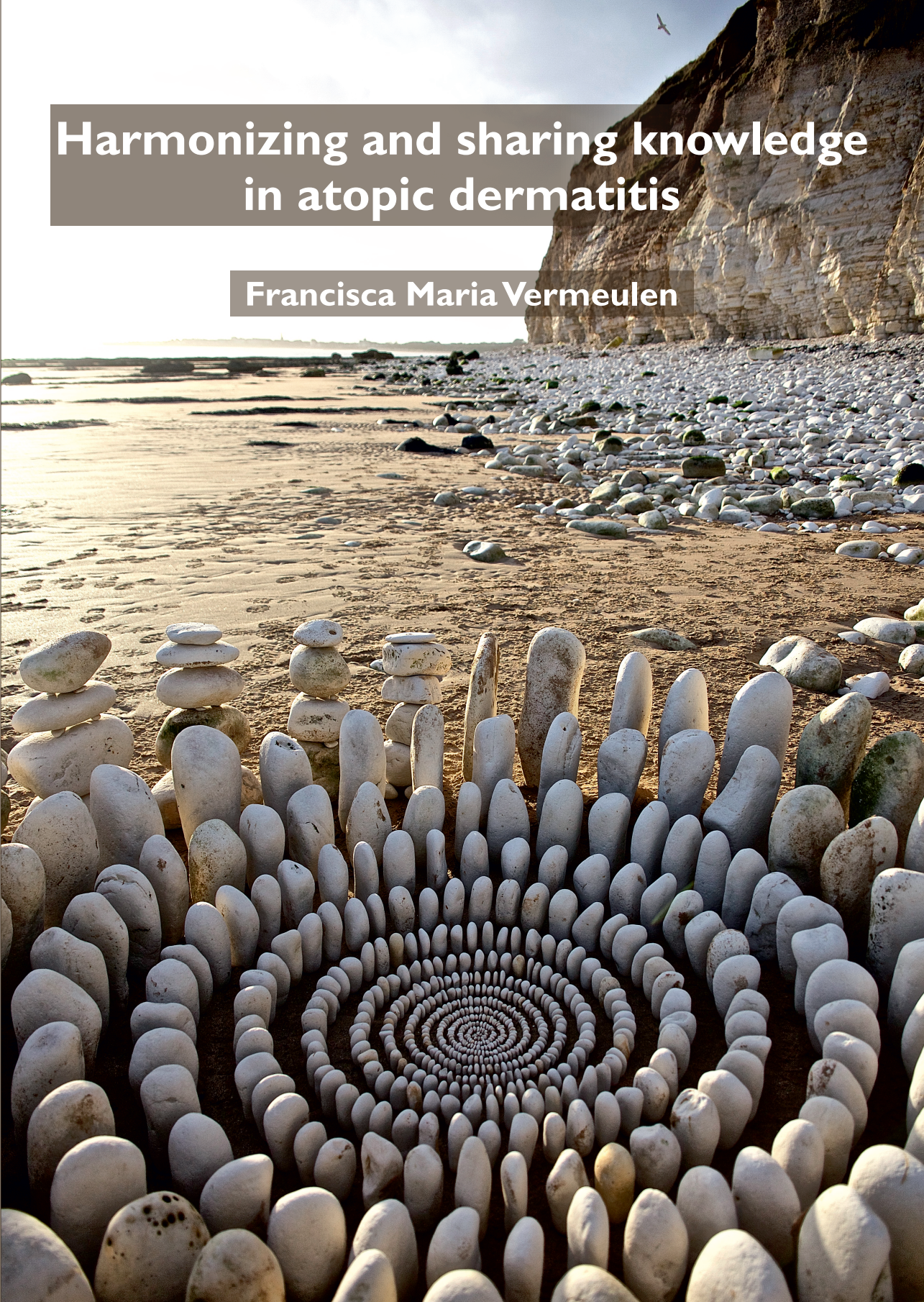
Harmonizing and sharing knowledge in atopic dermatitis

Francisca Maria Vermeulen



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Chapter 1

General introduction and outline of thesis

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Atopic dermatitis (AD) or atopic eczema (AE) is a chronic, fluctuating, inflammatory skin disease that affects up to 24.6% of children[1] and up to 10.2% of adults.[2] The onset is mostly during (early) childhood and about one third of patients still have AD throughout adulthood.[3] It is a polymorphic disease, presenting with signs like i.a. erythema, edema/papulation, excoriations, squamae/desquamation and lichenification in varying degrees.[4] It is most likely caused by a disruption in the skin barrier, a T-cell driven skin inflammation, an altered microbiome of the skin and genetic factors (i.a. filaggrin-null mutations). It is thought that environmental and lifestyle factors also influence AD and its severity.[5] AD is often accompanied by other allergic conditions like food allergy, allergic rhinitis or conjunctivitis, asthma and eosinophilic esophagitis.[6] There are indications that AD is more than a disease of the skin only. Due to a systemic inflammatory component, comorbidities like cardiovascular disease may accompany AD in patients.[7,8]

AD is characterized by symptoms of itch and pain and severely affects patients' quality of life (QoL). It has a substantial impact on school, work, home and social life.[9–11] Patients with AD have more mental health issues and give lower rates to their overall health compared to people without AD.[12] One study that examined QoL in children with chronic diseases showed that only cerebral palsy had a greater effect on QoL than generalized AD.[13] AD also influences family live, with up to 40% of patients and caregivers indicating that their own or their child's AD effects other family members.[9] The economic burden of AD is high. This can be expressed in costs per patient per year and in disability-adjusted lifeyears (DALYs). The costs per patient per year vary; from €351[14] to €20.695.[15] Laughter et al. found that of all skin diseases, AD has the highest disease burden when this was measured by DALYs.[14]

Most patients can be sufficiently treated with avoidance of trigger factors, patient education and topical therapy consisting of emollients and topical steroids, tar or calcineurin inhibitors. However, up to 30% of patients have moderate-to-severe disease,[5] many of which require phototherapy or systemic therapy in order to control their AD. With more severe disease, itch, scratching and pain increases, QoL decreases even further[12] and a risk of cardiovascular disease may increase too.[7] For many years dermatologists have had access to few therapies for their moderate-to-severe AD patients. Evidence supporting these therapies is scarce and of varying quality. With the burden that AD poses on patients and society, it is essential that the care for these patients improves. New, promising therapies like dupilumab have better short-term evidence profiles and might result in a treatment revolution for AD patients. However, these are very costly, not widely available therapies and (especially long-term) experience with these therapies is still limited. The importance of the conventional therapies (emollients and topical steroids, tar and/or calcineurin inhibitors, phototherapy and systemic therapies like ciclosporin, off-label methotrexate (MTX), azathioprine and mycophenolate acid) can therefore not be neglected.

This thesis focuses on two ways to improve the treatment for AD patients: 1. by improvement of the conventional treatment of moderate-to-severe AD patients, by both building on and strengthening the evidence base for phototherapies and

systemic therapies; and 2. by the addition of Shared Decision Making (SDM) to the AD treatment arsenal. SDM has shown, amongst others, to improve patient's knowledge and treatment satisfaction[16] and might even improve clinical outcomes[17] but is hardly used in dermatology. It might therefore be a good addition for AD treatment.

Treatments (both on and off-label) for moderate-to-severe AD

If AD cannot be controlled with topical therapies, a next step can be phototherapy. Phototherapy seems to be effective through several mechanisms. It may facilitate immunosuppression (i.a. by apoptosis of T-cells), suppression of colonisation of Staphylococcus Aureus and Pityrosporum Orbiculare on the skin, and prevention of antigens entering the skin by a thickened stratum corneum.[18] Different types of phototherapy are available: narrow-band UVB (NB-UVB, 311-313nm), broad-band UVB (BB-UVB, 280-315nm), UVAB (280-400nm), UVA1 (340-400nm), psoralen plus UVA (PUVA) and UVA (315-400nm). Currently the best evidence is available for the application of NB-UVB and UVA1 in AD patients.[18,19] More research towards these treatment modalities is needed.[18] While phototherapies can be perfect for the treatment of some AD patients, caution should be taken into account as there are concerns about early skin aging[20] and prolonged or repeated treatment cycles are not recommended.

Apart from phototherapy, systemic immunomodulatory therapies can be considered for patients with uncontrolled AD disease. Examples are ciclosporin, MTX, azathioprine, mycophenolate acid and oral prednisolone. Recently the biological dupilumab and Janus Kinase (JAK) inhibitor baricitinib were introduced. Currently, the European Medicines Agency (EMA) has approved ciclosporin and dupilumab for adult and adolescent AD patients[21,22] and baricitinib[23] for adult AD patients only. Dupilumab and prednisolone are the only treatments for adult AD patients approved by the United States (US) Food and Drug Administration (FDA).[24] All other systemic therapies are prescribed off-label. A therapy is regarded off-label when it is used in a way that is not registered in the Summary of Product Characteristics (which includes the agreed terms of use of a certain product).[25]

As most evidence on efficacy is available for ciclosporin, when considering the conventional therapies, this is currently considered the first-line option for systemic therapy.[26,27] However, common side-effects like hypertension and a nephrotoxic effect limit its use and the recommended therapy duration.[27] The evidence for the off-label conventional therapies MTX, azathioprine and mycophenolate acid is more scarce. For these therapies only a few RCTs and multiple retrospective studies exist supporting their effectiveness.[26–29] These therapies have however been frequently prescribed by clinicians in AD treatment. For MTX the use is mostly limited by liver toxicity and teratogenicity. For azathioprine the potential myelotoxic effect and a potential increased risk of non-melanoma skin cancer and lymphoma are the main concerns. Gastrointestinal symptoms, leukopenia and thrombocytopenia are the most seen adverse events for mycophenolate acid.

New treatments, especially for moderate-to-severe AD, are emerging.[30] Dupilumab, a human monoclonal antibody that inhibits the interleukin (IL) 4 receptor and inhibits IL 4 and IL 13 signalling, was the first new treatment approved in both the

United States and Europe in 2017. More biologicals that target IL4 (mepolizumab), IL12/23 (Ustekinumab), IL13 (lebrikizumab, tralokinumab), IL 31 (nemolizumab) and potentially IL 22 (Fezakinumab) are on their way as well as JAK inhibitors (i.a. baricitinib, abrocitinib, upadacitinib).[31,32] Although novel therapies have promising efficacy profiles,[31] long-term evidence on their safety profiles is missing.[33] Conventional systemic therapies like ciclosporin have more well-known side-effect profiles,[34] lower direct medical costs and will probably be more accessible to a wide group of AD patients than biologics.[35] It is therefore of importance that we keep paying attention to the conventional therapies in the treatment of AD and that more evidence will continue to be collected, for instance with the aid of well designed, long-term, prospective patient cohorts.

Harmonizing outcome measures for AD research registries

Evidence of the efficacy, effectiveness and safety of the conventional therapies is scarce, resulting in mostly off-label prescription of these therapies. New research for these therapies should ideally compare both new and conventional therapies in head-to-head trials. Randomized controlled trials (RCTs) are still the golden standard in research but have their limitations. They usually do not compare more than 2 or 3 different therapies and have very strict inclusion criteria. RCTs will not be performed for all treatment options that are available and therefore do not provide enough data for all head-to-head comparisons. They also do not reflect on real-life patients with AD. Well designed, long-term, prospective patient cohorts could contribute in the gathering of information on e.g. subgroups like elderly, pregnant patients or patients with comorbidities.[36,37]

The data from these cohorts could be gathered by registries, which should have sufficient amounts of patients in order to provide high quality evidence. In order to do so, all (inter-) national registries on this topic should be able to compare and pool data with each other. This can only be accomplished if all registries collect the same data, i.e. domains and domain items ("what to measure"), measurement instruments for these domain items ("how to measure") and standards for when to measure these items. In AD research many different outcome measures have been used in the past, most without or with limited validation and not always relevant to AD patients. The result is an inability to compare and pool data, and above all waste of research.[38–40] For this problem, Core Outcome Sets have been introduced. A Core Outcome Set (COS) is a minimum set of outcome domains and measurement instruments that should be collected and reported in all clinical trials for a certain disease.[41]

A platform for the development, strengthening and implementation of COS initiatives in dermatology was established in 2014; the Cochrane Skin (CS) – Core Outcome Set Initiative (COUSIN).[42] For AD, the Harmonising Outcomes Measures for Eczema (HOME) initiative has taken the first steps to harmonize and standardize outcome measures in AD research and clinical practice.[43] Four core outcome domains have been defined for AD trials: clinician-reported signs, patient-reported symptoms, health-related quality of life and long-term control. The core outcome measurement instruments for these domains are the Eczema Area and Severity Index (EASI, for the domain clinician-reported signs), the Patient-oriented Eczema Measure (POEM)

and Numerical Rating Scale (NRS)-11 for peak itch over the past 24 hours (for the domain patient-reported symptoms), the Dermatology Quality of Life Index (DLQI, for adults), Children's Dermatology Life Quality Index (CDLQI, for children) and Infant's Dermatitis Quality of Life Index (IDQoL, for infants) (for the domain health-related quality of life), and the Recap of Atopic Eczema (RECAP) or Atopic Dermatitis Control Test (ADCT) (for the domain long-term control).[44]

For registries, the TREatment of ATopic eczema (TREAT) Registry Taskforce (https://treat-registry-taskforce.org/) was founded to pursue harmonization of data collection for adult and paediatric AD patient registries in which phototherapies and systemic therapies are registered. This is done through multiple consensus exercises and the definition of core domains and domain items which should ultimately result in one core dataset that can be used by all AD research registries. The Taskforce has already undertaken the next step to define a core dataset for national AD registries.[45] Through an international Delphi exercise and consensus meeting in which all important stakeholders were included from over 30 countries, consensus was found on a core dataset of 'what to measure' domain items.[46] Next, consensus should be found on how and when to measure this core dataset.

Harmonizing prescribing practices

In the past, survey studies of the TREAT Registry Taskforce initiative have investigated the prescribing practices of the conventional therapies in paediatric AD patients in Europe and Northern America[47,48] and in adult AD patients in the UK.[49] These studies have shown varying prescribing practices and varying factors influencing these prescribing practices among dermatologists. Until now the prescribing practices of dermatologists regarding conventional therapies for adult AD patients in continental Europe are unknown. Especially with the upcoming new therapies, a new survey is necessary to provide the current prescription landscape which can serve as a comparison to the future landscape in which biologics are routine clinical practice.

Improving knowledge on off-label MTX prescriptions

As the TREAT survey studies have shown that MTX is often prescribed off-label and the evidence for the prescription is still insufficient, it is of clinical importance to provide an overview of the current evidence that is available for the off-label use of MTX in dermatological conditions. In 2016 the British Association of Dermatologists already published a guideline for the prescription of MTX in dermatology which also provided an overview of the available evidence in off-label MTX use[50] but as this guideline only included evidence up until October 2015 this needs an update.

Shared Decision Making

In Shared Decision Making (SDM) patients and clinicians not only share the best available evidence that is available for a certain treatment decision. Patients are also encouraged to consider the harms and benefits of certain options so that their values and preferences can be considered when taking a decision. SDM therefore promotes

patient engagement and is more respectful towards patient autonomy than the more paternalistic relationship formerly used between patients and clinicians.[51]

The best treatment option depends on several aspects. It depends not only on the best available evidence but also on patient aspects (i.a. comorbidity, co-medication, psychological burden of the disease), patient preferences (i.a. mode and frequency of administration, necessity to come to the hospital for, and frequency of control visits, and consideration of possible side-effects) and disease aspects (i.a. location and extent of the disease). Diseases in which no golden standard is available for the treatment and in which values of patients are of importance, are especially suitable for SDM.[52] It is therefore remarkable that in Dermatology SDM is not applied more as dermatological patients could greatly benefit from SDM.

SDM is applied more and more worldwide and several studies have shown that patients want to actively be involved in decision making.[53] In the Netherlands, a survey study amongst 7851 participants (patients from several medical specialties) demonstrated that 67% of the participants always want to be actively involved, and 27% sometimes.[54] Within Dermatology little research has been done within this field. One study showed that 71% of psoriasis patients want to be actively involved[55] while another showed that 80% of melanoma patients want to be involved.[56] In the Netherlands no research has been performed towards the experienced need for SDM by patients and dermatologists.

Currently, no uniform approach for the application of SDM is available and many different approaches have been suggested in multiple studies.[57] Stiggelbout et al. suggest 4 steps: 1) acknowledge that a treatment decision has to be made and that the patient's opinion is important, 2) make a comparison of the different treatment options and consider the different benefits and harms of these options, 3) consider the patient's preferences, and support the patient in their consideration, and 4) verify in which way a patient wants to be involved in the decision making process, make a decision and discuss possible follow-up.[52]

To actively involve patients in the decision making process tools are available: Patient Decision Aids (PDAs). These PDAs should contain information on different treatment options and their potential benefits and harms, and should help elicit patients' preferences and values related to the treatment.[58] PDAs have been shown to increase patients' knowledge, improve doctor-patient communication and treatment satisfaction, reduce decisional conflict, and help patients make more value-congruent choices.[16] Moreover, patients who are more actively involved in their decision making process may experience better clinical outcomes and may be more prone to adhere to their treatment plans.[17] Several forms of PDAs exist. PDAs can be online tools that provide much information and are able to help patients identify their own values. They can also exist in more compact forms that can be used during a consultation; these are called Encounter Decision Aids (EDA).[59,60]

A few online PDAs exist for dermatological diseases, i.a. acne, psoriasis, shingles, basal cell carcinoma (https://decisionaid.ohri.ca/AZinvent.php). For melanoma, psoriasis and actinic keratosis EDAs exist. Up until recently, no PDAs were available in Dutch for dermatological patients.

Aims & outline of this thesis

The main aim of this thesis is to contribute to the improvement of the treatment of moderate-to-severe AD patients. This is done through: 1. The harmonization of outcome measurement instruments used in AD research registries. 2. The collection of more evidence on the use of conventional (on- and off-label) phototherapies and systemic therapies for AD. 3. The initiation of research towards SDM in the Netherlands and the implementation of two Dutch EDAs for AD patients.

For this purpose, the following chapters were created:

Part I: Harmonization of outcome measurement instruments used in AD research registries

In **chapter 2** we continued our work on the core dataset for AD research registries for which the 'what to measure' dataset was already established. Through consensus meetings with several stakeholders and experts in the field of AD two more steps were completed. First, consensus was found on the measurement instruments that will be used to measure the previously defined 'what to measure' items. Second, consensus was found on 'when to measure' these items.

Part II: Collecting more evidence on the use of conventional phototherapies and systemic therapies in adult AD patients

In **chapter 3** we gathered more evidence on the prescribing practices of dermatologists who treat adult AD patients with phototherapies and systemic therapies. With this study we not only aimed to provide insight into the prescribing practices and the use of off-label therapies in AD treatment, but also into the reasons for and against the prescription of these therapies. This might improve the experience with, and prescribing of the conventional phototherapies and systemic therapies, and might also provide valuable information for guideline developers.

In **chapter 4** we broadened our view. We performed a systematic review (SR) to find out what evidence is available on the off-label prescription of methotrexate; not only in AD, but in all dermatological diseases. This evidence will not only help guideline developers but also clinicians who wish to prescribe methotrexate off-label and require an overview of the available evidence to do so.

Part III: Initiation of research towards, and implementing SDM in Dermatology in the Netherlands

In **chapter 5** we started with the essentials for SDM in the Netherlands: do Dutch patients and dermatologists want to apply SDM in a dermatological setting? If we want to improve SDM in a dermatological setting in the Netherlands, we first need to know if patients and dermatologists are already applying SDM, if they are willing to apply SDM, which characteristics make them more or less prone to apply SDM and what they experience as possible facilitators and barriers for the application of SDM. AD and psoriasis are both common skin diseases with many treatment options that are preference sensitive. We therefore decided that these skin diseases were best to start our research with.

Up until recently, no PDAs for skin diseases were available for Dutch patients. Because PDAs are developed for patients, it is important that they are available in their native language. We decided to start with the development of EDAs, which are more easily incorporated in a busy dermatological practice because they are more compact PDAs. In **chapter 6** we therefore developed three EDAs; one that provides an overview of topical therapies versus phototherapies and systemic therapies, one that provides an overview of the different systemic therapies and one that provides information about different biologics that are used in psoriasis treatment. In this chapter we also elaborate on how we developed these EDAs, in hope of inspiring other researchers to do the same and to provide them with a framework to do so.

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Part I

Harmonization of outcome measurement instruments used in AD research registries

Chapter 2

TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries

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Abstract

Background

Comparative, real-life and long-term evidence on the effectiveness and safety of photo- and systemic therapy in moderate-to-severe atopic eczema (AE) is limited. Such data must come from well-designed prospective patient registries. Standardisation of data collection is needed for direct comparisons and data pooling.

Objectives

To reach consensus on *how* and *when* to measure the previously defined domain items of the TREatment of Atopic eczema (TREAT) Registry Taskforce core dataset for research registries for paediatric and adult AE patients.

Methods

Proposals for the measurement instruments were based on the recommendations of the Harmonising Outcome Measures for Eczema (HOME) initiative, the existing AE database of TREATgermany, expert opinions and systematic reviews of the literature. The proposals were discussed at multiple face-to-face consensus meetings, one teleconference and via email. The frequency of follow-up visits was determined by an expert survey.

Results

A total of 16 experts from 7 countries participated in the 'how to measure' consensus process and 12 external experts were consulted. Consensus was reached for all domain items on how they should be measured by assigning measurement instruments. A minimum follow-up frequency of initially 4 weeks after commencing treatment, then every 3 months while on treatment and every 6 months while off treatment was defined.

Conclusions

This core dataset for national AE research registries will aid the comparability and pooling of data across centres and country borders and enable international collaboration to assess the long-term effectiveness and safety of photo- and systemic therapy used in patients with AE.

Introduction

A significant number of paediatric and adult patients with moderate-to-severe atopic eczema (AE) may require photo- or systemic immunomodulatory therapy at some point during their life. For adults, ciclosporin, and recently dupilumab, are currently the only systemic therapies that are approved by the European Medicines Agency (EMA)[1,2] while only dupilumab has been approved by the United States (US) Food and Drug Administration (FDA).[3] For children there are no approved systemic therapies, although our European and North American treatment surveys show that they are regularly prescribed.[4,5] While there is some evidence on the short-term effectiveness of photo- and systemic immuno-modulatory therapies, there is a clear lack of head-to-head comparison trials and a paucity of data on the long-term effectiveness and safety of such treatments.[6,7] Since randomized controlled trials (RCTs) have very strict inclusion criteria, important subgroups of patients (for instance those with co-morbidities) are commonly excluded and therefore evidence in real-life populations is missing. All of this requires data collection from well-defined patient cohorts.[8–10]

In order to harmonise data collection for such observational cohorts, the TREatment of ATopic eczema (TREAT) Registry Taskforce initiated a consensus exercise to develop a core set of domains and domain items for AE treatment research registries. After an international Delphi study and consensus meeting the core dataset ('what to measure') was agreed on, consisting of 19 domains with 69 corresponding domain items (49 at baseline and 20 at follow-up).[11,12]

As the next step in this consensus finding process, we performed a consensus exercise to define how and when to measure the core domain items to fully harmonise data collection within national AE treatment research registries and prevent heterogeneity.[13,14]

Materials and Methods

Study design

To establish a core set of measurement instruments ('how to measure') three face-to-face expert consensus meetings, one teleconference (TC) and final discussions via email were arranged. For this process we used the following sources to guide decision making:

1. We used the recommendations from the Harmonising Outcome Measures for Eczema (HOME) initiative where possible, for instance with regard to the capture of clinical signs, patient-reported outcomes and quality of life.[15–17]
2. Relevant literature, in particular systematic reviews considering measurement instruments in AE.[7,13,14,18–20]
3. The existing AE database of TREATgermany[21] that already included over 100 patients at the start of this study.
4. Personal communications with experts in the field of measurement instruments for specific domain items. (e.g. K. McElhone from the UK psoriasis biologics register (BADBIR), personal communication, May 18, 2017)
5. The current usage of measurement instruments in clinical practice and clinical experience of the participants.

During all meetings feasibility and current common practice were kept in mind.

All meetings were chaired by either Professor Phyllis Spuls or Professor Carsten Flohr. During each session, the evidence for each suggested measurement instrument was presented in form of a Power Point presentation and written handouts, followed by whole group discussions. These discussions were iterative and continued until full consensus was achieved. Voting was done by a show of hands and was therefore not anonymous. Whenever possible, validated measurement instruments were selected. If multiple validated instruments were available decisions were based on (in order of importance): 1. the HOME recommendations, 2. quality of the validation studies and 3. the feasibility and in particular the potential to be used in different countries and the number of available translations of the measurement instrument. In case consensus on domain items could not be reached immediately during the meetings, for instance due to a lack of evidence, items were assigned to participating TREAT members for further investigation taking into account their areas of expertise. These items were then re-discussed at the next consensus meeting. The three face-to-face consensus meetings were audio recorded for reference at the next meetings.

To define when the domain items should be measured ('when to measure'), in September 2017 we conducted an online survey among all participants using SurveyMonkey software. Options put to the vote were based on current clinical practice (Fig. S1). The results of the survey were discussed and approved in a small group via email.

Participants

Participants were physicians, patients, and non-clinical researchers (i.e. health economists, epidemiologists/methodologists) from the TREAT Registry Taskforce with an interest in AE and/or AE measurement instruments. We also consulted external experts through personal communications (mostly email) from e.g. the Coronel Institute of Occupational Health and the Medical Psychology Department of the Academic Medical Centre in Amsterdam (AMC) for items considering work and health and items considering treatment adherence.

Definition of consensus

Consensus was predefined both for the 'how' and 'when to measure'. Consensus for the 'how to measure' was achieved when 100% of the participants present during the consensus meeting agreed on the measurement instrument. Consensus on the follow-up frequency and the visit window ('when to measure') was achieved when the majority of the participants voted for one of the options.

Results

How to measure

In March, May and June 2017 four consensus meetings were held. The first by TC, the other three by face-to-face meetings in London, Amsterdam and Nantes. A total of 16 participants met (for details see Fig. S2), all members of the TREAT Registry Taskforce, including 11 academic dermatologists, 1 dermatology resident, 1 dermatology PhD student, 1 patient/patient representative, 1 epidemiologist/ methodologist and 1 health economist. A total of 11 experts were consulted for specific items.

During the face-to-face meetings slight alterations were made to the 'what to measure' core dataset. In order to make the core dataset as feasible as possible some domain items were merged with others. The items 'medical history', 'follow-up (FU) safety bloods', 'adverse events that cause stop or switch of therapy or change in dosage' and 'probability of relationship with treatment' are now captured as part of other items (for details see Table 1). Additionally, the items 'other significant illnesses' and 'other medication relevant for AE treatment response' were added as they were not previously captured in the 'what to measure' core dataset. After these alterations, the final 'what to measure' core dataset consists of 70 items; 50 baseline items and 20 follow-up items (see Table 1). For all items consensus was reached on the measurement instruments.

Details on specific domain items

Ethnicity

We reviewed all ethnicity classifications we had access to based on a literature search, including the one used by the UK Biobank, the German National Cohort and the

British Association of Dermatologists' Biologic Interventions Register (BADBIR). The classification system shown in Table 1 was made (based on all these reviewed classification systems) and was selected as this system allows patients and physicians to choose from an extensive list of ethnicities. The option to select and specify two ethnicities is given as well. To capture migration, country of birth of patient and parents was added.

Educational status

Educational status is an important predictor of health and disease.[22] For this item the International Standard Classification of Education (ISCED) system was chosen. The ISCED has for instance been adopted by the United Nations Educational, Scientific and Cultural Organization (UNESCO) General Conference and consists of definitions that have been agreed on internationally. Further, it facilitates the comparison of education systems from different countries. The group agreed that each country will translate this classification to its national educational classification.

It was decided to record the highest completed educational level; from the parent or child in case of a child or from the patient themselves if adult.

Use of validated diagnostic criteria

Both the quality of the gathered data and the feasibility of the registry were considered. Many lists of diagnostic criteria for AE are available and reviewed (e.g. the UK Working Party criteria, the Hanifin & Rajka criteria, the refined Millennium Criteria[23]). Although in clinical practice a diagnosis of AE is often made without the use of specific diagnostic criteria, the use of validated diagnostic criteria is nevertheless desirable within the context of national AE treatment research registries. During the consensus exercise we decided to give national registries the option to decide which validated diagnostic criteria they would like to use. Also, the option 'physician-diagnosed' was added in case no diagnostic criteria were used.

Previous and current photo- and systemic therapy

In addition to recording the type, dose and outcome of past therapies, we also recommend to capture the number of treatment courses, the average treatment (maintenance) dose, and whether adverse events associated with these treatments occurred. Where available, we also recommend to record the cumulative dose of phototherapy. It was decided to add investigational therapies to the registry (both for past and current systemic therapy) even though during the initial Delphi exercise this was voted out.

Current topical treatments

The question was whether or not to register the potency of corticosteroids as the classification differs between countries. For feasibility reasons it was therefore decided to recommend registration of the potency using the known national classification system, but this is not mandatory.

Table 1: Core dataset of domains, domain items and measurement instruments to be captured in national atopic eczema treatment registries

Domains	Domain Items	How To Measure	Comments
Demographics	Date of birth Date of enrolment into registry	1. Date 2. Date	
	Gender	1. Male | Female | Other	
	Ethnicity	1. Country of birth of patient and parents 2. Ethnicity of patient (possibility to select two options): White (Europe, Russia, Middle East, North Africa, USA, Canada, Australia) | Black-African, Afro Caribbean | African-American | Asian-Chinese | South Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh) | Asian – other (Korea, China north of Huai-River) | Japanese | Hispanic or Latino | Mixed – please specify | Other – please specify	
	Educational status	1. ISCED classification (for both adults and children): ISCED 0: Early childhood education ISCED 1: Primary education ISCED 2: Lower secondary education ISCED 3: Upper secondary education ISCED 4: Post-secondary non-tertiary education ISCED 5: Short-cycle tertiary education ISCED 6: Bachelor's or equivalent level ISCED 7: Master's or equivalent level ISCED 8: Doctoral or equivalent level	• This item will be assessed repeatedly • Use the highest completed education level; from child or parents if a child or from the patient themselves if adult • Will have to be translated for each country to its national educational classification
	Current occupation or education	1. 1. Eurostat classification 1 – 8: Employed | Self-employed | Disability pension (unable to work)| Retired | Student or pupil | Engaged on home duties | Unemployed | Other – please specify	This item will be assessed repeatedly
AE diagnosis	How diagnosis AE is established	1. 1. Clinically Y | N 2. Histopathology Y | N	
	Use of validated diagnostic criteria	1. Physician diagnosis alone | Hanifin & Rajka Criteria | UK Working Party Diagnostic Criteria | AAD/Eichenfield Criteria | Refined Millennium Criteria | Schultz-Larsen Criteria | Kang and Tian Criteria | Diepgen Criteria | Danish Allergen Research Centre Criteria | Saeki's JDA Criteria	Each country can decide which of these criteria they want to give as options

Domains	Domain Items	How To Measure	Comments
	Date of onset AE	1. Year	
Past AE treatments	Phototherapy	1. Y | N 2. NB-UVB | BB-UVB | UVB (unspecified) | UVA | UVA1 | UVAB |PUVA (oral or other) | Other | (possibility to select multiple options) 3. How many courses (numerical) | Cumulative dose (J/cm^2) (Optional) | When (start year) (Optional) | Number of treatments within a course (numerical) (Optional) | Outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side effects, cumulative dose, disease remission, other), c. adverse event (Y | N)	• UVB (unspecified) if type is unknown • This is only medical history. If current it should be recorded under 'current AE treatments'
	Systemic therapy	1. Y | N 2. Ciclosporin | Azathioprine | Methotrexate | Mycophenolate acid | Systemic corticosteroids | Dupilumab | Omalizumab | Other – please specify | Investigational medication – please specify | (possibility to select multiple options) 3. How many courses (numerical) | When (start month + year) (Optional) | Duration (free text) | Average treatment (maintenance) dose (Optional) | Outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side effects, cumulative dose, disease remission, other), c. adverse event (Y | N)	• With definitions for average treatment (maintenance) dose (see Fig. S4) • This is only medical history. If current it should be recorded under 'current AE treatments'
	Topical treatments for AE	1. Y | N 2. Corticosteroids | Calcineurin inhibitors | Tar-ointments | Crisaborole | Other | (possibility to select multiple options)	• Only registered for the past year • This is only medical history. If current it should be recorded under 'current AE treatments'
	Day hospital care treatments for AE (outpatient)	1. Y | N 2. Duration (cumulative treatment days)	• Only registered for the past year • This is only medical history. If current it should be recorded under 'current AE treatments'
	Hospitalisation for AE	1. Y | N 2. Duration (cumulative days)	• Only registered for the past year • This is only medical history. If current it should be recorded under 'current AE treatments'

Domains	Domain Items	How To Measure	Comments
Current AE treatments	Phototherapy	1. Y | N 2. NB-UVB | BB-UVB | UVA | UVA1 | UVAB | PUVA (oral or other) | Other 3. Start date | Cumulative dose (J/cm^2) | Stop date	
	Systemic therapy	1. Y | N 2. Ciclosporin | Azathioprine | Methotrexate | Mycophenolate acid | Systemic corticosteroids | Dupilumab | Omalizumab | Other – please specify | Investigational medication – please specify | (possibility to select multiple options) 3. Start date | Start dose | Current dose | Stop date	With definitions for average treatment (maintenance) dose (see Fig. S4)
	Topical treatments	1. Y | N 2. Corticosteroids | Calcineurin inhibitors | Tar ointments | Crisaborole | Other | (possibility to select multiple options) 3. Classification of steroids and calcineurin-inhibitors (Optional) 4. Frequency ('how many times a week do you use it?') (Optional)	If classification is registered use the national official potency classification
	Amount of topical creams/ointments used per week	1. <30 gram | 30-60 gram | 60-100 gram | >100 gram	This is exclusive additive-free, bland emollients
Family history of AE or allergic diseases	Family history of AE or allergic diseases	1. Y | N 2. Atopic eczema | Asthma | Allergic rhinoconjunctivitis | Atopic eye disease | Eosinophilic oesophagitis | Other | (possibility to select multiple options)	• Y if 1st degree relative (parents or children) • According to the patient or physician-diagnosed
Allergic co-morbidities	Asthma	1. Physician diagnosed Y | N	
	Allergic rhinoconjunctivitis	1. Physician diagnosed Y | N	
	Atopic eye disease	1. Physician diagnosed Y | N	
	Eosinophilic oesophagitis	1. Physician diagnosed Y | N	

Domains	Domain Items	How To Measure	Comments
	Food allergies	1. Do you have a food allergy currently? Y | N 2. If yes, is at least one food allergy diagnosed by a doctor? Y | N 3. If yes, how was this diagnosis made? Double-blind placebo-controlled oral food challenge | Open food challenge | Skin prick tests | Scratch tests | Positive food allergen specific IgE test | Other (e.g. Atopy Patch Test) | Unknown	
	Contact allergies	1. Have you ever been tested for contact allergies with patch tests? Y | N| Unknown 2. If yes, what was the outcome? Positive | Negative| Unknown	
Other past and current co-morbidities	Malignancies	1. Y | N 2. When (year) 3. Type of malignancy (free text) 4. Active | Remission | Relapsed	MedDRA categories will be used for this item as much as possible
	Serious infections	1. Y | N 2. When (year) 3. Type of infection (free text) 4. Active | Latent | Resolved (cured)	• MedDRA categories will be used for this item as much as possible • Includes 'medical history' (tuberculosis, HIV, hepatitis B or C); original item of domain baseline assessments
	Other significant illnesses	1. Y | N 2. When (year) 3. Type of illness (free text) 4. Active | Remission | Resolved (cured) | Relapsed	MedDRA categories will be used for this item as much as possible
Current concomitant medication (i.e. other than specific AE medication)	Antihistamines	1. Y | N 2. Oral | Topical	
	Antibiotics	1. Y | N 2. Oral | Topical	
	Other medication relevant for AE treatment response	1. Y | N 2. Which (free text)	• Includes 'immunotherapy' • Relevant according to judgement of treating physician

Domains	Domain Items	How To Measure	Comments
	Immunosuppressives for other inflammatory diseases	1. Y | N 2. Which (free text) 3. Indication: Inflammatory bowel disease | Rheumatoid arthritis | Other – please specify 4. Start date | Stop date 5. Current dose (free text)	
Baseline general AE questions	Exposures that trigger disease flares	1. Y | N 2. Stress | Infection | Weather conditions | Sweating/Exercise | Exposure to aero-allergens | Other | (possibility to select multiple options)	
	Episodes of skin infection	1. Y | N 2. Bacterial skin infection (folliculitis, impetigo, etc.) | Viral skin infection (herpes simplex virus (HSV) infection, mollusca contagiosa, etc.) | (possibility to select multiple options)	
	Days lost from usual activities (e.g. work, study)	1. Y | N 2. Days per month (free text)	Average number of days in the past 3 months
Baseline physical examination	Fitzpatrick skin type	1. I | II | III | IV | V | VI	
	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): Skin folds around the eye(s) | Neck (front) | Flexures of the arm(s) | Flexures of the leg(s) | Front of ankle(s) |Not applicaple 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): Face | Extensor of elbows | Arms | Extensor of knees | Legs | Hands |Not applicaple 3. Presence of (Y | N): (History of) Pompholyx | Discoid eczema | Nodular prurigo | Follicular eczema | Ichthyosis | Keratosis pilaris | Palmar hyperlinearity | Erythroderma | Skin infection (if Y: bacterial/viral/fungal | sample taken Y | N)	For definitions on these phenotypical and morphological characteristics see Figure S3
Baseline physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (Optional)	Objective or full SCORAD. If the full SCORAD is used, the objective and subjective SCORAD need to be reported separately
	Investigator/physician global assessment	1. vIGA-AD™ scale (5-point)	

Domains	Domain Items	How To Measure	Comments
	Patient-reported symptoms	1. POEM 2. Peak Pruritus NRS (0-10) past 24 hours 3. Peak VAS pain (0-10) past 24 hours (Optional)	
	Patient global assessment	1. PGA 5-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	• Adults EQ-5D-5L; children EQ-5D-Y; caregivers (proxies) EQ-5D-Y and EQ-5D-5L • Awaiting the index score for the EQ-5D-Y
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	DLQI > 16 years; CDLQI 4-16 years; IDQoL < 4 years
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (5-point likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (5-point likert scale)	• The wording may change in the future if a validated measurement tool becomes available • Satisfaction with care is broad and includes for instance satisfaction with treatment, physician and the hospital
	Impact of AE on the family	1. FDLQI	• Needs to be filled out within the visit window (according to the patients visit) by adult family members or the partner of the patient • Preferably the FDLQI is answered by the same person every time
Baseline investigations	Full blood count	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	Normal/abnormal according to local standards
	Liver function	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	Normal/abnormal according to local standards
	Kidney profile	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	Normal/abnormal according to local standards

Domains	Domain Items	How To Measure	Comments
	Evaluating TPMT level prior to azathioprine use	1. Y | N | not applicable 2. Low or absent | Intermediate | Normal or high	
Baseline management	Main reasons for choosing specific treatment (systemic or phototherapy)	1. Existent comorbidities and/or results of baseline investigations including abnormal laboratory results | Patient age | Anticipation of pregnancy and other family planning issues for both males and females | History of prior systemic therapies (incl. response) | Drug safety and side effect profile | Therapeutic profile: a. speed of onset, b. magnitude of effect, c. better long-term control after drug is stopped | Accessibility of the treatment (including licensing) | Patient preferences | Other | (possibility to select 3 options)	
	Relative contraindication(s) for selected treatment	1. Y | N 2. Which (free text)	
Follow up general AE questions	Days lost from usual activities	1. Y | N 2. Days per month (free text)	Average number of days since the last visit
	Change in diagnosis after enrolment	1. Y | N 2. CTCL | Other	
	Date of death and relation to AE	1. Date |Not applicaple 2. Not related | Doubtful | Possible | Probable | Very likely | Definite	
Follow up physical examination	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): Skin folds around the eye(s) |Neck (front) | Flexures of the arm(s) | Flexures of the leg(s) | Front of ankle(s) |Not applicaple 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): Face | Extensor of elbows | Arms | Extensor of knees | Legs | Hands |Not applicaple 3. Presence of (Y | N): (History of) Pompholyx | Discoid eczema | Nodular prurigo | Follicular eczema | Ichthyosis | Keratosis pilaris | Palmar hyperlinearity | Erythroderma | Skin infection (if Y: bacterial/viral/fungal | sample taken Y | N)	Same comment(s) as for baseline item
Follow up physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (Optional)	Same comment(s) as for baseline item

Domains	Domain Items	How To Measure	Comments
	Investigator/physician global assessment	1. vIGA-AD™ scale (5-point)	
	Patient-reported symptoms	1. POEM 2. Peak Pruritus NRS scale (0-10) past 24 hours 3. Peak VAS pain (0-10) past 24 hours (Optional)	
	Patient global assessment	1. PGA 5-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	Same comment(s) as for baseline item
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	Same comment(s) as for baseline item
	Reporting of disease control	-	HOME results showed that for now this should be registered by repeated measurements of clinical signs, symptoms, quality of life and a patient global instrument (a specific instrument is not yet defined by HOME)
	Adherence to treatment between appointments	1. MARS (Optional)	To be adjusted for AE, until then optional
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (5-point likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (5-point likert scale) 3. PsoSaT (Optional)	• PsoSat to be adjusted for AE • Further comment(s) same as for baseline item
	Impact of AE on the family	1. FDLQI	Same comment(s) as for baseline item
Follow up investigations	Full blood count	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	• Previously captured as 'safety bloods' • Further comment(s) same as for baseline item
	Liver function	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	• Previously captured as 'safety bloods' • Further comment(s) same as for baseline item

Domains	Domain Items	How To Measure	Comments
	Kidney profile	1. Y | N 2. Normal | Abnormal 3. Clinically relevant Y | N	• Previously captured as 'safety bloods' • Further comment(s) same as for baseline item
Follow up adverse events	Severe adverse events	1. Y | N 2. Diagnosis (free text) 3. In case of a serious adverse event: Death | Life-threatening | Hospitalisation or prolonged hospitalisation of existing hospitalisation | Persistent or significant disability | Congenital anomaly | Important medical event which requires medical intervention | Not applicable | (possibility to select multiple options) 4. Relatedness: Not related | Doubtful | Possible | Probable | Very likely | Definite 5. Stop | Switch of therapy | Change in dosage | Not applicable	• MedDRA categories will be used for this item as much as possible • Severe according to judgement of treating physician
Follow up management	Reason for switching therapy	1. Efficacy | Inefficacy | Adverse event(s) | Interaction with other medication | Child wish | Patient request | Other | Not applicable | (possibility to select multiple options)	
	Reason for discontinuation of therapy	1. Efficacy | Inefficacy | Adverse event(s) | Interaction with other medication | Child wish | Patient request | Other | Not applicaple | (possibility to select multiple options)	

Abbreviations: AAD, American Academy of Dermatology; AE, Atopic Eczema; BB-UVB, Broad-band ultraviolet B; CDLQI, Children's Dermatology Life Quality Index; CTCL, Cutaneous T cell lymphoma; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol five-Dimensional; FDLQI, Family Dermatology Life Quality Index; HSV, Herpes simplex virus; HIV, Human immunodeficiency virus; HOME, Harmonising Outcome Measures for Eczema; IDQoL, Infant's Dermatitis Quality of Life Index; IgE, Immunoglobulin E; ISCED, International Standard Classification of Education; JDA, Japanese Dermatological Association; MARS, Medication Adherence Report Scale; MedDRA, Medical Dictionary for Regulatory Activities; NB-UVB, Narrow-band ultraviolet B; NRS, Numerical Rating Scale; PGA, Patient Global Assessment; POEM, Patient Oriented Eczema Measure; PsoSat, Psoriasis Satisfaction questionnaire; PUVA, Psoralen and ultraviolet A; QoLIAD, Quality of Life Index for Atopic Dermatitis; SCORAD, SCORing Atopic Dermatitis; TPMT, Thiopurine methyltransferase; UK, United Kingdom; USA, United States of America; UVA, Ultraviolet A; UVAB, Ultraviolet A plus ultraviolet B; UVB, Ultraviolet B; VAS, Visual Analogue Scale; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis.

Malignancies, serious infections, other significant illnesses

While only past malignancies and past serious infections were voted in during the Delphi exercise, the knowledge of current malignancies, infections and other comorbidities provides us with important information for safety and subgroup analyses. Thus, these items were added. The item 'medical history' (tuberculosis, HIV, hepatitis B or C), which was previously voted in during the Delphi exercise, is now captured as part of the item 'past serious infections'.

Other medication relevant for AE treatment response

Although not voted in during the 'what to measure' Delphi process, this item has been added, as such therapies (e.g. immunotherapy or aeroallergens) might need to be considered as a confounder of the response to AE treatments.

Days lost from usual activities

Part of the costs of AE are associated with decreased productivity or days lost from work.[24] Registration of the days lost from work is important to register for health technology assessment and cost-effectiveness research. However, this would bias results towards those patients in productive areas. Hence, the name of this item was changed to 'days lost from usual activities'.

