9

CSG-COUSIN scientific meeting, Berlin, Germany	2017	0.7
CSG-COUSIN scientific meeting, Amsterdam, the Netherlands	2017	0.7
European Dermato-Epidemiology Network (EDEN), Madrid, Spain	2018	0.7
National conferences		
Dermatologen in Opleiding (DIO) dagen, Amersfoort	2015-2020	0.4
Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren	2015	0.6
Refereeravonden Amsterdam UMC	2015-2020	0.1
Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren	2016	0.6
Therapeutic Drug Monitoring (TDM) of Biologics: Progress in Chronic Inflammatory Diseases symposium, Amsterdam Wetenschappelijke vergaderingen Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV)	2016 2015-2020	0.3 0.6
2. Teaching		
Supervising		
Scientific internship, Mikkie Kuipers (bachelor student)	2014	1.0
Scientific internship, Marisa Tjong Joe Wai (master student)	2015	2.0
3. Other		
Clinical scientific meeting, Department of Dermatology (weekly), Amsterdam, the Netherlands Member steering group Psoriasis, Department of Dermatology AMC, Amsterdam, the Netherlands	2014-2020 2014-2016	2.1 0.3
Conducting phase II, III and IV studies as trial doctor, Department of Dermatology, AMC, Amsterdam, the Netherlands Member methods group guideline psoriasis, Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV), Utrecht, the Netherlands	2014-2016 2014-2017	68 0.8
Journal club AMC Dermatology residents, Amsterdam (the Netherlands)	2017	0.2

Occasional reviewer for the Journal of Investigative Dermatology, Acta Dermato-Venereologica and British Journal of Dermatology	2014-2020	1.4

Dankwoord

"It's not how we fall. It's how we get back up again." *Patrick Ness*

Graag wil ik op deze plek iedereen bedanken die in de afgelopen jaren een bijdrage heeft geleverd aan mijn persoonlijke en wetenschappelijke ontwikkeling en aan de totstandkoming van dit proefschrift.

Allereerst gaat mijn dank uit naar alle patiënten die hebben deelgenomen aan de verschillende studies beschreven in dit proefschrift. Jullie inzet en bereidheid om die extra stap te zetten ter verbetering van de (dermatologische) zorg is essentieel en van onschatbare waarde.

Prof. dr. P.I. Spuls, beste Phyllis, bedankt voor de kansen die je me hebt gegeven om me op wetenschappelijk gebied te ontwikkelen en voor je vertrouwen in mij vanaf het allereerste begin. Ik heb veel geleerd van onze samenwerking. Een aantal uitdagingen had ik graag overgeslagen, maar het heeft me veerkrachtiger gemaakt en waardevolle inzichten gegeven en daar ben ik dankbaar voor.

Dr. B.A. Hutten, beste Barbara, wij ontmoetten elkaar in 2015 toen we jouw hulp goed konden gebruiken om structuur aan te brengen in de verzamelde data uit verschillende Europese patiënten registers. Bedankt voor je waardevolle input bij het analyseren en interpreteren van deze data en de daarop volgende studies.

Geachte leden van de leescommissie, prof. dr. D.L.P. Baeten, dr. D.M.W. Balak, dr. M.W. Langendam, dr. L.L.A. Lecluse, prof. dr. M.A. de Rie, prof. dr. T. Rustemeyer en prof. dr. H.J.C. de Vries, hartelijk dank voor de bereidheid zitting te nemen in mijn promotiecommissie en voor de genomen tijd en moeite om mijn proefschrift te beoordelen.