Skin examination

Treatment response might be influenced by the phenotype of AE. Therefore, we suggest to document if certain phenotypical and morphological characteristics are present. For definitions on these characteristics see Figure S3.

Details on physician- and patient-reported domain items

Physician-assessed clinical signs and patient-reported symptoms

For all items HOME recommendations were followed, i.e. the Eczema Area and Severity Index (EASI) was selected for the item 'physician-assessed clinical signs'[15] and the Patient-Oriented Eczema Measure (POEM) for the item 'patient-reported symptoms'.[16,25,26]

Patient-reported symptoms

At HOME V it was agreed that the inclusion of intensity of itch should be investigated as the POEM only measures frequency of itch.[17] Schoch et al. and Phan et al. found that the Numerical Rating Scale (NRS)-11 for itch has good reliability and validity and that recall bias increases with the recall period.[18,27] NRS-11 was therefore added to the item 'patient-reported symptoms' and after consultation with external experts it was decided to register the peak itch for the past 24 hours.[28] Reporting of disease control. For this item, which is analogous to the long-term control domain as defined by HOME, HOME V has recommended to use repeated measurements of the long-term control subdomains: clinical signs, symptoms, quality of life and a patient global instrument.[17]

Investigator/physician global assessment

Futamura et al. concluded that global assessments are often used in AE research but comparisons are hard because there are no standardised definitions.[29] As a result, the International Eczema Council (IEC) and Eli Lilly and Company (Lilly) have worked on a validated 5-point investigator global assessment (IGA) scale which was incorporated in the core dataset for this item.[30]
(http://www.eczemacouncil.org/research/investigator-global-assessment-scale/)

Patient global assessment

Little research has been done towards the PGA. This subdomain of the long-term control domain has been discussed during HOME V, but as yet stays undefined.[17] However, since we decided to use the 5-point IGA scale, the 5-point PGA for the item 'patient global assessment' was chosen.

Skin-specific quality of life score

For this item, during the HOME IV (adults) and HOME V (children) meetings it was concluded that there is currently no measurement instrument that can be recommended.[16,17,19,20] Considering feasibility and the most commonly used instruments, it was decided to use the Dermatology Life Quality Index (DLQI), the Children's DLQI (CDLQI) and the Infants' Dermatitis Quality of Life Index (IDQoL). Further validation work on the DLQI was recently published by Patel et al.[31]

Generic quality of life score

Feasibility, access to different languages and the high degree of usage were the main reasons to choose the EQ-5D-5L (adults) and the EQ-5D- N(children) as the preferred measurement instruments for this item.

Patient-reported satisfaction with AE care received, impact of AE on the family, adherence to treatment between appointments

We recommend the use of an adapted PsoSat Questionnaire, a questionnaire that measures the treatment satisfaction in psoriasis patients,[32] the Family Dermatology Life Quality Index (FDLQI)[33] and the Medication Adherence Report Scale (MARS), which was originally developed for the adherence with oral medication in asthma but can be easily adapted for AE patients.[34] The MARS will be optional until it is validated for AE.

When to measure

Thirteen out of 16 participants (81%) completed the survey. Eight out of 13 (62%) voted for a minimum follow-up frequency of every three months while on therapy; 7 out of 13 participants (54%) voted for an extra visit 4 weeks after baseline. 7 out of 13 participants (54%) voted for a minimum follow-up frequency while off therapy of every 6 months. The recommended visit window for patients both on and off therapy was set at 1 month (58% and 50%). An overview is shown in Table 2.

Table 2 – When to measure the domain items for national atopic eczema treatment registries

Category	When to measure
Follow-up frequency while on therapy	4 weeks, 3 months and then every 3 months
Follow-up frequency while off therapy	Every 6 months
Visit window	1 Month

Discussion

This consensus study identified 70 measurement instruments for the domain items previously agreed on during our Delphi study for AE research registries that capture data on adults and children with moderate-to-severe AE on photo- and systemic immunomodulatory therapies. By doing so, a complete core dataset is now available for usage by researchers worldwide.

Strengths and limitations

Our recommendations for core domains and domain items for data collection were based on a carefully conducted international Delphi process that over 400 stakeholders (physicians, nurses, patients, methodologists, regulatory body and industry representatives) from over 30 countries contributed to. The results of this Delphi directly fed into the 'how to measure' recommendations presented here.[12] In addition, proposals for the measurement instruments were based on the recommendations from the HOME initiative. Although primarily meant for clinical trials and not specifically for research registries, the HOME recommendations represent international consensus on core outcomes based on validation studies and systematic reviews. Experts that participated in the HOME initiative participated in this study as well, allowing us to benefit from their expertise.

Further, a patient and experts in the field of AE and/or AE measurement instruments were involved, which strengthened our recommendations and provided insight into important aspects that will play a role during implementation of the core dataset.

As for potential limitations, the final decisions on the 'how to measure' were made by a relatively small group for feasibility reasons, which did not include representatives from regulatory bodies or pharmaceutical industry. However, where required expertise was not available within the group, external experts were consulted. Also, due to the fact that observational studies need large numbers of patients, this core dataset will need to be implemented in many research facilities. Although this might prove to be a challenge, we think that, since many of the items from the core dataset are already registered in clinical practice, this will not become a problem. Although we had a very experienced patient representative, who also was the Chair of the Dutch Association for People with Atopic Dermatitis, it would have been desirable to include more patient representatives in this consensus process. Finally, for a number of domain items no underlying systematic reviews of the evidence were available. This meant that in this study expert opinion played a bigger role than for instance in the HOME initiative.

Recommendations for future work

As a next step, the feasibility of the core dataset and the proposed follow up frequencies need to be tested. As part of such feasibility work it is important to keep in mind that our recommendations apply to research registries, rather than record keeping in routine clinical practice. We are also encouraged that the larger TREATgermany dataset appears feasible to local investigators in its current form.[21]

This core dataset will allow the international dermatology community to generate, compare and pool data of AE patients on photo- and systemic therapies across country borders to answer important questions on long-term effectiveness, safety and cost-effectiveness of these therapies, some of which can only be addressed with very large patient numbers (e.g. on rare adverse events). We are working on a standardised data collection/storage platform to facilitate uniform data collection, pooling and analyses. In the long-term, we hope that our recommendations and the analyses generated by national treatment registries will complement the more short-term results from RCTs and ultimately aid the standardisation and optimisation of patient management.

As the uptake of this core dataset by new national AE registries is vital, we encourage colleagues to contact us through our website (treat-registry-taskforce.org), to extend this collaborative project not just within Europe but also beyond.

Acknowledgements

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Supplemental Material

Figure S1 – When to measure the domain items, survey

Figure S1 – When to measure the domain items, survey

1. What should be the minimum follow up frequency for registry data entry while on therapy, starting from baseline?

- ○ 4 Wks, 3 months and then every 3 months
- ○ 3 Months, 6 months and then every 6 months
- ○ Every 3 months
- ○ Every 6 months
- ○ 4 Wks, 3 months, 6 months and then every 6 months
- ○ Other (please specify)

2. What should be the minimum follow up frequency for registry data entry, while off therapy (after discontinuation of therapy)?

- ○ Every 3 months
- ○ 6 Months, 12 months and then annually
- ○ 3 Months, 6 months and then every 6 months
- ○ Annually
- ○ Every 6 months
- ○ Other (please specify)

3. Should we define a visit window?

- ○ Yes
- ○ No

4. If yes, what should be the visit window for follow up visits while on therapy?

- ○ +/- 1 week
- ○ +/- 2 weeks
- ○ +/- 1 month
- ○ Other (please specify)

5. If yes, what should be the visit window for follow up visits while off therapy (after discontinuation of therapy)?

- ○ +/- 1 week
- ○ +/- 2 months
- ○ +/- 2 weeks
- ○ +/- 3 months
- ○ +/- 1 month
- ○ Other (please specify)

Figure S2 – Overview of attending participants

MEETING	Academic dermatologist	Dermatology resident	Dermatology PhD student	Patient/ patient representative	Epidemiologist/ methodologist	Health economist
Teleconference	6	1	1	-	1	-
London	10	1	1	1	1	1
Amsterdam	4	1	1	1	1	-
Nantes	6	1	-	-	1	-

Figure S3 - Definitions on phenotypical and morphological characteristics

CONSENSUS

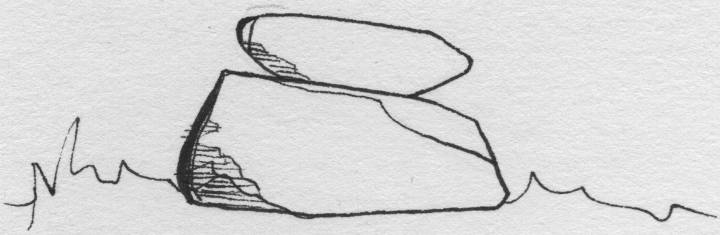
Pompholyx:	Vesicular eczema
Discoid eczema:	≥ 5 Circular patches in total, ≥ 2cm diameter each
Nodular prurigo:	≥ 5 Palpable nodules of the skin from long-term scratching (usually on the legs or arms), ≥ 1cm diameter each
Follicular eczema:	Widespread eczematous hair follicle involvement, more commonly seen in darker skin types
Ichthyosis:	Widespread fine scale predominantly affecting the non-flexural areas of the limbs and body
Keratosis pilaris:	Thickening around the base of hair follicles over upper arms, thighs or cheeks
Erythroderma:	≥ 90% BSA (Body Surface Area) involvement

Figure S4 – Average treatment (maintenance) dose

CONSENSUS		
Ciclosporin: < 2.5 mg/kg/day 2.5 - 3.5 mg/kg/day 3.6 - 4.5 mg/kg/day 4.6 - 5.0 mg/kg/day > 5.0 mg/kg/day Unknown		**Oral corticosteroids:** < 0.5 mg/kg/day 0.5 - 1.0 mg/kg/day > 1.0 mg/kg/day Unknown
Azathioprine: < 1 mg/kg/day 1 - 2 mg/kg/day 2.1 - 3 mg/kg/day > 3 mg/kg/day Unknown		**Dupilumab:** < 300 mg every other week 300 mg every other week 300 mg every week > 300 mg every week Other - please specify Unknown
Methotrexate (adults): < 5 mg/week 5 - 10 mg/week 11 - 15 mg/week 16 - 20 mg/week 21 - 25 mg/week > 25 mg/week Unknown	**Methotrexate (children)**: < 0.1 mg/kg/week 0.1 - 0.2 mg/kg/week 0.21 - 0.3 mg/kg/week 0.31 - 0.4 mg/kg/week > 0.4 mg/kg/week Unknown	**Omalizumab:** < 300 mg every four weeks 300 mg every four weeks > 300 mg every four weeks Other - please specify Unknown
Mycophenolate acid (adults): < 1 g/day 1 - 1.5 g/day 1.6 - 2 g/day > 2 g/day Unknown	**Mycophenolate acid (children):** < 30 mg/kg/day 30 - 40 mg/kg/day 41 - 50 mg/kg/day > 50 mg/kg/day Unknown	

Part II

Collecting more evidence on the use of conventional phototherapies and systemic therapies in adult AD patients



Chapter 3

The European TREatment of ATopic eczema Taskforce (TREAT) Survey; prescribing practices in Europe for phototherapy and systemic therapy in moderate-to-severe adult atopic eczema patients

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Summary (abstract)

Background

For many years dermatologists have had access to few therapies for patients with moderate-to-severe atopic eczema (AE). New promising therapies are entering the market but conventional phototherapies and systemic therapies have more well-known safety-profiles, lower cost and wider availability.

Objectives

To provide insight into current prescribing practices of conventional photo- and systemic immunomodulatory therapies for adults with AE and the factors influencing these prescribing practices before biologics and other novel therapeutics become routine clinical practice.

Methods

In this exploratory study dermatologists were invited to participate in an online survey via a mailing list of the European Academy of Dermatology and Venereology and national societies. Data were collected on participant characteristics (including clinical practices data), the use of phototherapies and systemic therapies and factors influencing their use.

Results

From 30 European countries, 238 out of 361 dermatologists willing to participate (65.9%) completed the survey. For phototherapy (ever prescribed by 84.7%), most preferred narrow-band ultraviolet-B as first line of choice (80.9%) and psoralen and ultraviolet-A as second line (21.6%). For systemic therapy (ever prescribed by 95.2%) ciclosporin (54.1%), oral corticosteroids (32.6%) and methotrexate (30.7%) were used first line. Dermatologists mostly relied on personal experience for prescribing phototherapy and systemic therapy. Few prescribed azathioprine (59%) and mycophenolate acid (37.1%), mostly due to a lack of personal experience.

Conclusions

This study provides insight into prescribing practices for conventional photo- and systemic therapies in Europe and shows that off-label therapies are also preferred as first line choice of systemic therapy.

Introduction

For many years dermatologists have only had a small array of available therapies for their moderate-to-severe atopic eczema (AE) patients - and no robust guidance for these therapies as the supporting evidence for phototherapy and systemic immunomodulatory therapy has been of varying quality and only a few long-term studies are available.[1–5] Currently, the European Medicines Agency (EMA) has approved ciclosporin and dupilumab for adult AE patients[6,7] while dupilumab and prednisolone are the only treatments for adult AE patients approved by the United States (US) Food and Drug Administration (FDA).[8,9] Although novel therapies have promising efficacy profiles,[10] long-term evidence on their safety profiles is missing.[11] Conventional systemic therapies like ciclosporin have more well-known side-effect profiles,[12] lower direct medical costs and will probably be more accessible to a wide group of AE patients than biologics.[13] We therefore still see a need to pursue a better evidence-profile for the usage of conventional phototherapies and systemic therapies.

Survey studies investigating the prescribing practices of conventional photo- and systemic therapies of the TREatment of ATopic eczema (TREAT) Registry Taskforce initiative (https://treat-registry-taskforce.org) have been performed in paediatric AE patients in Europe and Northern America[14,15] and in adult AE patients in the UK.[16] These studies have shown varying prescribing practices and varying factors influencing these prescribing practices among dermatologists. As the arrival of new biologics will probably influence the prescribing practices, we believe it is important to determine what the current treatment approaches and reasons for or against prescribing therapies for adult AE patients in continental Europe are.

This study will contribute to a clearer view on the usage and prescribing practices of *conventional* phototherapies and systemic therapies, and especially on factors for or against prescribing certain treatments. Ultimately this might aid in the development of better evidence-profiles for these therapies and more uniform treatment algorithms.

Participants and Methods

Study design

We conducted an online, anonymous, multiple-response survey among European dermatologists caring for adult moderate-to-severe AE patients. For the purpose of the survey, moderate-to-severe AE was defined as AE that is not adequately controlled by standard and optimised topical treatment (including emollients, topical steroids, topical calcineurin inhibitors and coal tar). Participants were asked to make decisions for patients who did not have an acute flare.

The survey was developed in Snap Surveys software, was available in English language only and was pilot tested before going live. As this study is not a part of the Medical Research Involving Human Subjects Act (WMO), a Medical Ethics Committee (MEC) was not consulted. The survey was live from 5 March 2018 till 28 September 2018. A total of 5 reminders were sent to participants that did not complete the survey.

Survey questionnaire

Both the protocol for and the questions used in the survey were based on previous surveys performed by Proudfoot et al.,[14] Totri et al.[15] and Taylor et al.,[16] and were slightly adapted for the purpose of this survey. The survey consisted of 135 questions in total, spread over 5 different sections: "demographics", "treatment options", "phototherapy", "systemic therapy" and "future work".

The following demographics of the participants were collected: age, gender, country of work, type of workplace (e.g. university teaching hospital or private practice), ethnicity of patient cohorts, years of experience, average number of treated patients per 3 months, number of referred or initiated patients on phototherapy or systemic therapy and the 5 most generally used measurement instruments for AE.

In the treatment options section, participants were queried about their 1st, 2nd and 3rd line choice of therapy, assuming the scenario that day care treatment (intensive topical therapy, potentially combined with bathing therapy, psychosocial support, education and phototherapy, 2-3 times a week), hospital admission, phototherapy and systemic therapy were available. Participants were also asked which treatments were available at their centre.

Subsequently, for phototherapy and systemic therapy, participants were asked if they prescribed the treatments and, if so, how often. If participants did not prescribe phototherapy and/or systemic therapy they were directed towards the next section or towards the end of the survey, depending on the answers given. Questions were then asked about participants 1st, 2nd and 3rd line choice of therapy. In the phototherapy section several options were offered: broad band ultraviolet-B (BB-UVB), narrow band UVB (NB-UVB), ultraviolet-A plus ultraviolet-B (UVAB), psoralen and ultraviolet-A (PUVA), ultraviolet-A (UVA) and UVA1. In the systemic therapy section the options were: ciclosporin, azathioprine, methotrexate, mycophenolate acid, oral corticosteroids and 'other'. For all 1st, 2nd and 3th line choice questions participants were able to select multiple therapies. Participants were queried about different subgroups (i.a. patients

with relative contra-indications, pregnant patients or elderly) in which they prescribed certain systemic therapies. In addition, for each treatment option participants were asked about dosing, duration of treatment, discontinuation regimens and reasons for or against prescribing a particular therapy (for phototherapy overall, and for systemic therapy overall and per treatment, see Tables S1 – S6). At the end of the questionnaire, participants had the opportunity to highlight current gaps in knowledge that they would like to see addressed.

Participants

Eligible were dermatologists and dermatology residents in Europe. Since Taylor et al. already performed a survey amongst UK dermatologists treating adult AE patients,[16] dermatologists and dermatology residents from the UK were excluded. A mailing list of EADV members and 41 national societies (Table S7) were used to distribute an invitation to register for participation in the survey. Those who were willing to participate were asked to register with their email address after which they received a personal link to the survey. To avoid duplicate answers from the same participant, the list of all email addresses was screened manually and duplicates were removed.

Statistical analyses

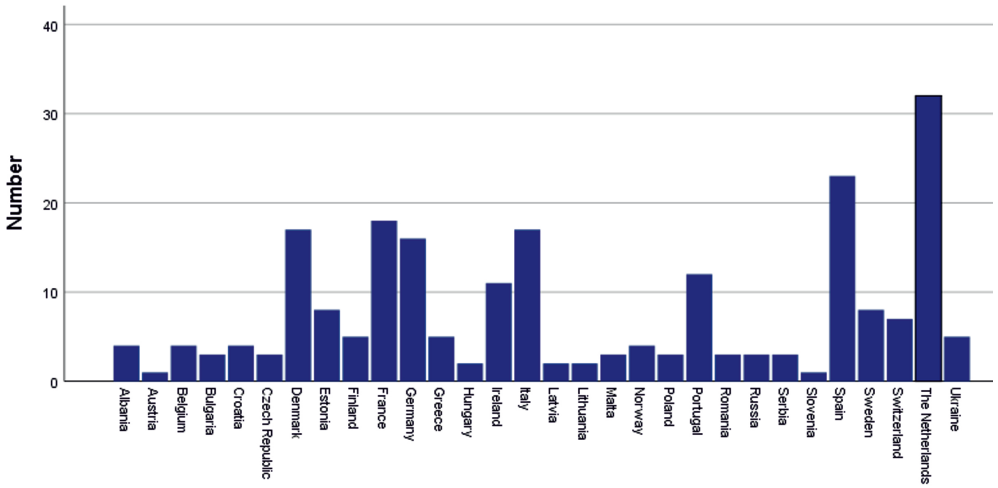
Descriptive statistics were primarily used for the statistical analyses. To identify differences in participant characteristics and choice of systemic therapy, a chi-square test for categorical variables was used. A p-value of < 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS 25 and R Statistical Software version 3.50.

Results

Study population

In total, 361 dermatologists/dermatology residents registered for participation in the survey. Of these, 238 completed the survey (65.9%). Four participants were excluded due to being based in the UK, 4 for not prescribing phototherapy or systemic therapy in adult AE patients and 1 for being a general practitioner instead of a dermatologist or dermatology resident. Participants originated from 30 different countries (Fig. 1). Of the remaining 229 participants, 135 (59%) were female and the majority worked in a university teaching hospital (148 of 229; 64.6%). A total of 100 (43.7%) participants treated AE patients for over 20 years and 70 (30.6%) for 11-20 years, indicating that the majority of the participants had a significant amount of expertise. Participants were consulted by patients with a white ethnicity for the majority of their time (98.3%) and occasionally by Asian-Chinese (76.0%), Black-African/ Afro-Carribean (70.3%), and South-Asian patients (69.0%). The SCORing Atopic Dermatitis (SCORAD) scale (67.7%), Dermatology Quality of Life Index (DLQI, 56.3%), Eczema Area and Severity Index (EASI, 54.6%), Investigator Global Assessment (IGA) scale (33.6%) and the visual analogue scale (VAS) for itch (23.1%) were the five most frequently used measurement instruments. An overview of participant and professional characteristics is given in Table 1.

Figure 1 – Country of work of participants



General prescribing behaviour

95 (41.5%) participants indicated to prescribe photo(chemo)therapy as their first line choice of therapy for moderate-to-severe AE patients, followed by day care therapy (90/229; 39.3%) and systemic therapy (61/229; 26.6%). As second line, systemic therapy (114/229; 49.8%) and photo(chemo)therapy (88/229; 38.4%) were mostly selected. An overview of the availability of phototherapy and systemic therapies for participating

countries can be found in Figures 2a-c. When participants were queried about their vision on the most relevant studies for the treatment of moderate-to-severe AE, they indicated that especially long-term safety, long-term control/efficacy and head-to-head trials are of importance. As gaps of evidence participants mentioned education of patients, data on efficacy, safety and duration of treatment of current conventional systemic therapies, data for personalised medicine using biomarkers and treatment of itch specifically.

Phototherapy

Of all participants, 194 (84.7%) indicated to use phototherapy as a treatment for their adult AE patients. Of these participants, 32 (16.5%) indicated to primarily prescribe phototherapy, 59 (30.4%) indicated to use this often, 64 (33%) sometimes and 39 (20.1%) rarely. 157 Participants (80.9%) prescribed NB-UVB as first line UV therapy, followed by BB-UVB (15/194; 7.7%) and UVAB therapy (12/194; 6.2%). PUVA was most frequently prescribed as second line UV treatment (42/194; 21.6%), followed by BB-UVB (32/194; 16.5%) and UVAB (28/194; 14.4%). PUVA (25/194; 12.9%) and UVA1 (9/194; 4.6%) were mostly selected as third line choice of UV therapy (Fig. 3a). The most important reason for the use of phototherapy was personal experience with the treatment (114/194; 58.8%) and the most important reason against was the unavailability of phototherapy at a centre (16/35; 45.7) (Tables S1-S2).

Figure 2a – Availability photo(chemo)therapy in 30 European countries

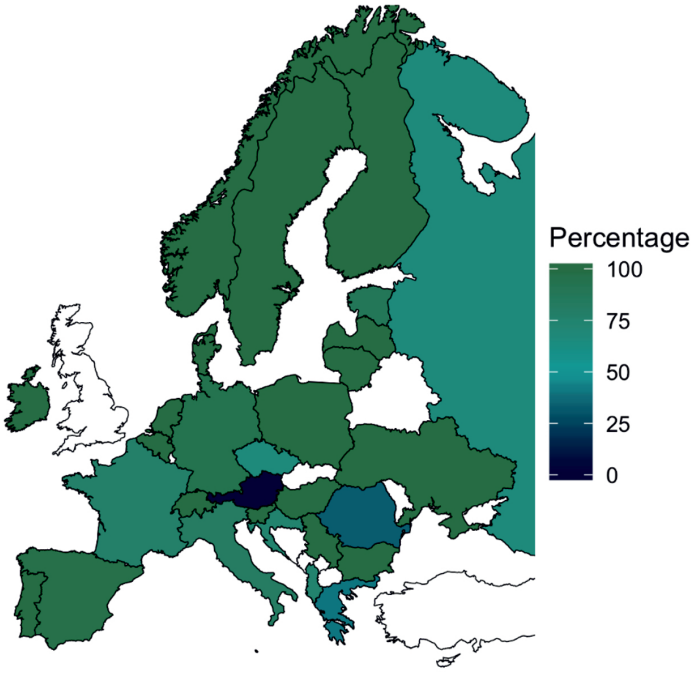


Figure 2b – Availability systemic therapy in 30 European countries

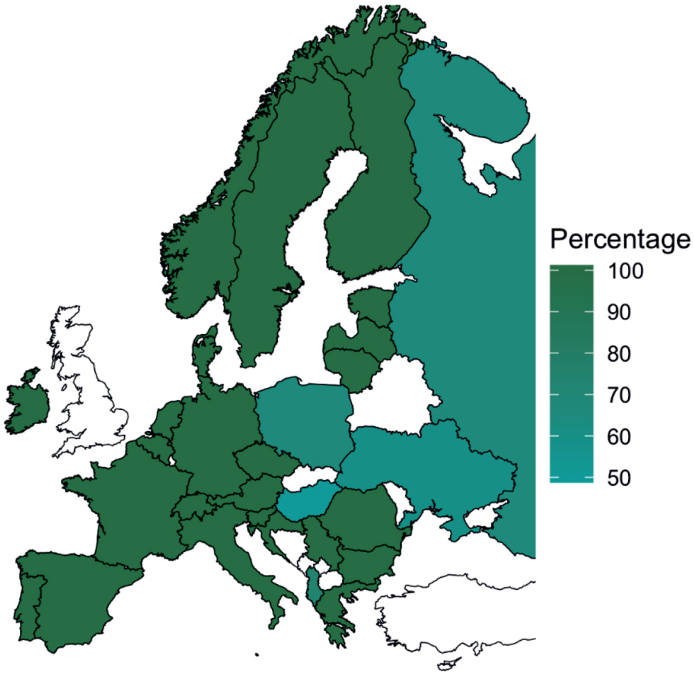


Figure 2c – Availability dupilumab in 30 European countries

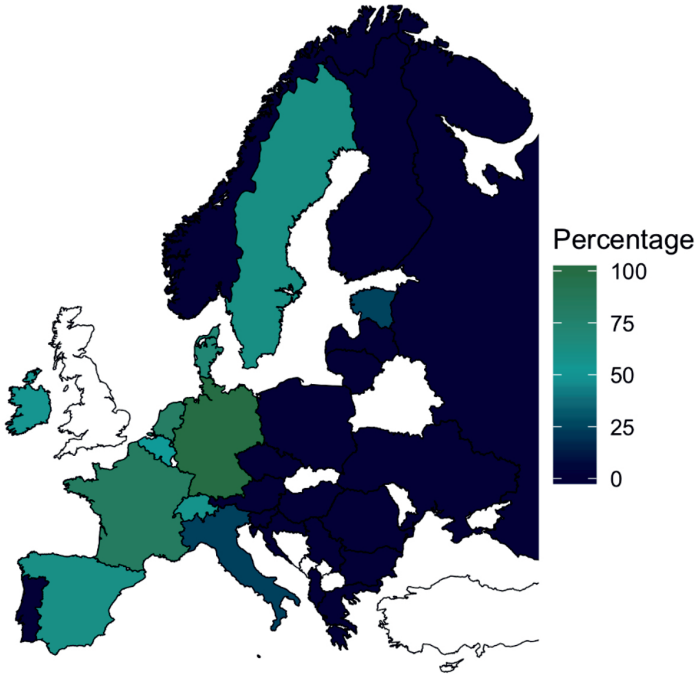


Figure 3a – First, second and third line choice of phototherapy

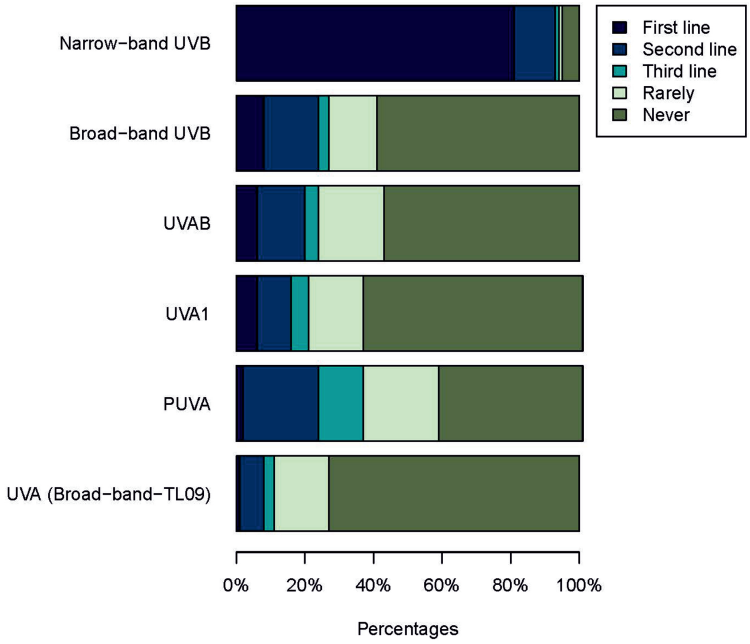


Figure 3b – First, second and third line choice of systemic therapy

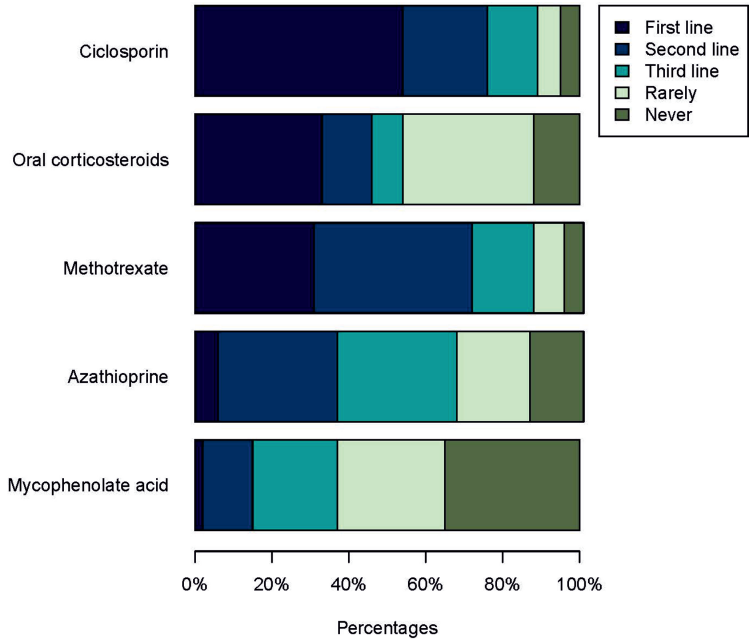


Table 1 – Participant characteristics (including professional characteristics)

Characteristics	N (%)
Age	
• 20-30	16 (7.0)
• 31-40	54 (23.6)
• 41-50	66 (28.8)
• 51-60	67 (29.3)
• > 60	26 (11.4)
Gender	
• Female	135 (59.0)
• Male	94 (41.0)
Type of workplace	
• Community	1 (0.4)
• General hospital	38 (16.6)
• Private practice	42 (18.3)
• University teaching hospital	148 (64.6)
Years of experience	
• 0-4 years	14 (6.1)
• 5-10 years	45 (19.7)
• 11-20 years	70 (30.6)
• > 20 years	100 (43.7)
Number of treated patients per 3 months	
• < 10	30 (13.1)
• 10-50	116 (50.7)
• 51-100	58 (25.3)
• 101-200	17 (7.4)
• > 200	8 (3.5)
Number of patients with moderate-to-severe AE in population	
• < 5%	34 (14.8)
• 5-10%	59 (25.8)
• 11-25%	55 (24.0)
• 26-40%	31 (13.5)
• 41-60%	24 (10.5)
• > 60%	26 (11.4)
Number of initiated patients on photo-or systemic therapy per 3 months	
• 0 patients	1 (0.4)
• 1-5 patients	109 (47.6)
• 6-10 patients	62 (27.1)
• 11-20 patients	35 (15.3)
• > 20 patients	22 (9.6)

Systemic therapy and dosing schedules

A total of 218 participants (95.2%) indicated to prescribe systemic therapy for adults suffering from AE. Multiple treatments were prescribed as first line choice of therapy: ciclosporin by 118 (54.1%), oral corticosteroids by 71 (32.6%) and methotrexate by 67 (30.7%). Azathioprine and mycophenolate acid were only prescribed as first line choice of treatment by 12 (5.5%) and 4 (1.8%) participants. Methotrexate (89/218; 40.8%), azathioprine (67/218; 30.7%) and ciclosporin (49/218; 22.5%) were mostly prescribed as second line treatment. Azathioprine (67/218; 30.7%), mycophenolate acid (48/218; 22.0%) and methotrexate (34/218; 15.6%) were most frequently selected as third line treatments (Fig. 3b). First line methotrexate prescription was highest in university teaching hospitals (38% compared to 18% and 15% for general hospital and private practice), while prescription in third line was more frequent in general hospitals (24% compared to 12% and 15% for private practice and university hospitals respectively). In addition, private practices prescribed less methotrexate compared to the other workplaces (p-value=0.0053; Table S8c). Mycophenolate acid was mostly prescribed by university-based dermatologists (15% and 28% for second and third line, respectively). Dermatologists from general hospitals and private practices rarely (39% and 18%) or never (39% and 65%) prescribed mycophenolate acid, respectively (p-value <0.0001; Table S8d). There was no significant difference between type of workplace and prescription pattern of the other systemic therapies (Tables S8a, S8b and S8e). We found that the following other demographic variables also significantly affected the responses. Less experienced participants more frequently prescribed mycophenolate acid for first and third line. Mycophenolate acid was more frequently prescribed in second and third line when more patients were initiated on phototherapy and systemic therapy (per 3 months) while participants prescribed less mycophenolate acid when less patients were initiated. Females were also more conservative in prescribing mycophenolate acid. Participants were more likely to prescribe oral corticosteroids first, second or third line when they treated less moderate-to-severe AE patients. Azathioprine was most frequently prescribed as second line in all participants and third line in participants treating 10-100 patients per 3 months, but more frequently rarely or never when <10 or >200 patients per 3 months were treated. Younger participants prescribed methotrexate more first and second line while older participants did this rarely or never (chi-square tables can be sent upon request).

First, second and third line choices of systemic therapy grouped by country (only those with >10 participants) are presented in Table S9-11. These tables show that dermatologists in Denmark and Ireland more often prescribe methotrexate as first line of choice (88.2%/90.9% vs. 30.7% on average), that especially dermatologists in The Netherlands more often prescribe ciclosporin as first line systemic agent (86.8% vs. 54.1% on average) and that oral corticosteroids are most frequently prescribed as first line of choice in Spain (56.5% vs. 32.6% on average). Table 2 shows prescribing practices in subgroups. Oral corticosteroids and ciclosporin are prescribed to both pregnant (110 (50.5%) and 64 (29.4%) respectively) and lactating patients (102 (46.8%) and 41 (18.8%) respectively). Methotrexate was the most preferred therapy in the category for patients with comorbidities (78/218; 35.8%) and in elderly (106/218; 48.6%).

Table 2 – Prescription of systemic medication in subgroups

	Ciclosporin	Azathioprine	Methotrexate	Mycophenolate acid	Oral corticosteroids
Patients with relative contra-indications	44 (20.2)	21 (9.6)	45 (20.6)	28 (12.8)	66 (30.3)
Pregnant patients	64 (29.4)	8 (3.7)	2 (0.9)	2 (0.9)	110 (50.5)
Lactating patients	41 (18.8)	7 (3.2)	2 (0.9)	2 (0.9)	102 (46.8)
Obese patients	72 (33.0)	49 (22.5)	84 (38.5)	31 (14.2)	25 (11.5)
Teenagers	127 (58.3)	37 (17.0)	63 (28.9)	26 (11.9)	41 (18.8)
Patients with malignant disease (current or history)	16 (7.3)	7 (3.2)	74 (33.9)	7 (3.2)	82 (37.6)
Patients with comorbidities	36 (16.5)	35 (16.1)	78 (35.8)	33 (15.1)	40 (18.3)
Elderly	34 (15.6)	44 (20.2)	106 (48.6)	27 (12.4)	39 (17.9)

N=218. *This table only shows in which subgroups participants would prescribe certain therapies. Relative and absolute contraindications such as pregnancy and lactation during MTX use are not shown but should always be considered when making a choice for systemic therapy.*

Not all systemic therapies were prescribed by all participants. Ciclosporin was prescribed by 201 (87.8%) participants, methotrexate by 199 (86.9%), oral corticosteroids by 184 (80.3%), azathioprine by 135 (59.0%), and mycophenolate acid by only 85 participants (37.1%). Table 3 provides information on the frequency of use, the initial and maximum dosing schedules and the average and maximum duration on therapy. It shows for example that ciclosporin and oral corticosteroids are mainly discontinued by titration over 1 month, while azathioprine, methotrexate and mycophenolate acid are discontinued without titration. Therapies that were mentioned as 'other' therapies used for moderate-to-severe AE were 'antibiotics' (not specified), omalizumab, rituximab, alitretinoin, photopheresis, dupilumab, 'study medication' (not specified), intravenous immunoglobulin, tacrolimus and tofacitinib.

Of the 199 participants that prescribed methotrexate, 100 (50.3%) indicated never to give a test dose of methotrexate, while 36 (18.1%) indicated to give a test dose of 7.5 mg, 23 (11.6%) of 10 mg, 21 (10.6%) of 5 mg and 7 (3.5%) of 2.5 mg. Oral corticosteroids were given for an acute flare (179/184; 97.3%), during initiation of other immunosuppression (73/184; 39.7%), in addition to other immunosuppression (23/184; 12.5%) and only rarely as ongoing treatment (6/184; 3.3%). In general, participants indicated that especially their own clinical experience (140/218; 64.2%), baseline tests and comorbidities (128/218; 58.7%), a low potential long-term side effect profile (123/218; 56.4%), sufficient medium term (>3 months) efficacy (118/218; 54.1%) and their knowledge of national/international guidelines (115/218; 52.8%) influenced their choice for systemic therapy (Table S3). Dermatologists of Denmark (17 participants in total) and Ireland (11 participants in total) mainly indicated that a better long-term

efficacy (14/17; 82.4% and 10/11; 90.9% respectively), a low potential acute (8/17; 47.1% and 7/11; 63.6%) and long-term (12/17; 70.6% and 4/11; 36.4%) side effect profile, knowledge of international guidelines (10/17; 58.5% and 4/11; 36.4%), knowledge of expert opinions (6/17; 35.3% and 8/11; 72.7%) and personal experience with the treatment (10/17; 58.8% and 10/11; 90.9%) were reasons for their prescription of methotrexate.

Perceived barriers for prescribing systemic therapy (not prescribed by 11 participants) were a high potential acute side-effect profile (6/11; 54.4%), a suspected risk of long-term organ toxicity (5/11; 45.5%), comorbidities (5/11; 45.5%) and patient preferences (5/11; 45.5%) (Table S4). Both azathioprine (not prescribed by 83 participants) and mycophenolate acid (not prescribed by 133 participants) were hardly prescribed as first line choice, mainly due to a lack of personal experience (50/83; 60.2% and 78/133; 58.6%). Other reasons for and against prescribing specific systemic therapies are given in Tables S5 and S6.

Table 3. –Dosing and discontinuation regimens of systemic therapy

Ciclosporin, N (%)		Azathioprine, N (%)		Methotrexate, N (%)		Mycophenolate acid, N (%)		Oral corticosteroids, N (%)	
Frequency of use									
• Rarely (<10% of patients)	72 (35.8)	• Rarely (<10% of patients)	82 (60.7)	• Rarely (<10% of patients)	79 (39.7)	• Rarely (<10% of patients)	70 (82.4)	• Rarely (<10% of patients)	80 (43.5)
• Sometimes (11-25% of patients)	70 (34.8)	• Sometimes (11-25% of patients)	44 (32.6)	• Sometimes (11-25% of patients)	54 (27.1)	• Sometimes (11-25% of patients)	14 (16.5)	• Sometimes (11-25% of patients)	58 (31.5)
• Often (26-50% of patients)	48 (23.9)	• Often (26-50% of patients)	9 (6.7)	• Often (26-50% of patients)	41 (20.6)	• Often (26-50% of patients)	1 (1.2)	• Often (26-50% of patients)	38 (20.7)
• Mostly (>50% of patients)	11 (5.5)	• Mostly (> 50% of patients)	0 (0.0)	• Mostly (>50% of patients)	25 (12.6)	• Mostly (>50% of patients)	0 (0.0)	• Mostly (>50% of patients)	8 (4.3)
Initial dose									
• <2.5 mg/kg/day	22 (10.9)	• <1 mg/kg/day	20 (14.8)	• <5 mg/week	6 (3.0)	• <1 g /day	11 (12.9)	• <0.5 mg/kg/day	75 (40.8)
• 2.5-3.5 mg/kg/day	110 (54.7)	• 1-2 mg/kg/day	98 (72.6)	• 5-10 mg/week	60 (30.2)	• 1-1.5 g/day	40 (47.1)	• 0.5-1.0 mg/kg/day	107 (58.2)
• 3.6-4.5 mg/kg/day	37 (18.4)	• 2.1-3 mg/kg/day	17 (12.6)	• 11-15 mg/week	109 (54.8)	• 1.6-2 g/day	32 (37.6)	• >1.0 mg/kg/day	2 (1.1)
• 4.6-5.0 mg/kg/day	32 (15.9)	• >3 mg/kg/day	0 (0.0)	• 16-20 mg/week	22 (11.1)	• >2 g/day	2 (2.4)		
• >5.0 mg/kg/day	0 (0.0)			• 21-25 mg/week	2 (1.0)				
				• >25 mg/week	0 (0.0)				
Maximum dose									
• <2.5 mg/kg/day	2 (1.0)	• <1 mg/kg/day	2 (1.5)	• <5 mg/week	1 (0.5)	• <1 g /day	2 (2.4)	• <0.5 mg/kg/day	24 (13.0)
• 2.5-3.5 mg/kg/day	32 (15.9)	• 1-2 mg/kg/day	53 (39.3)	• 5-10 mg/week	8 (4.0)	• 1-1.5 g/day	12 (14.1)	• 0.5-1.0 mg/kg/day	146 (79.3)
• 3.6-4.5 mg/kg/day	42 (20.9)	• 2.1-3 mg/kg/day	76 (56.3)	• 11-15 mg/week	33 (16.6)	• 1.6-2 g/day	51 (60.0)	• >1.0 mg/kg/day	14 (7.6)
• 4.6-5.0 mg/kg/day	120 (59.7)	• >3 mg/kg/day	4 (3.0)	• 16-20 mg/week	69 (34.7)	• >2 g/day	20 (23.5)		
• >5.0 mg/kg/day	5 (2.5)			• 21-25 mg/week	87 (43.7)				
				• >25 mg/week	1 (0.5)				
Average duration									
• 0-3 months	21 (10.4)	• 0-3 months	12 (8.9)	• 0-3 months	13 (6.5)	• 0-3 months	3 (3.5)	• <4 weeks	143 (77.7)
• 4-6 months	86 (42.8)	• 4-6 months	15 (11.1)	• 4-6 months	25 (12.6)	• 4-6 months	10 (11.8)	• 1-3 months	36 (19.6)
• 7-12 months	61 (30.3)	• 7-12 months	43 (31.9)	• 7-12 months	47 (23.6)	• 7-12 months	31 (36.5)	• 4-6 months	4 (2.2)
• 13-18 months	21 (10.4)	• 13-18 months	27 (20.0)	• 13-18 months	36 (18.1)	• 13-18 months	17 (20.0)	• 7-12 months	1 (0.5)
• 19-24 months	10 (5.0)	• 19-24 months	22 (16.3)	• 19-24 months	34 (17.1)	• 19-24 months	11 (12.9)	• 13-18 months	0 (0.0)
• >24 months	2 (1.0)	• >24 months	16 (11.9)	• >24 months	44 (22.1)	• >24 months	13 (15.3)	• 19-24 months	0 (0.0)
								• >24 months	0 (0.0)

Maximum duration									
• 0-3 months	3 (1.5)	• 0-3 months	2 (1.5)	• 0-3 months	3 (1.5)	• 0-3 months	2 (2.4)	• <4 weeks	74 (40.2)
• 4-6 months	27 (13.4)	• 4-6 months	12 (8.9)	• 4-6 months	14 (7.0)	• 4-6 months	2 (2.4)	• 1-3 months	80 (43.5)
• 7-12 months	64 (31.8)	• 7-12 months	17 (12.6)	• 7-12 months	23 (11.6)	• 7-12 months	13 (15.3)	• 4-6 months	24 (13.0)
• 13-18 months	25 (12.4)	• 13-18 months	10 (7.4)	• 13-18 months	16 (8.0)	• 13-18 months	8 (9.4)	• 7-12 months	3 (1.6)
• 19-24 months	55 (27.4)	• 19-24 months	27 (20.0)	• 19-24 months	15 (7.5)	• 19-24 months	13 (15.3)	• 13-18 months	0 (0.0)
• >24 months	27 (13.4)	• >24 months	67 (49.6)	• >24 months	128 (64.3)	• >24 months	47 (55.3)	• 19-24 months	1 (0.5)
								• >24 months	2 (1.1)
Discontinuation regimen									
• Titrate dose over 1 week	12 (6.0)	• Titrate dose over 1 week	5 (3.7)	• Titrate dose over 1 week	5 (2.5)	• Titrate dose over 1 week	5 (5.9)	• Titrate dose over 1 week	52 (28.3)
• Titrate dose over 1 month	80 (39.8)	• Titrate dose over 1 month	47 (34.8)	• Titrate dose over 1 month	46 (23.1)	• Titrate dose over 1 month	24 (28.2)	• Titrate dose over 1 month	76 (41.3)
• Halve dose every 2 weeks	47 (23.4)	• Halve dose every 2 weeks	27 (20.0)	• Halve dose every 2 weeks	36 (18.1)	• Halve dose every 2 weeks	20 (23.5)	• Halve dose every 2 weeks	33 (17.9)
• Discontinue without titration	50 (24.9)	• Discontinue without titration	50 (37.0)	• Discontinue without titration	94 (47.2)	• Discontinue without titration	33 (38.8)	• Discontinue without titration	15 (8.2)

Ciclosporin N=201; azathioprine N=135; methotrexate N=199, mycophenolate acid N=85, oral corticosteroids N=184

Discussion

The prescribing of phototherapy and systemic immunomodulatory treatments for AE varies across European countries. Despite the fact that clinical experience seemed the most relevant reason for or against prescribing certain therapies, the majority of dermatologists seem to prescribe treatments according to current guidelines.[12,17–20]

In this study NB-UVB and PUVA were found to be first and second line choice of therapies for photo(chemo)therapy. This corresponds with results from the UK TREAT adult survey,[16] but only partly with the recommendations that can be found in guidelines. Garritsen et al.[2] found that NB-UVB and UVA1 appear to be the most effective phototherapies based on the available evidence. In our study UVA1 was only prescribed by a small minority of the physicians. However, since we did not query participants about their availability of specific phototherapies, this could be based on a low availability of UVA1. A more recent study by Ling et al. shows that, if NB-UVB is not effective in severe AE, PUVA therapy may also be considered.[21]

Ciclosporin was found to be the preferred first line systemic therapy, which is in line with multiple guidelines and both the European and North American paediatric TREAT surveys.[14,15,17,19,20] It does not correspond, however, with the results of the UK adult treatment survey, in which azathioprine was preferred as first line systemic therapy.[16] Although more than half of the dermatologists favoured ciclosporin as first line therapy, a large proportion of dermatologists did not and preferred oral corticosteroids (32.6%) or methotrexate (30.7%) as first line treatment. This is interesting, as during the course of our study ciclosporin was the only licensed systemic agent for AE in Europe.[6]

As second line treatment methotrexate and azathioprine were most frequently selected. In most guidelines no specific second line therapy is suggested but recommendations are made that methotrexate, azathioprine and mycophenolate acid are all three options to consider when ciclosporin fails to achieve results in the treatment of AE.[17,19,20]

"No significant difference was found between type of workplace and prescription pattern for ciclosporin, azathioprine and oral corticosteroids. For ciclosporin this could be explained by the participants' knowledge of guidelines (as first choice therapy) and the wider evidence base for ciclosporin (see Table S5). For oral corticosteroids this might be explained by their historically very regular prescription by both academic and non-academic dermatologists.

Another interesting finding is that the majority of dermatologists prescribed ciclosporin for a maximum period of 18 months, while in daily practice some patients seem to tolerate ciclosporin for longer periods.[22] Further, we found that both ciclosporin and oral corticosteroids are mainly prescribed for pregnant or lactating patients. This is in accordance with the recent position paper from the European Task Force on Atopic Dermatitis (ETFAD) on the treatment of parental AE during pregnancy and lactation.[23] Oral corticosteroids were found to be most frequently prescribed for an acute flare (97.3%) or during initiation of other immunosuppression (39.7%), which is in line with a recent consensus paper on systemic corticosteroids published by the International Eczema Council.[24] It is not in line however with the fact that 32.6%

of the participants prescribe oral corticosteroids as first line therapy in the case of moderate-to-severe AE patients who did not have an acute flare – which was the case on which participants based their decision for their 1st, 2nd and 3rd therapy. When questioned about methotrexate, almost half of dermatologists indicated to use a test dose before start of therapy while the ETFAD and the American Academy of Dermatology (AAD) guidelines do not mention the use of a test dose.[13,19] Methotrexate was further mostly preferred as therapy for elderly and patients with comorbidities. This might be explained by the fact that dermatologists historically have broad experience with the prescription of methotrexate in other skin diseases - such as psoriasis - and in different subgroups of patients. Also, methotrexate has a lower acute toxicity risk compared with e.g. ciclosporin and is suitable for long-term use. For example in elderly more hypertension and/or kidney dysfunction is seen, and therefore the use of methotrexate could be preferred above ciclosporin.

Strengths and limitations

A total of 229 completed surveys from 30 countries were analysed in this study, providing a representation of practice within Europe (academic dermatologists: 64.6%; non-academic dermatologists: 35.4%). Since data was collected on both phototherapies and systemic therapies, this study provides a complete view on the treatment of moderate-to-severe AE patients in Europe before the standard use of biologics for AE, although the fact that the majority of the countries had less than 5 participants might influence the results. In this study only dermatologists who treated moderate-to-severe AE patients regularly were included. As for limitations, selection bias may play a role in our study. The majority of dermatologists in our study was based in an academic hospital. In our study participants were not queried about the simultaneous use of two systemic therapies. Recall-bias could play a role as the data that participants provided were not checked with their prescription data. Our inter-country data show some interesting differences between countries. These results need to be interpreted carefully though as more participants per country are needed for reliable inter-country analyses and calculations on statistically significant differences.

Future work

The results from this study provide evidence that next to (on-label) ciclosporin, phototherapies and off-label systemic therapies are chosen by dermatologists as first choice of treatment for moderate-to-severe AE patients. This is yet another reason to refine the guidance provided to dermatologists treating adult AE patients. Large, well-designed prospective patient cohorts (for real-life data) or (living) network meta-analyses[25] might provide the data that are needed, and might provide guidance on the treatment of e.g. subgroups. The TREAT Registry Taskforce[26] has developed a core dataset which can aid in gathering comparable data[27,28] and which is used in many national research registries already. (https://treat-registry-taskforce.org/)

As a next step, it might be interesting to compare the results of this study with insurance company data. Also, as the treatment of AE will very likely change with the further introduction of new developments - even more in the (near) future as our understanding of the molecular basis of AE is advancing and phenotypes

and biomarkers that characterize these phenotypes are being unravelled more and more[29] – it might be very interesting to re-evaluate the prescribing practices in moderate-to-severe AE in the future and see how these changes have influenced patient care.

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Supplementary material

Table S1 – Reasons for prescribing photo(chemo)therapy

Reasons FOR photo(chemo)therapy	N (%)
Sufficient short term (<3 months) efficacy	77 (39.7)
Sufficient medium term (>3 months) efficacy	103 (53.1)
Sufficient long term (>12 months) efficacy	28 (14.4)
Low potential acute side effect profile	102 (52.6)
Low potential long-term side effect profile	95 (49.0)
My knowledge of the evidence base for treatment efficacy including support by RCTs	62 (32.0)
My knowledge of national/international guidelines	75 (38.7)
My knowledge of expert opinion disseminated through lectures/clinical meetings	40 (20.6)
My own clinical experience	114 (58.8)
Costs	53 (27.3)
Comorbidities	75 (38.7)
Other	5 (2.6)

* Participants were able to select multiple reasons. N=194

Table S2 – Reasons against prescribing photo(chemo)therapy

Reasons AGAINST photo(chemo)therapy	**N (%)**
Insufficient effect in previous patients	7 (20.0)
Insufficient short-term (<3 months) efficacy	3 (8.6)
Insufficient medium-term (>3 months) efficacy	4 (11.4)
Insufficient long-term (> 12 months) efficacy	8 (22.9)
High potential acute side-effect profile	7 (20.0)
High potential long-term side-effect profile	5 (14.3)
Relative contraindication due to previous UV therapy (cumulative dose)	5 (14.3)
Lack of guidelines	4 (11.4)
Lack of evidence base for treatment efficacy	5 (14.3)
Lack of personal experience	9 (25.7)
Colleague(s) with more experience in the use of photo(chemo)therapy	11 (31.4)
Patient preferences	10 (28.6)
Logistics (not available in centre)	16 (45.7)
Costs	3 (8.6)
Other	2 (5.7)

* Participants were able to select multiple reasons. N=35

Table S3 – Reasons for prescribing systemic therapy

Reasons FOR systemic therapy	**N (%)**
Sufficient short term (<3 months) efficacy	87 (39.9)
Sufficient medium term (>3 months) efficacy	118 (54.1)
Sufficient long term (>12 months) efficacy	103 (47.2)
Low potential acute side effect profile	112 (51.4)
Low potential long-term side effect profile	123 (56.4)
Baseline tests and co-morbidities	128 (58.7)
My knowledge of the evidence base for treatment efficacy including support by RCTs	107 (49.1)
My knowledge of national/international guidelines	115 (52.8)
My knowledge of expert opinion disseminated through lectures/clinical meetings	84 (38.5)
My own clinical experience	140 (64.2)
Costs	57 (26.1)
Comorbidities	98 (45.0)
Other	0 (0.0)

* Participants were able to select multiple reasons. N= 218

Table S4 – Reasons against prescribing systemic therapy

Reasons AGAINST systemic therapy	**N (%)**
Insufficient effect in previous patients	0 (0.0)
Insufficient short-term (<3 months) efficacy	0 (0.0)
Insufficient medium-term (>3 months) efficacy	0 (0.0)
Insufficient long-term (> 12 months) efficacy	0 (0.0)
High potential acute side-effect profile	6 (54.4)
High potential long-term side-effect profile	4 (36.4)
Suspected risk of long-term organ toxicity	5 (45.5)
Necessity for blood monitoring	2 (18.2)
Lack of prescribing indication (due to off-label use)	2 (18.2)
Lack of guidelines	4 (36.4)
Lack of evidence base for treatment efficacy	1 (9.1)
Lack of personal experience	4 (36.4)
Colleague(s) with more experience in the use of systemic agents	3 (27.3)
Costs	4 (36.3)
Comorbidities	5 (45.5)
Patient preferences	5 (45.5)
Logistics (not available in centre)	2 (18.2)
Other	0 (0.0)

* Participants were able to select multiple reasons. N=11

Table S5 – Reasons for prescribing specific systemic therapies

Reasons FOR prescribing, N (%)	Ciclosporin	Azathioprine	Methotrexate	Mycophenolate acid	Oral corticosteroids
Sufficient short term (<3 months) efficacy	130 (64.7)	26 (19.3)	37 (18.6)	16 (18.8)	152 (82.6)
Sufficient medium term (>3 months) efficacy	88 (43.8)	79 (58.5)	109 (54.8)	47 (55.3)	12 (6.5)
Sufficient long term (>12 months) efficacy	39 (19.4)	73 (54.1)	122 (61.3)	45 (52.9)	12 (6.5)
Low potential acute side effect profile	60 (29.9)	46 (34.1)	87 (43.7)	32 (37.6)	64 (34.8)
Low potential long-term side effect profile	23 (11.4)	33 (24.4)	87 (43.7)	33 (38.8)	17 (9.2)
Baseline tests and co-morbidities	64 (31.8)	45 (33.3)	71 (35.7)	21 (24.7)	40 (21.7)
My knowledge of the evidence base for treatment efficacy including support by RCTs	99 (49.3)	54 (40.0)	78 (39.2)	33 (38.8)	42 (22.8)
My knowledge of national/international guidelines	98 (48.8)	56 (41.5)	88 (44.2)	37 (43.5)	59 (32.1)
My knowledge of expert opinion disseminated through lectures/clinical meetings	55 (27.4)	44 (32.6)	72 (36.2)	35 (41.2)	39 (21.2)
My own clinical experience	116 (57.7)	73 (54.1)	134 (67.3)	45 (52.9)	121 (65.8)
Costs	24 (11.9)	21 (15.6)	66 (33.2)	7 (8.2)	46 (25.0)
Comorbidities	23 (11.4)	26 (19.3)	41 (20.6)	20 (23.5)	27 (14.7)
Other	3 (1.5)	4 (3.0)	2 (1.0)	2 (2.4)	4 (2.2)

* Participants were able to select multiple reasons. Ciclosporin N=201; azathioprine N=135; methotrexate N=199, mycophenolate acid N=85, oral corticosteroid

Table S6 – Reasons against prescribing specific systemic therapies

Reasons AGAINST prescribing, N (%)	Ciclosporin	Azathioprine	Methotrexate	Mycophenolate acid	Oral corticosteroids
Insufficient effect in previous patients	1 (5.9)	9 (10.8)	4 (21.1)	16 (12.0)	3 (8.8)
Insufficient short-term (<3 months) efficacy	1 (5.9)	1 (1.2)	3 (15.8)	3 (2.3)	4 (11.8)
Insufficient medium-term (>3 months) efficacy	0 (0.0)	1 (1.2)	0 (0.0)	3 (2.3)	11 (32.4)
Insufficient long-term (> 12 months) efficacy	1 (5.9)	1 (1.2)	0 (0.0)	3 (2.3)	12 (35.3)
High potential acute side-effect profile	5 (29.4)	18 (21.7)	3 (15.8)	5 (3.8)	18 (52.9)
High potential long-term side-effect profile	2 (11.8)	18 (21.7)	4 (21.1)	8 (6.0)	27 (79.4)
Suspected risk of long-term organ toxicity	4 (23.5)	15 (18.1)	3 (15.8)	4 (3.0)	9 (26.5)
Necessity for blood monitoring	2 (11.8)	6 (7.2)	2 (10.5)	1 (0.8)	2 (5.9)
Lack of prescribing indication (due to off-label use)	3 (17.6)	19 (22.9)	3 (15.8)	24 (18.0)	2 (5.9)
Lack of guidelines	2 (11.8)	15 (18.1)	2 (10.5)	16 (12.0)	7 (20.6)
Lack of evidence base for treatment efficacy	2 (11.8)	15 (18.1)	4 (21.1)	16 (12.0)	12 (35.3)
Lack of personal experience	7 (41.2)	50 (60.2)	6 (31.6)	78 (58.6)	2 (5.9)
Colleague(s) with more experience in the use of systemic agents	2 (11.8)	9 (10.8)	2 (10.5)	13 (9.8)	1 (2.9)
Costs	2 (11.8)	0 (0.0)	0 (0.0)	13 (9.8)	0 (0.0)
Comorbidities	1 (5.9)	4 (4.8)	0 (0.0)	0 (0.0)	11 (32.4)
Patient preferences	2 (11.8)	6 (7.2)	3 (15.8)	8 (6.0)	0 (0.0)
Logistics (not available in centre)	6 (35.3)	3 (3.6)	2 (10.5)	25 (18.8)	0 (0.0)
Other	5 (29.4)	8 (9.6)	1 (5.3)	14 (10.5)	5 (14.7)

* Participants were able to select multiple reasons. Ciclosporin N=17; azathioprine N=83; methotrexate N=19; mycophenolate acid N=133, oral corticosteroids N=34.

Table S7 – National societies that received an invitation for the TREAT survey

Country	Society
Austria	Austrian Society for Dermatology and Venereology
Belarus	Belarusian Society of Dermatovenereologists and Cosmetologists
Belgium	"Belgian Society of Dermatology & Venereology"
Bulgaria	Bulgarian Dermatological Society
Croatia	Croatian Dermatovenerological Society of the Croatian
Cyprus	Cyprus Society of Dermatology and Venerology
Czech Republic	Czech Dermatovenereology Society
Denmark	Dansk Dermatologisk Selskab (Danish Dermatological Society)
Estonia	Estonian Society for Dermatovenereologists
Finland	Finnish Society of Dermatology (Suomen Ihotautilääkäriyhdistys)
France	French Society of Dermatology
	Société Francophone de Recherche Dermatologique
Georgia	Georgian Association of Dermatology and Venereology
Germany	German Dermatological Society
Greece	"The Hellenic Society of Dermatology & Venereology"
Hungary	Hungarian Dermatological Society
Iceland	Icelandic Dermatological Society
Ireland	Irish Association of Dermatologists
Italy	Association of Italian Clinical Dermatologists
	Association of the Italian Women Dermatologists
	Italian Association of Hospital Dermatologists
	The Italian Society of Medical, Surgical, Aesthetic Dermatology and Sexually Transmitted Diseases
Latvia	Association of Dermato-Venerologists of Latvia
Lithuania	Lithuanian Association of Dermatovenereologists
Malta	"Maltese Association of Dermatology & Venereology"
Macedonia	Macedonian dermatovenerologic society
Netherlands	NVDV Dutch Society of Dermatology and Venerology
Norway	Norwegian Society of Dermatology and Venereology (NSDV)
Poland	Polish Dermatological Society
Portugal	Portuguese Society of Dermatology and Venereology
Romania	Romanian Society of Dermatology
Russia	Russian Society of Dermatovenerologists and Cosmetologists
Serbia	Serbian Association of Dermatovenereologists
Slovakia	Slovak Dermatovenereological Society
Slovenia	Slovenian Society of Dermatology and Venereology
Spain	Spanish Academy of Dermatology and Venereology
Sweden	Swedish Society for Dermatology and Venereology
Switzerland	"Swiss Society of Dermatology & Venerology"
Turkey	Society of Dermatovenereology (Turkey)
	Turkish Society of Dermatology
Other	Nordic Dermatology Association (Norway, Finland, Iceland, Sweden, Denmark)

Table S8a – Prescription pattern of workplace and ciclosporin

	First line	Second line	Third line	Rarely	Never
Community	100% (1)	0% (0)	0% (0)	0% (0)	0% (0)
General hospital	55% (18)	18% (6)	9% (3)	9% (3)	9% (3)
Private practice	57% (23)	20% (8)	5% (2)	5% (2)	12% (5)
University teaching hospital	53% (76)	24% (35)	16% (23)	5% (7)	2% (3)

N=201

Table S8b – Prescription pattern of workplace and azathioprine

	First line	Second line	Third line	Rarely	Never
Community	0% (0)	100% (1)	0% (0)	0% (0)	0% (0)
General hospital	3% (1)	33% (11)	33% (11)	24% (8)	6% (2)
Private practice	2% (1)	20% (8)	28% (11)	22% (9)	28% (11)
University teaching hospital	7% (10)	33% (47)	31% (45)	17% (25)	12% (17)

N=135

Table S8c – Prescription pattern of workplace and methotrexate

	First line	Second line	Third line	Rarely	Never
Community	100% (1)	0% (0)	0% (0)	0% (0)	0% (0)
General hospital	18% (6)	42% (14)	24% (8)	12% (4)	3% (1)
Private practice	15% (6)	40% (16)	12% (5)	20% (8)	12% (5)
University teaching hospital	38% (54)	41% (59)	15% (21)	4% (6)	3% (4)

N=199

Table S8d – Prescription pattern of workplace and mycophenolate acid

	First line	Second line	Third line	Rarely	Never
Community	100% (1)	0% (0)	0% (0)	0% (0)	0% (0)
General hospital	0% (0)	9% (3)	12% (4)	39% (13)	39% (13)
Private practice	0% (0)	10% (4)	8% (3)	18% (7)	65% (26)
University teaching hospital	2% (3)	15% (22)	28% (41)	28% (40)	26% (38)

N=85

Table S8e – Prescription pattern of workplace and oral corticosteroids

	First line	Second line	Third line	Rarely	Never
Community	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)
General hospital	39% (13)	15% (5)	12% (4)	30% (10)	3% (1)
Private practice	40% (16)	12% (5)	10% (4)	28% (11)	10% (4)
University teaching hospital	29% (42)	13% (19)	6% (9)	36% (52)	15% (22)

N=184

Table S9 – First line systemic therapy per country

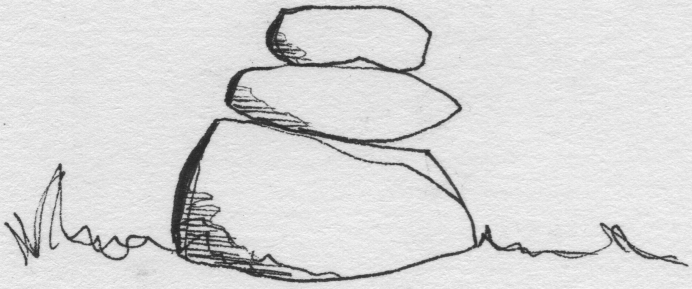
Country (Number of participants)	Ciclosporin N (%)	Azathioprine N (%)	Methotrexate N (%)	Mycophenolate acid N (%)	Oral corticosteroids N (%)
Denmark (17)	2 (11.8)	2 (11.8)	15 (88.2)	0 (0)	1 (5.9)
France (18)	8 (44.4)	0 (0)	9 (50.0)	0 (0)	0 (0)
Germany (16)	11 (68.8)	1 (6.3)	0 (0)	0 (0)	4 (25.0)
Ireland (11)	3 (27.3)	0 (0)	10 (90.9)	0 (0)	4 (36.4)
Italy (17)	12 (70.6)	0 (0)	0 (0)	0 (0)	8 (47.1)
The Netherlands (32)	22 (86.8)	1 (3.1)	10 (31.3)	3 (9.4)	13 (40.6)
Portugal (12)	8 (66.7)	3 (25.0)	3 (25.0)	0 (0)	3 (25.0)
Spain (23)	15 (65.2)	2 (8.7)	3 (13.0)	0 (0)	13 (56.5)

Table S10 – Second line systemic therapy per country

Country (Number of participants)	Ciclosporin N (%)	Azathioprine N (%)	Methotrexate N (%)	Mycophenolate acid N (%)	Oral corticosteroids N (%)
	N (%)	N (%)	N (%)		
Denmark (17)	2 (11.8)	13 (76.5)	2 (11.8)	1 (5.9)	1 (5.9)
France (18)	6 (33.3)	2 (11.1)	7 (38.9)	2 (11.1)	1 (5.6)
Germany (16)	3 (18.8)	2 (12.5)	5 (31.3)	1 (6.3)	0 (0)
Ireland (11)	1 (9.1)	5 (45.5)	0 (0)	0 (0)	0 (0)
Italy (17)	5 (29.4)	4 (23.5)	9 (52.9)	2 (11.8)	4 (23.5)
The Netherlands (32)	7 (21.9)	15 (46.9)	18 (56.3)	8 (25.0)	5 (15.6)
Portugal (12)	4 (33.3)	2 (16.7)	5 (41.7)	1 (8.3)	2 (16.7)
Spain (23)	5 (21.7)	6 (26.1)	14 (60.9)	4 (17.4)	2 (8.7)

Table S11 – Third line systemic therapy per country

Country (Number of participants)	Ciclosporin N (%)	Azathioprine N (%)	Methotrexate N (%)	Mycophenolate acid N (%)	Oral corticosteroids N (%)
Denmark (17)	7 (41.2)	2 (11.8)	0 (0)	5 (29.4)	1 (5.9)
France (18)	1 (5.6)	7 (38.9)	0 (0)	3 (16.7)	0 (0)
Germany (16)	0 (0)	6 (37.5)	7 (43.8)	9 (56.3)	0 (0)
Ireland (11)	5 (45.5)	1 (9.1)	0 (0)	4 (36.4)	1 (9.1)
Italy (17)	0 (0)	7 (41.2)	3 (17.6)	4 (23.5)	1 (5.9)
The Netherlands (32)	2 (6.3)	9 (28.1)	3 (9.4)	8 (25.5)	3 (9.4)
Portugal (12)	0 (0)	3 (25.0)	4 (33.3)	2 (16.7)	3 (25.0)
Spain (23)	2 (8.7)	9 (39.1)	4 (17.4)	7 (30.4)	2 (8.7)



Chapter 4

Off-label use of methotrexate in dermatological practice – a systematic review with GRADE approach

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Summary (abstract)

A drug is prescribed 'off-label' when it is an authorized drug which is used in a way that is not described in the Summary of Product Characteristics. Methotrexate is one of the drugs often used for off-label dermatological indications, probably since it is effective, cheap and available worldwide. Off-label prescription is only legal when physicians justify the treatment through the available scientific knowledge at one's disposal.

Our objective is therefore to summarise evidence for the effectiveness, efficacy and safety of the off-label use of methotrexate in dermatology.

We searched MEDLINE, EMBASE and CENTRAL for studies (RCTs, cohort studies, case series and in grey literature) concerning evidence for the effectiveness, efficacy and safety of the off-label treatment of methotrexate in dermatological indications up to November 2019. We used the rating system GRADE (Grading of Recommendations Assessment, Development and Evaluation, which rates outcomes instead of studies) to assess the quality of the evidence. The search retrieved 34.583 hits of which 3566 were selected after title and abstract screening. After full text screening 143 studies were included concerning 3688 patients. We found evidence for the effectiveness, efficacy and safety of the off-label use of methotrexate in 31 dermatological diseases. According to GRADE, most evidence was of low quality. Four monitored outcomes in atopic dermatitis, systemic lupus erythematosus, systemic sclerosis and morphea were of moderate quality. To optimize the quality of the current available evidence, we need high quality studies in which well-characterized patients are treated with standardized treatments regimens using patients and physician relevant well validated outcomes ideally core outcome sets.

Introduction

The use of off-label prescriptions is common in dermatology and varies from 14 to 73% of cases.[1–3] When a drug is prescribed 'off-label' it is an authorized drug (by e.g. the European Medicines Agency or the U.S. Food And Drug Administration) which is used in a way that is not described in the Summary of Product Characteristics (which includes the agreed terms of use of a certain product e.g. indication, dosage and frequency).[4] Examples of frequently off-label prescribed drugs in dermatology are azathioprine and dapsone.[5,6] The common prescription of off-label therapies in dermatology may be due to the time needed for market approval for an indication and the fact that over 3000 different skin diseases exist.[1] Also, the high costs for designing a new drug and the considerable time needed for the approval of a drug may play a role (combined with the low revenue of an expiring patent).[3]

Methotrexate (MTX) is a drug that is regularly prescribed off-label in dermatology. For example, a recent survey study showed that almost a third of all participating dermatologists preferred MTX as their first choice of therapy for atopic dermatitis (AD).[7] The usage of MTX has many advantages; it is widely available, the safety-profile is well known and it has low costs.[8,9] There is no European legislation available for the prescription of off-label drugs, this is delegated to the different member states.[10] Off-label prescription is legal in the Netherlands, as long as certain guidelines are followed;[11] physicians have to make sure that their patients and concerning pharmacists are aware of the fact that the drug is prescribed off-label. They should also be able to justify the off-label treatment through the available scientific knowledge and guidelines, and consider the risk-benefit balance for the patient and therapy as positive.[1,12]

In the past, three overviews of the off-label use of MTX in dermatology have been published. In 2012 and 2015, Shen et al. and Diani et al. respectively published a review[13,14] and in 2016 the British Association of Dermatologists published a guideline for the prescription of MTX in dermatology which also provided an overview of the available evidence in off-label MTX use in dermatology.[15] With this systematic review (SR) we aimed to provide a new, updated overview on the off-label use of MTX which might help dermatologists in their off-label prescription decision making. Where possible, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was applied.[16]

Participants and Methods

Inclusion and exclusion criteria

This systematic review was registered in Prospero (registration number: CRD42018081028).[17] All randomised controlled trials (RCTs), cohort studies and case series (with ≥ 5 patients) in which MTX was used off-label in a dermatological disease and in which the effectiveness, efficacy and/or safety was discussed, were included. If articles discussed information about off-label MTX use in a systemic disease, articles were only added if information on effectiveness/efficacy on dermatological abnormalities was also given. If patients had systemic disease, only the patients with cutaneous involvement were described. Many studies provided information on a combination of off-label MTX with other treatments. In this SR we decided to only add studies that combined corticosteroids (topical, oral, intramuscular, or intravenous) with MTX. Excluded were (systematic) reviews, duplicate publications, conference abstracts and questionnaire based surveys, articles of which the full-text was not available, articles in other languages than English, French, German or Dutch, articles in which on-label, topical or intralesional use of MTX or only side-effects of MTX were discussed, animal studies, and in-vitro studies.

Literature search

The MEDLINE and EMBASE databases were searched up to November 6, 2019. The CENTRAL database was searched up to November 13, 2019. In addition, the reference lists of the included articles were searched for eligible articles. Systematic reviews were used as second check for the literature search done by the authors. The complete search strategy can be found in Fig. 1.

Figure 1 – Search strategy for MEDLINE, EMBASE and CENTRAL

Search no.	Term(s)
1	derm*:jt
2	methotrexate
3	methotrexate:ti OR amethopterin:ti OR mexate:ti
4	methotrexate:ab OR amethopterin:ab OR mexate:ab
5	#2 OR #3 OR #4
6	#1 AND #5
7	'skin disease'/exp
8	#5 AND #7
9	#6 OR #8
10	#9 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim) AND [humans]/lim AND [2016-2019]/py

Study selection and data-extraction

First, all search results were merged and duplicates were removed. The titles and/or abstracts were screened by two independent researchers. Of the selected articles, the full-text was retrieved and screened for eligibility by the same authors, taking the in- and exclusion criteria into account. Reasons for exclusions were documented.

Data-extraction was performed by two independent researchers and collected on digital predefined data-extraction forms. Data was collected on the publication date, study population (number, age, sex, type of dermatologic disease and previous therapies), study design (study type), concomitant medication, duration of treatment and follow-up, dosage of MTX, efficacy/effectiveness, including type of outcomes used, time to effect and duration of remission if available, and safety data. Both adverse events (AEs) and serious adverse events (SAEs) were collected. SAEs were defined as any untoward medical occurrence that required inpatient hospitalisation of prolonging of existing hospitalization, was life threatening, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was reported in the study as such or that resulted in death. Whenever possible, data were reported with a mean and a range. For outcome measurements, changes in mean from baseline to end of treatment were reported.

For all different stages, discrepancies were resolved by discussion and, if needed, a third researcher (PS) was consulted.

Data-analysis – GRADE approach

For the evaluation of the quality of evidence GRADE was used. Further, all criteria for applying or using GRADE were followed.[18] The quality of an outcome can fall in four categories; very low, low, moderate or high.[19] As the outcomes from the case series and cohort studies in all included studies were very likely graded as very low, GRADE evidence profiles were only made for RCTs. Risk ratio's and absolute risk differences used in GRADE evidence profiles were calculated with Reverence Manager (RevMan). To guarantee quality of the reporting of this SR, the PRISMA statement was followed.[20]

Results

Study selection and data-extraction

Figure 2 – Flowchart summarizing the selection process for studies concerning off-label treatment with methotrexate in dermatological diseases.

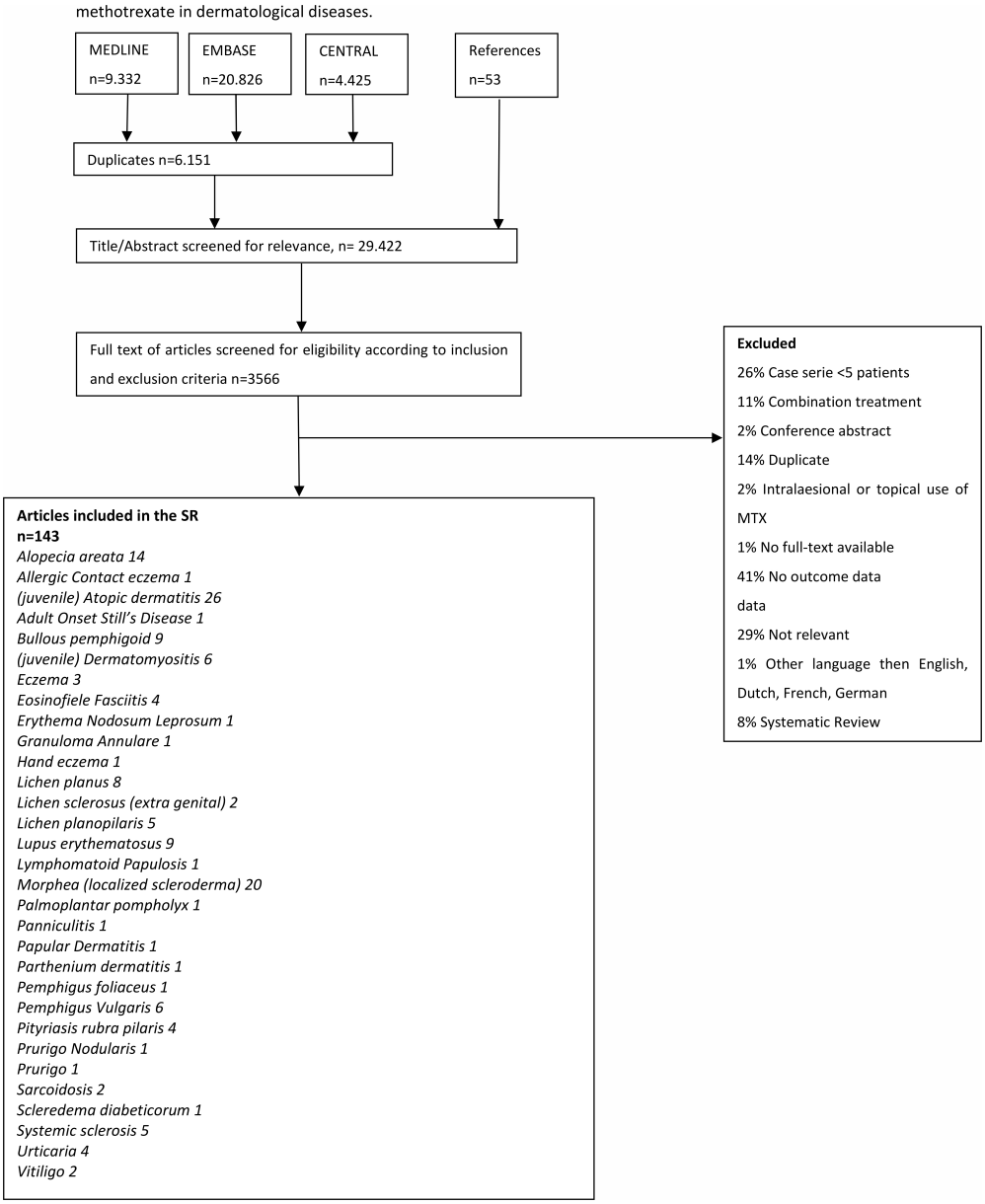

Fig. 2 summarizes the selection process. The literature search identified 34.583 hits of which 6151 were duplicates. After screening based on title/abstract 3566 studies were selected. Articles were mainly excluded due to lack of relevance (e.g. MTX in a non-skin disease). After full text screening, 143 articles were included, of which 14 RCTs, 29 cohort studies and 100 case series. In total around – some studies did not state exact how many patients they included[21] – 3688 patients with 31 different dermatologic diseases were included.

Data-extraction

Below the results per disease are given. Only the most remarkable findings were described. In Table 1 and corresponding abbreviation list in the supplemental material, an overview of all available extracted study characteristics can be found. Unknown values are reported as 'Unk', ranges of age, treatment duration, maximal duration, maximal dose, mean duration of remission together with male/female ratio are left empty when not reported to compress the tables format.

Concomitant medication was used in almost all studies, in 22 articles this concomitant use was not reported. In 40 of the 143 studies corticosteroids were used in combination with MTX. Prednisone was the concomitant medication most frequently prescribed (n=39). In twelve studies the usage of systemic corticosteroids in general without specification of systemic or topical use was described. Four studies reported the corticosteroid sparing effect of MTX as an outcome.[22–25] The concomitant use of folic acid, was mentioned in 47 studies, the dosage varied from 1 –5 mg daily[26–41] to 5-25 mg weekly[42–48]. Dosages or frequencies were often not described.[49–72] The maximum reported treatment duration was 132 months[30], but most study patients were treated for a mean duration of less than 24 months. The used dosage of MTX ranged from 0.2 mg/kg daily till 37.5 mg weekly. In children MTX was prescribed mostly in mg /kg[56] or mg/m^2.[73] The outcome measures that were used were very heterogeneous; primary outcome measures can be found in Table 2. The time to effect and mean duration of disease remission was regularly absent but ranged from 1-104 weeks and from 2.5 to 121 months, respectively. Details of the reported AEs and SAEs can be found in Table 2, in 21 studies AEs and in 61 studies SAEs were not mentioned. The absence of the reported AEs and SAEs in some studies may contribute to the lack of evidence regarding safety on off-label use of MTX in different dermatologic diseases.

Data-analysis – GRADE approach

The quality of the evidence of the RCTs can be found in the GRADE evidence profiles, Table S1 till S12.

Table 1 – Characteristics of included studies

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Chartaux	AA	[74] (2010)	Retrospective CS	MTX	Unk [6->24]	30
Alkeraye	AA	[75] (2017)	Prospective CS	Pred + MTX (14) Pred (6)	≥ 6	≥ 6
Anuset	AA	[76] (2016)	Retrospective CS	MTX	Unk	33 [6-81]
Chong	AA	[77] (2017)	CS	MTX	Unk	Unk
Droitcourt	AA	[59] (2012)	Retrospective CS	MTX	19 [3-30] (median)	8 [7-20]
Firooz	AA	[78] (2013)	Retrospective CS	MTX	Unk	14.4 [4-32]
Hammerschmidt	AA	[79] (2014)	Retrospective Co	MTX	Unk	13 [3-51]
Joly	AA	[80] (2006)	Retrospective CS	Pred+MTX (16) MTX (6)	Unk [9-27]	15
Landis	AA	[81] (2017)	Retrospective CS	MTX	Unk [1.5-Unk]	Unk
Lim	AA	[67] (2017)	Retrospective Co	MTX	7.025	Unk [12-20]
Lucas	AA	[58] (2016)	Retrospective CS	MTX	Unk [32.4 - 37.32]	Unk [2-72]
Royer	AA	[82] (2011)	Retrospective CS	MTX	14.2 (1-31)	Unk
Thi Van	AA	[83] (2019)	Prospective Co	MTX	4	6
Vano-Galvan	AA	[84] (2017)	Retrospective CS	MTX (10) MTX+Pred (5)	Unk	Unk
Anderson	AD	[85] (2019)	Retrospective CS	MTX	15.3	Unk
Baum	AD	[86] (2019)	Retrospective Co	MTX	Unk	Unk
Delcasso	AD	[87] (2018)	Retrospective Co	MTX	21	Unk
Deo	AD	[61] (2014)	Retrospective CS	MTX	9.5 [2–38]	Unk
Dvorakova*	AD	[88] (2017)	Retrospective CS	MTX	17.2 [5-33]	Unk [Unk-14]
El-Khalawany	AD	[63] (2013)	Randomized head to head trial	MTX (20) CSA (20)	3 [Unk]	3 [Unk]
Gerbens†	AD	[89] (2018)	Open-label observational follow-up study	MTX (17) AZA (18)	Unk [Unk-60]	Unk
Goujon	AD	[90] (2006)	Retrospective CS	MTX	Unk [1-30]	Unk
Goujon	AD	[28] (2017)	RCT	MTX (50) CSA (97)	6	Unk

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
33 (9/24)	Unk	PUVA (19), OCS (10), CST bolus (5)	Unk [15-25 mg]
14	Unk [21-72]	Pred 500 mg/d; 3 d/mo for 3 mo (14)	Unk [10-20 mg]
26 (8/18)	Unk	TCS (18), ICS (16), MNX (15), PT (14), DPCP (11), other (11)	Unk [15-20 mg]
14	Unk	TA (14)	0.2 mg/kg/d
20 (8/12)	33 [14-57] (median)	TCS (13), MNX (14), T TAC (1), PT (4), Pred (1)	Unk [12.5-25 mg]
10 (2/8)	29.6	Artifical hair transplant (1), AZA (2), clobetasol under occlusion (3), CST injection (1), DPCP (5), DTN (1), herbal medicine (1), levamisole (1), MNX (9), PUVA (2), Sul (2), T dinitrochlorobenzene (5), zinc (4)	Unk [5 mg/wk-37.5 mg/d]
31 (11/20)	40 [15-72]	T sensitizers (18), SCS (16)	Unk [10 -25 mg]
22 (7/15)	37.6	IV CS (4), Or CS (9), PUVA (22), TAC (3),TCS (22)	Unk [15-30 mg]
14 (4/10)	Unk [3-17]	Anthralin, excimer laser, IL or IM CST TCS, MNX, PT, Squaric Acid, Sul (No. Unk)	Unk [2.5-15 mg]
29 (16/13)	40.31 [16-65]	DPCP (2), Cry (8), CSTA (3), MPP (7), SCS (9), Sul (1), TCA sc (29), TCST (29), UVB (13)	14.5 mg [10-Unk]
5 (2/3)	Unk, ped	SCS, TCS (No. Unk)	Unk [17.5-25 mg]
14 (6/8)	14.7. (8-18)	Isoprinosine, oral CST, PT, UVA (No. Unk)	18.9 mg [15-25]
38 (31/7)	29.6	Unk	7.5 mg
15	Unk	Unk	Unk [15-25 mg]
55 (25/30)	10.6 [3.0-19.5]	AZA (3), CSA (6), MPA (3), MTX (5), UVB (21)	Unk [0.37 - 0.45 (oral)/ - 0.37 - 0.5 (sc) mg/kg] (1)
19	Unk	Unk	Unk
20 (8/12)	39	PT and/or CSA (15)	Unk; initial mean dose 21 mg
31 (14/17)	Unk	TA (31), PT (15), OCS (9), Or A (14), other (1)	0-5 Y: 7.5 mg 6-14 Y: 10 mg 15-18 Y: 15 mg (all median)
47 (32/15)	Unk	AB (18), AZA (8), CSA (8), NB-UVB PT (4), IVIG (1), SCS (16)	3.4 mg/kg
20 (12/8)	MTX: 11.2 [8-14]	TA (40), PT (Unk)	MTX: 7.5 mg/wk [Unk]
17 (10/7)	43.3	AZA (1), CSA (1)	Unk [10-22.5 mg]
20 (10/10)	26.3 [17-68]	Em (Unk), TCI (Unk), TCS (Unk)	Unk [7.5-25 mg]
50 (28/22)	32	TCS or TCI (50)	Unk [15 - 25 mg]

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Hegazy	AD	[91] (2017)	Retrospective Co	MTX	6	Unk
Ho	AD	[21] (2018)	Retrospective CS	MTX	Unk	>18
Knöpfel	AD	[56] (2018)	Retrospective CS	MTX	12.6	Unk
Lyakhovitsky	AD	[54] (2010)	Retrospective CS	MTX	Unk [2-3]	Unk [2-24]
Mittal	AD	[92] (2011)	CS	MTX	Unk [12-Unk]	Unk
Politiek	AD	[93] (2016)	Retrospective CS	MTX	7.4	Unk [Unk-2]
Purvis	AD	[51] (2019)	Retrospective CS	MTX	17 (median)	29
Rahman	AD	[94] (2014)	Retrospective CS	MTX	12	Unk
Roekevisch†	AD	[42] (2018)	Open-label observational follow-up study	AZA (18) MTX (17)	Unk [Unk-24]	Unk
Schram	AD	[43] (2011)	RCT	AZA (22) MTX (20)	3	3
Shah	AD	[30] (2018)	Retrospective Co	MTX	36.8 [1-132]	Unk
Syed	AD	[95] (2009)	Prospective CS	Placebo (30) MTX (30)	3	Unk
Taieb	AD	[96] (2019)	Retrospective CS	MTX	14 (median)	25 (median)
Vedie	AD	[97] (2016)	Retrospective co	MTX	20.4 - 27.9	57.8
Weatherhead	AD	[98] (2007)	Prospective CS	MTX	6	3
Zoller	AD	[69] (2008)	Retrospective CS	MTX	Mrz 28	Unk
Roberts	AD, NE	[45] (2010)	Retrospective CS	MTX	10.5 [3-30]	9 [1-22]
Patel	All CE	[99] (2018)	Retrospective Co	MTX	Unk [3.2-53.1]	Unk
Kalyoncu	AO SD	[100] (2016)	Retrospective Co	CS+MTX (117) CS+HCQ+MTX (85)	Unk	Unk
Bakker	BP	[47] (2013)	Retrospective CS	MTX	4	26.4 [3-96]
Bara	BP	[101] (2003)	CS	MTX	Unk	11.4 [4-23]
Dereure	BP	[102] (2002)	Prospective CS	MTX	Unk [2-Unk]	Unk [6 - Unk]
Du-Thanh	BP	[103] (2011)	Retrospective CS	MTX	8.48 [1-18]	Unk
Heilborn	BP	[62] (1999)	Prospective CS	MTX	Unk [3-24]	24
Kjellman	BP	[104] (2008)	Retrospective CS	MTX (61) MTX+pred (37)	Unk	26 (median) [0.5-77]
Kremer	BP	[105] (2017)	Retrospective CS	MTX	Unk	Unk
Kwatra	BP	[35] (2013)	Retrospective CS	MTX	25.3	Unk [20.4-66]
Paul	BP	[106] (1994)	Retrospective CS	MTX	Unk [10-39]	Unk [10-44]
Click	DM	[107] (2013)	Retrospective CS	MTX	Unk [4-Unk]	Unk