During my PhD period I have had the privilege to work with many (inter)national co-authors and colleagues which have inspired me. In particular I would like to thank Sun-Jine van Bezooijen, Simone Cazzaniga, Arnon Cohen, Anna-Christa de Vries, Martijn van Doorn, Ilan Feldhamer, Spyros Gkalpakiotis, Lotty Hooft, Elke de Jong, Eline de Keyser, Marisol Kooijmans-Otero, Gayle van der Kraaij, Jo Lambert, Miranda Langendam, Jacqueline Limpens, Stef Menting, Annelie Musters, Luigi Naldi, Jessica Nolte, Marcel Pasch, Errol Prens, Peter Wolf, Franz Quehenberger, Juul van den Reek, Menno de Rie, Theo Rispens, Ewoud Schuit, Robert Stern, Annick de Vries, Jeffrey Zweegers and the members of the updated psoriasis guideline.

Iedereen die betrokken was bij het recruteren en de follow-up van deelnemers van de verschillende studies: bedankt!

Lieve trial-team collega's, bedankt voor alle gezellige momenten en jullie steun tijdens mijn periode in het trial team en daarna. Lieve Marleen en Gabrielle, veel dank voor de goede gesprekken en fijne momenten die we hebben gedeeld. Jullie inzet bij het verzamelen van data voor de Optimap studie en de psoriasis database heeft een waardevolle bijdrage geleverd aan de publicaties in (onder andere) dit proefschrift.

Lieve Gayle, als mijn opvolgster gaf ik het Optimap stokje in het volste vertrouwen aan jou door. Je vrolijke en vaak kleurrijke verschijning en tomeloze inzet maken het een genoegen om met je samen te werken. Ik kijk uit naar jouw proefschrift!

Evelien Jagtman, veel dank voor het creatieve design van de kaft van dit proefschrift, ik word er vrolijk van en daar ben ik blij mee!

Lieve Reina, alweer bijna acht jaar geleden liep ik, uitgebreid voorbereid op een verwacht kritisch vragenvuur, enigszins zenuwachtig bij je binnen en niet veel later stond ik weer buiten met mijn eerste baan in handen. Veel dank voor je vertrouwen in mij en voor de kans die je mij gaf om me te ontwikkelen binnen de dermatologie, dit heeft de basis gelegd voor mijn verdere carrière. Oud-collega's van Medisch Centrum Wetering, bedankt voor de fijne en gezellige samenwerking, ik kijk er met plezier op terug!

Beste dr. Jan Mekkes, bedankt voor uw betrokkenheid bij mijn opleiding, promotie en persoonlijke ontwikkeling in de afgelopen jaren.

(Oud) arts-assistenten, stafleden en andere collegae van de afdeling dermatologie van het Amsterdam UMC en Huid MC, bedankt voor jullie interesse in mijn promotie onderzoek en voor de steun en gezelligheid tijdens onze fijne samenwerking.

Lieve vrienden en vriendinnen, dank voor de waardevolle vriendschappen die we samen hebben opgebouwd. Dank voor jullie humor, steun, kwetsbaarheid, openheid en voor het delen van zo veel mooie momenten en ervaringen. De liefde, energie en het plezier dat jullie mij geven is een belangrijke factor geweest in het voltooien van mijn proefschrift en het behalen van andere mijlpalen. Jullie zijn me enorm dierbaar en ik kijk uit naar nog veel meer toekomstige avonturen samen.

Dear international friends, you have broaden my world and the laughs and inspiring conversations have given me so much pleasure and support, thank you.

Lieve Hilde, Mariëlle, Wessel en Robin, vanaf de eerste ontmoeting heb ik me welkom en thuis gevoeld bij jullie. Dank voor jullie betrokkenheid bij mij en bij ons als gezin, ik geniet van alle momenten samen.