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
37	Unk	Unk	Unk [15-20 mg]
>300	Unk	Unk	15 mg
28 (24/4)	7.8 [2-18]	AZA (1), CSA (6), Or AB (Unk), Or CS (21), TCS (28), T AB (Unk)	Unk [0.2 - 0.5 mg/kg]
20 (12/8)	51.8 [20-85]	AH, CSA (3), PT (11), SCS (15), TCS	Unk [10-25 mg]
15 (10/5)	Unk [30-60]	Unk	Unk [10-15 mg]
89 (53/36)	50.7	Or immunosuppresive drugs (62)	13.6 mg [5-25]
43 (21/22)	Unk [2-16]	CSA (2), PT (2), Pred (1), Systemic treatment (5)	0.3 mg/kg (median)
30	8 [2-17] (median)	TA (30)	0.5 mg/kg [Unk-15]
17 (10/7)	43.3	Unk	14.5 mg [10-22.5]
20 (10/10)	43	CSA (Unk)	17.5 - 20 mg (week 12 and week 24)
41 (22/19)	45 [19-90]	AB (3), AZA (7), CSA (5), IM CS (12), MMF (1), MTX (3), OCS (17), other (1), PT (11)	Unk [7.5-25 mg]
30	Unk	Unk	0.1 mg/kg [5-7.5]
26 (13/13)	12 (median)	CS (12), other systemic immunosuppressive (4), PT (23)	Unk [0.3-0.6 mg/kg]
35	Unk	AZA, TCS (No.Unk)	Unk [15-20 mg]
12 (7/5)	37	TCS (12)	Unk [5-22.5 mg]
9 (6/3)	75 [52-85]	CSA (Unk), PT (Unk), SCS (Unk), TCI (Unk), TCS (9)	Unk [5-20 mg]
25	7 (3-16)	MTX (90)	Unk [5-15 mg]
32	Unk	Unk	Unk [Unk-30 mg]
Unk	Unk	Unk	Unk
6 (Unk)	Unk	Unk	Unk [5-15 mg]
16 (7/9)	84.6	Unk	Unk [10-15mg]
18 (7/11)	77.8	Potent TCS 2-3 wks (18)	Unk [7.5-12.5 mg]
70 (30/40)	82.7 [50-97]	Unk	9.8 mg
11 (4/7)	81 [73-91]	TCS (Unk)	Unk [5-12.5 mg]
98 (39/59)	Unk	Unk	Unk [2.5-17.5 mg]
6	Unk	CS (Unk)	Unk
16 (8/8)	71.4 [30-94]	Unk	Unk [2.5-15 mg]
8 (4/4)	73.5 (63-87)	AB (3), TCS (3), SCS (8)	Unk [5-20 mg]
8 (0/8)	39 [25-60]	IVIG (1), MPA (2), HCQ (6), AZA (1)	Unk [15-25 mg]

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Hornung	DM	[27] (2012)	Retrospective CS	MTX	Unk [2-3]	Unk
Kasteler	DM	[25] (1997)	Retrospective CS	MTX	Unk [3-22]	Unk
Ramanan	DM	[73] (2005)	Retrospective Co	MTX	45.5 (median)	48
Ruperto	DM	[108] (2016)	RCT	Pred (47) Pred+CSA (46) Pred+MTX (46)	Unk	35.5 (median)
Zieglschmid	DM	[109] (1995)	Retrospective CS	MTX	1.8-68.5	Unk
Chen	E	[110]8 (2016)	Co	MTX	22 [2-93]	Unk
Shaffrali	E	[111] (2003)	Retrospective CS	MTX	Unk [3-18]	Unk
Tétart	E	[48] (2011)	Retrospective CS	MTX	2.6	12
Berianu	EF	[112] (2015)	Retrospective CS	MTX	31.4 [12-84]	Unk [12-36]
Lebeaux	EF	[113] (2012)	Retrospective CS	MTX	24.7 [5-93]	Unk
Mertens	EF	[44] (2016)	Prospective Co	MTX	5	Unk
Kroft	EF/M/SS	[70] (2009)	Retrospective Co	MTX (47) MTX+CS (11)	Unk [10-16]	Unk
Hossain	ENL	[114] (2013)	Prospective CS	MTX	Unk [24-30]	24
Naka	GA	[52] (2018)	Retrospective Co	MTX	Unk [Unk-60]	Unk [Unk-72]
Politiek	HE	[115] (2016)	Retrospective Co	MTX	4.6	Unk [Unk-2]
Arfi	LE	[116] (1995)	CS	MTX	Unk [1-24]	Unk
Böhm	LE	[32] (1998)	Retrospective CS	MTX	Unk [1-12]	Unk
Böhm	LE	[117] (2003)	Retrospective CS	MTX	Unk [0.25-25]	27.9 [6-62]
Carneiro	LE	[118] (1999)	RCT	MTX (20) Placebo (21), 28 with skin involvement	6	Unk
Fruchter[§]	LE	[119] (2017)	Retrospective CS	MTX	Unk	58
Gansauge	LE	[53] (1997)	Prospective CS	MTX	6	Unk
Islam	LE	[120] (2012)	RCT	MTX (13) CQ (29)	6	6
Kan	LE	[121] (2016)	Retrospective Co	MTX	Unk	48
Wenzel	LE	[122] (2005)	Retrospective CS	MTX	25.6 [2-67]	Unk [Unk-24]
Chauhan	LP	[123] (2018)	Prospective CS	MTX (15) MTX + TCA (15)	Unk [$\leq$ 4]	Unk [$\leq$ 8]
Ilyas	LP	[38] (2016)	Prospective Co	MTX	3	3

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
11 (3/8)	61 [46-84]	SCS (11), AZA (4), MPA (1)	14.91 mg
13 (0/13)	48 [22-77]	AZA (1), Chlorambucil (1), CQ (7), HCQ (6), Pred (2), Quinacrine (2)	18.5 mg [2.5-30] (mean maximal dose)
31 (11/20)	8.4	Unk	15 mg/m^2
46 (16/30)	Unk	Pred (3)	15-20 mg/m^2
10 (1/9)	Unk [27-79]	Pred (8)	8 mg (mean initial) - 15.92 (max)
41 (27/14)	49 [18-83]	PT (14), CSA (30), MPA (9), AZA (7)	Unk [10-25 mg]
5 (2/3)	74.4 [67-83]	AZA, OCS, PT, TCS (No. Unk)	Unk [2.5-12.5 mg]
15 (11/4)	78	CSA (1), Pred (1), PT (5), TCS (15), TA (3)	9.7 mg
16 (8/8)	52 [30-75]	Pred (13), AZA (3), HCQ (2)	Unk
12	Unk	OCS (12)	Unk [15-30 mg]
12 (1/11)	Unk [37-69]	MTX (6), SCS (6)	288 mg/kg/month (median)
58 (18/40)	40 [13-67]	AB (7), antimalarials (5), AZA (1), Em (3), isotretinoin (3), penicillamine (5), PT (4), TCS (16), TCA lesional injection (1)	Unk [15-25 mg]
9 (7/2)	34 [23-52]	Clofazamine (9), Pred (9)	7.5 mg
11 (2/9)	60.7	Ada, AZA, dapson, kenalog injections, PT, SCS, TA, TCS, UVB (No. Unk)	Unk [12.5-15 mg]
42 (29/13)	53.2	Systemic treatment (7)	Unk [5-20 mg]
16	33 [16-48]	Unk	Unk [7.5-10 mg]
12 (6/6)	53 [28-86]	AZA (1), CQ (5), SCS (9), TCS (2)	Unk [10-25 mg]
22 (9/13)	46.5 [27-74]	Pred, antimalarials (No. Unk)	Unk [10-30 mg]
41 (2/39)	32.1	Antimalarial, immunosuppressive	Unk [15-20 mg]
27	Unk	HCQ sulfate (No. Unk), antimalarial (No. Unk)	16.6 mg
10	Unk	Antimalarials, Pred (No. Unk)	15 mg
13 (0/13)	24	Unk	10 mg
27	Unk	None	Unk
43 (13/30)	52 (19-86)	TA (43), antimalarials (31), AZA (6), dapsone (2), mmf (4)	Unk [7.5-20 mg]
30 (9/6, MTX), (8/7, MTX + TCA)	MTX: 46.33 [40-52] MTX + TCA: 45.53 [36-55]	Unk	Unk [Unk - 0.3 mg/kg]
55 (23/32)	37 [22-65]	Unk	15 mg

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Kanwar	LP	[37] (2013)	Prospective CS	MTX	Unk [Unk-24]	3
Lajevardi	LP	[124] (2016)	Prospective CS	MTX	3	3
Malekzad	LP	[31] (2012)	Prospective Co	MTX	Unk [8-Unk]	6
Torti	LP	[125] (2007)	Retrospective CS	MTX	Unk	27
Turan	LP	[126] (2009)	Retrospective CS	MTX	Unk [1-4]	6
Kortekangas-Savolainen	LP, vulvovaginal	[127] (2007)	Retrospective CS	MTX	Unk [6-36]	Unk [12-48]
Babahosseini	LPP	[128] (2019)	Retrospective CS	MTX	Unk	Unk
Bakhtiar	LPP	[129] (2018)	RCT	MTX (79) OCS (79)	2 [Unk]	Unk
Bulbul baskan	LPP	[130] (2017)	Retrospective CS	MTX (10) CSA (6)	Unk [3-6]	Unk
Kerkemeyer	LPP	[131] (2018)	Retrospective CS	MTX	Unk	Unk
Naeini	LPP	[132] (2017)	RCT	HCQ (14) MTX (15)	6	Unk
Karadag	LS	[133] (2018)	Prospective CS	MTX	12.6 [3-18]	10.6 [6-17]
Kreuter	LS	[134] (2009)	Retrospective CS	MTX	>6	4.7 [3-8]
Fernandez-de-Misa	LyP	[135] (2018)	Retrospective CS	MTX	Unk	52 [1-277] (median)
Bulur	M	[136] (2017)	Retrospective CS	MTX	Unk	5
Christen-Zaech	M	[34] (2008)	Retrospective CS	MTX	19.9 [3-52]	Unk
Cox	M	[60] (2008)	Retrospective CS	MTX (9) CSA (1)	23 [10-36]	Unk
Fitch	M	[66] (2006)	Retrospective CS	MTX	04. Jul	>6
Koch	M	[40] (2013)	Retrospective CS	MTX	19.6 [5.8-52.8]	55.2 [11.3 -162]
Kreuter	M	[137] (2005)	Prospective CS	MTX	9.8 [6-25]	>6
Li	M	[138] (2019)	Prospective Co	MTX mono (12) MTX with iv Cst (23) MTX with OCS (9)	12	Unk
Mertens	M	[64] (2016)	Retrospective Co	MTX	12.3 [1-65.3]	Unk
Mirsky	M	[139] (2012)	Retrospective Co	MTX	28.8	Unk [7.3-7.0]
Piram	M	[140] (2013)	Retrospective CS	MTX	24	Unk
Platsidaki	M	[49] (2017)	Retrospective CS	MTX	Unk [Unk-12]	21
Rattanakaemakorn	M	[68] (2017)	Retrospective CS	MTX	Unk [2-Unk]	Unk [7-33.6]

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
24 (8/16)	37.4 [9-63], 2 children [Unk]	Unk	Adults: 15 mg, children 0.35 mg/kg
18 (5/13)	53.8 [30-65]	MMF (4), SCS (11), TCI (3), TCS/IL CST (13)	15 mg
18 (8/10)	51.1 [22-80]	Unk	Unk [≤10 mg]
18	Unk	Unk	Unk [2.5-12.5 mg]
11 (3/8)	44.2 [27-55]	SCS (4), TCS (7)	Unk [15-20 mg]
5 (0/5)	57.6 [45-65]	Repeated vaginal dilatations (5), TAC (2), tetracycline (1), TCS (2)	7.5 mg
30	Unk	Unk	Unk
79 (47/32)	Unk	Unk	10 mg
10 (2/8)	Unk	Unk	Unk [10-15 mg]
7	Unk	Unk	Unk
15 (2/13)	44.9	Ac (2), CSA (4), isotretinoin (2), pioglitazone (1) SCS (8), TCS (15)	15 mg
6 (0/6)	53 [46-63]	Ac (2), Colchicine (3), TCS (6), UVA (2), NB UVB (1)	7.5 mg
7 (1/6)	67.6 [50-80]	Ac (1), NB-UVB PT (1), penicillin (3), T calcipotriene (1), TCS (7), UVA PT (3), PUVA (2)	15 mg
51	Unk	Unk	Unk [≤20 mg]
14	Unk	Colchicine, SCS, TCS (No. Unk)	Unk
39	9.8	Unk	Unk [0.3-0.5 mg/kg till 35 mg/wk]
9	7.4 [4-16]	D-penicillamine (2), CSA (2), SCS 30 mg/kg/d, 3 d/mo for 3 mo (10)	0.3 mg/kg
17 (6/11)	7.3	TCI (2), TCS (11), T vit D (11)	Unk [12.5-25 mg]
17 (9/8)	15.2 [4-25]	Unk	9.12 mg [2.5-15]
15 (6/9)	50.7 [18-73]	Penicillin (7), PUVA (6), SCS (4), TCS (3)	15 mg
44 (13/31)	12.6	Systemic treatment (7)	Unk [1 mg/kg, max 25 mg]
107 (30/77)	Unk	Unk	15 mg [5-26.9 mg]
90 (32/58)	10.2	MTX (90)	Unk [Unk-15 mg]
24	Unk	Unk	0,5 mg/kg
20 (3/17)	Unk	HCQ (3), penicilliamine (2), PUVA (20), SCS (20), TCI (20), TCS (20), vit D analogs (20)	15 mg
7 (3/4)	11.8	TCS (1)	Paediatric dose; Unk [2.5 mg-Unk], adult dose; Unk [10 mg-Unk]

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Seyger	M	[141] (1998)	Prospective CS	MTX	6	0
Shahidi	M	[41] (2018)	CS	MTX	18	Unk
Torok	M	[29] (2012)	Prospective Co	MTX	36	36.4
Uziel	M	[142] (2000)	Prospective CS	MTX	Unk [2-13]	Unk [8-30]
Weibel	M	[143] (2006)	Retrospective CS	MTX	Unk	35
Wlodek	M	[144] (2018)	Retrospective CS	MTX	Unk	Unk
Zulian	M	[50] (2011)	RCT	MTX (46) Placebo (24)	Unk [Unk-12]	40.3 [3-72]
Zulian‡	M	[55] (2012)	Prospective Co	MTX	27.5 [Unk - 72]	Unk
Torrelo	Pa	[145] (2017)	Retrospective CS	MTX	Unk [3-Unk]	Unk
Moustafa	PD	[146] (2015)	Retrospective CS	MTX	14.5 [2-65]	65
Rivitti	PF	[22] (1973)	Retrospective CS	MTX	Unk	Unk
Spring	PN	[147] (2014)	Retrospective CS	MTX	Unk [2-24]	Unk
Egan	PPP	[23] (1999)	Retrospective CS	MTX	Unk [1-Unk]	Unk [1-Unk]
Klejtman	Pr	[148] (2018)	Retrospective CS	MTX	Unk	16 [2-108] (median)
Sharma	PrD	[149] (2007)	Retrospective CS	MTX	Unk [6-Unk]	Unk
Allison	PRP	[150] (2002)	CS	MTX	Unk	Unk
Chapalain	PRP	[151] (1999)	Retrospective CS	MTX	12.1 [4.5-19.5]	Unk
Dicken	PRP	[152] (1994)	CS	MTX	6 [2-12]	Unk
Knowles	PRP	[153] (1970)	Retrospective CS	MTX	Unk [4-7]	Unk
Baum	PV	[33] (2012)	Retrospective CS	MTX	31 [6-96]	Unk [6-30]
Lever	PV	[154] (1972)	CS	Pred -> MTX (15) MTX -> pred (9)	Unk [10-106]	Unk
Mashkilleyson	PV	[155] (1988)	CS	MTX	Unk	Unk
Peck	PV	[24] (1971)	Retrospective CS	MTX	Unk	Unk [4-204]
Smith	PV	[156] (1999)	Retrospective CS	MTX	3	Unk [6-Unk]
Tran	PV	[39] (2013)	Retrospective CS	MTX	Unk [3-Unk]	Unk [26-Unk]
Lower	Sar	[157] (1995)	Prospective CS	MTX	Unk [24-Unk]	Unk [Unk-84]
Veien	Sar	[158] (1997)	Co	MTX	23 [1-72]	Unk

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
9 (2/7)	47.8 [34-71]	Systemic treatment, TA (No. Unk)	Unk [15-25 mg]
33 (5/28)	29 [10-61] (median)	Unk	Unk [15 mg-Unk]
36 (11/25)	7.9	CSA (2), MTX (1), TA (25)	1 mg/kg
10 (4/6)	6.8 [2-12]	D-penicillamine (1), naproxen (1), Pred (2), TCS (1)	Unk [0.3-0.6 mg/kg]
34 (11/23)	8.2 [2.3-15.2]	PT (1), systemic therapy (1), TCS (10)	Unk [10-12.4 mg/m^2]
8 (0/8)	62 (52-69) (median)	Bath PUVA (3), HCQ (3), Pred (3), TL-01 (1)	Unk [2.5-30 mg]
46 (34/12)	9	Antimycotics/AB (13), CSA (1), D-penicillamine (6), TCS (22)	15 mg/m^2 [Unk-20 mg]
65 (16/42)	9.4 [Unk]	Antimycotics/AB (13), CSA (1), D-penicillamine (6), TCS (22)	15 mg/m^2 [Unk-20 mg]
5 (1/4)	4.3 [1.5-8]	Unk	Unk [0.3-0.4 mg/kg)
12	63.5 (median)	Anti-pruritics (6), doxepin (2), neurontin (1), Pred (7)	Unk [2.5-10 mg]
8 (2/6)	24	MTX (8), OCS (Unk)	Unk [20-37.5 mg]
13 (4/9)	75.8	Antipruritic agents, PT, TCS (No. Unk)	Unk [7.5-20 mg]
5 (4/1)	50 [39-62]	SCS (4), TCS (5), PUVA (3), CSA (1), ET (1)	Unk [12.5-22.5 mg]
39 (16/23)	62 [28-94] (median)	Ac (4), AH (34), AZA (1), Capsaicin (1), CSA (4), Em (28), HCQ (1), MMF (1), Naltrexone (2), O CS (3), Pregabalin (5), PT (22), T TAC (10), TCS (38), Thalidomide (9)	15 mg [5-25]
7	Unk	TCS (7), sunscreens (7)	15 mg
5	Unk	Unk	Unk
5	67 [45-87]	AC (2), TCS (5),PUVA therapy (1)	Unk [15-25 mg]
8 (5/3)	Unk [35-74]	Vit A (3), isotretinoin (3)	Unk [10-25 mg]
6 (6/0)	48.3 [40-60]	Pred (2)	Unk [2.5-5mg/d till 75mg/wk]
30 (6/24)	54 [35-78]	AZA (18), dapsone (14), CSA (3), CP (2), MPA (1), IVIG (2)	15 mg
24	51.2 [20-79]	Pred, MTX (No. Unk)	Unk
53	Unk	Unk	Unk [25-50 mg (also in daily dosage)]
13 (3/10)	Unk [18-76]	CST (13)	Unk [10-50 mg]
9 (8/1)	59	AZA (Unk), CP (Unk), Pred (9)	Unk [7.5-17.5 mg]
23 (11/12)	54	AZA (3), dapsone (2), etanercept (1), IVIG (2), MMF (7), Pred (23), rituximab (2)	Unk [7.5-35 mg]
22	39	Antimalarial agents (Unk), nonsteroidals (Unk), Pred (3)	Unk [$\leq$15 mg]
16	51 [36-68]	Unk	Unk [Unk-25 mg]

Author	Disease	Reference (year of publication)	Study design	Treatment arms (no. of patients)	Mean treatment duration [range], mo	Mean FU duration [range], mo
Schanz	Scl	[71] (2013)	Prospective Co	MTX	Unk	Unk [6-12]
Breuckmann	SD	[72] (2005)	Retrospective CS	MTX	6	Unk
Herrick	SS	[159] (2017)	Prospective Co	MTX (65) MMF (118) CP (87)	24	Unk
Pope	SS	[160] (2001)	RCT	MTX (35) Placebo (36)	12	18 (median)
Sumanth	SS	[161] (2007)	Prospective CS	MTX	Unk [6-12]	Unk
Van den Hoogen	SS	[162] (1996)	RCT	MTX (17) Placebo (12)	24	24
Leducq	Ur	[163] (2019)	RCT	MTX (39) Placebo (36)	4.5	2
Perez	Ur	[65] (2010)	Retrospective CS	MTX	Unk	Unk
Sagi	Ur	[57] (2011)	Retrospective CS	MTX	4.5	8.3
Sharma	Ur	[164] (2014)	RCT	MTX (14) Placebo (15)	3	3.5 [0.5-9]
AlGhamdi	Vi	[36] (2013)	Prospective CS	MTX	6	9
Singh	Vi	[46] (2015)	Randomized comparative study	CST (25) MTX (25)	8	Unk

* 4 patients (AB 3, AZA 1, CSA 1) received concomitant systemic medication. Since this number is low compared to the total number of patients, we still included this study.

§ This study reported an inconsequent number of patients; 26 patients participated, but from 23 patients AE's were reported and from 19 patients effectiveness was reported.

† Follow-up study from Schram (2011)

‡ Follow-up study from Zulian (2011)

No. of patients (m/f)	Mean patients age [range], y	Previous treatments (no. of patients)	Mean weekly dose mtx [range]
22 (6/16)	52 (median)	Unk	15 mg
7 (5/2)	56 [39-65]	Unk	25 mg
65 (15/50)	Unk	Unk	Unk [20-25 mg]
35 (4/31)	47	CST (10)	Unk [10-17.5 mg]
33 (4/29)	31 [17-51]	Unk	15 mg
17	52 [32-75]	Colchicine (1), penicillamine (10), Pred (7), NSAID's (6)	15 mg
39 (11/28)	46.4	Colchicine (8), corticosteroids (22), montelukast (19)	Unk [0.2-0.25 mg/kg]
16 (5/11)	49 [30-75] (median)	AZA (9), colchicine (4), CSA (14), doxepin (6), H1-AH (16), HCQ (6), IVIG (3), montelukast (12), sedating AH (13), Sul/Dapsone (7)	Unk [10-15 mg]
8 (2/6)	8	AH (8), colchicine (Unk), dapsone (Unk), doxepin (Unk), IV hydrocortisone (4), Or Pred (1)	15 mg
14 (6/8)	34.21	AH (14)	15 mg
6 (4/2)	29	Unk	25 mg
25	38.6	Unk	10 mg

Table 2 – Efficacy of included studies

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Chartaux	AA	[74] (2010)	Complete hair regrowth: MTX+CTS: 12/19 MTX: 8/14	12	Unk
Alkeraye	AA	[75] (2017)	Responders (≥ 50% regrowth): 9/14 (pred + mtx), 2/6 (pred)	4	Unk
Anuset	AA	[76] (2016)	Total hair regrowth (100%): 15/26 Partial hair regrowth (50-100%): 6/26 Regrowth failure (<50%): 5/26	12	27 [6-72]
Chong	AA	[77] (2017)	Good response (≥ 50% hair regrowth): 6/14	8	Unk
Droitcourt	AA	[59] (2012)	Total or partial regrowth (after 12 mo): 14/20 Total regrowth (after 18 mo): 10/14 Partial regrowth (after 18 mo): 4/14	10 (median)	Unk
Firooz	AA	[78] (2013)	Regrowth of terminal hairs: 8/10	7.2	Unk
Hammerschmidt	AA	[79] (2014)	>50% regrowth: 21/31	Unk	6.3 mo (3)
Joly	AA	[80] (2006)	Complete regrowth: Pred+MTX: 11/16 MTX: 3/6	Unk	Unk
Landis	AA	[81] (2017)	Complete response: 4/11	Unk	Unk
Lim	AA	[67] (2017)	Complete response (100% regrowth): 14/29 Partial response 75-90% regrowth: 12/29 Poor response <50% regrowth: 3/29	Unk	Unk
Lucas	AA	[58] (2016)	Partial response 75-99% regrowth: 2/5 Poor response 25-49% regrowth: 1/5 No change or further loss: 2/5	Unk	Unk
Royer	AA	[82] (2011)	Regrowth >50%: 5/14 Regrowth <50%: 9/14	Dez 27	Unk
Thi Van	AA	[83] (2019)	Good response: 23/38 Medium response: 9/38 Poor response: 6/8	4	Unk
Vano-Galvan	AA	[84] (2017)	Complete response >75% regrowth: MTX: 0/10 MTX+Pred: 3/5 Partial response <75% regrowth: MTX: 5/10 MTX+Pred: 1/5	06.08.2012	Unk [6.3-6.8]
Anderson	AD	[85] (2019)	IGA 0-5: 6-9 months FU: 2.9 12-15 months FU: 2.4 Final visit: 2.7	< 8	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
CST 10-20 mg/d (19)	Elevated liver enzymes (4), lymphocytopenia (1), persistent nausea (2) **(patients)**	None
Pred 500 mg/d; 3 ds/mo	None	None
Pred 20 mg/d (23), "prophylactic osteoporosis treatment"	Acne (2), elevated liver enzymes (4), pneumocystosis pneumonia (1), steroidinduced cataract (1), weight gain (4) [both mtx and pred.] **(patients)**	None
Or CST 10 mg/kg/d, 3 d/mo for 3 mo	Abdominal discomfort (Unk)	None
IV Pred 500 mg/d, 3 d/mo for 3 mo, FA 5 mg	Nausea (2), neutropenia (1) **(patients)**	None
Or CST (10)	Acne (2), amenorrhea (1), anemia (1), herpes infection (1), hypertension (1), muscle cramp (2), weight gain (1)	None
IL CST, MNX, SCS	Elevated liverenzymes (2), leukopenia (3), nausea, epigastric pain and diarrhoea (3)	None
Or Pred 10-20 mg/d (16)	Abdominal pain, nausea, vomiting (1)	Unk
Pred (13)	Unk	Unk
FA (29)	Elevated liver enzymes (3), gastrointestinal discomfort (3), lymphopenia (1), reactivation of pulmonary tuberculosis (1)	Unk
FA (5)	Nausea (1)	None
SCS (8)	Herpes zoster (1), nausea (1)	None
Pred 24 mg/d, 3 ds/week (38)	None	Unk
Pred 0.5-1 mg/kg/d (5)	Elevated liver enzymes (4), weight gain (3)	None
TCS (51), nonsteroidal topicals (29)	Blurry vision (3), cellulitis (2), eczema herpeticum (1), fatigue (14), folliculitis (1), GI discomfort (17), headaches (9), low hematocrit and hemoglobin (2), molluscum (8), mouth sores (3), ocular herpes simplex (1), ringworm (1), staphylococcus aureus superinfection (22), transient elevated liver enzymes (5), verruca vulgaris (1) **(patients)**	Unk

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Baum	AD	[86] (2019)	Disease severity 6 Months: mild 20; moderate 7; severe 3	Unk	Unk
Delcasso	AD	[87] (2018)	SCORAD 50: After 3 months: 7/14 After 6 months: 5/8 After 12 months: 9/12	Unk	Unk
Deo	AD	[61] (2014)	>50% persistent improvement: 75% **(patients)** SCORAD reduction (n=9): 16 points	8	Unk
Dvorakova*	AD	[88] (2017)	Reduction disease severity: IGA decrease 2.35	11.3	Unk
El-Khalawany	AD	[63] (2013)	MEAN absolute SCORAD reduction: MTX: 26.3 (12 wks), 24.9 (24 wks) CSA: 25.0 (12 wks), 21.0 (24 wks)	03. Mai	5
Gerbens†	AD	[89] (2018)	MEAN absolute SCORAD reduction: MTX: 32.1 AZA: 32.1	Unk	Unk
Goujon	AD	[90] (2006)	>70% improvement: 13/20	02. Aug	Unk
Goujon	AD	[28] (2017)	SCORAD 50 after 8 weeks: MTX: 4/50 CSA: 18/43 SCORAD 50 after 24 weeks: MTX: 9/24 CSA: 22/31	Unk	Unk
Hegazy	AD	[91] (2017)	Complete response: 8/37	Unk	Unk
Ho	AD	[21] (2018)	Excellent control: >75%	Dez 24	Unk
Knöpfel	AD	[56] (2018)	Complete/almost complete clearance: 10/28 Marked improvement: 13/28 Mild improvement: 4/28 No improvement: 1/28	Unk	Unk
Lyakhovitsky	AD	[54] (2010)	Responders: 16/20	9.95 (mean), 2-12 (range)	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
FA 5 mg/d, CST	GI discomfort (3), alopecia (1)	None
EM +/- TCS (20)	GI discomfort (5), headache/weakness (5), hepatic cytolysis (3), infectious (3), lymphopenia (3) **(patients)**	None
FA 5 mg, 2d/wk, TCS, SAB or SCS (3)	Elevated liver enzymes (4), nausea (4)	Serious pyelonephritis needing hospitalisation (1), viral-induced exacerbation of asthma needing hospitalisation (1)
AB (3), AZA (1), CSA (1), OCS (7)	Anemia, elevated liverenzymes, fatigue (17), hyperbilirubinemia, lymphocytopenia, nausea/vomiting/abdominal pain (14), neutropeania	Bullous impetigo (1), chest tightness/ wheezing (1), hospitalisation for community acquired pneumonia (1), poststreptococcal glomerulonephritis (1)
FA (20)	Abnormal renal function test (1), anemia (6), abnormal liver enzymes (5), fatigue (6), fever (1), flu-like symptoms (1), GI discomfort (9), headache (3), leukopenia (2),nausea and vomiting (4), Or ulceration (4), pancytopenia (1) **(patients)**	Unk
AB, TCI, TCS, Or CST	Blood and lymphatic system disorders (14), cardiovascular disorders (6), ear and labyrinth disorders (4), gastrointestinal disorders (31), general and administration site conditions (25), hepatobiliary disorders (19), immune system disorders (1), infections (86), injury, poisoning and procedural complications (9), metabolism and nutrition disorders (1), musculoskeletal and connective tissue disorders (21), neoplasms (6), nervous system disorders (22), psychiatric disorders (3), renal and urinary disorders (6), reproductive system and breast disorders (2), respiratory, thoracic and medisastinal disorders (19), skin and subcutaneous tissue disorders (30), surgical and medical procedures (2)	Cholera (1), exacerbation of AD (1), myocardial infarction (2), respiratory problems (2), social reasons after trauma (1)
TCI, TCS	Elevated liverenzymes (2), lymphopenia (1), nausea (4)	Unk
Em, FA 5mg/d (50), TCI, TCI	Acne/virus papilloma (1), elevated liverenzymes (1), fatigue (6), gastrointestinal disorders (9), headache (1), infections (12), lymphocytopenia (1)	None
Unk	Unk side effects (3)	Unk
Em, TCI, TCS	Unk	Unk
FA (28), Or CST (1), TCS (28),	Elevated liverenzymes (5), headache (1), nausea (6), vomiting (1)	None
FA (20), SAH, TCS	Elevated liver enzymes (5), nausea (5), peripheral neuropathy (1)	None

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Mittal	AD	[92] (2011)	Excellent response: 7/15 Good response: 3/15 Poor response: 5/15	Unk	Unk
Politiek	AD	[93] (2016)	PGA1, good effect: 38/89 PGA2, moderate effect: 28/89 PGA3, failure of treatment: 12/89 Excluded: 11/89	Unk	Unk
Purvis	AD	[51] (2019)	A lot better: 23/43 Slightly better: 2/43 No change: 5/43 Excluded: 13/43	Unk	24 (median)
Rahman	AD	[94] (2014)	Good - excellent respons: 23/30 No response: 7/30	12	Unk
Roekevisch†	AD	[42] (2018)	SCORAD reduction (ITT) MTX: 37.8 AZA: 32.6	Unk	Unk
Schram	AD	[43] (2011)	MEAN absolute SCORAD reduction: MTX: 22.8 AZA: 21.7	Unk	Unk
Shah	AD	[30] (2018)	Excellent improvement: >75% 38/41 Good improvement: 50-75% 2/41 Partial improvement: 25-50% 1/41	04. Jun	Unk
Syed	AD	[95] (2009)	EASI50: MTX: 30/30 Placebo: 0/30	Unk	Unk
Taieb	AD	[96] (2019)	IGA decrease at least 2 points: 14/26	Unk	Unk
Vedie	AD	[97] (2016)	Responders: 15/28 Non-responders: 12/28 Lost to follow-up: 1/28	Unk	Unk
Weatherhead	AD	[98] (2007)	MEAN SASSAD reduction: 19 units	3	Unk
Zoller	AD	[69] (2008)	Complete remission: 6/9 Significant improvement: 3/9	04. Aug	Unk
Roberts	AD, NE	[45] (2010)	Clear: 16/25 Almost clear: 3/25 Ongoing: 3/25 Failed: 1/25 Lost to follow up: 2/25	42	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
SCS, TCS	None	None
Prednisolone 10-30 mg/d (26)	Aggravation of rosacea (1), alopecia (1), concentration problems (1), condylomata acuminata (1), depressive discomfort (1), elevated liver enzymes (2), fatigue (4), folliculitis (1), flu-like discomfort (1), gastrointestinal complaints (6), headache (3), pneumonia (1), shortness of breath (1), vision changes (1)	Unk
AB, AH, Em, FA 5 mg (43), TCS	Cataracts (1), gastrointestinal upset (4)	None
Unk	Unk	Unk
FA, weekly 5 mg (17)	Blood and lymphatic system disorders (11), eye disorders (4), gastrointestinal disorders (26), general disorders and administration site conditions (22), hepatobiliary disorders (11), infections (52), injury, poisoning, and precedural complications (4), musculoskeletal and connective tissue disorders (16), neoplams benign, malignant, and unspecified (3), nervous system disorders (2), renal and urinary disorders (6), reproductive system and breast disorders (2), respiratory, thoracic, and medistinal disorders (1), skin and subcutaneous tissue disorders (26), surgical and midcal procedures (2)	Exacerbations AD (1), hospitalization because of psychiatric comorbidity (1)
FA 5 mg (20)	Abnormalities in blood count (6), exacerbation of their eczema (3), gastrointestinal complaints (11), infections (14), increased liver enzymes (7)	None
AB (14), CSA 150mg (1), FA 5mg/d, 6ds/week (41), IM TCA (17), tapering doses of Pred (2), valacyclovir (1)	Decreased hemoglobin (1), transient decrease in platelets (1), elevated liver enzymes (8), fatigue (3), nausea (5)	None
Unk	None	Unk
SCS, TCS	Gastrointestinal discomfort (1), elevated liver enzymes (1), bone marrow suppression (3), mild fatigue (1)	Unk
AZA (7)	Asthenia (3), digestive disorders (4), hepatic dysfunction (7), infections (4), lymphopenia (2)	Folliculitis (1), herpetic recurrences (1)
Em, TCI, TCS	Elevated liver enzymes (2), herpes simplex (1), nausea (2)	None
Em, FA (9)	Numbness (1)	Unk
FA, weekly 5 mg (25)	Generalized exanthem (1), lethargy (1), mild lethargy (2), nausea (4), transient mouth ulceration (1)	None

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Patel	All CE	[99] (2018)	Complete clearance: 6/32 Partial clearance: 19/32 Failure: 6/32	Unk	Unk
Kalyoncu	AO SD	[100] (2016)	Remission with treatment: CST+MTX: 85/97 CST+MTX+HCQ: 68/81	Unk	18 (median)
Bakker	BP	[47] (2013)	Clinical Remission: 5/6	16	Unk
Bara	BP	[101] (2003)	Complete remission: 14/16	Unk	3 (in 1 pt)
Dereure	BP	[102] (2002)	Maintenance of complete clinical response: 17/18	Unk	7.8
Du-Thanh	BP	[103] (2011)	Complete clinical remission: TCS+MTX: 70/70 Maintenance of complete clinical remission: MTX: 53/70	Unk	2.5 [0.5-7]
Heilborn	BP	[62] (1999)	Marked and rapid decrease in disease activity: 11/11	<1	>24
Kjellman	BP	[104] (2008)	Remission rate: MTX: 26/31 MTX+pred: 13/37	44-80	Unk
Kremer	BP	[105] (2017)	Disease control: 6/6	Unk	Unk
Kwatra	BP	[35] (2013)	Complete remission: 15/16	15.2	Unk
Paul	BP	[106] (1994)	Clearance and significant decrease in the need for systemic corticosteroids: 5/8	Apr 88	Unk
Click	DM	[107] (2013)	Substantial clearing/near response: 3/8	Unk	Unk
Hornung	DM	[27] (2012)	CDASI decrease: 8.6	Unk	Unk
Kasteler	DM	[25] (1997)	CST sparing effect: 10/13	Unk	Unk
Ramanan	DM	[73] (2005)	Median time to discontinuation prednisone: MTX: 10 mo Control: 27 mo	Unk	Unk
Ruperto	DM	[108] (2016)	PRINTO20 Pred: 51% Pred+CSA: 70% Pred+MTX: 72%	Unk	Unk
Zieglschmid	DM	[109] (1995)	Improvement of cutaneous disease: 9/10	Unk	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
Unk	Anemia (5), elevated creatinine (3), elevated liver enzymes (10), fatigue (5), gastrointestinal discomfort (7), leukopenia (2), thrombocytopenia (1)	None
CST 43.9 mg/d	Unk	Unk
FA 5mg/week (6)	Unk	None
0.5% clobetasol, max 20 g/d (10)	Anemia, thrombopenia, colon ulcerations, pancytopenia (events)	None
TCS	Decrease in hemoglobin (6), weary (5) **(patients)**	None
Superpotent TCS (70)	Anemia (7), asthenia (1), depression (1), GD ulceration (3), interstitial pneumopathy (1), leucopenia (2), liver cytolysis (2), Or ulceration (2), pancytopenia (1), pulmonary embolism (1), respiratory tract infection (1), thrombocytopenia (2)	Death (6, 1 MTX related due to respiratory tract infection in a setting of MTX related pancytopenia). Other: Unk.
FA (3), TCS	Anemia (1), nausea and anorexia (1), pyoderma (2)	Unk
Pred (37)	anemia (1), alveolitis (1), elevated liver enzymes (1) GI discomfort (2)	Unk
CST (6)	Unk	Unk
FA 1 mg/d, tapered pred 20-60 mg/d	GI intolerance (1), mild nausea and dyspepsia (2), worsening of anemia (1)	None
Or CST (8)	Anemia (1), nausea (1), thrombocytopenia (1)	None
TCS (8)	Alopecia (1), leukopenia (1)	None
FA 5mg/d (11), Pred 5-20 mg/d (9)	Abces on injection place (1)	Herpes encephalitis (1), pancytopenia (1), urothelial carcinoma (1)
Or Pred (10)	Mild malaise (2), transient nausea (6)	Unk
AZA (1), CSA (1), Cyclophosphamide (1), HCQ (6), IVIg (15), Pred 2m/g/kg/d (31)	Cellulitis of the metacarpophalangeal joint (1), elevated liver enzymes (6), fungal vaginitis (1), herpes zoster (1)	Unk
Pred 2 mg/kg, after induction phase tapered to 0.25 mg/kg (46)	Cardiac disorders (1), endocrine disorders (9), eye disorders (3), gastrointestinal disorders (9), general disorders and administration site conditions (2), infections and infestations (14), investigations (6), metabolism and nutrition disorders (4), musculoskeletal and connective tissue disorders (4), nervous system disorders (2), psychiatric disorders (4), skin and subcutaneous disorders (9), vascular disorders (1)	Dermohypodermitis (1), paronychia (1)
OCS, Pred, sunscreens, TCS	Alopecia (1), gastrointestinal distress (2), abnormal liver biopsy (2), lung disease (1), leukopenia (1), mild hepatic fibrosis (2), stomatitis (3)	Unk

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Chen	E	[110] (2016)	Control of disease: 15/41	Unk	Unk
Shaffrali	E	[111] (2003)	Successful response: 4/5 No successful response: 1/5	Unk	Unk
Tétart	E	[48] (2011)	Complete response: no skin-lesions: 11/15 Partial response: still skin-lesions 4/15	Unk	Unk
Berianu	EF	[112] (2015)	Complete remission: 9/16	26	27.1 [7-36]
Lebeaux	EF	[113] (2012)	Complete remission: 4/12	Unk	Unk
Mertens	EF	[44] (2016)	MEDIAN difference modified skin score: 9	Unk	Unk
Kroft	EF/M/SS	[70] (2009)	Clinical improvement: MTX: 38/47 MTX+CS: 11/11	Unk	Unk
Hossain	ENL	[114] (2013)	Persistent remission: 9/9	04. Aug	Unk
Naka	GA	[52] (2018)	Complete resolution: 3/11 Partial resolution: 4/11 No improvement: 4/11	≥4	Unk
Politiek	HE	[115] (2016)	PGA1, good effect: 14/42 PGA2, moderate effect: 14/42 PGA3, failure of treatment: 9/42 Excluded: 5/42	Unk	Unk
Arfi	LE	[116] (1995)	Improvement: 16/16	Unk	Unk
Böhm	LE	[32] (1998)	Improvement: 10/12 Complete response: 6/12 Partial response: 4/12	02. Jun	5-24 (in 5 pts)
Böhm	LE	[117] (2003)	Complete response: 15/22 Clinical improvement: 21/22	8 [2-22]	Unk
Carneiro	LE	[118] (1999)	Presence of cutaneous lesions: MTX: 3/20 Placebo: 16/21	Unk	Unk
Fruchter[§]	LE	[119] (2017)	≥50% improvement: 10/19	Unk	Unk
Gansauge	LE	[53] (1997)	Resolve of cutaneous lesions: 8/10	Unk	Unk
Islam	LE	[120] (2012)	Number of patients with skin rash: MTX: 0/13 CQ: 3/19	24	Unk
Kan	LE	[121] (2016)	Both the MTX and AZA clusters appeared to have better clinical outcomes and lower total medical costs relative to CST monotherapy.	Unk	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
Unk	Elevated liver enzymes (3), elevated creatinine (3), increased procollagen type III aminoterminal peptide (3), nausea (4) **(patients)**	None
Prednisolone 5 mg/d (1)	Abdominal pain (1), flu-like illness (1), liver enzyme elevation (1)	Unk
FA 10 mg/week (12)	Malaise (1), renal insufficiency (1), stomach aches (2), transient lymphopenia (1)	Unk
Pred (15)	Unk	Unk
Pred (12)	Unk	Unk
Analgesics, antiemetics, FA 5-25 mg/week, SCS ≤15 mg/d	Alopecia (4), gastrointestinal discomfort (9), mild stomatitis (5)	None
FA (not routinely and exact dose not indicated), SCS (6)	Unk	Unk
Pred tapered from 30-40 mg/d (9)	Crusted scabies (1), extensive pityriasis versicolor (1), facial swelling (1), multiple folliculitis (2), weight gain (1)	None
FA (11)	Diarrhoea (2), gastrointestinal upset (2), hair loss (2)	None
OCS (7)	Fatigue (1), gastrointestinal complaints (3), headache (2), hematoma (1), suspicion of an allergic reaction to folic acid or MTX (1), urinary tract infection (1)	Unk
Pred 5-30 mg	Elevated liver enzymes (2) **(patients)**	None
GCS systemic (6), TCS (3)	Elevated liver enzymes (3) **(patients)**	None
FA 5 mg/d (Unk)	Elevated liver enzymes and vomitus (10)	None
SCS <0.5 mg/kg/d	Diarrhoea (5), dyspepsia (9), elevated liverenzymes (31), infection (4), nausea (6), oral ulcer (6), urticaria (1), weakness (5)	Unk
Unk	Adverse events, details unknown (6)	Unk
Pred, FA	Elevated liver enzymes (2), general malaise (4) **(patients)**	None
Unk	Anorexia and nausea (7), elevated liverenzymes (2)	None
HCQ (Unk), Or CST (Unk)	Unk	Unk

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Wenzel	LE	[122] (2005)	Significant clinical improvment in CLAI: 42/43	0.5-2	Unk
Chauhan	LP	[123] (2018)	Mean CSS reduction (%): MTX: 53.31 MTX + TCA: 83.53 Mean VAS reduction (%): MTX: 65.31 MTX + TCA: 93.29 Mean QLIQ reduction (%) MTX: 80.26 MTX + TCA: 96.00	16	Unk
Ilyas	LP	[38] (2016)	>50% clearance of cutaneous lesions: 35/55	Unk	Unk
Kanwar	LP	[37] (2013)	Complete remission: 14/24	2	Unk [3-Unk]
Lajevardi	LP	[26] (2016)	TS score reduction: 2.06	Unk	Unk
Malekzad	LP	[31] (2012)	Excellent improvement >75%: 12/15 Mild improvement <75%: 3/15 Unresponsive: 1/15	2	6
Torti	LP	[125] (2007)	Substantial improvement: >75% clear 10/18 Moderate improvement 25-75% clear: 6/18 No response <25% clear: 2/18	Unk	Unk
Turan	LP	[126] (2009)	Complete response: 10/11	4	Unk
Kortekangas-Savolainen	LP, vulvovaginal	[127] (2007)	Long-term symptom relief: 6/6	Unk	6
Babahosseini	LPP	[128] (2019)	Complete responders: 10/26 Partial responders: 12/26 Non-responders: 4/26	9	Unk
Bakhtiar	LPP	[129] (2018)	Effective: 63/79	Unk	Unk
Bulbul baskan	LPP	[130] (2017)	Clinical response: MTX: 10/10 CSA 6/6	Unk	Unk
Kerkemeyer	LPP	[131] (2018)	Partial improvement: 1/7	Unk	Unk
Naeini	LPP	[132] (2017)	LPP Activity Index points decrease: MTX: 2.46 HCQ: 0.67	Unk	Unk
Karadag	LS	[133] (2018)	Median total clinical score reduction: 11.5	Unk	Unk
Kreuter	LS	[134] (2009)	Softening of sclerotic skin and elimination of signs of active disease: 14/15	Unk	>6
Fernandez-de-Misa	LyP	[135] (2018)	Complete response: 25/51	Unk	Unk
Bulur	M	[136] (2017)	Clinical improvement: 14/14	Unk	Unk
Christen-Zaech	M	[34] (2008)	Less induration, violaceous coloration: 38/39	Unk	6 (in 3 pts)

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
Antimalarials (19), low dose prednisolone (18)	Elevated liverenzymes (23), fatigue (11), GI discomfort (22), infections (2), minor hair loss (2)	None
TCA 0.1% oral paste 3 times/d	Anemia (1), nausea (1)	None
FA 1mg/d (55)	Elevated liverenzymes (Unk), leucopenia (Unk), nausea (4)	Unk
FA 5 mg/d, 2 D/Wk	Deranged liver function abnormality (4), marginal decrease in haemoglobin (6), reduced appetite (2)	Unk
FA 1mg/d (18)	Epigastric pain (1), nausea (1), pityriasis rosea (1)	Elevation of liverenzymes (1)
Em, FA 1 mg/d (18), SAH	Elevated liver enzymes (1), anemia (1)	None
Systemic antifungals, TCS, TAC	Unk	Unk
Unk	Fatigue (1), nausea (1)	Unk
TCS (3)	Hair loss (1), herpes simplex (1)	Unk
TCS (26)	Anemia (1), dizziness (1), ecchymosis (1), edema (1), erythema (2), fatigue (1), headache (1), hypertension (1), LFT rising (7), stupor (1)	Unk
Unk	None	None
Unk	None	None
Unk	Unk	Unk
None	Elevated liver enzymes (1)	None
IV MP 1000mg/d, for 3 D	None	None
MP (15), Pred 5 mg/d (Unk)	Diabetes Mellitus (2), increase of glucose level (2), mild nausea and headache (3), weight gain (1)	None
Unk	Unk	Unk
Unk	None	None
Or CST 0.5 - 1 mg/kg/d (34), FA 1 mg/d (39)	Elevated liver enzymes (1), GI discomfort (5) **(patients)**	None

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Cox	M	[60] (2008)	Responders: 8/10	3 (median)	6 [2-12]
Fitch	M	[66] (2006)	Inactive lesions: 16/17	MTX: 24.4 , MTX+CST: 9.2	Unk
Koch	M	[40] (2013)	Disease inactivity: 17/17	8.4	21
Kreuter	M	[137] (2005)	Decrease of clinical score: MD 6	12	None
Li	M	[138] (2019)	PGA-A, mLoSSI, LSCAM scores decreased in all groups 44/44, no significant differences in treatment failure between groups	Unk	Unk
Mertens	M	[64] (2016)	Stop due to disease remission: 48/107	Unk	Unk
Mirsky	M	[139] (2012)	No disease relapses: 31/90	Unk	20.4
Piram	M	[140] (2013)	Significant disease improvement MTX+CST combined compared to MTX or CST alone: OR 5 (95% CI, 1.2-20.7)	Unk	Unk
Platsidaki	M	[49] (2017)	Very good response: 6/20 Good response: 10/20 Fair response: 2/20 Failed treatment 2/20	$\leq$12	Unk
Rattanakaemakorn	M	[68] (2017)	Responders, improvement: 7/7	8	Unk
Seyger	M	[141] (1998)	Significant improvement on MSS and VAS for tightness, no significant improvement on durometer and VAS for itching	Unk	Unk
Shahidi	M	[41] (2018)	mLoSSI, LoSDI and MRI: showed significant improvement	Unk	Unk
Torok	M	[29] (2012)	Significant mLosSI improvement after 1.77 mo: 36/36	4.32	Unk
Uziel	M	[142] (2000)	Inactive lesions: 9/11	Aug 52	Unk
Weibel	M	[143] (2006)	Arrest of disease progression: 32/34	22.8	Unk
Wlodek	M	[144] (2018)	Very well response: 4/8	Unk	Unk
Zulian	M	[50] (2011)	Decrease in target skin lesion activity MTX: -44.4% Placebo: -12.1%	Unk	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
SCS 30 mg/kg/d, 3 d/mo (9), FA (10)	Hyperglycaemia, nausea, varicella zoster (1) **(patients)**	None
FA (19), Or CST (12), TCS	Elevated glucose (1), elevated liver enzymes (1), weight gain (2), weight gain and mild cushingoid features (several)	Unk
FA 1mg/d (17), Or Pred (9)	Unk	Unk
MP (7)	Nausea (3), headache (3), elevation of liver enzymes (1)	None
Pred (32)	Blurred vision (1), gastro-intenstinal problems (11), hair thinning (1), infection (3), laboratory abnormalities (3), lip and nasal ulcer (1), medication intolerance (5), mood problems (5), seizure recurrence (1)	Dehydration/gastroenteritis (1)
FA (78), SCS (37)	Depression (1), fatigue (3), GI discomfort (7), haematotoxicity (2), headache (1), hepatotoxicity (5), pulmonary discomfort (3), renal impairment (1)	Unk
Unk	Unk	Unk
Calcipotriene (29), HCQ (20), methylprednisolone 21 mg/kg (20), Or CST 0,8 mg/kg (6), tacrolimus (14), TCS (33), UVB (3), vit A or vit E TA (Unk)	Headache, nausea	Unk
FA (20), TA	Abdominal pain (4), elevated liver enzymes (1), nausea (4)	None
FA, daily (7)	Mild nausea (1)	Unk
Unk	Elevated liver enzymes (4), fatigue (2), nausea (2) stomatitis (3), weight loss (1)	None
FA 1 mg/d, methylprednisolone 20-30 mg/kg/month	Alopecia (6), anorexia (1), fatigue (13), headache (5), hypokalemia (8), leukopenia (2), nausea (11), striae rubrae (7)	None
FA 1 mg/d(36), Pred 0.25-2 mg/kg/d (36)	Anticipator emesis (7), cushingoid facies (23), elevated liver enzymes (1), light striae (2), oral candidiasis (1)	None
D-penicillamine (1), IV MP (8), naproxen (1), Pred (3)	Elevated liverenzymes (1), leukopenia (1), nausea (1)	Unk
IV MP (34), CST	Abdominal discomfort (4), elevated liverenzymes (6), headache (3), lymphopenia (4), mouth ulcers (3), nausea (14)	None
Topical imiquimod (1)	Back pain (1), elevated liver enzymes (1), P3NP elevation (1), urinary symptoms (1)	None
FA (46), Pred 1mg/kg	Alopecia (2), fatigue (2), headache (5), hepatotoxicity (3), nausea (8)	None

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Zulian±	M	[55] (2012)	Responders: 48/65 Relapse: 10/65 Lost-to-follow-up: 7/65	Unk	Unk [25.6-Unk]
Torrelo	Pa	[145] (2017)	Good control of active symptoms and signs and no reappearance of further attacks: 5/5	Unk	Unk
Moustafa	PD	[146] (2015)	Disease control: 8	Unk	Unk
Rivitti	PF	[22] (1973)	Good response: 1/8 Slight improvement: 2/8 No improvement: 5/8	Unk	Unk
Spring	PN	[147] (2014)	Decrease PNASI/PNRS >75%: 10/13 Tend to improvement: 2/13 Relapse: 1/13	Unk	Unk
Egan	PPP	[23] (1999)	CST sparing effect: 5/5	4	Unk
Klejtman	Pr	[148] (2018)	Objective complete response: 16/28 Subjective complete response 19/28	9.6	19
Sharma	PrD	[149] (2007)	MEAN DASI reduction: 7.9	Unk	Unk
Allison	PRP	[150] (2002)	Poor response: 5/5	Unk	Unk
Chapalain	PRP	[151] (1999)	Significant improvement: 3/5 Complete clearance: 2/5	4	Unk
Dicken	PRP	[152] (1994)	Favorable response (clearing): 8/8	Unk	Unk
Knowles	PRP	[153] (1970)	Complete clearance: 6/6	Apr 40	Unk
Baum	PV	[33] (2012)	Treatment response: 16/19	Unk	Unk
Lever	PV	[154] (1972)	Freedom of lesions: Pred -> MTX: 7/15 MTX -> pred: 2/9	Unk	Unk [4-121]
Mashkilleyson	PV	[155] (1988)	Effective: 42/53 Not effective: 6/53 Further exacerbation of the disease: 3/53 Discontinue due to drug induced side effects: 2/53	0.36	Unk
Peck	PV	[24] (1971)	Lowering antibodies with a correlation with clinical activity: 13/13 Steroid sparing: 13/13	Unk	Unk
Smith	PV	[156] (1999)	Pred stopped in 6 months: 6/9	Unk	Unk [7-55 d]
Tran	PV	[39] (2013)	Improvement in clinical symptoms: 21/23	Unk	Unk [0-26]
Lower	Sar	[157] (1995)	Responders: 16/23 Non-responders: 1/23 Unk: 5	Unk	Unk

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
FA (65)	Elevated liverenzymes (3), headache (7), nausea (16), transitory hair loss and fatigue (2)	None
Pred 1 mg/kg/d (5)	Unk	Unk
Unk	Diarrhoea (1), elevated creatinine (9), fatigue (1), hair loss (2), minimally reduces hemoglobin (1), solar purpura (2)	Unk
SCS, TCA 4-24 mg (8)	None	Death by bronchopneumonia (1)
Em, TCS	Fatigue (1), liver enzyme elevation (1), nausea (1), typical side effects (Unk)	Unk
TCS (3), SCS (4)	GI discomfort (1)	None
Unk	Anaemia (1), asthenia (1), cutaneous abscess (1), elevated liverenzymes (4), hair loss (1), hepataocarcinoma (1), gastrointestinal discomfort (2)	Unk
Prednisolone $\leq$30 mg/d	Dermatophytosis (4), folliculitis (4), furuncles (4)	Unk
Unk	Unk	Unk
Unk	Cytolysis (1)	None
TCS	None	None
TA	GI discomfort (1)	Unk
TA	Unk	Unk
Unk	Leukopenia (2)	
SCS (53)	Gastric ulcer (3), herpes simplex (4), moniliasis (2), necrotizing gingivitis (Unk), pneumonia (8), pyoderma (4), TBC (3)	0-7 pts (exact number unclear)
Calcium folinate (10), CST (13)	Gastrointestinal discomfort (1), leukopenia (1), mouth lesions (7), nausea (2)	Unk
Pred (9)	Liver enzyme elevation (2), nausea (1)	Unk
FA 1 mg/d, TCA injections, TCS	Haematocrit decrease (1), abnormalities on liver ultrasound (1)	Unk
Antimalarial agents, nonsteroidals, pred (3)	Cough (1), hepatotoxicity (6), mouth sores, nausea	Leukopenia requiring hospitalization (1)

Author	Disease	Reference (year of publication)	Efficacy/ effectiveness*	Time to effect, wk	Mean duration of remission [range], mo
Veien	Sar	[158] (1997)	Clearing skin lesions: 12/16	16 - 104	Unk
Schanz	Scl	[71] (2013)	Responders: 12/22 Stable disease: 10/22	Unk	Unk
Breuckmann	SD	[72] (2005)	No response: 7/7	NA	NA
Herrick	SS	[159] (2017)	mRSS reduction: MTX: -4.0 MMF: -3.8 CP: -3.5	Unk	Unk
Pope	SS	[160] (2001)	No significant differences in UCLA skin score, modified Rodnan score and MD global assessment	Unk	Unk
Sumanth	SS	[161] (2007)	Improvement of skin score: Excellent: 1/33 Moderate: 4/33 Mild: 12/33 None: 3/33 Deterioration: 5/33 Lost-to-follow-up: 8/33	Unk	Unk
Van den Hoogen	SS	[162] (1996)	Significant improvement of TSS and VAS: MTX: 8/17 Placebo: 1/12	Unk	Unk
Leducq	Ur	[163] (2019)	Complete urticaria remission (ITT): MTX: 3/38 Placebo: 0/32	Unk	Unk
Perez	Ur	[65] (2010)	Responders: 12/16 Steroid sparing: 2/16	Unk	Unk
Sagi	Ur	[57] (2011)	Complete clinical remission: 7/8 No response: 1/8	03. Mai	Unk [4-15]
Sharma	Ur	[164] (2014)	>2/3 of baseline urticaria scores achieved: MTX: 3.5/10 Placebo: 3.67/7	Unk	Unk
AlGhamdi	Vi	[36] (2013)	Clinical improvement: no change (6/6)	Unk	Unk
Singh	Vi	[46] (2015)	New vitiliginous lesions: MTX: 6/25 CST 7/25	Unk	Unk

* at the end of treatment duration, see reference for definition of outcomes

Concomitant medication (no. of patients)	AE's (no. of events)	SAE's (no. of events)
Unk	Elevated liver enzymes (2), fatigue (2), nausea (6), stomatitis (1)	None
FA 5 mg (22), Prednisolone 1mg/kg after induction phase tapered (22)	Unk	Unk
FA	Unk	Unk
Unk	Unk	Unk
Additional MTX 1.25-3.5 mg/week (11)	Oral ulcers (1)	MTX (3), placebo (7)
Unk	Nausea/vomitnig (3), fever (2), edema (2), increased bilirubin (2), alopecia (92), anorexia (1), dyspnoea (1), headache (1), elevated liver enzymes (1), upper respiratory tract infection (1), angioedema (1), fever (1)	Unk
Pred <10 mg/d	Elevated liver enzymes (6), headache (1), pancytopenia (1)	Renal crisis (1), sudden death (1)
H1-AH (39)	Anemia (4), asthenia (4), cholestasis (5), elevated liver enzymes (17), gastrointestinal discomfort (17), headache (3), insomnia (1), leukopenia (4), lymphopenia (3), nasopharyngitis (5), neutropenia (1), respiratory tract infection (4), urinary tract infection (1)	Cerebrovascular stroke (1), unstable angina (1)
FA 5 mg (16), Prednisolone 10-60 mg/d (16)	Dyspnoea (1), fatigue, hair thinning	Unk
AH (5), FA 5 mg (8), Pred (8)	Gastrointestinal discomfort (2), liver enzymes elevation (1), subjective fatigue (1)	None
Levocetirizine 5 mg/d (Unk)	Liver enzyme elevation (2), uncontrollable nausea (1), vomiting (1)	None
FA, 5 mg/d	None	None
FA 5 mg/week	Nausea (4), severe nausea (1)	None

Results per disease

Alopecia areata (AA)

Fourteen studies[58,59,67,74–84] were found including 285 patients. These studies were mainly retrospective case series (n=7), no RCTs were found. Four case series included solely children.[58,77,81,82] In all case series about half of the patients experienced hair regrowth of at least 50%. In those case series where a complete hair regrowth of 100% was seen, MTX treatment was combined with at least one topical or systemic corticosteroid.

(Juvenile) Atopic dermatitis (AD)

Twenty-six studies including 1056 patients were found for AD, the most in this SR. Three RCTs, two observational follow-up studies, five retrospective cohorts and 16 case series were reported.[21,28,30,42,43,45,51,54,56,61,63,69,85–98] In the RCT of El-Khalawany[63], in which MTX was compared to ciclosporin in 40 children, no significant difference in SCORing Atopic Dermatitis index (SCORAD) reduction was found (Table S1. GRADE evidence profile). Goujon et al.[28] compared MTX to ciclosporin in 147 adults (Table S2. GRADE evidence profile). On their primary endpoint (SCORAD 50, which means a SCORAD reduction of 50% after eight weeks) they found that MTX was inferior to ciclosporin, while after 20 weeks the clinical improvement was similar. This could be explained by the fact that MTX therapy may need at least 8-12 weeks before reaching its full potential. Schram et al.[43] compared MTX to azathioprine in 42 adults with a primary endpoint at 12 weeks and a follow-up until 24 weeks (Table S3. GRADE evidence profile). This study shows that SCORAD reduction scores from MTX treatment were similar to azathioprine treatment. These findings were confirmed by the two and five years observational follow-up studies, from Roekevisch et al.[42] and Gerbens et al.[89], respectively. In the case series approximately half of the patients experienced effectiveness of MTX.

Bullous pemphigoid (BP)

Only case series[35,47,62,101–106] (n=9) were found of which two were prospective. In total 249 patients were enrolled. In the study of Heilborn et al.[62] eleven elderly patients were treated in total. All patients responded in the first month. Outcome measurements in all studies were clearance of disease or good response, remission of disease or long term disease control. These case series reported successes in 80-100% of the treated patients.

(Juvenile) Dermatomyositis (DM)

In the literature search six studies were found, including one RCT[108], one cohort study[73] and four case series[25,27,107,109] in which 119 patients were included. Ramanan et al.[73] and Ruperto et al.[108] studied the paediatric form of DM, the other studies included adults only. Ruperto et al.[108] conducted a multicentre, randomised, open-label superiority trial. A total of 139 patients were included. 47 Patients were randomised to prednisone alone, 46 received MTX combined with ciclosporin and 46 prednisone with MTX (Table S4. GRADE evidence profile). After six months 51% of the patients in the prednisone

group, 70% of the patients in the prednisone/ciclosporin group and 72% patients in the prednisone/MTX group achieved the Paediatric Rheumatology International Trials Organization 20 (PRINTO)[108] (p=0.0228; difference between prednisone alone and the two combination groups). The case series and cohort study imply MTX can be effective in prednisone tapering and disease reduction.

Eczema (E, other than atopic dermatitis)

One cohort study[110] and two retrospective case series[48,111] were found eligible. In total 61 patients were studied. The two case series focused specific on eczema in the elderly (mean age 74.4[111] and 78[48] years) the cohort study[110] reported different subtypes of eczema in one study (atopic/pompholyx/discoid/unclassified). In the cohort study 15/41 patients achieved the effectiveness outcome 'control of disease'. Effectiveness was assessed as good or complete response in the elderly eczema studies, which was achieved by 15/20 patients.

Eosinophilic fasciitis (EF)

Four studies were found in the literature in which 45 patients were studied. The prospective cohort study from Mertens et al.[44] saw a median difference in modified skin score of 9 points. The retrospective cohort study from Kroft et al.[70] included i.a. five patients with EF but did not report effectiveness. The found case series[112,113] imply that MTX combined with or without corticosteroids for the treatment of EF can be effective and shows signs of improvement in 60-80% of the patients.

Lupus erythematosus (LE)

Two RCTs, six case series and one cohort study were found in which 211 patients were studied. The RCT from Carneiro et al.[118] studied 41 patients, of which 21 participants received MTX, the other 20 placebo. Only 28 patients had skin involvement (Table S5. GRADE evidence profile). Both treatment groups received concomitant systemic corticosteroids. In the MTX group, 12 patients had cutaneous lesions at the start of the study. This number reduced to three patients after six months of treatment. The 16 patients with placebo and cutaneous lesions showed no reduction. This difference was significant (p<0.001). Islam et al.[120] included 42 patients with cutaneous and articular lupus erythematosus. 13 patients received MTX and 29 patients chloroquine (Table S6. GRADE evidence profile). At the start of the study six patients in the MTX group and 19 patient in the chloroquine group had a skin rash. After 24 weeks this number reduced to zero patients and three patients, respectively (no significant difference). In the cohort study and case series[32,53,116,117,119,121,122] at least half of the patients showed a clinical response >50%.

Lichen planus (LP)

In total, two cohort studies[31,38] and six case series[26,37,123,125–127] were included in which 155 patients (generalized, mucocutaneous and vulvovaginal) were treated with MTX. Effectiveness was assessed using the percentage of patients achieving either complete response, remission or reduction in disease severity. The use of MTX for the treatment

of LP led to a complete response, substantial improvement or symptom relief in all treated patients.

Lichen planopilaris (LPP)

Two RCTs and three retrospective case series were eligible, in which 141 patients were studied.[128–132] Bakhtiar et al.[129] conducted a RCT in which 79 patients with generalized lichen planus were treated with MTX and 79 patients with oral corticosteroids (Table S7. GRADE evidence profile). The responses were analysed after eight weeks by a Visual Analogue Scale (VAS) from 0-10, in which 6-7 was considered a good response and >7 an excellent response. MTX was effective in 80% of the patients and oral corticosteroids in 72% of the patients, for which no significant difference was found. In the RCT from Naeini et al.[132] 29 patients were included of which 15 were treated with MTX and 14 with hydroxychloroquine for six months (Table S8. GRADE evidence profile). Efficacy was assessed using the Lichen Planopilaris Activity Index (LPPAI). After six months mean decrease in LPPAI in the MTX group was significantly higher compared to the hydroxychloroquine group (3.3. [2.09] vs 1.51 [0.91], p=0.01).

In the case serie of Bulbul Baskan[130], the clinical response of MTX versus ciclosporin treatment was compared. They found a clinical response of 100% in both groups.[130] In all case series 47 patients were included in total of which 80-100% of the patients showed at least partial clinical response.[128,130,131]

Morphea (M, localized scleroderma)

In total, twenty studies were included; one RCT, four cohort studies and 15 case serie studies. Six-hundred and forty-four patients were included and 14 studies included children.[29,34,40,50,55,60,66,68,136,138–140,142,143] One RCT on juvenile morphea was found which was published by Zulian et al.[50] In this study, 70 patients were included (46 to the MTX group, 24 to the placebo group). Both groups received oral prednisone for the first three months (Table S9. GRADE evidence profile). Response was quantified clinically (physician's and patient's global assessment and Childhood Health Assessment questionnaires), by thermography and by a computerized scoring system (CSS). Zulian et al. reported an initial response in all patients, a relapse in 15 MTX-treated patients (32.6%) and in 17 placebo-treated patients (70.8%). The mean skin score (measured with the CSS) decreased in the MTX group, but not in the placebo group. In 527 patients which were included in the case series[34,40,41,49,55,60,66,68,136,137,140–144] and cohort studies,[29,64,138,139] different outcomes were measured, varying from clinical response to improvement of the modified Localized Scleroderma Severity Index (mLoSSI). A good response was showed by 80-100% of the patients.

Pityriasis rubra pilaris (PRP)

Four small case series involving the use of MTX in patients with PRP were found.[150–153] Twenty-four patients were studied in total. The responses varied: from poor response in all participants[150] to complete clearance in all participants.[152,153]

Pemphigus vulgaris (PV)

Six case series were found. In these studies 152 patients were studied. Lever et al.[154] studied 24 patients with PV that were treated with MTX and prednisone. They conclude that patients who receive MTX in the early phase of their disease need less treatment duration, dosage and maintenance use of prednisone. In all case series[24,33,39,154–156] over 80% of the patients showed improvement in the reported outcome measures.

Sarcoidosis (Sar)

Only two case studies originating from 1977 and 1995 with 38 patients in total were found to be eligible.[157,158] Efficacy was assessed measuring the number of patients that were responders (n=16) or showed clearing of skin lesions (n=12).

Systemic sclerosis (SS)

Four eligible studies were found. One cohort study[159], one prospective case serie[161] and two RCTs.[160,162] In total, 150 patients were included. Van den Hoogen et al.[162] performed a double blind-RCT (Table S10. GRADE evidence profile) including 29 patients. Seventeen patients received intramuscular MTX and 12 patients received placebo. The response to treatment was evaluated by a self-made set of criteria; the total skin score (TSS), the VAS of general well-being (0-100), lung diffusion capacity (DLco) and presence or absence of digital ulcerations. Van den Hoogen et al. reported that a significantly larger number of patients receiving MTX (n=8 (53%)) who completed the first 24 weeks of the study had responded favourably compared to patients receiving placebo (n=1, (10%), p=0.03). The authors conclude that although the study sample was small, the results suggest low dose MTX seems to be more effective than placebo according to their response criteria.

Pope et al.[160] performed a RCT (Table S10. GRADE evidence profile), including 71 patients. Patients were randomised to MTX (n=35) or placebo (n=36). Efficacy was quantified subjectively by the patient and the physician and objectively by the University of California, Los Angeles (UCLA) skin score and a modified Rodnan's skin score. No significant difference was found between the two treatment groups. However, a trend in favour of the MTX treatment was seen in Rodnan skin score, ULCA skin score, DLco, and physician global assessment.

The case series and cohort study concluded that at least half of the 98 patients treated with MTX were responders.

Urticaria (Ur)

Four studies were found in which 77 patients were treated.[57,65,163,164] Two studies were RCTs[163,164] and two studies involved case series.[57,65] Leducq et al.[163] performed a randomised-placebo controlled trial (Table S11. GRADE evidence profile) in which 75 patients were included. Thirty-nine patients used MTX, 36 placebo. Effectiveness was defined as complete remission. In the intention-to-treat analysis three patients in the MTX group and 0 patients in the placebo group achieved this endpoint at week 18 (p=0.24).

Sharma et al.[164] performed a randomised placebo controlled trial with 29 patients with H1-antihistaminics resistant urticaria (Table S11. GRADE evidence profile). 14 patients used MTX and 15 patients placebo. Effectiveness was defined as -67.7% on primary outcomes (wheal score, pruritus score, wheal size, wheal duration, wheal episodes, days/week with urticaria). Three-and-a-half of the ten patients (35%) in the MTX group and 3.67 of the seven patients (52%) in the placebo group achieved 67.7% reduction of the primary outcomes. It is unclear how to interpret this. In the case series about 75% responded to MTX.

Vitiligo (Vi)

Two studies were found in which 31 patients were studied; one randomised comparative study[36] and one prospective case serie.[46] Efficacy was assessed in Alghamdi&Khurrum[36] as no change in vitiligo lesions, which occurred in all six patients. Singh et al.[46] performed a prospective randomised open label study (Table S12. GRADE evidence profile). Fifty-two patients were included in the study. Twenty-six patients were treated with MTX and 26 patients with oral mini pulse (OMP) corticosteroids. In the MTX group six of 25 patients developed new vitiligous lesions, compared to seven of 25 patients in the OMP group. The difference was not significant. Both groups showed a similar reduction in the Vitiligo Disease Activity (VIDA) score and the Vitiligo Area Scoring Index (VASI).

Adult onset still's disease (AoSD), Allergic contact eczema (All CE), Erythema nodosum leprosum (ENL), Granuloma annulare (GA), Hand eczema (HE), Lichen sclerosis (extragenital) (LS), Lymphomatoid papulosis (LP), Panniculitis (Pa), Papular dermatitis (PD), Parthenium dermatitis (PrD), Pemphigus foliaceus (PF), Palmoplantar pompholyx (PPP), Prurigo nodularis (PN), Prurigo (Pr), Scleredema diabetoricum (SD), Scleroderma (Scl)

For all these diseases only one[22,23,52,71,72,99,100,114,115,135,145–149] or two[133,134] case series were found. These studies all had a small sample size and very low quality of evidence. The study from Kalyoncu[100] with adult onset Still's Disease did include 202 patients which received MTX, the study from Patel[99] 32 with allergic contact eczema and the study from Politiek[115] 42 with hand eczema. In Table 1 and 2 details on the studies can be found.

Safety

The majority of the studies reported AEs and some studies reported SAEs as well. Most commonly reported AEs involved gastrointestinal complaints as nausea, vomiting or diarrhoea and elevation of liver enzymes. Details on all AEs can be found in Table 2. SAEs reported were; a serious pyelonephritis needing hospitalisation,[61] a viral-induced exacerbation of asthma needing hospitalisation,[61] bullous impetigo,[88] chest tightness/wheezing,[88] hospitalisation for community acquired pneumonia,[88] post streptococcal glomerulonephritis,[88] cholera[89], exacerbations of AD[42,89] myocardial infarction,[89] respiratory problems[89], hospitalization for social reasons after trauma,[89] hospitalization because of psychiatric comorbidity,[42] folliculitis,[97] herpetic recurrences,[97]

six cases of death (one MTX related due to respiratory tract infection in a setting of MTX-related pancytopenia, other unknown),[103] herpes encephalitis,[27] pancytopenia,[27] urothelial carcinoma,[27] dermohypodermitis,[108] paronychia,[108] elevation of liverenzymes,[26] dehydration/gastroenteritis,[138] death by bronchopneumonia,[22] leukopenia requiring hospitalization,[157] renal crisis,[162] sudden death,[162] cerebrovascular stroke,[163] unstable angina,[163] and there were 17 SAEs reported with an unknown origin.[155,160]

Quality

Most evidence was of very low quality, and for only four diseases (atopic dermatitis, morphea, systemic lupus erythematosus and systemic sclerosis) studies of moderate quality could be found. See Table S1 till S12 for all GRADE tables.

Discussion

This SR provides a new overview of the available literature for the off-label use of MTX in dermatology. This overview was updated compared to the BAD guideline[15] and two earlier reviews[13,14] and used GRADE to rate the quality of evidence of the included RCTs. It is intended as a basis for off-label MTX guidance in dermatology, which might catalyse optimal off-label prescription in daily practice and can contribute to the development of a research agenda around MTX use in dermatology.

The quality of the different included evidence in this SR altered; for cutaneous systemic lupus erythematosus,[118] systemic sclerosis,[160] atopic dermatitis[28] and morphea[50] evidence of moderate quality could be found. Most evidence was found for the treatment of atopic dermatitis with MTX. MTX therefore seems to be a treatment option in both adults and children with AD. For other diseases only evidence of low quality was found. A few reasons for the lack of high quality evidence exist; first, only 14 RCTs in dermatological off-label MTX prescription have been found. Most evidence involves retrospective poor quality case series or cohort studies. In the GRADE system[16] these types of studies all start with a very low quality. Furthermore, they have very small sample sizes and show heterogeneity in study characteristics, outcomes and outcome measures used.

The MTX dosages used in the included studies ranged widely, from 0.2 mg/kg daily till 37.5 mg weekly. It can be discussed if especially the high dosages are necessary in dermatological diseases. When looking at the EDF guideline for psoriasis this does not seem to be the case. Here, 15 mg till a maximum of 25 mg weekly are recommended[165]. The EDF guideline recommended to give folic acid during treatment of MTX, which was only done in 47 of the included studies. They also recommended to give MTX subcutaneously. In many of our included studies MTX was given orally instead. The maximum reported treatment duration was 132 months. The EDF guideline does not give a recommendation on treatment duration. However, Visser et al. suggest in a Rheumatology guideline that MTX treatment is safe for long-term use.[166] The adverse events that were most commonly reported were gastrointestinal complaints like nausea, vomiting or diarrhoea and elevation of liver enzymes. This corresponds with an overview of important side-effects as reported for psoriasis.

Strengths and limitations

Our SR highlights the lack of high quality evidence for the off-label use of MTX in dermatology and present knowledge gaps which may contribute to a future research agenda.

The risk of publication bias may exist, as negative results probably are not published. We had to deal with the fact that outcomes used in the included studies turned out to be very heterogeneous which made comparisons and pooling impossible. Many studies used outcomes with a poor definition, e.g. 'treatment response'. We decided to include these studies, to provide a complete overview of the literature. Several studies on the efficacy of MTX are ongoing according to ClinicalTrials.gov; those studies involve skin diseases such as vitiligo, bullous pemphigoid, Takayasu arteritis, granulomatosis with

polyangiitis, giant cell arteritis and erythema nodosum leprosum. As the results of these studies were not published by the time of the closure of our search these studies were not included in this SR. This SR should be updated frequently or evolve in a living SR.[167]

Future work

Despite the emergence of drugs like biologics, we believe that MTX has a place in the treatment of dermatological diseases, due to the low price, wide availability and the long experience with the drug in this specialism. High quality evidence for MTX for different dermatosis is needed and accompanying up-to-date guidelines are of great importance.[168] As physicians are ethically required to discuss off-label prescription with their patients, Shared Decision Making (SDM) is important to prescribe this type of treatment as well. In SDM physicians and patients decide together which treatment is the best option for the patient and base their decision on the best available evidence and the values and preferences of patients.[169]

To optimize the evidence for off-label use of MTX in dermatology, we need high quality studies in which well-characterized patients are treated with standardized treatments regimens using patients and physician relevant well validated outcomes, ideally core outcome sets. This can also involve the publication of results of ineffectiveness or unsafety of the drug for certain diseases. There is a need for harmonization of the use of MTX dosages, screening and outcome measures used. A lack of long term and safety data exists as well. As prospective RCTs will probably not be set up, prospective cohort studies of cases in clinical practice with a clear case definition or diagnostic criteria, severity measures and patient reported outcomes could help to improve the evidence. An example of this study type is the international TREAT (TREating ATopic dermatitis) Registry Taskforce which registers the use, effectiveness and safety of systemic therapies (including MTX) in patients with atopic dermatitis.[170] Such studies are required to improve quality of care for patients in which off-label MTX is prescribed.

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Supplementary material I

Table S1 GRADE evidence profile: MTX compared to CSA for atopic dermatitis

Table S2 GRADE evidence profile: MTX compared to CSA for atopic dermatitis

Table S3 GRADE evidence profile: MTX compared to AZA for atopic dermatitis in

Table S4 GRADE evidence profile: Pred compared to pred+MTX for dermatomyositis

Table S5 GRADE evidence profile: MTX compared to Or CST for Lichen Planopilaris

Table S6 GRADE evidence profile: MTX compared to HCQ for refractory lichen planopilaris

Table S7 GRADE evidence profile: MTX compared to placebo for cutaneous SLE

Table S8 GRADE evidence profile: MTX compared to CQ for cutaneous SLE

Table S10 GRADE evidence profile: MTX compared to placebo for systemic scleroris

Table S11 GRADE evidence profile: MTX compared to placebo for chronic urticaria

Table S12 GRADE evidence profile: OMP compared to MTX for vitiligo

Atopic Dermatitis Table S1 – GRADE evidence profile: MTX compared to CSA for atopic dermatitis

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Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	CSA	Relative (95% CI)	Absolute (95% CI)	Certainty
SCORAD after the end of treatment period (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	mean 2 lower (6.78 lower to 2.78 higher)	⊕○○○ VERY LOW
Absolute reduction in SCORAD at the end of treatment period from baseline (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	mean 1.24 points lower (3.5 lower to 5.98 higher)	⊕○○○ VERY LOW
SCORAD after the end of follow-up period (follow up: 24 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	mean 3.89 higher (2.86 lower to 10.64 higher)	⊕○○○ VERY LOW
Absolute reduction in SCORAD at the end of follow-up period from baseline (follow up: 24 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	mean 3.89 higher (2.86 lower to 10.64 higher)	⊕○○○ VERY LOW
Adverse events (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 43 AEs occured in total. Reported AEs were GI discomfort (9), anemia (6), fatigue (6), elevated liver enzymes (5), nausea and vomiting (4), oral ulceration (4), headache (3), leukopenia (2), pancytopenia (1), abnormal renal function test (1), fever (1) and flu-like symptoms (1). No SAEs were mentioned.				⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CSA:** Ciclosporin; **MTX:** Methotrexate; **SAE:** Serious adverse event; **SCORAD:** Scoring atopic dermatitis

Explanations

a. Downgraded one level for risk of bias due to unclear allocation concealment and blinding of participants, personnel and outcome assessors. There was no data on patients lost to follow-up.

b. Downgraded two levels for imprecision due to a small sample size and a wide confidence interval that included both no effect and beneficial or harmful effect.

Table S2 – GRADE evidence profile: MTX compared to CSA for atopic dermatitis

Bibliography: Goujon, C. et al., *Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial.* The journal of Allergy and Clinical Immunology. In Practice, 2018. 6(2): 562–569.e3. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	CSA	Relative (95% CI)	Absolute (95% CI)	Certainty
SCORAD 50 (≥50% reduction) (follow up: 12 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	7/36 (19.4%)	21/41 (51.2%)	**RR 0.38** (0.18 to 0.79)	**32 fewer per 100** (from 52 fewer to 12 fewer)[c]	⊕○○○ VERY LOW
SCORAD 50 (≥50% reduction) (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	9/23 (39.1%)	22/31 (71.0%)	**RR 0.55** (0.32 to 0.96)	**32 fewer per 100** (from 57 fewer to 6 fewer)[c]	⊕○○○ VERY LOW
EASI 50 (≥50% reduction) (follow up: 12 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	16/37 (43.2%)	31/41 (75.6%)	**RR 0.57** (0.38 to 0.86)	**32 fewer per 100** (from 53 fewer to 12 fewer)[c]	⊕○○○ VERY LOW
EASI 50 (≥50% reduction) (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	20/23 (87.0%)	25/31 (80.6%)	**RR 1.08** (0.85 to 1.36)	**6 more per 100** (from 13 fewer to 26 more)[c]	⊕○○○ VERY LOW
DLQI (≤5) (follow up: 12 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	15/37 (40.5%)	28/41 (68.3%)	**RR 0.59** (0.38 to 0.92)	**28 fewer per 100** (from 49 fewer to 6 fewer)[c]	⊕○○○ VERY LOW
DLQI (≤5) (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	15/23 (65.2%)	25/31 (80.6%)	**RR 0.81** (0.57 to 1.14)	**215 fewer per 100** (from 39 fewer to 8 more)[c]	⊕○○○ VERY LOW

Adverse events (follow up: 24 weeks)								
1	randomised trials	serious[a]	not serious	serious	serious[b]	none	In the MTX group 31 AEs occured in total. Reported AEs were infections (12), gastro-intestinal disorders (9), fatigue (6), acne/virus papilloma (1), elevated liverenzymes (1), headache (1), lymphocytopenia (1). There were no SAEs.	⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CSA:** Ciclosporin; *DLQI:* Dermatology life quality index; *EASI:* Eczema area severity index; **MTX:** Methotrexate; **SAE:** Serious adverse event; **SCORAD:** Scoring atopic dermatitis

Explanations
a. Downgraded one level for risk of bias due to a lack of blinding of patients and physicians. Randomization, concealment of allocation and blinding of outcome assessors were adequate.
b. Downgraded one level for imprecision due to a small sample size and because the 90% CI includes both neglectable and appreciable benefit or appreciable harm (the non-inferiority limit was -20%).
c. Calculated with Review Manager.

Table S3 – GRADE evidence profile: MTX compared to AZA for atopic dermatitis in

Bibliography: Schram, M. E. et al., *A randomized trial of methotrexate versus azathioprine for severe atopic eczema.* The Journal of allergy and clinical immunology, 2011. 128(2): p. 353–359. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	AZA	Relative (95% CI)	Absolute (95% CI)	Certainty
Mean change in SCORAD (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean **0.5 points lower** (8.22 lower to 7.22 higher)	⊕○○○ VERY LOW
SCORAD reduction of 50% (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	8/20 (40.0%)	10/22 (45.5%)	**RR 0.88** (0.43 to 1.78)	**5 fewer per 100** (from 35 fewer to 24 more)[c]	⊕○○○ VERY LOW
Change in mean IGA (follow up: 12 weeks; Scale from: 0 to 6)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean **0.4 points lower** (0.89 lower to 0.09 higher)	⊕○○○ VERY LOW
Achieving mild disease (follow up: 12 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	15/20 (75.0%)	15/22 (68.2%)	**RR 1.10** (0.75 to 1.61)	**7 more per 100** (from 20 fewer to 34 more)[c]	⊕○○○ VERY LOW
Mean change in EASI (follow up: 12 weeks; Scale from: 0 to 72)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean **0.2 lower** (6.36 lower to 6.76 higher)	⊕○○○ VERY LOW
Mean change in POEM (follow up: 12 weeks; Scale from: 0 to 28)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean **1 lower** (5.07 lower to 3.07 higher)	⊕○○○ VERY LOW

Adverse Events (follow up: 24 weeks)								
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 112 AEs occured in total. Frequently reported AEs were infections (14), gastro-intestinal complaints (11), elevated liver enzymes (7), abnormalities in blood count (6) and exacerbation of eczema (3). There were no SAEs.	⊕○○○ VERY LOW

AE: Adverse event; *AZA:* Azathioprine; **CI:** Confidence interval; *EASI:* Eczema area severity index; *IGA:* Investigator global assessment; **MTX:** Methotrexate; *POEM:* Patient oriented eczema measure; *RR:* Risk ratio; **SAE:** Serious adverse event; **SCORAD:** Scoring atopic dermatitis

Explanations

a. Downgraded one level for risk of bias; no allocation concealment since patients were not blinded. Randomization, concealment of allocation and blinding of researchers was adequate. Concomitant topical corticosteroids and oral antihistamines were allowed. Rescue medication of maximal 2 courses of oral prednisolone was allowed, but this was not considered serious enough to downgrade for risk of bias.

b. Downgraded two levels for imprecision due to small sample size and a wide confidence interval that includes both no effect and (beneficial or harmful) effect.

c. Calculated with Review Manager

Dermatomyositis

Table S4 – GRADE evidence profile: Pred compared to pred+MTX for dermatomyositis

Bibliography: Ruperto, N. et al., *Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial.* Lancet (London, England), 2016. 387(10019): p. 671–678. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pred	pred+MTX	Relative (95% CI)	Absolute (95% CI)	Certainty
Achieving PRINTO 20 (follow up: 6 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/47 (51.1%)	33/46 (71.7%)	**RR 0.71** (0.51 to 0.99)	**21 fewer per 100** (from 40 fewer to 1 fewer)[c]	⊕⊕◯◯ LOW
Achieving PRINTO 50, 70 or 90 (follow up: 24 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	No exact data was provided. For achieving PRINTO 50 or 70, there was a significant difference between the combination of prednisone plus MTX versus prednisone alone.				⊕⊕◯◯ LOW
Achieving clinical remission proportion of patients (follow up: 60 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b,d]	none	8/47 (17.0%)	15/46 (32.6%)	**RR 0.52** (0.25 to 1.11)	**16 fewer per 100** (from 33 fewer to 33 more)[c]	⊕◯◯◯ VERY LOW
Achieving clinical remission proportion of patients (follow up: 60 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/47 (63.8%)	17/46 (37.0%)	**RR 1.73** (1.12 to 2.67)	**27 more per 100** (from 7 more to 46 more)[c]	⊕⊕◯◯ LOW
Achieving discontinuation of prednisone (follow up: 60 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b,d]	none	19/47 (40.4%)	25/46 (54.3%)	**RR 0.74** (0.48 to 1.15)	**14 fewer per 100** (from 34 fewer to 6 more)[c]	⊕◯◯◯ VERY LOW

Adverse events (follow up: 60 months)								
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	A total of 52 AEs were reported in the prednisone group compared to 74 in the prednisone + MTX group. The most frequently reported AEs in the MTX group were infections (30%). Reported SAEs were dermohypodermitis (1) and paronychia (1).	⊕⊕◯◯ LOW

AE: Adverse event; **CI:** Confidence interval; **MTX:** Methotrexate; **pred:** Prednisone; **PRINTO:** Pediatric rheumatology international trials organisation; *RR:* Risk ratio; **SAE:** Serious adverse event

Explanations
a. Downgraded one level for risk of bias due to lack of blinding of participants, clinicians (treating and assessing) and statisticians, which accounts for a high risk of performance and detection bias.
b. Downgraded one level for imprecision due to a small sample size and wide confidence intervals.
c. Calculated with Review Manager.
d. Downgraded one level for imprecision due to a wide confidence interval that includes both no effect and (beneficial or harmful) effect.

Lupus erythematosus

Table S5 – GRADE evidence profile: MTX compared to placebo for cutaneous SLE

Bibliography: Carneiro, J. R. and Sato, E. I., *Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus.* The Journal of Rheumatology, 1999. 26(6): p. 1275–1279. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
Achieving PRINTO 20 (follow up: 6 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/20 (15.0%)	16/21 (76.2%)	**RR 0.20** (0.07 to 0.57)	**61 fewer per 100** (from 85 fewer to 37 fewer)[c]	⊕○○○ VERY LOW
Mean change in SLEDAI (follow up: 6 months; Score from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Data was insufficient to calculate a mean, SD, MD or CI. After 6 months the SLEDAI significantly decreased in the MTX group compared to baseline scores. In the placebo group the mean SLEDAI was significantly higher after 6 months compared to baseline scores. The difference in SLEDAI between placebo and MTX groups was significant.				⊕○○○ VERY LOW
Achieving 50% decrease in prednisone dose (follow up: 6 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	13/20 (65.0%)	1/21 (4.8%)	**RR 13.65** (1.96 to 94.95)	**60 more per 100** (from 37 more to 83 more)[c]	⊕○○○ VERY LOW
Mean change in SLEDAI (follow up: 6 months; Score from: 0 to 108)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	In the MTX group 67 AEs occured in total. Reported AEs were elevated liverenzymes (31), dyspepsia (9), nausea (6), oral ulceration (6), weakness (5) diarrhea (5), infection (4) and urticaria (1). No SAEs were mentioned.				⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event; **SLE:** Systemic lupus erythematosus; **SLEDAI:** Systemic lupus erythematosus disease activity index

Explanations
a. Downgraded one level for risk of bias due to allocation concealment.
b. Downgraded two levels for imprecision due to very small sample size.
c. Calculated with Review Manager.

Table S6 – GRADE evidence profile: MTX compared to CQ for cutaneous SLE

Bibliography: Islam, M. N. et al., *Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus.* International journal of rheumatic diseases, 2012. 15(1): p. 62–68. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	CQ	Relative (95% CI)	Absolute (95% CI)	Certainty
Number of subjects with skin rash (follow up: mean 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	0/13 (0.0%)	3/24 (12.5%)	**RR 0.41** (0.02 to 6.95)	**13 fewer per 100** (from 29 fewer to 4 more)[c]	⊕◯◯◯ VERY LOW
Adverse events (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	In the MTX group 9 AEs occured in total. Reported AEs were anorexia and nausea (7) and elevated liver enzymes (2). There were no SAEs.				⊕◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CQ:** Chloroquine; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event; **SLE:** Systemic lupus erythematosus

Explanations
a. Downgraded one level for risk of bias due to allocation concealment.
b. Downgraded two levels for very small sample size.
c. Calculated with Review Manager.