Lieve Tom, mijn grote broer, en ik jouw inmiddels niet meer zo kleine maar gelukkig voor altijd jongste zusje ☺. Dank voor je luisterend oor en adviezen op momenten dat ik dat nodig had. De ervaringen die we vanaf onze jeugd hebben gedeeld zijn ontelbaar, ik ervaar het als een groot geluk en voorrecht om zo'n hechte band te hebben kunnen opbouwen met jou en met Milou. Lieve Milou, mijn grote zus, jij weet als geen ander wat het bewandelen van deze route met zich meebrengt, en het was voor mij fijn om ervaringen te kunnen delen. Ik geniet van onze momenten samen en de ervaringen die we delen, zoals onze mooie reis naar Brazilië. Fijn dat je binnenkort een heerlijke nieuwe plek hebt om te wonen, ik ben blij dat je nog even in Amsterdam blijft! Lieve Diana, de verbinding die ik met jou voel gaat dwars door alle (cultuur)verschillen en landsgrenzen heen, ik ben zo blij dat je in ons leven bent gekomen, dank voor je liefde en betrokkenheid, ook bij onze kleine prinses Ella. Lieve Amelie, Elena en Lucas, jullie vormen een grote bron van liefde en geluk.

Lieve paranimfen, wat fijn dat jullie op deze belangrijke dag naast mij willen staan.

Lieve Mel, jij reist al met mij mee vanaf het begin van onze studententijd in Groningen. Als enige twee uit het Oosten van het land voelden we ons al snel thuis bij elkaar. Inmiddels zijn we vele jaren verder en zijn er weinig dingen die we niet samen hebben meegemaakt en gedeeld. Ik ben zo blij met onze onvoorwaardelijke vriendschap, en kijk met veel plezier uit naar nog veel mooie momenten, ook samen met Ella en Lucie ☺

Lieve Louise, Loupie, prinses, wat een geluk dat we samen het pad der wetenschap (en opleiding) hebben mogen bewandelen. Al snel reikte onze verbinding tot ver buiten de deuren van het ziekenhuis en was een ware vriendschap ontstaan. Zoveel hilarische en mooie momenten beleefd, dank voor je vele spreekbeurten over de vogels langs de route naar het AMC, je relativeringsvermogen en je steun en betrokkenheid.

Lieve papa en mama, dank voor jullie onvoorwaardelijke liefde en voor de aanmoediging, steun en kansen die jullie mij hebben gegeven.

Lieve Marnix, mijn grote liefde, de dankbaarheid die ik ervaar voor het geduld, de liefde en de steun die ik van jou heb mogen ontvangen is niet in woorden te vangen. Jij geeft me de ruimte om te groeien, en vangt me op als dat nodig is. Ik ben zo trots op jou, en op ons, en kijk met heel veel plezier uit naar onze toekomst samen.

Lieve Ella, mijn andere grote (kleine) liefde, je bent de spiegel van mijn ziel en vormt een grote bron van inspiratie. Ik geniet intens van je onbevangen schaterlach en je avontuurlijke ontdekkingsreis. Dat we nog heel lang samen van het leven mogen genieten.

About the author

Celine Ingrid Michelle Busard was born in Nijmegen on July 1st 1986. After finishing high school at the Thorbecke Scholengemeenschap in Zwolle, she moved to Groningen in 2005 to attend medical school at the State University Groningen. After obtaining her doctoral degree in 2010, she did her scientific internship at the department of Dermatology Academic Medical Centre (AMC) in Amsterdam under supervision of prof. dr. P.I. Spuls. It concerned a literature study about the evidence on systemic combination treatments, which initiated her interest for research. In June 2013 she graduated from medical school and worked as a resident not in training (ANIOS) in a clinic specialized in the treatment of dermatological diseases, during this period she developed a special interest in Dermatology. One year later, she returned to the department of Dermatology at the AMC to start a PhD project focusing on optimization of systemic treatment in psoriasis. Under the supervision of prof. dr. P.I. Spuls and dr. B.A. Hutten she performed clinical studies on (combinations of) systemic antipsoriatic agents and she immersed herself in the assessment of high-quality literature studies and standardization of outcome reporting in clinical studies, which led to the formation of this thesis. During her PhD period she was involved in conducting clinical trials and she contributed to the update of the national psoriasis guideline. In June 2017, she started her residency Dermatology at the AMC in Amsterdam under supervision of dr. J.R. Mekkes. Celine lives together with Marnix Dreise and their daughter Ella in Amsterdam.