Table S7 – GRADE evidence profile: MTX compared to Or CST for Lichen Planopilaris

Bibliography: Bakhtiar, R., Noor, S. M., and Paracha, M. M., *Effectiveness of Oral Methotrexate Therapy versus Systemic Corticosteroid Therapy in Treatment of Generalised Lichen Planus*. Journal of the College of Physicians and Surgeons–Pakistan : JCPSP, 2018. 28(7): p. 505–508. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MTX**	**Or CST**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Number of subjects with skin rash (follow up: mean 24 weeks)											
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	63/97 (64.9%)	47/79 (59.5%)	**RR 1.09** (0.86 to 1.38)	**5 more per 100** (from 9 fewer to 20 more)[c]	⊕○○○ VERY LOW
Number of subjects with skin rash (follow up: mean 24 weeks)											
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	In the MTX group no AEs occured. No SAEs were mentioned.				⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **Or CST:** Oral corticosteroids; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event

Explanations

a. Downgraded two levels for risk of bias, poor clarification of randomization, unclear outcome and lack of blinding of participants.

b. Downgraded one level for imprecision due to a small sample size.

c. Calculated with Review Manager

Table S8 – GRADE evidence profile: MTX compared to HCQ for refractory Lichen Planopilaris

Bibliography: Naeini, F. F. et al., *Clinical Efficacy and Safety of Methotrexate versus Hydroxychloroquine in Preventing Lichen Planopilaris Progress: A Randomized Clinical Trial.* International journal of preventive medicine, 2017. 8: p. 37. epublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	HCQ	Relative (95% CI)	Absolute (95% CI)	Certainty
Change in LPPAI - month 6 (follow up: 6 months; Score from 0 to 10)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	15	14	-	mean **1.95 higher** (0.79 higher to 3.11 higher)	⊕○○○ VERY LOW
Global photographic assessment 1 - slightly decreased (follow up: 6 months)											
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	2/15 (13.3%)	1/14 (7.1%)	**RR 1.87** (0.19 to 18.38)	**6 more per 100** (from 16 fewer to 28 more)[d]	⊕○○○ VERY LOW
Global photographic assessment 2 - slightly decreased (follow up: 6 months)											
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	1/15 (6.7%)	0/14 (0.0%)	**RR 2.81** (0.12 to 63.38)	**7 more per 100** (from 10 fewer to 24 more)[d]	⊕○○○ VERY LOW
Adverse events (follow up: 6 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 1 AE occured in total. The reported AE was elevated liver enzymes (1). There were no SAEs.				⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **HCQ:** Hydroxychloroquine; **LPPAI:** Lichen planopilaris activity index; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event

Explanations
a. Downgraded one level for risk of bias due to unclear sequence generation and no blinding of participants.
b. Downgraded two levels for imprecision due to a very small sample size.
c. Downgraded one level for risk of bias due to an unclear sequence generation.
d. Calculated with Review Manager.

Morphea

Table S9 – GRADE evidence profile: MTX compared to placebo for morphea

Bibliography: Zulian, F. et al., *Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial.* Arthritis and rheumatism, 2011. 63(7): p. 1998–2006. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
Target skin lesion activity (follow up: 12 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	46	24	-	MD **32.3 percent lower** (37.92 lower to 26.68 lower)	⊕⊕◯◯ LOW
Change in SSR (follow up: 12 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	46	24	-	mean **0.31 lower** (0.35 lower to 0.27 lower)	⊕⊕◯◯ LOW
Development of new lesions (follow up: 12 months)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	3/46 (6.5%)	4/24 (16.7%)	**RR 0.39** (0.10 to 1.61)	**10 fewer per 100** (from 27 fewer to 6 more)[d]	⊕◯◯◯ VERY LOW
Achieving individual response (follow up: 12 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	31/46 (67.4%)	7/24 (29.2%)	**RR 2.31** (1.20 to 4.45)	**38 more per 100** (from 16 more to 61 more)[d]	⊕⊕◯◯ LOW
Adverse events (follow up: 6 months)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	In the MTX group 26 AEs occured in total, of which 20 were MTX treatment related. Reported AEs related to MTX treatment were nausea (8), headache (5), hepatotoxicity (3), alopecia (2) and fatigue (2). There were no SAEs.				⊕⊕◯◯ LOW

AE: Adverse event; **CI:** Confidence interval; MD: Mean difference; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event; **SSR:** Skin score rate

Explanations
a. Downgraded one level for risk of bias due to lack of allocation concealment.
b. Downgraded one level for imprecision due to a low sample size.
c. Downgraded one level for imprecision due to a wide confidence interval that includes both no effect and (beneficial or harmful) effect.
d. Calculated with Review Manager

Table S10 – GRADE evidence profile: MTX compared to placebo for systemic scleroris

Bibliography: Pope, J. E. et al., *A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma.* Arthritis and rheumatism, 2001. 44(6): p. 1351–1358. ppublish
van den Hoogen, F. H. et al., *Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial.* British journal of rheumatology, 1996. 35(4): p. 364–372. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
Mean change in UCLA skin score (follow up: 12 months; Scale from 0 - 30)											
1	randomised trials	not serious[a]	not serious	not serious	very serious[b]	none	27	24	-	MD **2.45 lower** (2.74 lower to 2.16 lower)	⊕⊕◯◯ LOW
Mean change in modified RSS (follow up: 12 months; Scale from 0 - 78)											
1	randomised trials	not serious[a]	not serious	not serious	very serious[b]	none	27	24	-	MD **5.9 lower** (6.56 lower to 5.25 lower)	⊕⊕◯◯ LOW
Change in MD global assessment (follow up: 12 months)											
1	randomised trials	not serious[a]	not serious	not serious	very serious[b]	none	At 12 months the difference was statistically significant (4.2 ± 0.5 and 5.5 ± 0.4 in the MTX and placebo groups, respectively; P 0.035).				⊕⊕◯◯ LOW
Response to treatment (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/15 (53.3%)	1/10 (10.0%)	**RR 5.33** (0.78 to 36.33)	**43 more per 100** (from 12 more to 75 more)	⊕◯◯◯ VERY LOW
Mean change in TSS (follow up: 24 weeks; Scale from: 0 to 5)											
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	10	-	mean **1.9 lower** (5.19 lower to 1.39 higher)	⊕◯◯◯ VERY LOW
Mean change in VAS general well-being (follow up: 24 weeks; Scale from: 0 to 10)											
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	10	-	mean **5.5 higher** (6.86 lower to 17.86 higher)	⊕◯◯◯ VERY LOW

Adverse events (follow up: 5.5-12 months)								
1	randomised trials	serious[e]	not serious	not serious	serious[f]	none	In the MTX group 11 AEs occured in total. Reported AEs were elevated liver enzymes (6), oral ulceration (1), pancytopenia (1) and headache (1). Two SAEs were reported: sudden death presumably due to acute myocardial infarction (1) and renal crisis (1).	⊕⊕◯◯ LOW

AE: Adverse event; **CI:** Confidence interval; **Dlco:** Lung diffusion capacity; MD: Mean difference; **MTX:** Methotrexate; *RR:* Risk ratio; **RSS:** Rodnan skin score; **SAE:** Serious adverse event; **TSS:** Total skin score; **UCLA:** University of California Los Angeles; **VAS:** Visual analogue scale

Explanations

a. No downgrading for risk of bias. Randomization, concealment of allocation and blinding of patients was adequate. Data was analysed per protocol and intention to treat. Results were adjusted for differences in baseline characteristics (differences in sex distribution and prednisone use).

b. Downgraded two levels for imprecision due to very small sample size.

c. Downgraded one level for risk of bias due to possible inadequate allocation concealment since groups were balanced for disease duration and extent of skin involvement.

d. Downgraded two levels for imprecision due to small sample size and wide confidence intervals that includes both (beneficial and harmful) effects.

e. Downgraded one level for risk of bias due to possible inadequate allocation concealment since in 1 study groups were balanced for disease duration and extent of skin involvement.

f. Downgraded one level for imprecision due to small sample size.

Table S11 – GRADE evidence profile: MTX compared to placebo for chronic urticaria

Bibliography: Leducq, S. et al., *Efficacy and safety of methotrexate versus placebo as add-on therapy to H1 antihistamines for patients with difficult-to-treat chronic spontaneous urticaria: A randomized, controlled trial.* Journal of the American Academy of Dermatology, 2020. 82(1): p. 240–243. ppublish
Sharma, V. K. et al., *A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria.* Indian journal of dermatology, venereology and leprology, 2014. 80(2): p. 122–128. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
Primary outcome (follow up: 12 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	The sentence 'Out of 17 patients who completed therapy, the primary outcome was achieved by 3.5 ± 1.9 (out of 10) patients in the methotrexate group and by 3.67 ± 1.03 (out of 7) patients in the placebo group (P > 0.05).' is unclear to interpret.				⊕○○○ VERY LOW
Wheal score (follow up: 12 weeks; Scale from: 0 to 3)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	14	15	-	mean **3.36 lower** (3.52 lower to 3.2 lower)	⊕○○○ VERY LOW
Pruritus score (follow up: 12 weeks; Scale from 0 to 3)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	14	15	-	mean **0.24 higher** (0.09 higher to 0.39 higher)	⊕○○○ VERY LOW
Complete remission (follow up: mean 18 weeks)											
1	randomised trials	serious[c]	not serious	not serious[d]	very serious[e]	none	3/38 (7.9%)	0/32 (0.0%)	**RR 5.92** (0.32 to 110.56)	**0.8 more per 100** (from 0.2 fewer to 0.2 more)[f]	⊕○○○ VERY LOW
Self-assessment of pruritus (follow up: 18 weeks)											
1	randomised trials	serious[c]	not serious	not serious	very serious[e]	none	The MD in the MTX group was 15.0 with an Q1-Q3 range [3.5-32.7] and in the placebo group 15.6 with an Q1-Q3 range range[6.4-51.1]. The difference was 0.6 points.				⊕○○○ VERY LOW
Self-assessment of quality of sleep (follow up: 18 weeks; Scale from 0 to 100)											
1	randomised trials	serious[c]	not serious	not serious	very serious[e]	none	The MD in the MTX group was 84.5 with an Q1-Q3 range [67.5-95.3] and in the placebo group 77.7 with an Q1-Q3 range [68.4-89.6]. The difference was 6.8 points.				⊕○○○ VERY LOW

Adverse events (follow up: 12-18 weeks)								
1	randomised trials	serious[g]	not serious	not serious	very serious[e]	none	A total of 74 AEs were reported in the MTX group. Reported AEs were elevated liver enzymes (19), gastrointestinal discomfort (17), cholestasis (5), nasopharyngitis (5), anemia (4), asthenia (4), leukopenia (4), respiratory tract infection (4), lymphopenia (3), headache (3), insomnia (1), nausea/vomiting (1), neutropenia (1) and urinary tract infection (1). Reported SAEs were cerebrovascular stroke (1) and unstable angina (1).	⊕○○○ VERY LOW

AE: Adverse event; **MD:** Mean difference; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event

Explanations

a. Downgraded one level for risk of bias since no assessments were made for incomplete data.

b. Downgraded two levels for imprecision due to a very small sample size.

c. Downgraded one level for risk of bias due to selective outcome reporting, because not all secondary outcomes are reported (including the baseline), and many patients were lost to follow-up.

d. No downgrading for indirectness; possible differences in baseline characteristics in the intervention and control group are not reported. However we did not find reasons to assume these differences exist.

e. Downgraded two levels for imprecision due to a small sample size and a small number of events.

f. Calculated with Review Manager.

g. Downgraded one level for risk of bias due to the facts that no assessments were made for incomplete data, there was selective outcome reporting, not all secondary outcomes were reported (including the baseline) and many patients were lost to follow-up.

Table S12 – GRADE evidence profile: OMP compared to MTX for vitiligo

Bibliography: Singh, H. et al., *A Randomized Comparative Study of Oral Corticosteroid Minipulse and Low-Dose Oral Methotrexate in the Treatment of Unstable Vitiligo.* Dermatology (Basel, Switzerland), 2015. 231(3): p. 286–290. ppublish

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OMP	MTX	Relative (95% CI)	Absolute (95% CI)	Certainty
Development of new lesions (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	7/25 (28.0%)	6/25 (24.0%)	**RR 1.17** (0.46 to 2.98)	**0.8 more per 100** (from 20 fewer to 28 more)[c]	⊕○○○ VERY LOW
Reduction in mean VIDA (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	No exact data was provided. Both groups showed a similar reduction in the VIDA score.				⊕○○○ VERY LOW
Reduction in mean VASI (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	No exact data was provided. Both groups demonstrated reduction in the VASI score.				⊕○○○ VERY LOW
Achieving >50% repigmentation (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	9/25 (36.0%)	14/25 (56.0%)	**RR 0.64** (0.34 to 1.20)	**20 fewer per 100** (from 47 fewer to 7 more)[c]	⊕○○○ VERY LOW
Achieving no repigmentation (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	10/25 (40.0%)	16/25 (64.0%)	**RR 0.63** (0.36 to 1.10)	**24 fewer per 100** (from 51 fewer to 3 more)[c]	⊕○○○ VERY LOW
Reduction in mean VASI (follow up: 24 weeks)											
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 5 AEs occured in total. Reported AEs were not severe nausea (4) and severe nausea (1). There were no SAEs.				⊕○○○ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **OMP:** Oral corticosteroid minipulse; **MTX:** Methotrexate; *RR:* Risk ratio; **SAE:** Serious adverse event; **VIDA:** Vitiligo disease activity; **VASI:** Vitiligo area scoring index

Explanations

a. Downgraded one level for risk of bias due to a lack of blinding of participants and investigators. Analysis was done according to the worst-case-scenario.

b. Downgraded two levels for imprecision due to small sample size and a wide confidence interval that includes both no effect and (beneficial or harmful) effect.

c. Calculated with Review Manager.

Supplementary Material II

Abbreviations Table 1 and Table 2

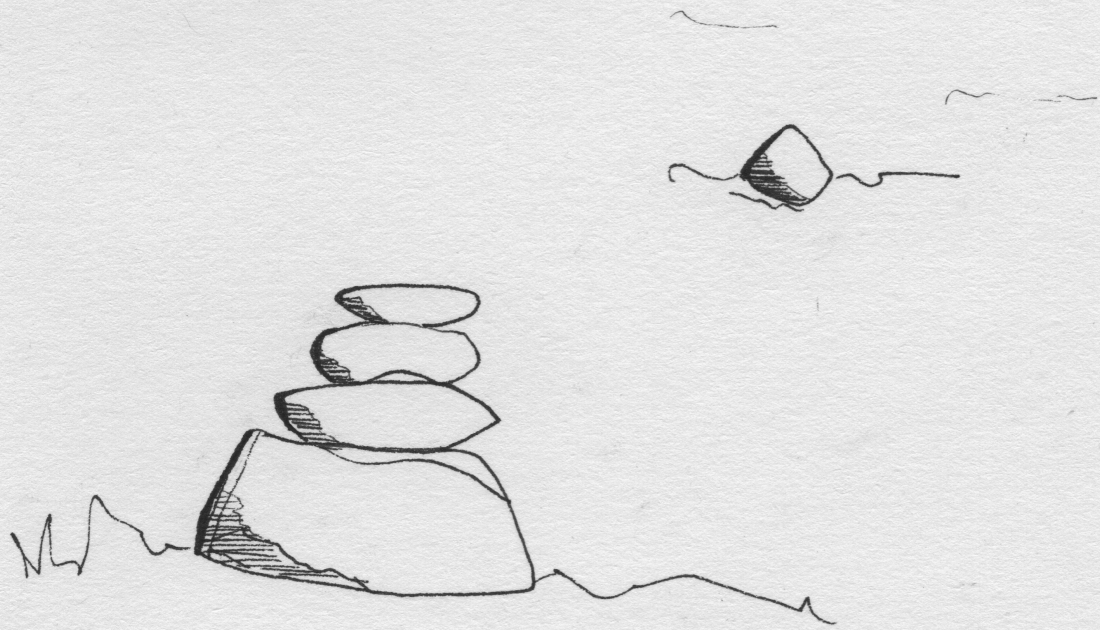
A	Antibodies
AA	Alopecia areata
AB	Antibiotics
Ac	Acitretin
AD	Atopic dermatitis
AH	Antihistamines
All CE	Allergic Contact Eczema
AO	Adult onset
AZA	Azathioprine
BP	Bullous pemphigoid
BSA	Body surface area
Co	Cohort study
CP	Cyclophosphamide
CQ	Chloroquine
Cry	Cryotherapy
CS	Case series
CSA	Ciclosporin
CSS	Clinical severity score
CST	Corticosteroids
D	Day
DM	Dermatomyositis
DPCP	Diphenciprone
DTN	Dithranol
E	Eczema
EC	Eosinophil count
EF	Eosinophilic fasciitis
Em	Emollients
ENL	Eythema Nodosum Leprosum
ET	Etretinate
FA	Folic acid
G	Gram
GA	Granuloma Annulare
GD	Gastroduodenal
GCS	Glucocorticosteroids
GI	Gastrointestinal
GPA	Granulomatosis with polyangiitis (Wegener's granulomatosis)
HCQ	Hydroxychloroquine
ICS	Intravenous corticosteroids
IL	Intralesional
ITT	Intention to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
LE	Lupus erythematosus

LP	Lichen planus
LPP	Lichen planopilaris
LS	Lichen Sclerosus (extra genital)
LyP	Lymphomatoid papulosis
M	Morphea
Mg	Milligram
MMF	Mycophenolate Mofetil
MNX	Minoxidil
Mo	Month
MP	Methylprednisolone
MPA	Mycophenolate acid
MPP	Methylprednisolone pulse
MTX	Methotrexate
NA	Not applicable
NE	Nummular Eczema
NB	Narrow band
Or	Oral
OCS	Oral Corticosteroids
Pa	Panniculitis
PB	Placebo
PD	Papular Dermatitis
Ped	Pediatric
PGA	Patient Global Assessment
PF	Pemphigus Foliaceus, epidemical, fogo selvagem
PP	Per protocol
PPP	Palmoplantar pompholyx
PN	Prurigo Nodularis
Pred	Prednisone
Pr	Prurigo
PrD	Parthenium Dermatitis
PRP	Pityriasis rubra pilaris
Pt	Patient
PT	Phototherapy
Pts	Patients
PUVA	Psoralen – ultraviolet-A
PV	Pemphigus vulgaris
QLQI	Quality of life impairment questionnaire score
RCT	Randomised Controlled Trial
SAB	Systemic antibiotics
SAH	Systemic Antihistamines
Sar	Sarcoidosis
Sc	Subcutaneous
SCORAD	SCORing of Atopic Dermatitis
SCS	Systemic corticosteroids
Scl	Scleroderma
SD	Sclerodema diabeticorum

Sul	Sulfasalazine
SS	Systemic sclerosis
T	Topical
TAC	Tacrolimus
TA	Topical agents
TCA	Triamcinolone
TCS	Topical corticosteroids
TCI	Topical calcineurin inhibitor
Unk	Unknown
Ur	Urticaria
UVA	Ultraviolet-A
UVB	Ultraviolet-B
VAS	Visual analogue scale
Vi	Vitiligo
Vit	Vitamin
Wk	Week
Y	Year

Part III

Initiation of research towards, and implementing SDM in Dermatology in the Netherlands



Chapter 5

The current extent of and need for shared decision making in atopic dermatitis and psoriasis in the Netherlands: An online survey study amongst patients and physicians

G.E. van der Kraaij MD, F.M. Vermeulen MD, P.M.G. Smeets MD, E.M.A. Smets PhD, Ph. I. Spuls MD Ph

Abstract

Background

In shared decision making (SDM) patients and physicians work together to choose the best treatment option for an individual patient. Atopic dermatitis (AD) and psoriasis are particularly suitable for SDM, considering that the best treatment option depends on a patient's preferences and values (preference-sensitive decisions). Currently it is unknown to what extent SDM is applied in treatment decisions for these diseases in The Netherlands.

Objectives

Primary, to assess the current extent of SDM in AD and psoriasis in the Netherlands amongst patients and dermatologists. Secondary, to assess the degree to which patients and physicians endorse SDM, to explore which characteristics are related to their preference to be involved in SDM and to identify which barriers and facilitators for SDM they perceive.

Methods

Two similar online surveys, one for patients with AD or psoriasis and one for (resident) dermatologists, were carried out. The surveys comprised validated questionnaires (Shared Decision Making Questionnaire (SDM-Q; range 0-100), Control Preference Scale) and study-specific statements mainly regarding barriers and facilitators for SDM.

Results

The responses of 219 patients and 147 physicians were analysed. Dermatologists experienced significantly more SDM than patients (SDM-Q 82 vs 55;$p<0.01$). Most patients and dermatologists prefer to share treatment decisions. Mainly facilitators for SDM were perceived, including the positive perception of patients and dermatologists regarding SDM. The perceived barriers included lack of continuity of care by the same physician and lack of time.

Conclusion

Despite the dermatologists' optimistic perspective, patients experience a limited extent of SDM and physicians should be aware of this gap. Improvement of SDM in AD and psoriasis is needed. The positive attitude of patients and dermatologists towards the process and outcome of SDM are important facilitators, while barriers were mainly perceived on an organizational level.

Introduction

In shared decision making (SDM) patients and physicians work together to make healthcare decisions, based on the best available evidence, clinical expertise and patients' values.[1,2] It is a shift from a paternalistic relationship towards a more equal collaboration between patients and physicians.[3] Arguments for SDM today are mainly based on ethical principles such as respect of patients' autonomy and values.[4] In literature there is no uniform definition for SDM, but several suggestions of what steps or elements should be incorporated in a consultation in order to perform SDM are made.

Stiggelbout et al describe four steps: 1) inform the patient that a decision has to be made, and that the patient's opinion is important, 2) explain the options and the pros and cons of each relevant option, 3) discuss the patient's preferences, and support the patient in deliberation, and 4) discuss the patient's decisional role, make or defer the decision and discuss possible follow-up. Other researchers propose three[5] or nine[6] steps which are similar in essence.

SDM is especially suitable for preference-sensitive decisions. In such decisions the available options are comparable regarding benefits and harms, and the best option depends on patients' values. Many treatment decisions in dermatology are preference-sensitive and therefore suitable for SDM.[2,7,8] In this study we focus on treatment decisions in Atopic Dermatitis (AD) and psoriasis; two chronic inflammatory skin diseases with several available treatment options in which the best option is largely dependent on patients' (psychological) burden of disease, preference and values.

Patient decision aids (PDAs) are tools that support patients and physicians in the process of SDM by providing information about risks and benefits of treatment options and helping to identify patients' personal values. The use of PDAs improves patients' knowledge, helps them feel more clear about their values and promotes patients' engagement and autonomy leading to more value-congruent choices.[9] The need for decision aids in psoriasis was previously addressed.[7,10]

However, little is known about the current extent in which SDM is applied in daily clinical practice in dermatology, or in AD and psoriasis specifically. Furthermore, no research was performed towards the aspiration of patients and dermatologists to apply SDM in daily practice.

Yet, a survey amongst 7851 Dutch patients with various diseases showed that the majority of respondents want to be involved in decision making (67% always, 27% sometimes).[11] Twenty-two percent of participants in this survey responded that no treatment options were discussed at all, which emphasized the need for improvement of SDM in The Netherlands.

If we identify a need to improve SDM in AD and psoriasis, and we can identify the perceived barriers and facilitators, suitable strategies towards improvement of patient care with SDM can be made accordingly.

Objectives

Primary

- To assess the extent to which patients and dermatologists experience SDM when making a treatment decision in AD or psoriasis.

Secondary

- To explore to what degree patients and dermatologists prefer to be involved in SDM for treatment decisions for topical-, photo-, or systemic therapy in AD and psoriasis.
- To explore which characteristics of patients and dermatologists are related to their preference to be involved in SDM.
- To explore which barriers and facilitators for SDM are perceived by patients and dermatologists.

Methods

Study design:

For this exploratory survey study we developed two comparable online surveys, for patients and dermatologists respectively, which were carried out using LimeSurvey version 2.6.7-LTS. The questionnaires took about 10 minutes to complete. All data were collected anonymously, which required completion in a single attempt since data could not be saved. The Medical Ethics Committee of the Amsterdam UMC approved the study and waived the need for a written informed consent.

Participants:

Inclusion criteria for patients were an age of 18 years or older, a diagnosis of AD or psoriasis and a treatment visit with a dermatologist or dermatology resident in the past 2 years. The patient questionnaire was accessible via the Dutch national patient associations; Association for People with Atopic Dermatitis (VMCE) and Psoriasis patients the Netherlands (PN). For AD patients, the survey was e-mailed to all members and a link to the survey was placed on the VMCE website and social media platforms. For psoriasis patients a link was placed on the PN website and social media platforms, an invitation to participate was published in the PN magazine, and flyers were spread during World Psoriasis Day 2018.

Dermatologists and dermatology residents (further referred to as dermatologists) were eligible to participate if they were practicing in the Netherlands and a member of the Dutch Society of Dermatology and Venereology (NVDV). They were invited by email and a single reminder was sent after one month.

Questionnaires:

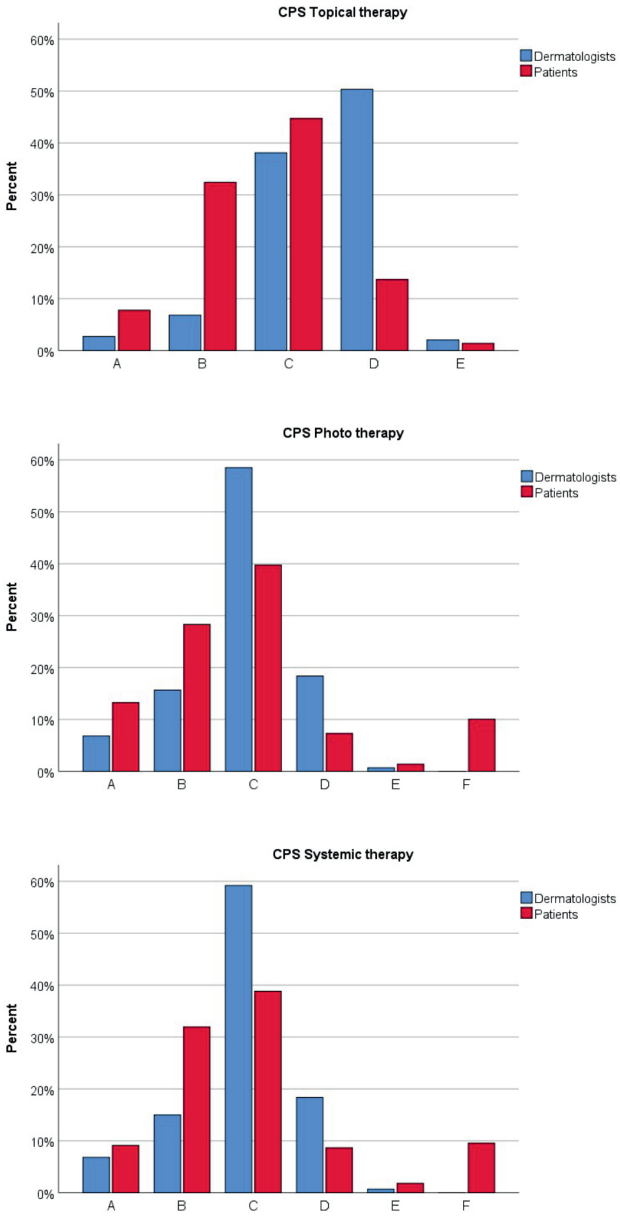
The surveys consisted of validated measures and study-specific statements developed by the research group. To measure the extent to which SDM is currently experienced when making a treatment decision for AD or psoriasis, we used the validated Dutch translation of the nine-item Shared Decision Making Questionnaire (SDM-Q), consisting of a patient questionnaire (SDM-Q-9) and a similar version for physicians (SDM-Q-doc).[12] Originally these questionnaires were designed to evaluate the extent of SDM after a consultation. We slightly adapted them to make them applicable for consultations in general, following Kunneman et al.[13]

Each of the nine items was scored on a 6-point Likert scale from 0 (no SDM) to 5 (optimum SDM) resulting in a score of 0-45, which was then converted to a 0-100 scale.

To define to what extent participants want to be involved in SDM we used the Control Preference Scale (CPS).[14] The CPS was originally designed for patients and comprises a single question to indicate their desired role in treatment decision-making (Fig. 3). When we used the CPS for the treatment of phototherapy or systemic therapy we added the option '(F) I don't know what treatment with phototherapy/systemic

therapy entails and skip this question'. The questions were slightly adapted in the physicians' questionnaire to reflect their perspective (Fig. 3).

Figure 3 – Control Preference Scale (CPS)



Dermatologists: (A) I prefer to leave all treatment decisions to my patient; (B) I prefer that my patient makes the final treatment decision after seriously considering my opinion; (C) I prefer that the patient and I share responsibility for deciding which treatment is best; (D) I prefer that I make the final treatment decision, but seriously considers my patient's opinion; (E) I prefer to make the final treatment decision.

Patients: (A) I prefer to make the final treatment decision; (B) I prefer to make the final treatment decision after seriously considering my doctor's opinion; (C) I prefer that my doctor and I share responsibility for deciding which treatment is best; (D) I prefer that my doctor makes the final treatment decision, but seriously considers my opinion; (E) I prefer to leave all treatment decisions to my doctor; (F) I don't know what treatment with phototherapy/systemic therapy encounters and skip this question.

Additional study-specific statements (responded to on a 4-point Likert scale from totally agree to totally disagree; Table 2a, 2b) were included to explore the barriers and facilitators patients and dermatologists experience and to further explore the extent of SDM they experience. The statements regarding perceived barriers and facilitators were based on previous studies.[15–18] They were classified in; 1) factors related to healthcare organisation such as time for a consultation and continuity of treating physician and 2) factors related to the decision making interaction such as believes about the importance of one's role in SDM.[16] The statements regarding the extent of SDM were based on the Observing Patient Involvement (OPTION) 5 instrument.[19]

Statistical analysis:

Data were analysed using IBM SPSS Version 25. The results of the SDM-Q-9 questionnaires were compared with a Mann-Whitney U test since data were not normally distributed. The CPS scales of patients and dermatologists were compared with a Chi-square test. To define any patient or physician characteristics which correlated with (predict) the desire for SDM a Somers' d test was performed. A value under 0.3 predicts less than 30% of the outcome, which was considered 'little if any correlation'.[20] Results of the additional statements were presented descriptively.

Results

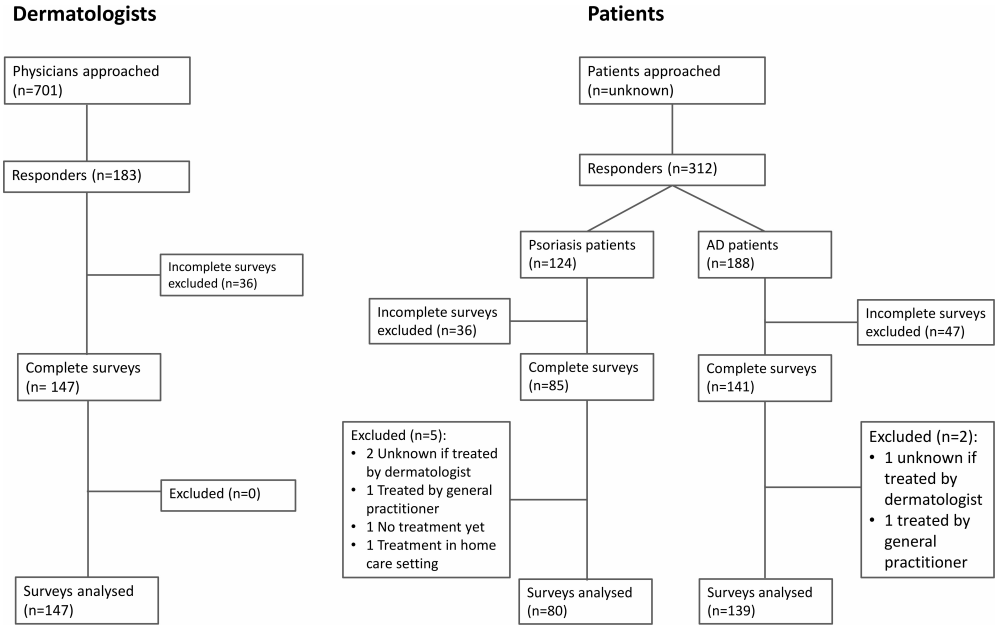
Participants

We invited an unknown number of patients (due to the strategy as described in the methods section) and 701 physicians. Incomplete surveys were excluded from analysis: 47 for patients with AD, 39 for patients with psoriasis and 36 for dermatologists.

Seven patients were excluded because it was unknown if they were treated by a dermatologist (n=3), were treated by a general practitioner (n=2), in a home care setting (n=1) or because no treatment decision was made yet (n=1).

We analysed the responses of 139 patients with AD, 80 patients with psoriasis and 147 dermatologists (Fig. 1). Demographic (and for dermatologists professional) characteristics of the participants are summarized in Table 1.

Figure 1 – Flowchart of participants.



AD = Atopic dermatitis. Incomplete surveys were defined as missing ≥ 10 items.

Almost all dermatologists (97%) were familiar with the term 'SDM' before participating in this study and 18% had previously followed a training or lecture about SDM. About half of the patients (52%) were familiar with the term 'SDM' before this study.

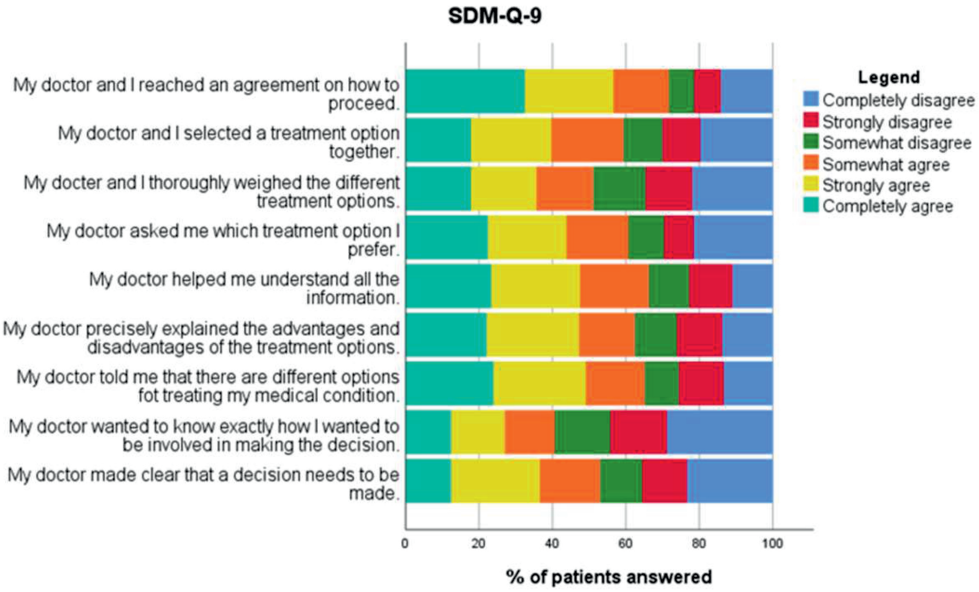
Table 1: Demographics of participating patients and dermatologists

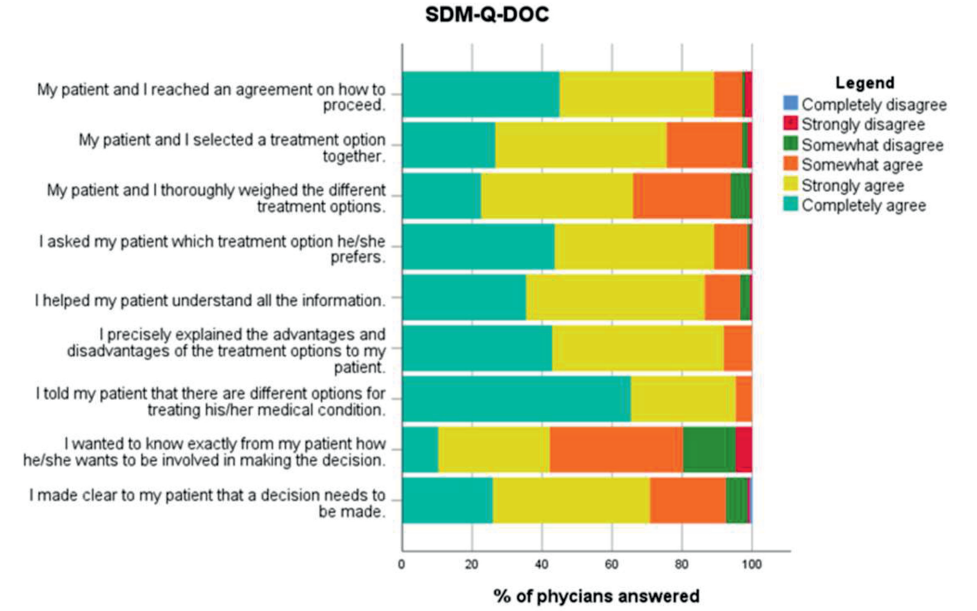
	Patients n=219
Men	63 (29)
Age, yr	
< 30	28 (13)
30 - 39	37 (17)
40 - 49	53 (24)
50 - 59	52 (24)
≥ 60	49 (22)
Skin disease	
Psoriasis	80 (37)
Atopic dermatitis	139 (63)
Disease duration, yr	
< 1	2 (1)
01. Mai	16 (7)
06. Okt	17 (8)
Nov 15	16 (7)
>15	168 (77)
Last or current treatment	
Topical	182 (83)*
Phototherapy	55 (25)
Systemic therapy	90 (41)
Education	
ISCED 0 - 1	4 (2)
ISCED 2	31 (14)
ISCED 3 - 4	75 (34)
ISCED 5 - 6	70 (32)
ISCED 7 - 8	39 (18)

	Dermatologists n=147 (%)
Men	45 (31)
Age, yr	
< 30	10 (7)
30 - 39	57 (39)
40 - 49	34 (23)
50 - 59	38 (26)
≥ 60	8 (5)
Experience, yr	
Resident	31 (21)
< 5	36 (25)
05. Sep	16 (11)
Okt 19	30 (20)
20 - 29	31 (21)
≥ 30	3 (2)
Work setting	
Academic hospital	35 (24)
Non-academic hospital	85 (58)
Private practice	27 (18)
Planned time new patient visit, min	
5	0 (0)
10	83 (57)
15	37 (25)
20	16 (11)
≥ 25	11 (8)
Planned time follow-up visit, min	
5	21 (14)
10	106 (72)
15	18 (12)
20	2 (1)
≥ 25	0 (0)

Yr = year, min = minutes, ISCED = International Standard Classification of Education
* More options could be selected e.g. topical and systemic therapy.

Figure 2 – Experienced extent of SDM by patients and dermatologists measured with SDM-Q-9 and SDM-Q-DOC respectively.





SDM = Shared decision making, SDM-Q-9 = 9-item shared decision making questionnaire for patients, SDM-Q-DOC = 9-item shared decision making questionnaire for physicians.

The extent to which patients and dermatologists experience SDM

The mean total score of the SDM-Q questionnaire (range 0-100) was significantly higher for dermatologists, 82 (95% CI 80; 83) compared to 55 for patients (95% CI 51; 58, p<0.01), indicating that dermatologists experienced a higher degree of SDM compared to patients. The largest discrepancy between patients and dermatologists was found for the statement that different treatment options were discussed (Fig. 2). There was no difference between patients with AD or psoriasis (54 vs. 55, p=0.82) in the extent to which they experienced SDM.

Notably, 56 patients (26%) indicated that their dermatologist had not discussed different treatment options. Of these patients, 63% had started with topical therapy, 14% with phototherapy and 23% with systemic therapy.

Most dermatologists (87%) reported to discuss the option of no treatment, but only 33% of the patients reported this. Of the dermatologists, 68% reported to ask patients which treatment aspects they find important (e.g. onset of action or side effects) and 60% of the patients indicated to have been asked this.

The degree to which patients and dermatologists prefer to be involved in SDM

Regarding treatment decisions for topical therapy, most dermatologists (50%) indicated to 'prefer to make the final treatment decision, but seriously consider the patients opinion'. For both photo-and systemic therapy 59% of the dermatologists preferred to make a shared decision. For biologics specifically, 36% preferred to share the responsibility and 38% preferred to make the final treatment decision but seriously consider the patients opinion.

Most patients preferred 'to share the responsibility with their doctor' when making a treatment decision for topical therapy (45%), phototherapy (40%) or systemic therapy (39%). However, a substantial part of patients, (around 30% for all three therapy groups) 'prefers to make the treatment decision after seriously considering my doctors opinion' (Fig. 3).

The patients and dermatologists characteristics related to their preference for SDM.

We did not identify a relevant correlation (defined as Somers d ≥ 0.3) between dermatologists' years of experience and the preference for SDM in topical therapy (Somers' d -0.18, p<0.01) photo therapy (Somers' d -0.02, p=0.75) or systemic therapy (Somers' d -0.02, p=0.75). The same applied for work setting (Somers' d -0.09, p=0.20; d 0.07, p=0.28; d 0.07, p=0.34) or planned consultation time (Somers' d 0.14, p=0.04; Somers' d 0.01, p=0.85; Somers' d 0.00, p=1.00) and topical- photo- or systemic therapy respectively. Previously followed courses or lectures about SDM did correlate with an enhanced preference for SDM in respectively topical-, photo- and systemic therapy (Somers' d 0.30, p=0.01; Somers' d 0.31, p< 0.01; Somers' d 0.34, p<0.01)

For patients no correlation was found between age and the preference for SDM in topical-, photo- or systemic therapy (Somers' d 0.04, p=0.40; Somers' d 0.04, p=0.31; Somers' d 0.05, p=0.31 respectively). The same applied for disease duration (Somers'

d -0.05, p=0.55; Somers' d -0.07, p=0.37; Somers' d -0.16, p=0.051) or highest level of education (Somers' d -0.11, p<0.05; Somers' d -0.003, p=0.96; Somers' d 0.09, p=0.12) and topical, photo- or systemic therapy respectively.

The perceived barriers and facilitators for SDM

The barriers or facilitators regarding healthcare organisation

The most frequently reported barrier to participate in SDM by patients (72%) was a lack of continuity in treating physician (Table 2b). Time constraints were mentioned as a barrier for SDM by 38% of the dermatologists and 15% agreed with the statement that SDM is not realistic because it takes too much time (Table 2a). No correlation could be found between the level of agreement with this statement and the actual planned time for a consultation (for a new patient or a follow-up visit; Somers' d -0.17 and Somers' d -0.01 respectively).

Barriers or facilitators regarding the decision making interaction.

All participating dermatologists (100%) believed that SDM is important and nearly all patients agreed. Also, both patients and dermatologists considered AD and psoriasis suitable for SDM.

Most dermatologists (82%) assumed that patients want to be involved in SDM, and 75% of patients felt that dermatologists want them to be involved in the treatment decision. Both patients and dermatologists reported to believe that SDM contributes to better treatment choices, improved treatment satisfaction and adherence. All of these findings facilitate SDM.

A barrier might be that 50% of the dermatologists believed that they are most capable of choosing the best suitable treatment. Also, 39% of dermatologists considered patients' knowledge about the disease and treatment options sufficient to participate in SDM. In contrast, most patients (81%) believed their knowledge is sufficient for SDM and 93% reported to feel confident to participate in SDM. Yet, the majority of patients (59%) indicated that they prefer to receive more information before participating in SDM.

Patients reported most frequently to have received information about their treatment options directly from their dermatologist (89%), a website they found themselves (29%) and by patients societies (25%). Twelve (5%) patients received no information at all (Table 3).

A table or chart with an overview of treatment options was considered relatively most helpful by 32 patients out of 36 (89%). Leaflets from the hospital were considered helpful least often (Table 3).

Fifty-nine patients (27%) preferred to receive information in a different way than they had received (Table 3). Most of these patients (n=40, 68%) preferred a chart or table with an overview of treatment options.

Table 2a – Responses on study-specific statements – dermatologists (n=147)

Statements for dermatologists	Totally disagree N (%)	Disagree N (%)	Agree N (%)	Totally Agree N (%)
Barriers or facilitators regarding healthcare organisation				
SDM is not realistic because it takes too much time.	29 (20)	96 (65)	21 (14)	1 (1)
I do not have enough time to let patients participate in the treatment decision.	17 (12)	74 (50)	45 (31)	11 (8)
Physician payment should be based on how well they do on SDM.	67 (46)	65 (44)	10 (7)	5 (3)
Barriers or facilitators regarding the decision making interaction				
Treatment decisions in psoriasis are suitable for SDM.	1 (1)	9 (6)	95 (65)	42 (29)
Treatment decisions in AD are suitable for SDM.	1 (1)	14 (10)	97 (66)	35 (24)
SDM is important	0 (0)	0 (0)	83 (57)	64 (44)
SDM is low on my priorities.	47 (32)	87 (59)	12 (8)	1 (1)
SDM improves satisfaction with the treatment.	0 (0)	9 (6)	93 (63)	45 (31)
SDM improves treatment adherence.	0 (0)	7 (5)	90 (61)	50 (34)
SDM decreases decisional conflict in patients.	7 (5)	66 (45)	60 (41)	14 (10)
SDM leads to better treatment decisions.	0 (0)	22 (15)	90 (61)	35 (24)
Patients want to participate in the treatment decision	1 (1)	25 (17)	98 (67)	23 (16)
Patients have sufficient knowledge of their disease to participate in SDM.	9 (6)	81 (55)	52 (35)	5 (3)
Patients know what treatment aspects they find important.	0 (0)	24 (16)	110 (75)	13 (9)
I ask patients if they want to be involved in the treatment decision.	6 (4)	54 (37)	69 (47)	18 (12)
I find patients that want to be involved in the treatment decision difficult patients.	55 (80)	80 (54)	9 (6)	3 (2)
I believe that as a physician I am most capable of choosing the best suitable treatment for a patient.	13 (60)	60 (41)	70 (48)	4 (3)
Patients should trust physicians to make all treatment decisions for them.	19 (85)	85 (58)	36 (25)	7 (5)

Wrong treatment decisions can be made because of SDM.	37 (91)	91 (62)	18 (12)	1 (1)
I discuss only the treatment options that I consider appropriate for a patient.	4 (3)	41 (28)	85 (58)	17 (12)
Patients can only participate in SDM if their knowledge is sufficient and they are confident enough to discuss treatment options with their physician.	3 (2)	40 (27)	80 (54)	24 (16)
Decision aids with a summary of pros and cons of treatments (such as online decision aids or option grids) would be useful.	0 (0)	10 (7)	84 (57)	53 (36)
Statements regarding the extent of SDM				
I discuss the option of no treatment.	1 (1)	18 (12)	104 (71)	24 (16)
I ask patients what treatment aspects they find important (e.g. onset of action, drug survival or long term safety).	1 (1)	45 (31)	92 (63)	9 (6)
I check if a patient understood the treatment options correctly (e.g. by asking to summarize the options).	3 (2)	62 (42)	71 (48)	11 (8)

SDM = Shared decision making

Table 2b – Responses on study-specific statements – Patients (n=219)

Statements for dermatologists	**Totally disagree** N (%)	**Disagree** N (%)	**Agree** N (%)	**Totally Agree** N (%)
Barriers or facilitators regarding healthcare organisation				
Physicians have enough time for SDM.	21 (10)	75 (34)	95 (43)	28 (13)
If I am always treated by another physician, I find it more difficult to participate in the treatment decision.	18 (8)	43 (20)	97 (44)	61 (28)
I prefer to consider the treatment options at home before I can participate in the treatment decision.	9 (4)	52 (24)	123 (56)	35 (16)
Barriers or facilitators regarding the decision making interaction				
SDM is important	1 (1)	3 (1)	96 (44)	119 (54)
SDM improves satisfaction with the chosen treatment for me.	1 (1)	11 (5)	144 (66)	63 (29)
SDM improves treatment adherence for me.	6 (3)	30 (14)	130 (59)	53 (24)

SDM limits my doubts about the chosen treatment.	6 (3)	20 (9)	142 (65)	51 (23)
SDM leads to the best therapy for me.	2 (1)	27 (12)	141 (64)	49 (22)
Physicians want patients to participate in SDM.	5 (2)	49 (22)	115 (53)	50 (23)
My knowledge is sufficient to participate in the treatment decision.	6 (3)	35 (16)	111 (51)	67 (31)
My knowledge of my disease and previous treatments is as important as the knowledge of the physician.	3 (1)	26 (12)	109 (50)	81 (37)
I know which treatment aspects I find important (e.g. how quick it works or what side effects occur on the long-term).	3 (1)	15 (7)	112 (51)	89 (41)
I am afraid that physicians think I am a burden when I get involved in the treatment decision, and that this negatively influences the treatment outcome.	64 (29)	111 (51)	29 (13)	15 (7)
Physicians know best which treatment suits me best.	10 (5)	80 (37)	110 (50)	19 (9)
I am afraid to make a wrong decision when I am involved in the treatment decision.	76 (35)	106 (48)	30 (14)	7 (3)
I feel confident enough to participate in the treatment decision.	2 (1)	13 (6)	120 (55)	84 (38)
The words that physicians use in their explanation are too difficult to participate in the treatment decision.	47 (22)	129 (59)	36 (16)	7 (3)
Statements regarding the extent of SDM				
Physicians discuss the option of no treatment.	61 (61)	86 (39)	68 (31)	4 (2)
Physicians ask me which treatment aspects I find important (e.g. how quick it works or what side effects occur on the long-term).	21 (10)	66 (30)	91 (41)	41 (19)
Physicians check if I understood the treatment options correctly (e.g. by asking me to summarize the options).	19 (9)	70 (32)	107 (49)	23 (11)
I prefer to receive more information before I can participate in the decision for my treatment.	8 (4)	60 (27)	120 (55)	31 (14)

SDM = Shared decision making

Table 3: Current way and preferred ways to provide information about treatment options as reported by patients and dermatologists.

	Information provided – dermatologists (n=147)	Information received – patients (n=219)	The received information was helpful – patients (n=173) (% of patients who received that information)	I prefer to receive information in another way – patients (n=59) (% of patients who received that information)	Preferred way to receive information – patients who preferred to receive information another way (n=59) (% of patients who received that information)
	n (%)	n (%)	n (%)	n (%)	n (%)
Consultation physician	147 (100)	195 (89)	163 (85)	42 (22)	23 (39)
Consultation nurse/assistant	58 (39)	55 (22)	27 (49)	4 (7)	11 (19)
Table with treatment options	34 (23)	36 (16)	32 (89)	4 (11)	40 (68)
Friends and family	NA	28 (13)	13 (46)	8 (17)	0 (0)
Leaflets from hospital	131 (89)	35 (16)	10 (29)	2 (6)	11 (19)
Patient society	NA	55 (25)	22 (40)	8 (15)	10 (17)
Websites recommended by hospital	73 (50)	10 (5)	4 (40)	0 (0)	18 (30)
Website I found myself	NA	63 (29)	NA	20 (32)	1 (2)
No information	0 (0)	12 (5)	NA	11 (92)	NA
Other	9 (6)	9 (4)	NA	0 (0)	0 (0)

NA = not applicable. For each statement on ore more answers could be given.

Discussion

Taking into account the four steps for SDM as described by Stiggelbout et al, we found that (step 1) 37% of the patients (strongly or totally) agree with the statement that it was made clear that a treatment decision had to be made. This number is low compared to other studies, but these were not performed on dermatology patients.[21,22]

Concerning step 2, about half of the patients report (to strongly or totally agree) that different treatment options including the pros and cons were discussed and a quarter reported that no options were discussed. More complete information about the treatment options seems necessary, which was also demonstrated in a Canadian survey study amongst psoriasis patients.[23] Other studies confirm that patients want more information than what physicians expect.[22,24] Decision aids are particularly helpful here and they have shown to improve patients' knowledge and risk perception.[9] Also, the use of decision aids can meet the preference of the majority of the patients (72%) to consider the treatment options at home.

For step 3, 44% of the patients reported (to strongly or totally agree) that their preferences towards therapies were discussed and 60% reported they were asked which treatment aspects they found important. Only 35% (strongly or totally) agrees that the options were thoroughly weighted. In a systematic review it was reported that patient preferences were discussed in only 1 of 17 studies, and on a level below baseline skills.[21] Unlike in our study these outcomes were objectively measured. Nevertheless it seems that dermatologists in the Netherlands perform relatively well on this step. Finally, regarding step 4, 27% of patients report (to strongly or totally agree) that their dermatologists asked if and how they wanted to be involved in the treatment decision and 39% reported that the treatment decision was shared. This was slightly higher than the 29% reported in the Canadian survey.[23]

There is quite a difference between patients and dermatologists in the reported extent of SDM (althoughconclusions should be taken carefully as the patients in this study were not patients of the participating dermatologists). Possibly, several aspects of SDM are discussed by dermatologists, but are not remembered by patients or not recalled correctly as reported in several studies.[13,25,26] However, one could argue that in that case SDM was not performed satisfactorily, and improvement is nevertheless necessary. Additionally, it is known that both patients and physicians subjectively report higher levels of SDM compared to what is objectively measured when consultations are audiotaped.[27,28] Being aware of the lower experienced extent of SDM by patients might encourage dermatologists to make more efforts to improve SDM. Previously followed courses or lectures about SDM were the only characteristic in dermatologists that correlated with an enhanced preference for SDM. We could not identify any patients' characteristics that correlate with the preference for SDM, but the groups are relatively small for this analysis. Nevertheless we suggest that no patients are excluded from SDM beforehand.

Regarding the barriers and facilitators for SDM, mostly facilitators were found. Both patients and dermatologists acknowledge each other's willingness to apply SDM and both groups believe that SDM results in improvement of patient care. These facilitators are also most frequently reported in literature.[29] Barriers are most often perceived on

an organisational level, such as continuity in treating physician and lack of time. One way to address these issues could be to involve other healthcare practitioners such as (specialized) nurses to further explain treatment options before making the final decision with the dermatologist. Other often reported barriers are lack of applicability due to patient characteristics or clinical situation, but these were not confirmed in our study.[29]

Strengths and limitations

Our study compares the views of patients and dermatologists, which helps to obtain a complete picture of the current situation. Like all survey studies, this study is prone to recall bias and there might be a selection bias since patients and dermatologists with an interest in SDM are more likely to participate. The participating patients were not treaded by the participating dermatologists. Incomplete surveys were not included in analysis. Reasons for discontinuation were not collected, but possibly the need to finish the survey in a single attempt has played a role. Patients were recruited via the national patient societies, and their members might be more actively involved with disease management. This study lacks objective measurements of the extent of SDM, therefore it is not to say if the differences between patients and dermatologists are accountable to one group.

Future perspective

The results of this study show that improvement of SDM in AD and psoriasis is needed. Potential steps to accomplish this include education on the concept of SDM and training in communication skills for physicians on how to attain SDM during a consultation.[30] Preferred ways are consultation simulations with trained actors or colleagues and include not only treating physicians but also other involved healthcare professionals.[4,22,31] Furthermore, since only half of the patients were familiar with SDM, patient education is important to create awareness about SDM and encourage patients to actively participate in the treatment decision. Decision aids are appreciated by patients and are helpful to improve SDM. Compact 1-page encounter decision aids have recently been developed for AD and psoriasis in the Netherlands.[9,32–34] However, they cannot replace the consultation between patients and their dermatologist. Although patients and dermatologists presume beneficial effects of SDM, data on the effect of SDM on treatment satisfaction and adherence are lacking and clinical trials are needed.

Conclusion

Both patients and dermatologists prefer SDM for treatment decisions in AD and psoriasis. Despite the dermatologists optimistic perspective, the extent of SDM that patients experience is limited and physicians should be aware of this gap. Improvement of SDM in AD and psoriasis is needed in all four steps. The positive attitude of patients and dermatologists towards the process and outcome of SDM are important facilitators. The most important perceived barriers include a lack of continuity of care by the same physician and a lack of time. Further steps to improve SDM in dermatology can include

training of physicians, education in patients, and the development and implementation support tools such as decision aids.

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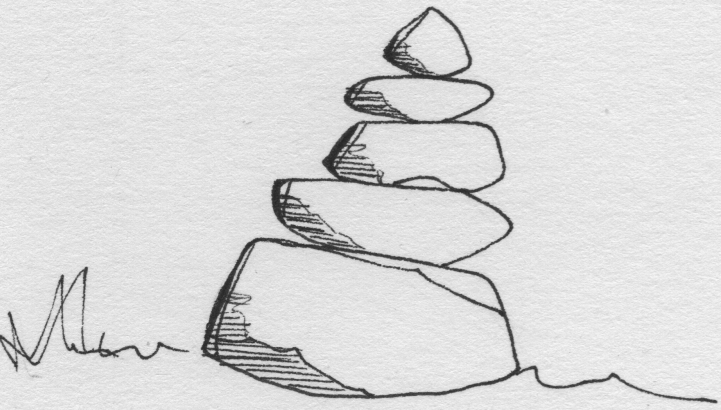

Chapter 6

Towards more Shared Decision Making in dermatology: the steps taken for evidence-based Decision Cards on psoriasis and atopic eczema treatments

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Abstract

In Shared Decision Making (SDM) patients and physicians make treatment decisions together, based on the best available evidence and the values and preferences of patients. SDM is very suitable for the dermatological practice, but is infrequently applied by dermatologists.

To support SDM in dermatology we developed Decision Cards; one-page overviews of possible treatment options which are used during a patient-physician consultation. Decision Cards provide answers to patients' most frequently asked questions based on (inter)national guidelines, Summary of Product Characteristics, relevant literature and clinical expertise. Three evidence-based Decision Cards were developed; one for biologicals or apremilast in psoriasis, and two for atopic eczema: one for topical, photo- or systemic therapy and one only for systemic therapy. More cards for psoriasis are under development. Patients, dermatologists and researchers collaborated in the development of the Decision Cards. The framework used for the development is shared to support others in the development process.

Introduction

Shared decision making (SDM) can be defined as an approach where physicians and patients share the best available evidence when faced with the task of making decisions, in order to choose the therapy which best suits a patient's values, preferences and needs.[1]

Tan et al. and Anstey et al. wrote articles advocating more integration of SDM in dermatology.[2,3] Many skin diseases have multiple treatment options, usually without one best treatment. The best treatment depends on disease aspects (such as extent and location of the lesions), patient aspects (such as comorbidity, co-medication and physical and emotional burden of the disease), and patient preferences (e.g. the frequency and route of administration, number of hospital visits or the need for controls). These aspects can vary between patients, but also in the same patient over time. Such preference-sensitive treatment decisions are most suitable for SDM.[4]

Three steps have been proposed to apply SDM during a consultation: 1) acknowledge that a treatment decision has to be made and explore what role the patient wants in this decision making process, 2) compare treatment options and discuss the benefits and harms of these options, 3) make a treatment decision that best suits the patient's expectations, needs and lifestyle guided by the experience of the healthcare team.[5]

Patient decision aids (PDAs) are tools to support patients in the decision making process, by providing information about treatment options and helping patients to identify their values. Encounter decision aids (EDAs) are PDAs developed for use during a consultation.[6,7]

The use of a decision aid improves patients' knowledge and the likelihood of patients making decisions more congruent to their values.[8] It improves doctor patient communication and satisfaction with the treatment decision and decision making process compared to usual care.[8] This may enhance treatment compliance, but studies report different outcomes on this subject.[8]

The challenge in the development of decision aids is to provide scientifically correct information, which is helpful and understandable for patients. They are therefore preferably developed according to an established format. We developed Decision Cards, one-page EDAs with an overview of different treatment options based on the questions most frequently asked by patients. They are similar to Option Grids, designed and studied extensively by the group of Glynn Elwyn[9–12] and make the treatment options easy to discuss because they are standardised and visually displayed.[13] Decision cards are preferably read through by patients and physicians together (although patients can take them home too, as long as they engage in the decision making process), and support the discussion of individual patient's values and preferences which are therefore only partly incorporated on the cards itself.[9,14]

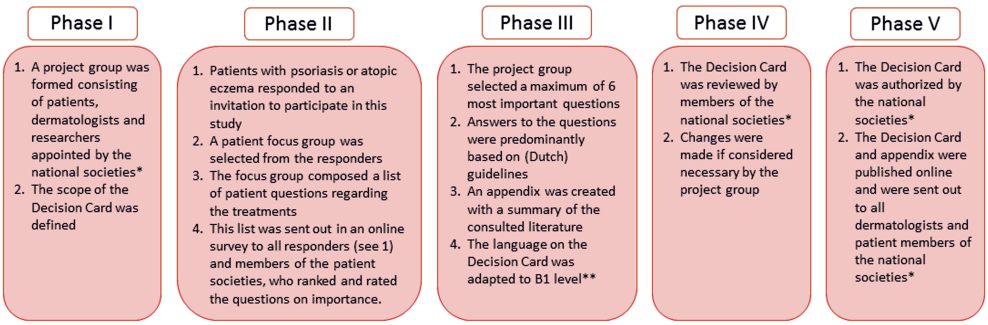
Up until now no Option Grids or Decision Cards were available in Dutch for any dermatological diseases, nor are such tools available in English for AE. Since Decision Cards are designed for patients, it is important that they are available in the native language of a patient, and suitable for daily practice in a specific country.

We decided to developed Decision Cards for psoriasis and AE, since treatment decisions for these diseases are preference sensitive, many treatment options are available for these diseases and because psoriasis and AE are common diseases, meaning many patients can benefit. In this study we describe the used framework, which may serve as an example for the development of EDAs for other dermatological diseases.

Materials and Methods

For the development of the Decision Cards a previously established framework was used in which a clear order of consecutive steps was provided (Fig. 1).[15] This framework complies with the Dutch Protocol for the development of decision aids with guidelines,[16] and was developed by the Knowledge Institute of the Dutch Association of Medical Specialists and the Netherlands Patients Federation. Both have been the initiators for the development of Decision Cards for multiple diseases. The format was inspired by the format of the Dartmouth Institute for Option Grids (not published). The development and usage of Option Grids have been investigated for many years, but its trademark restrains development of Option Grids by other researchers.[9–12]

Figure 1 – Summary of the used framework for the development of a Decision Card



*Dutch National Society for Dermatology and Venereology and patient societies Skin patients the Netherlands and Dutch Association for People with Atopic Dermatitis.

** According to the Common European Framework of Reference for Languages.

During the first phase, two project groups were formed; one for the development of a psoriasis Decision Card and one for the AE Decision Cards. Both project groups consisted of dermatologists affiliated with the Dutch National Society for Dermatology and Venereology (NVDV), patients, patient representatives of the national dermatology patient association (Skin Patients the Netherlands and Association for People with Atopic Dermatitis), researchers and project advisors experienced in the development of Decision Cards.

A Decision Card contains a maximum of 6 treatments due to the limited amount of space that is available (one side of standard size A4 paper).[13] Therefore the project groups defined a specific treatment category (e.g. systemic or topical therapies) and patient group (e.g. adults or children) per Decision Card. The project group selected treatment categories in which the need for more information on the treatment decision was most necessary. Only treatments currently captured by the Dutch national guidelines were eligible.

In the second phase, an invitation was sent out via email to a cohort of psoriasis and AE patients. Of those who were willing to participate in this project, a selection was made for participation in a focus group, pursuing a group of equal distribution in age, sex, residence, education level and expertise with multiple treatments. Three focus groups consisting of 5 psoriasis patients, 8 AE patients for the first and 4 AE patients

for the second AE Decision Card composed a list of important questions regarding the treatments. Next, the project group added more questions based on their clinical expertise. An online survey with the complete list of questions was then sent to all psoriasis and AE patients of the cohort, members of the national patient societies and a link to the survey was placed on the patient societies websites. In this survey, patients were asked to judge the questions in 2 different ways:

- By rating the questions with a number from 1-10 (with 10 being the most important).
- By ranking the questions from most important to least important. If a question was ranked most important by a patient it received 1 point, the 2nd question received 0.5 point, the 3rd 0.33, the 4th 0.25 and the 5th 0.2 point. After the 5th question no points were awarded. The total of points was then calculated for each question. Questions with the highest score were overall ranked as most important.

In the third phase, a maximum of 6 most important questions were selected based on the patient surveys. If questions did not make this cut-off but were often encountered in clinical practice according to the dermatologists, attempts were made to merge them with other, already included questions. In order to formulate answers to these questions, evidence from (inter)national guidelines (from the Netherlands,[17,18] the United Kingdom,[19] the United States of America[20,21] and the European Dermatology Forum[22,23]) and summary of product characteristics (SmPC) texts was used. In case of discrepancies between guidelines, the national guideline was followed. If the consulted guidelines did not provide the answers, recent systematic reviews, meta-analyses and other (preferably randomized controlled) studies were consulted. Only if necessary, answers were based on expert opinions. Appendices were created containing a summary of the available and consulted literature and the rationale why certain information was or was not selected to be used for the answers on the Decision Cards.[24–26]

In order to make the Decision Cards as accessible as possible to all patient groups the language used on the Decision Cards was adapted to B1 level according to the Common European Framework of Reference for Languages.[27] After finalising the first draft of the Decision Cards, members of the NVDV and the Dutch patient societies for psoriasis and AE were invited for feedback (fourth phase). In addition to the original framework, we invited the Association Innovative Medicines (the industry association for the Dutch branches of innovative pharmaceutical companies) to provide feedback as well. The received suggestions for modifications were then re-evaluated by the project group and, only if considered necessary, the answers on the Decision Cards were adjusted. The reasons for or against implementing the suggestions were collected and summarised in the appendix of the corresponding Decision Card. After this last step the Decision Cards were finalised and sent out to the NVDV and patient societies for approval and authorization (fifth phase). Finally, the Decision Cards were published online on https://consultkaart.nl.

The Decision Cards were linked to the national guidelines to ensure updates of the guidelines are followed by an update of the Decision Cards.

Results

The project group of the psoriasis Decision Card consisted of one dermatologist, one dermatology researcher, two patient representatives and one project advisor. The project group of the two AE Decision Cards consisted of two dermatologists, one dermatology researcher, three patient representatives and one project advisor.

Three Decision Cards were developed (See Table 1-3). For psoriasis one for biologics or apremilast in psoriasis vulgaris, as this is the most frequently encountered treatment decision in our (third line) hospital. For AE two cards were developed: one for systemic medication in AE (AE I) and one for different types of treatment in AE (topical, phototherapy or systemic therapy, AE II). All three Decision Cards were designed for adult patients.

In February and March 2017, the online surveys with the proposed questions for the psoriasis and AE I Decision Cards were carried out. The survey for Decision Card AE II followed in August and September 2017. Thirty-four patients with psoriasis, 76 (AE I) and 60 (AE II) patients with AE filled out the surveys. Characteristics of the patients are described in Table 4. The most important questions including the mean rating score (0-10) and weighted ranking are described per survey in Tables S1, S2 and S3.

For psoriasis the selected questions were:

- *What does this treatment entail?*
  Route and frequency of administration, hospital visits and blood tests were incorporated.
- *What is the effect of the treatment?*
  We showed: 1) the percentage of patients achieving a good effect, defined as Psoriasis Area and Severity Index (PASI) 75 (75% improvement of the PASI) after 3-4 months, 2) the time until onset of action (TOA),[28] defined as the time until 25% of patients achieve PASI 75 and 3) drug survival after 3 years.
- *What are the most common side effects that occur in 10 or more of 100 patients (≥10%)?*
  The very frequent side effects according to the SmPC texts were added. After extensive discussions in the project group, the risk for depression and sleep loss in apremilast were additionally added, since this is mentioned explicitly in the SmPC text.
- *Does this treatment affect my other disorders or medication?*
  Since psoriatic arthritis (PsA) is relatively common in patients with severe psoriasis the effect of the drugs on PsA was added.[17] Furthermore, diseases which are related and more common in patients with psoriasis (inflammatory bowel disease, multiple sclerosis and systemic lupus erythematosus), and diseases that make a clear distinction in the preference for certain drugs such as heart failure, were discussed.

Table 1 – Decision Card 'Atopic eczema: treatment options for systemic drugs in adults. (AE I)'

Are you 18 years or older and diagnosed with psoriasis? Do you consider starting a treatment with a biological or apremilast? This Decision Card can support you and your doctor when discussing treatment options. The Decision Card is based on the Dutch Psoriasis guideline 2017, newer drugs are not (yet) listed. These treatments are generally not suitable for patients with severe active infections or cancer, and for pregnant or breastfeeding women. If you also use other immune suppressing drugs there may be more risks of side effects. During treatment live vaccines should be avoided. It is recommended to get the annual flu vaccine.

	Apremilast, 2015 (Otezla)	Adalimumab, 2007 (Humira, Amgevita, Hulio, Hyrimoz, Imraldi)	Etanercept, 2004 (Enbrel, Benepali, Erelzi)	Secukinumab, 2015 (Cosentyx)	Ustekinumab, 2008 (Stelara)	Infliximab, 2005 (Remicade, Remsima, Inflectra)
What does this treatment entail?	• Two pills are taken a day • The intake is increased from 10mg to 30 mg. • A blood test will be done before start of treatment and during treatment only if necessary.	• Self-applied injection. • Two injections in the first week and thereafter 1 injection every other week. • A blood test will be done before start of treatment and every 3 – 6 months during treatment.	• Self-applied injection. • One or 2 times a week. • A blood test will be done before start of treatment and every 3 – 6 months during treatment.	• Self-applied injections: 2 at a time. • The first month once a week, thereafter once a month. • A blood test will be done before start of treatment and every 3 – 6 months during treatment.	• Self-applied injection or injection at the hospital. • Week 0 and 4. Thereafter once every 12 weeks. • A blood test will be done before start of treatment and every 3 – 6 months during treatment.	• An infusion is given at the hospital. • Week 0, 2 and 6, thereafter once every 8 weeks. • A blood test will be done before start of treatment and every • 3 – 6 months during treatment.
What is the effect of the treatment?	• The first effect can be noticed after 9-11 weeks.* • 34 of 100 patients (34%) notice a good effect.** • Unknown how many patients still benefit from this drug after 3 years.	• The first effect can be noticed after 4-5 weeks.* • 70 of 100 patients (70%) notice a good effect.* • After 3 years 56 of 100 patients (56%) still benefit from this drug.	• The first effect can be noticed after 6-7 weeks.* • 41 of 100 patients (41%) notice a good effect.** • After 3 years 51 of 100 patients (51%) still benefit from this drug.	• The first effect can be noticed after 3-4 weeks.* • 78 of 100 patients (78%) notice a good effect.** • Unknown how many patients still benefit from this drug after 3 years.	• The first effect can be noticed after 4-5 weeks.* • 72 of 100 patients (72%) notice a good effect.** • After 3 years 79 of 100 patients (79%) still benefit from this drug.	• The first effect can be noticed after 3-4 weeks.* • 57 of 100 patients (57%) notice a good effect.** • After 3 years 51 of 100 patients (51%) still benefit from this drug.
What are the most common side effects that occur in 10 or more of 100 patients (≥10%)?	• Gastro-intestinal complaints • Weight loss • Although not very common, there is a slightly higher risk of mental disorders such as sleep loss and depression.	• Infections • Headache • Rash • Muscle aches • Gastro-intestinal complaints • Redness or itch at the injection site • Abnormalities in your blood test results	• Infections • Hives • Redness or itch at the injection site	• Infections	• There are no known very common side effects for this drug, however every drug can have side effects.	• Infections • Gastro-intestinal complaints • Headache • Allergic reactions • during or after infusion

Does this treatment effect my other disorders or medication?	• If you use i.a. rifampicin, anti-epileptics or St John's Worth, apremilast is less effective. • If you have a congenital metabolic disorder this drug might not be suitable. • In psoriatic arthritis this drug is usually not recommended.	• Do not use this drug in severe heart failure. • If you have Multiple Sclerosis (MS) or Systemic Lupus Erythematosus (SLE) this drug is less suitable. • In psoriatic arthritis this drug is preferred.	• Do not use this drug in severe heart failure. • If you use medication for diabetes your blood sugar levels can lower after starting this treatment. • If you have Multiple Sclerosis (MS) this drug is less suitable. • In psoriatic arthritis this drug is preferred.	• Caution is advised in patients with Crohn's disease or ulcerative colitis. • In psoriatic arthritis this drug is less preferred.	• In psoriatic arthritis this drug is less preferred.	• Do not use this drug in severe heart failure. • If you have Multiple Sclerosis (MS) or Systemic Lupus Erythematosus (SLE) this drug is less suitable. • In psoriatic arthritis this drug is preferred.

*Time until Onset of Action (TOA): time until 25% of patients achieve PASI 75. **PASI 75 after 12-16 weeks. PASI = Psoriasis Area and Severity Index.

Table 2 – Decision Card 'Atopic eczema: treatment options for systemic drugs in adults. (AE I)'

Have you been diagnosed with Atopic Eczema? This Decision Card can support you and your doctor when discussing treatment options for systemic drugs. It is based on the Dutch guideline Atopic eczema 2014. Systemic dugs are drugs that work throughout the whole body. All drugs suppress the inflammatory response and/or suppress the immune system, which improves your eczema. These drugs may increase the risk for infections and cancer. During treatment, live vaccines should be avoided. Do you doubt between a treatment with an ointment or cream, phototherapy or a systemic treatment? Then please use the Decision Card "Atopic Eczema: treatment options in adults".

	Ciclosporin	Azathioprine	Methotrexate	Mycophenolate, mycophenolic acid	Prednisone
What does this treatment entail?	• Two pills are taken a day; before, during or after a meal. • This drug can be used for 1 to 2 years, and sometimes longer.	• Two pills are taken a day; 1 hour before or 3 hours after a meal. • This drug can be used for 1 year, some people use it several years.	• One pill or self-applied injection is taken a week; 1 hour before or 1.5 to 2 hours after a meal. • This drug can be used more than 5 years.	• Two pills are taken a day; before, during or after a meal. • Some people use this drug for several years.	• One pill is taken a day; before or during a meal. • It is not recommended to use this drug for a long time. In severe and acute flares you can take this drug for 2 to 3 weeks.
What is the effect on my signs and symptoms? And how quickly do they improve?	• Good effect on the signs and symptoms. • Good effect on itch. • The signs and symptoms reduce within 2 to 6 weeks.	• Moderate effect on the signs and symptoms. • Moderate effect on itch. • The signs and symptoms reduce within a few weeks to a few months.	• Moderate effect on the signs and symptoms. • Moderate effect on itch. • The signs and symptoms reduce within a few to 10 weeks.	• Moderate effect on the signs and symptoms. • Probably a moderate effect on itch. • The signs and symptoms reduce within a few weeks to a few months.	• Very good effect on the signs and symptoms. • Very good effect on itch. • The signs and symptoms reduce within 1 day to a few days.
What are the very frequent side effects that occur in 10 or more of 100 patients (≥10%)?	• Increased blood fats (such as cholesterol) • Tremors • Headache • High blood pressure • Excessive hair growth on the face/body • Impaired kidney function	• Shortage of white blood cells due to impaired bone marrow function	• Decreased appetite • Nausea, vomiting, stomach ache • Inflammation and ulceration of the mucous membranes of the mouth and throat • Stomach and oesophagus complaints • Impaired liver function	• Blood poisoning • Shortage of white blood cells • Shortage of platelets • Anaemia • Nausea, vomiting, stomach ache, diarrhea	• There are many 'frequent' side effects (in 1 to 10 of 100 patients (1-10%) such as disturbed blood sugar levels, mood swings and fluid retention.
Which disorders may worsen when you use this drug?	• Impaired kidney function • Disorders of the liver • High blood pressure • Gout	• Impaired liver function • Impaired bone marrow function • Pancreatitis • Gout	• Disorders of the liver or kidney • Impaired bone marrow function • Poor lung function or lung fibrosis (scarring of lung tissue) • Immune disorders • Gastric ulcer • Gout	• Gout	• Gastric or duodenal ulcer • Diabetes • High blood pressure • Osteoporosis • Mental disorders

When should you not use this drug?	• Are you pregnant or do you want to become pregnant? Then only use this drug under strict supervision of your doctor. • Are you breastfeeding? Then do not use this drug.	• Are you pregnant, do you want to become pregnant, or are you breastfeeding? Or do you want to become a father? Then do not use this drug.	• Are you pregnant, do you want to become pregnant, or are you breastfeeding? Or do you want to become a father? Then do not use this drug. • Limit your alcohol consumption to a minimum.	• Are you pregnant, do you want to become pregnant, or are you breastfeeding? Or do you want to become a father? Then do not use this drug. • Are you pregnant or do you want to become pregnant? Then only use this drug under strict supervision of your doctor. • Are you breastfeeding? Then do not use this drug.

Table 3 – Decision Card 'Atopic eczema: treatment options in adults. (AE II)'

Have you been diagnosed with Atopic Eczema? This Decision Card can support you and your doctor when discussing the options for treatment. It is based on the Dutch guideline Atopic eczema 2014. All treatments inhibit the inflammatory response and/or suppress the immune system, which improves your eczema. Are you and your doctor considering systemic medication? Then please also use the Decision Card "Atopic Eczema: possibilities for systemic treatment in adults". Systemic drugs are drugs that work throughout the whole body.

	Ointment, cream or lotion			Phototherapy (UVA, UVB)	Systemic drugs
	Corticosteroids	Calcineurin inhibitors	Coal tar		
What does this treatment entail?	Corticosteroids are applied on the skin 1 or 2 times a day, for 2 to 7 days a week. How long corticosteroids need to be applied depends on: • The severity of your eczema. • The strength of the corticosteroids. Strength: 1, 2, 3, or 4, of which 4 is the strongest. • How often the ointment is applied. • Where on the body it is applied.	• Calcineurin inhibitors are applied on the skin 1 or 2 times a day, for 2 to 7 days a week. • It is safe to use this for a long time.	• Coal tar is applied on your skin 1 or 2 times a day. You can do this every day. • It is safe to use this for a long time.	• Visits to the outpatient clinic are needed for this treatment; 2 to 3 times a week over a period of 6 to 12 weeks. • In consultation with your doctor, treatment at home may be possible.	• The specific type of drug influences the frequency and length of treatment. • These drugs (pills or injections) are taken 1 time a week to 2 times a day. • The drugs can be used for a couple of weeks to several years.
What is the chance that signs (such as redness and scaling) and itch decrease?	• This depends on the strength, how often it is applied and whether it is an ointment, cream or lotion: • Good effect on signs. • Good effect on itch.	• This depends on the strength: • Moderate to good effect on signs. • Moderate to good effect on itch.	• Moderate effect on signs. • Possibly good effect on itch.	• Moderate to good effect on signs. • Moderate to good effect on itch.	• This depends on the drug: • Moderate to very good effect on signs. • Moderate to very good effect on itch.
What are the most important side effects which can occur?	• This depends on the strength, how often and where on the body it is applied: • Pimples • The skin can become lighter • Red, itching bumps around the mouth • A thinner skin resulting in small blood vessels becoming more visible and small bruises or stretchmarks	• These side effects can occur on the skin where you apply the drug: • Burning sensation • Itch • Redness and irritation in the face when drinking alcohol	• Skin irritation • Allergic reaction • Inflamed hair follicles • Pimples • Unpleasant smell • Discolouring of your skin, hair, clothing and bedsheets	• Dry skin • Red skin • Burning sensation of the skin • Risk of premature skin aging • Higher risk of skin cancer	• These drugs can have many side effects. We refer to the Decision Card "Atopic eczema: treatment options for systemic drugs in adults".

What can I no longer do with this treatment?	• There are no limitations.	• Limit the amount or prevent sun exposition to your skin.	• Limit the amount or prevent sun exposition to your skin.	• Limit the amount of sun exposition to your skin.	• Avoid alcohol completely or limit your use in combination with specific medications.
Are you pregnant, do you want to become pregnant or are you breastfeeding?	• This treatment is possible under supervision of your doctor.	• Do not use this treatment.	• Do not use this treatment.	• There are no limitations.	• Most treatments cannot be used. In some cases treatment is possible under strict supervision of your doctor.

Table 4: Characteristics of the patients participating in the surveys.

	Psoriasis N (%)	Atopic Eczema I – systemic treatment N (%)	Atopic Eczema II – any treatment N (%)
Number of participants	34	76	60
% Men	13 (38 %)	14 (18%)	14 (24%)
Age < 18	0	2 (3%)	1 (2%)
Age 18-30	1 (3%)	4 (5%)	3 (5%)
Age 31-50	9 (27%)	19 (25%)	16 (27%)
Age 51-70	24 (70%)	47 (62%)	34 (56%)
Age > 70	0	4 (5%)	6 (10%)
Disease duration > 5 year	32 (95%)	67 (88%)	52 (86%)
Diagnosed with nail psoriasis	20 (59%)	NA	NA
Diagnosed with psoriatic arthritis	21 (62%)	NA	NA
Highest level of education			
Higher education ISCED 6-8	11 (32%)	11 (14%)	Unknown
Secondary education ISCED 3-5	9 (27%)	30 (38%)	Unknown
Lower education ISCED 0-2	14 (18%)	14 (19%)	Unknown

NA = not applicable, ISCED = International Standard Classification of Education.

For AE I the questions were:

- *What does this treatment entail?*
  The route and frequency of administration, need to take the drugs with or without a meal and the possible duration of treatment were incorporated.
- *What is the effect on my signs and symptoms? And how quickly do they improve?*
  Due to severe heterogeneity in the study reported outcomes on clinical signs and itch, the project group had to take multiple different treatment effects into consideration. After careful comparison the project group categorised the treatment effects in a 4-point ordinal scale ranging from no effect to very good effect.
- *What are the very frequent side effects that occur in 10 or more of 100 patients (≥10%)?*
  The very frequent side effects according to the SmPC text were reported.
- *Which disorders may worsen when you use this drug?*
  The absolute contra-indications derived from the Dutch guideline were added.[18]

- *When should you not use this drug?*
  An advice for parents wishing to have children (both men and women), breastfeeding and alcohol use was discussed.

For AE II the questions were:

- *What does this treatment entail?*
  The route and frequency of the drug and the possible duration of treatment were added. For topical corticosteroids we mentioned that the strength of the drug, the severity of AE, frequency and location of application all influence the treatment duration.
- *What is the chance that signs (such as redness and scaling) and itch decrease?*
  The same 4-point ordinal scale as used in the AE I Decision Card was applied. Strength, frequency and type of ointment were added as influential factors for corticosteroids and strength only for calcineurin inhibitors.
- *What are the most important side effects which can occur?* For topical corticosteroids, coal tar and phototherapy no very frequent side effects are known. Therefore the Dutch guideline was followed for the most important side effects for these therapies.
- *What can I no longer do with this treatment? Are you pregnant, do you want to become pregnant or are you breastfeeding?*
  SmPC texts were used for these questions, as well as information of the treatments acquired from the pharmaceutical companies. If no information was available, expert opinions were incorporated.

Discussion

In chronic illnesses, such as psoriasis and AE, it is especially important for patients to adopt a more active role in decision making as throughout the course of the disease multiple treatment decisions can be made.[3,29] The need for decision aids in dermatology, and especially short and feasible decision aids for busy clinicians, was previously indicated by Tan et al,[2] and is also highlighted by research that has shown time-constraints are one of the most important perceived barriers for physicians for the application of SDM.[30] Decision Cards are compact tools and provide the most important information to make comparisons in a glance - which is sometimes all that is needed to make a decision.[1–3,13] We therefore believe Decision Cards are useful support tools to improve SDM in the dermatological setting and are optimistic that they will find their way into daily practice. We hope that by sharing our experience, others will be able to develop Decision Cards to further enhance SDM.

Two other EDAs for dermatologic diseases could be found. One EDA for psoriasis was presented in the British Association of Dermatologists (BAD) guidelines for biologic therapy for psoriasis 2017.[19] The treatments discussed in this EDA are slightly different since ixekizumab was discussed and apremilast was not. Also, more and slightly different questions are answered: start dosages are not discussed; effectiveness is registered as PASI 90 instead of PASI 75; drug survival after one instead of three years is mentioned; and side effects causing a termination of the treatment or an admission into the hospital due to infections are provided. Another EDA was found for actinic keratosis, but no methods for the development were reported.[31]

Strengths and limitations

The Decision Cards provided in this study were based on the previously described framework,[15] which was based on the format of the Dartmouth Institute, and has been used for many Decision Cards already. Since the Knowledge Institute successfully developed multiple Decision Cards, expertise from their advisors was beneficial for the development of our cards. Because the questions on the Decision Cards were defined as most important by patients, they provide relevant information for patients when facing a treatment decision. Data used to answer these questions were derived from (inter)national guidelines, systematic reviews, international SmPC texts and, if necessary, primary research and clinical expertise. Relevant stakeholders, affiliated to dermatological, pharmaceutical and patient organisations, were involved (either in the development phase or in the reviewing phase) which creates a good support base for the implementation and use of the Decision Cards. To provide transparency, for each Decision Card an appendix was made in which the quality of evidence of the consulted literature can be found. Because the cards are linked to the national guidelines, updates of the guidelines will guarantee updates of the Decision Cards. Since the Decision Cards are in Dutch and the language was adapted to the B1 level according to the Common European Framework of Reference for Languages, the Decision Cards will be useful for many psoriasis and AE patients in the Netherlands. For the purpose of this article, we provide English versions of the Decision Cards that were loosely translated from the Dutch Decision Cards.

A few limitations need to be mentioned. Due to the limited space on a Decision Card only a selection of questions, treatments and information could be included. Also, not for all treatment options sufficient evidence to answer the questions properly was available. Since this might influence the treatment decision it was mentioned on the Decision Cards whenever applicable. As the surveys for the most important questions were dispersed via a link on patient societies websites, we unfortunately cannot calculate response rates. In both psoriasis and AE research many different outcome measures are used.[32–34] Due to this heterogeneity it is hard to compare evidence. Preferably, future studies should report core outcomes.[35] To promote high quality control criteria for PDAs, the International Patient Decision Aids Standards (IPDAS) criteria were developed.[36] Unfortunately, these criteria are not yet suitable for EDAs due to their compact size but hopefully will be applicable in the near future.[14] Lastly, since the Dutch treatment guidelines were leading in the development of these Decision Cards, not all available treatments were discussed and the answers provided on the Decision Cards can differ from other guidelines. Physicians from other countries are advised to check if these decision cards are suitable for their country. There is a need to update the Decision Cards regularly in the future with the best available evidence. In order to do so, it might be favourable to base Decision Cards on living, international guidelines in the future, and adapt them to the availability of therapies in each specific country. If living, international guidelines will not become available in the near future, the Decision Cards should be updated with every guideline update, as is currently agreed upon.

Future perspective

Preferably, in the future more Decision Cards will be developed, especially for topical, photo and systemic therapies in psoriasis and eventually also for the (newer) biologics in both psoriasis and AE. In addition, the impact of Decision Cards on SDM in clinical practice should be evaluated and it might be helpful to develop EDAs that present information more graphically instead of textually.

To fully benefit from decision aids it is important that they are properly implemented. This will require a change in clinical routine and more attention for SDM during a consultation.[5] Even though some physicians feel SDM takes up too much time, SDM might also save time in the long run, through better compliance, better outcomes and selecting the right treatment the first time a treatment-decision needs to be made.[8] Decision Cards should not replace the conversation between the patient and physician, and physicians should provide patients with extra information if the decision card is not entirely suitable to their personal situation. Furthermore, if we want to properly inform our patients and enhance SDM correctly, the quality of decision aids is of importance. We therefore believe there is a need to harmonise the development of decision aids, including EDAs. For this reason, we have started a collaboration with multiple other dermatology departments in The Netherlands to reduce duplication of effort and resource expenditure and we would like to encourage others to do the same.

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Table S1 – The most important questions defined by psoriasis patients when starting a biological or apremilast.

I want to know…	Mean rating (range 0-10)	Ranking (weighted score)
How often I should use the drug	9.7	3.4
What the side effects and risks are	9.6	17.7
How long the drug works on the long term	9.5	10.1
What happens if I stop using the drug	9.5	5.0
If this drug affects other drugs that I take or diseases that I have	9.4	13.9
How the drug works	9.3	11.6
If I have to go to the outpatient clinic to get the drug	9.2	0.5
How likely is that itching (and pain) reduces	9.2	3.1
How quickly I can see results	9.0	4.8
How likely it is that the drug does not work	8.9	1.4
If I can drive with the drug	8.8	1.5
How often I have to visit the outpatient clinic	8.7	1.3
How the drug affects my daily functioning, such as work, sports, etc.	8.7	0.9
If I can drink alcohol with the drug	8.2	0.7
If the drug is harmful during pregnancy	4.1	1.0

Table S2 – The most important questions defined by atopic eczema patients when starting systemic treatment.

I want to know…	Mean rating (range 0-10)	Ranking (weighted score)
How likely it is that itching (and pain) reduces	9.1	26.0
What the side effects and risks are	9.1	54.0
If this drug affects other drugs that I take or diseases that I have	8.7	22.1
How long I have to take the drug	8.6	10.7
How likely it is that the drug does not work	8.5	8.7
How quickly I can see results	8.4	18.5
If I can drive with the drug	8.4	6.3
How the drug works	8.3	10.8
How often I should use the drug and at what time of the day	8.2	6.0
If I can drink alcohol with the drug	6.7	1.1
If the drug is harmful during pregnancy	4.2	2.0
If I can breast-feed with this medication	4.1	0.7

Table S3 – The most important questions defined by atopic eczema patients when starting any treatment.

I want to know…	Mean rating (range 0-10)	Ranking (weighted score)
How likely it is that itching (and pain) reduces	9.5	20.2
What the side effects and risks are	9.3	18.6
How the treatment affects my daily functioning, such as work, sports, etc.	9.2	13.2
What the effect is	9.1	19.3
If this treatment affects other drugs that I take or diseases that I have	9.1	10.9
How the treatment works	9.1	10.8
If I can use the treatment myself (at home)	9.0	16.4
How long I have to use the treatment	8.6	7.4
How quickly I can see results	8.6	10.4
Whether I should continue with emollients in addition to treatment	8.3	3.4
How often I have to visit the outpatient clinic	8.0	2.4

Chapter 7

Discussion

Discussion and future perspectives of this thesis

The main aim of this thesis was to contribute to the improvement of the treatment of moderate-to-severe atopic dermatitis (AD) patients. This was done through:

1. The harmonization of outcome measurement instruments used in AD research registries.
2. The collection of more evidence on the use of conventional (on- and off-label) phototherapies and systemic therapies for AD.
3. The initiation of research towards Shared Decision Making (SDM) in the Netherlands and the implementation of two Dutch EDAs for AD patients.

Part I: Harmonization of outcome measurement instruments used in AD research registries

In **chapter 2** we focused on finding consensus on a complete core dataset for research registries that capture data on adults and children with moderate-to-severe AD receiving phototherapy or systemic immunomodulatory therapy. Consensus was previously found on the core domains and domain items (the "what to measure") for this core dataset.[1] In this study we aimed to find consensus for the measurement instruments used to measure these domain items (the "how to measure") and for follow-up frequencies to measure these items (the "when to measure"). Consensus was found through expert consensus meetings in which physicians, patients and non-clinical researchers (i.e. health economists, epidemiologists/methodologists) from the TREAT Registry Taskforce with an interest in AD and/or AD measurement instruments participated. For all domain items measurement instruments were identified and agreed on; the final 'how to measure' core dataset consists of 70 items. Further, a minimum follow-up frequency of initially 4 weeks after commencing treatment, then every 3 months while on treatment, and every 6 months while off treatment was agreed on. With 70 domain items included, the dataset is extensive. Multiple (mostly European) national AD research registries have already included, or have shown an interest in implementing this dataset in their registry, but have also addressed concerns about feasibility. A mapping exercise was therefore performed to determine which items of the dataset are already included into national registries and can be used for combined analyses, and which adjustments need to be made for future analyses. This might result in an adaptation of the core dataset in the future. Because the research landscape will keep on changing, the core dataset will be subjective to changes anyway. These changes follow the recommendations from HOME and CS - COUSIN. Ultimately the uptake of this dataset by multiple research registries will aid in achieving large patients numbers. Only then, and with the aid of a universal data collection platform, comparing and pooling of standardized data can take place and important clinical questions can be answered. The dataset presented in this thesis has been used already in studies evaluating the effectiveness and safety of dupilumab in real-life situations.[2,3] Analyses of the TREAT Registry Taskforce that are planned for the future include baseline characteristics, phenotypes, biomarkers and cost-effectiveness in AD, and analyses on subgroups of AD like pregnant women, children and patients with comorbidities/ contraindications. Biomarkers might play

a crucial role in the prediction of failure or success of certain treatments and might be the first step towards more personalized medicine in AD.[4] Eventually, this core dataset will be crucial to gain insight into the long-term effectiveness and safety of phototherapies and systemic therapies in AD, and will provide important information for clinical practice. Ultimately this may improve standardisation and optimisation of patient management.

Part II: Collecting more evidence on the use of conventional phototherapies and systemic therapies in adult AD patients

In **chapter 3** we collected data on the prescribing practices of (resident) dermatologists and their reasons for or against the prescription of phototherapies and systemic therapies for moderate-to-severe AD patients. We found that the prescribing of these therapies for adult AD patients varies across 30 included European countries. Clinical experience was the most important reason for prescription. A lack of experience was the most important reason against the prescription of certain therapies. A recent study by Fougerrouse et al. showed the same result.[5] Although the majority of dermatologists seem to prescribe treatments according to current guidelines, prescribing practices that differed from guidelines were also found.[6–10] For photo(chemo)therapy, NB-UVB and PUVA were found to be first and second line choice of therapy for most dermatologists. This is in line with a previous UK TREAT survey,[11] but not completely with guideline recommendations.[6–8] Currently, in the Netherlands a debate is ongoing about the use of phototherapy in AD. More evidence on the efficacy and cost-effectiveness might become necessary for reimbursement of this therapy by health insurers. This survey made a start on this topic and will be succeeded by another survey focusing solely on phototherapy in AD. Also, a Cochrane SR will be performed to gather the current evidence and its strength.[12] Ciclosporin was the most preferred first line systemic therapy, which corresponds with guideline recommendations.[6,7,9] A recent network meta-analysis also reports the possible superiority of ciclosporin in AD treatment.[13] However, a large proportion of dermatologists favoured methotrexate (MTX) or corticosteroids as first line treatment. MTX and azathioprine were most frequently selected as second line treatment. The study from Fougerousse et al. supports these results; in their study MTX was found to be frequently prescribed as first and second line treatment.[5] As during the course of our study ciclosporin was the only licensed systemic agent for AD in Europe, this is an interesting finding.[14] Also, the fact that corticosteroids were prescribed first line frequently in our study is remarkable, as participants were asked to make decisions based on a situation in which patients did not have an acute flare. The International Eczema Council has recently published a paper in which this is not recommended.[15] The more common use of MTX and corticosteroids could be explained by the fact that physicians have been working with these treatments for many years for other indications. Both MTX and corticosteroids are widely available (in contrast to other treatments like biologicals) and relatively low-priced. This shows – again – that we cannot rule out the importance of these (off-label) treatments.

Because not only (on-label) ciclosporin, but also phototherapies and off-label systemic therapies are chosen by dermatologists as first choice of treatment, we have provided

more evidence that it is crucial that the guidance for these therapies should be improved. Further, this study provides information on prescribing practices within Europe before the standard use of biologics in AD treatment. In a few years, when more biologics and JAK-inhibitors have entered the AD treatment arsenal, the treatment landscape might have changed radically. It will therefore be very interesting to repeat this study in the future. In conclusion, this study shows that we need well-designed RCTs, prospective observational studies and eventually, ideally, living meta-analyses[13] in order to complement the current evidence. This will help guide clinical practice and reduce prescribing variation. The core dataset that was discussed in **chapter 2** can be of great use for this.

In **chapter 4** we started with the collection of more evidence by performing a systematic review (SR) on the off-label use of MTX, not only in AD but also in other dermatologic diseases.

As the use of off-label prescriptions is common in dermatology (reported percentages vary from 14 to 73% of cases[16–18]), more guidance for these therapies is important. With this study we hope to provide a basis for off-label guidance in MTX usage, and thus optimal use of MTX in daily practice. Such an overview has been provided earlier, both by the British Association of Dermatologistis[19] and in the form of two reviews,[20,21] but an update was needed (last update 2015). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of the evidence of the included RCTs.[22] This system is used worldwide nowadays because it provides a grading system that is very transparent, methodologically accurate and user friendly.[22]

In this **chapter** we show that the quality of the evidence for off-label use of MTX for many dermatoses for which it is used is scarce. Most evidence was found for MTX use in AD, which might therefore be a treatment option that could be considered for on-label prescription, both in adults and children. For lupus erythematosus[23], systemic sclerosis[24], AD[25] and morphea[26] evidence of moderate quality could be found. For all other dermatological indications only evidence of (very) low quality was found. This is mostly due to the fact that most evidence for off-label MTX prescription was found in the form of retrospective poor quality case series or cohort studies with very small sample sizes and heterogeneity in the used outcomes and outcome measures. While some would argue that therefore case reports should not be included in these kinds of studies, others find that they can be of great value, for example in providing more evidence on the safety of a particular treatment.[27] We decided to include case reports to give a complete overview and to explore treatment options that need further research. The study characteristics were compared with the European Dermatology Forum guideline for the treatment of psoriasis (for which MTX treatment is on-label).[28] This showed that MTX was sometimes given in maximum dosages that might not be necessary in dermatological diseases, that only a minority of the studies included folic acid as concomitant medication – while this is recommended – and that subcutaneous usage of MTX might be applied more often. The side-effects that were most often found were gastrointestinal complaints like nausea, vomiting or diarrhoea and elevation of liver enzymes, which corresponds with the EDF guideline.

This SR provides physicians with an update of the evidence that is needed for developing guidelines for off-label MTX prescription in dermatology. More work needs to be done however - especially if we want to start prescribing MTX on-label for some of these diseases - due to the very low to moderate quality of evidence that was found. Also, for the prescription of MTX no dosage-finding studies have been done. With this SR we collected data on the dosages that are used. The next step will be a dose-finding study which will hopefully result in a consensus of the dosages that should be used when prescribing MTX in both AD and psoriasis. The results from this SR emphasize once more the need for more high quality data, and therefore also urge us to explore other options. Physicians are ethically required to discuss off-label treatments with patients. Patients will only be able to make well-considered decisions when they are well informed. SDM might play an important role in this matter.

Part III: Initiation of research towards, and implementing SDM in Dermatology in the Netherlands

Therefore, in **chapter 5**, we started with an inventory on the current extent of SDM in the Netherlands. We also looked into the degree in which patients and physicians are willing to support SDM, into the characteristics that are related to their preferences in SDM and into the facilitators and barriers patients and physicians experience when applying SDM.

Our primary objective was to assess the extent to which patients and dermatologists experience SDM. For this, we used the SDM-Q-9 (patients) and the SDM-Q-doc (physicians).

Higher scores on these questionnaires correspond to higher extents of SDM that are perceived. The mean total score of dermatologists was 82 while for patients this was 55. This shows that dermatologists experience a higher degree of SDM than patients. We found that only a minority of the patients agreed that their physician made it clear a decision had to be made, which is low compared to other (non-dermatologic) studies.[29,30] About half of the patients reported to have discussed different treatment options with their physician, while a quarter reported to not have discussed any options at all. Our study therefore confirms what other studies have found; that patients want to be better informed.[30–32] About half of the patients agreed that their preferences were discussed thoroughly, 35% reported that the options were carefully weighted before making a decision. This seems quite low but compared to a recent SR this is actually quite high.[29] As a last step for SDM, the treatment decision needs to be shared. 27% of the patients reported that they were asked what their preferable role in the decision making process was and 39% found that the treatment decision was shared, which is slightly higher than found in another study.[31]

Regarding our secondary objectives, we found that both patients and physicians would prefer to make treatment decisions on a shared basis. Only for dermatologists a characteristic that could be linked to a higher preference for SDM was found in the form of previously followed courses or lectures. Mostly facilitators for the application of SDM were found. Both patients and physicians are willing to apply SDM and see each other's willingness to apply SDM. Both also think SDM may improve patient

care. A lack of time and a lack of continuity in the treating physician were the most encountered barriers.

Overall, with this study we showed that improvement of SDM for AD and psoriasis in the Netherlands is desired. In other medical fields the use of and research towards SDM is much more common nowadays. A recent paper supports this vision for SDM in dermatology.[33] We therefore really need to catch up on SDM in dermatology. As both patients and physicians are willing to apply SDM, we should look into options that will accomplish this. One option is the education of both patients and physicians, so that patients are more aware of the fact that they can have a bigger role in their treatment decision, and physicians know better how to apply SDM in daily practice. Another option is the development of patient decision aids (PDAs).

In **chapter 6**, we therefore developed PDAs for different treatment situations in both AD and psoriasis. To support further implementation of SDM in dermatology, we also described how these PDAs were developed. AD and psoriasis require multiple treatment decisions through life which are preference sensitive and are therefore especially suitable for SDM.[34,35] Encounter decision aids (EDAs) are PDAs that can be used during a consultation.[36,37] Decision cards are a form of EDAs that are similar to Option Grids and show the most frequently asked questions from patients and their answers on one page.[38–41] Because our research and the research from Legare et al[42] showed that time constraints are a barrier to SDM, and Tan et al suggest that especially short and feasible decision aids might work in the dermatological setting,[43] we decided to develop Decision Cards to support SDM in AD and psoriasis in the Netherlands. In the literature, two EDAs for dermatologic indications could be found; one for biologic therapy in psoriasis which was developed by the British Association of Dermatologists[44] and one for actinic keratosis.[45] For AD no EDAs could be found. New PDAs have been developed though, for instance for psoriasis,[46] basal cell carcinoma[47] and lentigo maligna.[48] With all PDAs it is important to provide scientifically correct data. Ideally, PDAs are therefore based on quality control criteria. Such criteria are developed for PDAs – the International Patient Decision Aids Standards (IPDAS) criteria[49] – but these are not yet suitable for EDAs.[50] In order to still maintain a high quality of our Decision Cards, they were based on Option Grids. Option Grids were developed by Glynn Elwyn and his research group and have been studied extensively.[38–41]

While a first step might be the introduction of PDAs for several treatment decisions in dermatology, in the end it might be best if PDAs are adjusted to the country in which they are used, and are preferably based on living guidelines so they are updated regularly. In the meantime our Decision Cards were – whenever possible – based on guidelines for AD and psoriasis and will be updated when these guidelines are updated. Creating a PDA requires a lot of work, which will repeat itself every so many years due to updates of the guidelines. Ultimately, it might therefore be necessary that in the future PDAs are linked to living guidelines. We found that especially for AD it was difficult to obtain scientifically correct information, as there is much heterogeneity in outcome measures used in this research field. This shows once more the importance of pursuing more uniform data collection that can be shared and pooled among researchers.

These Decision Cards are a first step in the right direction for the implementation of SDM in dermatology, but more work will need to be done. More PDAs needs to be developed, the impact of PDAs on SDM in clinical practice needs to be evaluated, PDAs need to be properly implemented, and the information on which PDAs are based should be improved.

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Chapter 8

Summary and conclusion / Samenvatting en conclusie

Summary and conclusion

Atopic dermatitis (AD) is a chronic, inflammatory skin disease that affects up to 25% children and around 10% of adults. It presents with symptoms of itch and pain and has a substantial effect on patients' quality of life. Multiple (conventional) therapies exist, varying from avoidance of trigger factors, to topical therapy, phototherapy and systemic therapy. For most of these therapies the (long-term) evidence on efficacy, (cost)effectiveness and safety is scarce and of varying quality. As AD poses a high burden on patients and society, this requires us to aim for improvement of AD care. Randomized controlled trials (RCTs) are the golden standard for research but usually only compare a few therapies, and do not reflect on real-life patients. Well designed, long-term prospective patient registries could help to gather new evidence, if data collection is harmonised and international cooperation and data pooling can be established. Another way to improve AD care is by the addition of Shared Decision Making (SDM). Only limited research towards SDM in dermatology has been done, even though it has shown its benefits in other medical fields.

With this thesis we therefore focussed on the improvement of AD care, by harmonizing the outcome measurement instruments that are used in AD research registries (part I), by collecting more evidence on the conventional phototherapies and systemic therapies (part II), and by the initiation of more research towards, and development of tools for SDM in dermatology (part III).

Part I: Harmonization of outcome measurement instruments used in AD research registries

Core outcome sets (COS) have been introduced to provide researchers and clinicians with an agreed minimal set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. For AD research studies the Harmonising Outcomes Measures for Eczema (HOME) initiative has developed a COS; for AD clinical practice they are developing a Core Practice Set (CPS). For registries, the TREAT Registry Taskforce (https://treat-registry-taskforce.org) developed a core data set for the harmonisation of data collection, focussing on phototherapy and systemic therapy in moderate-to-severe AD patients. An international eDelphi exercise resulted in the 'what to measure' domain items of the core dataset. This needs to be complemented by core outcome measurement instruments and frequencies on which these domain items should be measured.

Therefore, in **chapter 2** we aimed to reach consensus on how and when to measure the domain items that were previously defined. Proposals for the measurement instruments (the "what to measure") were based on the recommendations from the HOME initiative, on (preferably) systematic reviews of the literature, the TREATgermany database and expert opinions. A survey was performed to define the "when to measure" follow-up frequency. Sixteen experts from seven countries participated, and 12 other experts were consulted. Eventually, consensus was reached for all 70 measurement instruments. The follow-up frequency was established at four weeks after starting treatment, then every three months while on treatment and every six months when off treatment. The complete core dataset will allow researchers

to compare and pool data on both national and international levels. It will help to answer important questions on the effectiveness and safety of phototherapy and systemic therapy in AD treatment. But first, this dataset will need to be implemented in research registries worldwide and its feasibility will need to be tested.

Part II: Collecting more evidence on the use of conventional phototherapies and systemic therapies in adult AD patients

Recently, biologics and Janus-Kinase (JAK) inhibitors have entered the treatment arsenal for moderate-to-severe AD patients. These therapies seem very promising, but have possible downsides too. Their availability is limited, the costs are high and (long-term) experience with these therapies is still limited. More information on long-term effectiveness and safety for the conventional therapies is needed, as currently most of these therapies are prescribed off-label.

Previous survey studies from the TREAT Registry Taskforce have investigated the prescribing practices of conventional phototherapies and systemic therapies for paediatric patients in Europe and Northern America and for adult patients in the UK. Such a survey has not been performed yet for the prescribing practices for adult AD patients in (continental) Europe. Because the treatment landscape will change drastically with the arrival of the new therapies, insight into these prescribing practices is necessary before the new therapies become routine clinical practice. In **chapter 3** we therefore invited dermatologists from 30 European countries to participate in an online survey. We collected data on participant characteristics, their prescribing practices with phototherapy or systemic therapy for adult AD patients and the factors that influenced their choices. Out of 361 dermatologists who were willing to participate, 238 (65.9%) completed the survey. Overall, phototherapy was preferred by most dermatologists (41.5%) for the treatment of moderate-to-severe AD. Most dermatologists (80.9%) preferred narrow-band ultraviolet-B (NB-UVB) as first choice of therapy and psoralen and ultraviolet-A (PUVA) as second (21.6%). Ciclosporin (54.1%), oral corticosteroids (32.6%) and methotrexate (MTX) (30.7%) were mostly used as first choice in systemic therapies. Personal experience was the most important reason for the prescription of both phototherapy and systemic therapy. A lack of personal experience was the most important reason against the use of azathioprine (prescribed by 59%) and mycophenolate acid (prescribed by 37.1%). The unavailability of phototherapy at a specific centre was an important reason against the use of it. This study has given us more insight into the fact that both on-label therapies (like ciclosporin) and off-label therapies (like MTX) are preferred by dermatologists when considering AD treatment.

In **chapter 4** we therefore summarized the evidence on the off-label use of MTX in dermatology. The databases MEDLINE, EMBASE and CENTRAL were searched to collect studies (RCTs, cohort studies, case series and grey literature) on the off-label use of MTX in dermatological diseases up until November 2019. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating system was used to evaluate the quality of the evidence (only for RCTs). A total of 34.583 studies were found, of which 143 studies were included after screening on duplicates,

title, abstract and full text. MTX was used off-label in 31 dermatologic diseases. Most evidence was of (very) low quality, mostly because of small sample sizes and heterogeneity in outcome measures that were used. Only a few RCTs could be included. Only for the use of MTX in AD, systemic lupus erythematosus, systemic sclerosis and morphea studies with evidence of moderate quality could be found.

To optimize the quality of off-label MTX treatment and justify its use, more high-quality evidence is needed.

Part III: Initiation of research towards, and implementing SDM in Dermatology in the Netherlands

In SDM, patients are more involved by physicians in the treatment decision making process, while considering the best available evidence and their values and preferences.

SDM is very suitable for the dermatological setting but only sporadically used by dermatologists, even though studies (mostly in other medical fields) have shown patients want to be more actively involved. In the Netherlands no research has been performed towards the experienced need for SDM by patients and dermatologists. In **chapter 5** we therefore performed a survey to assess the current extent of and need for SDM in AD and psoriasis in The Netherlands. We also looked into barriers and facilitators for SDM. Both physicians and patients participated. Two similar online surveys were distributed, one for patients with AD or psoriasis and one for (resident) dermatologists. The Shared Decision Making Questionnaire (SDM-Q) and the Control Preference Scale (CPS) were imbedded into the survey, together with statements about barriers and facilitators for SDM. We analyzed responses from 219 patients and 147 physicians. The results showed that dermatologists experienced a higher degree of SDM than patients (SDM-Q 82 vs 55;$p<0.01$). Further we found that the majority of patients and physicians wish to share the treatment decision. We mainly identified facilitators for SDM; both patients and physicians want to apply SDM and see the willingness of the other party to apply SDM too. Both believe SDM may improve patient care. Barriers were found in the form of a suggested lack of time for the application of SDM and a lack of continuity in the treating physicians.

This study showed that, while both patients and physicians are willing to apply SDM, AD and psoriasis patients in the Netherlands do experience a limited extent of SDM.

Patients decision aids (PDAs) can help in the process of actively involving patients. PDAs have been shown to have multiple beneficial effects; they increase the patients' knowledge, improve communication between the doctor and the patient, improve treatment satisfaction, help patients make choices that correspond better with their values and reduce decisional conflict. They might also help improve clinical outcomes and treatment adherence. Only a few PDAs exist for dermatology patients in The Netherlands. PDAs are available in different forms. Encounter decision aids (EDAs) are compact PDAs that consist of one-page overviews of treatment options with answers for the most frequently encountered questions. These can be used during a consultation. In **chapter 6** we developed three EDAs, two for AD (one for topical,

photo- or systemic therapy and one for systemic therapy only) and one for psoriasis (for biologicals or apremilast). We also elaborated on the steps that can be taken to develop other EDAs and the framework that we used. This framework complied with the Dutch Protocol for the development of decision aids and was inspired by the format used to develop Option Grids, which have been used and investigated for many years. While this is a first step for the implementation of SDM in dermatology in The Netherlands, we are not there yet. More PDAs or EDAs need to be developed, they need to be implemented and evaluated, and both physicians and patients will need to be educated. Also, quality criteria that apply to all sorts of PDAs should be developed.

Conclusion

With this thesis we have contributed to the harmonization of data collection for AD research registries, especially for phototherapy and systemic therapy. We have also provided more evidence for the use of conventional phototherapies and systemic therapies in moderate-to-severe AD patients, both by providing an oversight of the prescribing practices for these therapies in Europe and by providing an update on the off-label use of MTX in dermatology.

With this thesis SDM in dermatology has become one step closer; we now have better insight into the extent of and need for SDM in the Netherlands and have three tools that can be used to apply SDM.

More work needs to be done. More high-quality, long-term comparable research is needed. When we can truly harmonize and share this research in AD, we are up for another treatment revolution of which the patients will benefit.

Samenvatting en conclusie

Atopisch eczeem (AE) is een chronische inflammatoire huidziekte met een prevalentie tot bijna 25% bij kinderen en rondom de 10% bij volwassenen. Het presenteert zich met symptomen van jeuk en pijn en heeft een substantieel effect op de kwaliteit van leven van patiënten. AE heeft een hoge ziektelast voor zowel patiënten als voor de maatschappij. Meerdere (conventionele) therapieën bestaan, variërend van het vermijden van uitlokkende factoren, tot lokale therapie, lichttherapie en systemische therapie. Voor de meeste van deze therapieën is het (langdurige) bewijs voor de werkzaamheid, (kosten)effectiviteit en veiligheid beperkt en van variërende kwaliteit. Dit vereist dat we ernaar streven de behandeling te verbeteren. Gerandomiseerde, gecontroleerde onderzoeken (RCTs) zijn de gouden standaard voor onderzoek, maar vergelijken vaak maar een paar therapieën tegelijk, en patiëntkarakteristieken van patiënten die deelnemen aan RCTs zijn niet altijd gelijk aan die van patiënten in de dagelijkse praktijk.

Kwalitatief goede, lange termijn, prospectieve patiëntregisters kunnen daarom helpen met het verzamelen van nieuw bewijs, mits de datacollectie geharmoniseerd wordt, er internationaal wordt samengewerkt en data wordt gedeeld en samengevoegd.

Een andere manier om de behandeling van AE te verbeteren is door het toepassen van gezamenlijke besluitvorming. Er is beperkt onderzoek gedaan naar gezamenlijke besluitvorming in de dermatologie, terwijl dit in andere medische specialisaties al veel voordelen heeft laten zien. Dit proefschrift gaat daarom over het verbeteren van de behandeling van AE, door het harmoniseren van meetinstrumenten die gebruikt worden in AE onderzoek registers (deel I), door het verzamelen van meer bewijs voor de conventionele lichttherapieën en systemische therapieën (deel II) en door het initiëren van onderzoek naar, en het ontwikkelen van keuzetools voor gezamenlijke besluitvorming in de dermatologie (deel III).

Deel I: Harmoniseren van meetinstrumenten gebruikt in AE onderzoek registers

Core outcome sets (COS) zijn ontwikkeld, waarmee onderzoekers en clinici een minimale set van uitkomstmaten hebben die gemeten zouden moeten worden tijdens al het onderzoek naar een specifieke ziekte of populatie. Het Harmonising Outcomes Measures for Eczema (HOME) initiatief heeft een COS ontwikkeld die gebruikt kan worden bij AE onderzoek. Daarnaast werken ze aan een 'core practice set', welke in de klinische praktijk ingezet kan worden. De TREatment of ATopic eczema (TREAT) Registry Taskforce (https://treat-registry-taskforce.org/) heeft een dataset ontwikkelt die bijdraagt aan de harmonisatie van data collectie voor onderzoek registers, met name voor lichttherapie en systemische therapie bij matig-tot-ernstige AE patiënten. Een internationale eDelphi methode resulteerde in de 'what to measure' domein items die in deze dataset zijn vastgelegd. Dit moet nog gecomplementeerd worden met bijpassende meetinstrumenten (de 'how to measure') en frequenties waarin deze items gemeten zouden moeten worden (de 'when to measure').

Daarom hebben we in **hoofdstuk 2** ons ten doel gesteld consensus te bereiken over hoe en wanneer deze domein items gemeten zouden moeten worden. Voorstellen voor de meetinstrumenten werden gebaseerd op aanbevelingen van het HOME initiatief, op (bij voorkeur) systematische reviews van de literatuur, het TREAT register van Duitsland en meningen van experts. Een survey werd uitgevoerd om de follow-up frequentie te definiëren. Zestien experts uit zeven landen namen deel aan dit consensus-onderzoek, en 12 externe experts werden geconsulteerd. Uiteindelijk werd consensus bereikt voor alle 70 domein items. The follow-up frequentie werd vastgesteld op iedere vier weken na het starten van de behandeling, en daarna iedere drie maanden indien de behandeling voortgezet wordt of iedere zes maanden indien de behandeling gestopt wordt.

De complete dataset geeft onderzoekers de mogelijkheid om data te vergelijken en samen te voegen op zowel een nationaal, als een internationaal niveau. De dataset kan daardoor helpen in het beantwoorden van belangrijke vragen over de effectiviteit en veiligheid van lichttherapie en systemische therapie in AE. Allereerst moet de dataset echter geïmplementeerd worden in onderzoek registers wereldwijd. Daarnaast zal de praktische haalbaarheid getest moeten worden.

Deel II: Meer bewijs verzamelen over het gebruik van conventionele lichttherapie en systemische therapie bij volwassen AE patiënten

Recent zijn biologics en Janus-Kinase (JAK) remmers goedgekeurd voor de behandeling van matig-tot-ernstige AE patiënten. Deze therapieën lijken veelbelovend, maar hebben ook mogelijke nadelen. De beschikbaarheid is beperkt, de kosten zijn hoog en lange termijn ervaring met deze therapieën is beperkt. Meer informatie over lange termijn effectiviteit en veiligheid van de conventionele therapieën is daarom nodig, gezien het merendeel van deze therapieën momenteel off-label wordt voorgeschreven.

Met eerdere survey studies van de TREAT Registry Taskforce werd onderzoek gedaan naar het voorschrijfgedrag van conventionele lichttherapieën en systemische therapieën bij kinderen in Europa en Noord-Amerika en bij volwassenen in het Verenigd Koninkrijk. Een dergelijke survey studie is nog niet verricht naar het voorschrijfgedrag van deze therapieën bij volwassen AE patiënten in de rest van Europa.

Omdat de behandeling van AE patiënten drastisch zal veranderen met de komst van de biologics en JAK remmers, is het noodzakelijk ook inzicht te krijgen in dit voorschrijfgedrag. In **hoofdstuk 3** hebben we daarom dermatologen van 30 Europese landen uitgenodigd om deel te nemen aan een online survey. We verzamelden data over deelnemer karakteristieken, hun voorschrijfgedrag aangaande lichttherapie en systemische therapie bij volwassen AE patiënten, en factoren die hierin hun keuzes beïnvloedden. Van de 361 dermatologen die bereid waren deel te nemen, voltooiden 238 (65.9%) de survey. Over het algemeen hadden dermatologen een voorkeur voor lichttherapie (41.5%) voor de behandeling van matig-tot-ernstige AE patiënten. De meeste dermatologen hadden een voorkeur voor smalspectrum ultraviolet-B (NB-UVB) als eerste keus therapie (80.9%), en psoralenen en ultraviolet-A (PUVA) als tweede keus therapie (21.6%). Ciclosporine (54.1%), orale corticosteroïden (32.6%) en methotrexaat

(MTX) (30.7%) werden het meest frequent ingezet als eerste keus systemische therapie. Persoonlijke ervaring was de meest belangrijke reden voor het voorschrijven van zowel lichttherapie als systemische therapie. Een gebrek aan persoonlijke ervaring was de meest belangrijke reden waarom dermatologen geen azathioprine (door 59% voorgeschreven) of mycofenolzuur (door 37.1% voorgeschreven) voorschreven. Het niet beschikbaar zijn van lichttherapie in een specifiek centrum was de belangrijkste reden waarom dit niet ingezet werd. Deze studie heeft ons meer inzicht gegeven in het feit dat niet alleen on-label therapieën (zoals ciclosporine) maar ook off-label therapieën (zoals MTX) de voorkeur van dermatologen hebben als eerste keus behandeling van AE.

In **hoofdstuk 4** hebben we daarom het bewijs voor het off-label gebruik van MTX in de dermatologie op een rij gezet. De databases MEDLINE, EMBASE en CENTRAL werden geraadpleegd om gepubliceerde studies (RCTs, cohort studies, case series en grijze literatuur) tot aan november 2019 over het off-label gebruik van MTX in huidziekten te vinden.

Het 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) beoordeling systeem werd gebruikt om de kwaliteit van het gevonden bewijs te evalueren (alleen voor RCTs). In totaal werden 34.583 studies gevonden, waarvan na het verwijderen van duplicaten en screening op titel, abstract en volledige tekst, 143 studies werden geïncludeerd. MTX werd off-label toegepast in 31 verschillende soorten huidziekten. Het meeste bewijs was van (erg) lage kwaliteit, voornamelijk doordat maar weinig patiënten geïncludeerd werden in de studies, en door de hoge mate van heterogeniteit in uitkomstmaten die gebruikt werden. Slechts enkele RCTs konden worden geïncludeerd. Enkel voor het gebruik van MTX in AE, systemische lupus erythematosus, systemische sclerose en morfea kon bewijs van matige kwaliteit gevonden worden. Om de kwaliteit van off-label MTX behandeling te optimaliseren en het gebruik hiervan te rechtvaardigen, is meer bewijs van hoge kwaliteit nodig.

Deel III: Initiatie van onderzoek naar, en het implementeren van gezamenlijke besluitvorming in de dermatologie in Nederland

Bij gezamenlijke besluitvorming (ook wel 'samen beslissen' genoemd) worden patiënten meer betrokken door hun artsen bij het besluitvormingsproces, terwijl het best beschikbare bewijs en de waarden en voorkeuren van de patiënt hierin meegenomen worden. Gezamenlijke besluitvorming is zeer geschikt voor de dermatologische praktijk maar wordt slechts sporadisch ingezet door dermatologen, ondanks het feit dat meerdere studies (voornamelijk in andere medische specialismes) hebben laten zien dat patiënten meer betrokken willen worden. In Nederland is geen onderzoek naar de gewenste mate van samen beslissen onder patiënten en dermatologen verricht. Daarom hebben we in **hoofdstuk 5** een survey opgezet waarmee de behoefte aan en gewenste mate van samen beslissen in AE en psoriasis werd beoordeeld. Er werd ook gekeken naar barrières en faciliterende factoren voor het toepassen van gezamenlijke besluitvorming.

Patiënten en dermatologen namen deel aan de survey. Twee gelijke surveys werden verspreid; één voor patiënten met AE of psoriasis, en één voor dermatologen (al dan niet in opleiding). The survey werd gebaseerd op de 'Shared Decision Making Questionnaire' (SDM-Q) en de 'Control Preference Scale' (CPS). Daarnaast werden stellingen toegevoegd over barrières en faciliterende factoren voor gezamenlijke besluitvorming. De antwoorden van 219 patiënten en 147 dermatologen werden geanalyseerd. De resultaten lieten zien dat dermatologen lijken te denken dat gezamenlijke besluitvorming beter wordt toegepast dan dat de patiënten het ervaren (SDM-Q 82 vs 55;$p<0.01$). Verder werd gevonden dat het merendeel van de patiënten en dermatologen besluitvorming het liefste samen doen. Vooral faciliterende factoren werden geïdentificeerd. Zowel patiënten als dermatologen willen graag gezamenlijke besluitvorming toepassen en zien dat de andere partij hier ook toe bereid is. Beide partijen geloven dat gezamenlijke besluitvorming kan leiden tot betere patiëntenzorg. Barrières werden vooral gevonden in de vorm van een verwacht tekort aan tijd voor de toepassing van gezamenlijk besluitvorming en een te grote wisseling in de dermatologen die gezien werden. Deze studie heeft laten zien dat door AE en psoriasis patiënten in Nederland toch slechts in geringe mate gezamenlijke besluitvorming wordt ervaren, ondanks de bereidheid van patiënten en dermatologen om gezamenlijke besluitvorming toe te passen.

Keuzetools kunnen helpen om patiënten actiever te betrekken en meer gezamenlijke besluitvorming toe te passen. Van keuzetools is bekend dat zij meerdere voordelen hebben; zij vergroten de kennis van patiënten, verbeteren de communicatie tussen patiënten en hun behandelaar, verbeteren tevredenheid met de behandeling, helpen patiënten om keuzes te maken die beter overeenkomen met hun waardes en reduceren keuzestress. Ze zouden mogelijk ook helpen om uitkomsten van de therapie te verbeteren en meer therapietrouw te bewerkstelligen. Slechts een paar keuzetools zijn beschikbaar voor dermatologie patiënten in Nederland. Keuzetools zijn beschikbaar in verschillende vormen. Consultkaarten zijn compacte keuzetools waarbij op 1 pagina een overzicht wordt gegeven van de beschikbare behandelingen en antwoorden op de meest gestelde vragen over deze behandelingen. Deze keuzetools kunnen tijdens een consult ingezet worden.

In **hoofdstuk 6** hebben we daarom drie consultkaarten ontwikkeld waarvan twee voor AE (één voor lokale therapie, lichttherapie of systemische therapie en één voor enkel systemische therapie) en één voor psoriasis (biologics of apremilast). In dit hoofdstuk beschrijven we daarnaast welke stappen genomen kunnen worden om andere consultkaarten te ontwikkelen en aan welke kwaliteitscriteria voldaan moet worden/welk kwaliteitskader gevolgd werd. Deze eisen/dit kader komt overeen met het Nederlandse protocol voor de ontwikkeling van keuzehulpen en is zelf gebaseerd op het format voor de ontwikkeling van Option Grids. Option Grids zijn vrijwel identiek aan consultkaarten maar worden al vele jaren gebruikt en onderzocht. Met deze studie hebben we een eerste stap gezet voor de implementatie van gezamenlijke besluitvorming in de dermatologie in Nederland, maar we zijn er nog niet. Meer keuzetools zullen ontwikkeld moeten worden, ze zullen geïmplementeerd en geëvalueerd moeten worden, en zowel patiënten als artsen zullen onderwijs over gezamenlijke besluitvorming moeten krijgen. Daarnaast is het nodig dat

kwaliteitscriteria ontwikkeld worden die toegepast kunnen worden op alle soorten keuzetools.

Conclusie

Met dit proefschrift hebben we bijgedragen aan de harmonisatie van data collectie in onderzoek naar AE, voornamelijk voor lichttherapie en systemische therapie. We hebben meer bewijs gevonden voor het gebruik van lichttherapie en systemische therapie bij matig-tot-ernstige AE patiënten, zowel door een overzicht te geven van het voorschrijfgedrag van deze therapieën in Europa, als door een update te geven over het off-label gebruik van MTX in de dermatologie. Gezamenlijke besluitvorming in de dermatologie is door dit proefschrift ook een stap dichterbij gekomen; we hebben nu beter inzicht in de behoefte aan en de gewenste mate van gezamenlijke besluitvorming, en hebben drie consultkaarten voor AE en psoriasis ontwikkeld die in Nederland ingezet kunnen worden.

Er moet echter nog meer werk gedaan worden. Meer onderzoek van goede kwaliteit is noodzakelijk, met lange termijn en vergelijkbare data. Wanneer deze data daadwerkelijk geharmoniseerd en (inter)nationaal gedeeld wordt staan we aan de rand van een nieuwe behandelrevolutie binnen AE, en zullen vele patiënten daarvan uiteindelijk kunnen profiteren.

Chapter 9

Addendum

List of abbreviations

A	Antibodies
AA	Alopecia areata
AAD	American Academy of Dermatology
AB	Antibiotics
Ac	Acitretin
AD	Atopic dermatitis
ADCL	Atopic dermatitis control test
AE	Atopic eczema
AE	Adverse event (chapter 4)
AH	Antihistamines
All CE	Allergic Contact Eczema
AO	Adult onset
AZA	Azathioprine
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic and Immunomodulators Register
BB-UVB	Broadband ultraviolet B
BP	Bullous pemphigoid
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
COS	Core outcome set
CP	Cyclophosphamide
CPS	Control Preference Scale
CQ	Chloroquine
Cry	Cryotherapy
CS	Case series
CSA	Ciclosporin
CSG - COUSIN	Cochrane Skin Group - Core Outcome Set Initiative
CSS	Clinical severity score
CST	Corticosteroids
CTCL	Cutaneous T cell lymphoma
D	Day
DALY	Disability-adjusted lifeyears
DLco	Lung diffusion capacity
DLQI	Dermatology Quality of Life Index
DM	Dermatomyositis
DPCP	Diphenciprone
DTN	Dithranol
E	Eczema
EASI	Eczema Area and Severity Index
EDA	Encounter decision aid
EF	Eosinophilic fasciitis
E.g.	Exempli gratia (for example)
Em	Emollients
EMA	European Medicines Agency
ENL	Eythema Nodosum Leprosum
EQ-5D	EuroQol five-Dimensional
ET	Etretinate
ETFAD	European Task Force on Atopic Dermatitis
FA	Folic acid
FDA	Food and Drug Administration
FDLQI	Family Dermatology Life Quality Index
FU	Follow-up
G	Gram
GA	Granuloma Annulare
GD	Gastroduodenal

GCS	Glucocorticosteroids
GI	Gastrointestinal
GPA	Granulomatosis with polyangiitis (Wegener's granulomatosis)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCQ	Hydroxychloroquine
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
HOME	Harmonising Outcome Measures for Eczema
I.a.	Inter alia (among other things)
I.e.	Id est (that is)
ICS	Intravenous corticosteroids
IDQoL	Infant's Dermatitis Quality of Life Index
IGA	Investigator Global Assessment
IL	Intralesional (chapter 4)
IL	Interleukin (introduction)
IPDAS	International Patient Decision Aids Standards
ISCED	International Standard Classification of Education
ITT	Intention to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus Kinase
JDA	Japanese Dermatological Association
LE	Lupus erythematosus
LP	Lichen planus
LPP	Lichen planopilaris
LS	Lichen Sclerosus (extra genital)
LyP	Lymphomatoid papulosis
M	Morphea
MARS	Medication Adherence Report Scale
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mLoSSI	Modified Localized Scleroderma Severity Index
MMF	Mycophenolate Mofetil
MNX	Minoxidil
Mo	Month
MP	Methylprednisolone
MPA	Mycophenolate acid
MPP	Methylprednisolone pulse
MTX	Methotrexate
N	No
NA	Not applicable
NB-UVB,	Narrowband ultraviolet B
NE	Nummular Eczema
NRS	Numerical rating scale
NVDV	Dutch Society of Dermatology and Venereology
OCS	Oral Corticosteroids
OMP	Oral mini pulse
OPTION	Observing patient involvement
Or	Oral
Pa	Panniculitis
PASI	Psoriasis Area and Severity Index
PB	Placebo
PD	Papular Dermatitis
PDA	Patient decision aid
Ped	Pediatric
PF	Pemphigus Foliaceus
PGA	Patient Global Assessment
PhD	Doctor of Philosophy

PN	Prurigo Nodularis (chapter 4)
PN	Psoriasis patients the Netherlands (chapter 5)
POEM	Patient Oriented Eczema Measure
PP	Per protocol
PPP	Palmoplantar pompholyx
Pred	Prednisone
Pr	Prurigo
PrD	Parthenium Dermatitis
PRINTO	Paediatric Rheumatology International Trials Organization
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	Pityriasis rubra pilaris
PsA	Psoriatic arthritis
PsoSat	Psoriasis Satisfaction questionnaire
Pt	Patient
PT	Phototherapy
Pts	Patients
PUVA	Psoralen and ultraviolet A
PV	Pemphigus vulgaris
QLQI	Quality of life impairment questionnaire score
QoL	Quality of life
QoLIAD	Quality of Life Index for Atopic Dermatitis
RCT	Randomised Controlled Trial
RECAP	Recap of atopic eczema
RevMan	Reverence Manager
SAB	Systemic antibiotics
SAH	Systemic Antihistamines
Sar	Sarcoidosis
SAE	Serious adverse event
Sc	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SCS	Systemic corticosteroids
Scl	Scleroderma
SD	Sclerodema diabeticorum
SDM-Q	Shared decision making questionnaire
SDM-Q-9	9-item shared decision making questionnaire for patients;
SDM-Q-DOC	9-item shared decision making questionnaire for physicians
SmPC	Summary of product characteristics
SR	Systematic review
Sul	Sulfasalazine
SS	Systemic sclerosis
T	Topical
TAC	Tacrolimus
TA	Topical agents
TCA	Triamcinolone
TCS	Topical corticosteroids
TCI	Topical calcineurin inhibitor
TOA	Time until onset of action
TSS	Total skin score
SDM	Shared decision making
SPSS	Statistical Package for the Social Sciences
TPMT	Thiopurine methyltransferase
TREAT	TREatment of ATopic eczema
UCLA	University of California, Los Angeles
Unk	Unknown
UK	United Kingdom
Ur	Urticaria
US	United States
UVA	Ultraviolet A

UVAB	Ultraviolet A plus ultraviolet B
UVB	Ultraviolet B
VAS	Visual analogue scale
VASI	Vitiligo Area Scoring Index
Vi	Vitiligo
VIDA	Vitiligo Disease Activity
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
Vit	Vitamin
VMCE	Association for People with Atopic Dermatitis
Wk	Week
WMO	Medical Research Involving Human Subjects Act
Y	Yes (chapter 2)
Y	Year (chapter 4)

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Chapter 2

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List of Publications

F.M. Vermeulen,* A.M. van Huizen,* C.M.J.M. Bik, R. Borgonjen, S.A.T. Karsch, R. Kuin, L.A.A. Gerbens and P.I. Spuls. Off-label use of methotrexate in dermatological practice – a systematic review with GRADE approach. Submitted to the JEADV.
**both authors have contributed equally and share first authorship.*

F.M. Vermeulen,* G.E. van der Kraaij,* R.A. Tupker, A. Bijlsma, H. Blaauwbroek, F. Das, T. Geltink, J.S. van der Kraan, R. Kranenburg, D.J. van der Veen, K. Venhorst, P.I. Spuls. The steps towards evidence-based Decision Cards for psoriasis and atopic eczema. *Acta Derm Venereol 2020; 100: adv00337.*
**both authors have contributed equally and share first authorship.*

C. Flohr, A.L. Bosma, I. Garcia-Doval, L. Naldi, D. Prieto-Merino, F. Tesch, C.J. Apfelbacher, B.W.M. Arents, S. Barbarot, E. Baselga, M. Deleuran, L.F. Eichenfield, L.A.A. Gerbens, A.D. Irvine, A. Manca, P. Mendes-Bastos, M.A. Middelkamp-Hup, A. Roberts, J. Seneschal, Å. Svensson, J.P. Thyssen, T. Torres, **F.M. Vermeulen**, C. Vestergaard, L.B. von Kobyletzki, D. Wall, S. Weidinger, P.I. Spuls, J. Schmitt. TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for a European safety study of dupilumab and other systemic therapies in patients with atopic eczema. *Br J Dermatol. 2020 Jun; 182(6):1423-1429.*

F.M. Vermeulen, L.A.A. Gerbens, J. Schmitt, M. Deleuran, A.D. Irvine, K. Logan, W. Ouwerkerk, C. Vestergaard, C. Flohr, P.I. Spuls. The European TREatment of ATopic eczema Taskforce (TREAT) Survey; prescribing practices in Europe for photo- and systemic therapy in moderate-to-severe adult atopic eczema patients. *British Journal of Dermatology (2020) 183:1073–1082.*

G.E. van der Kraaij, **F.M. Vermeulen**, P.M. Smeets, E.M.A. Smets, P.I. Spuls. Patients and physicians' views on the current extent of, and need for Shared Decision Making in atopic dermatitis and psoriasis in The Netherlands. *JEADV 2020, 34:2574–2583.*

F.M. Vermeulen, L.A.A Gerbens, A.L. Bosma, C.J. Apfelbacher, A.D. Irvine, B.W.M. Arents, S. Barbarot, M. Deleuran, L.F. Eichenfield, A. Manca, J. Schmitt, C. Vestergaard, D. Wall, S. Weidinger, M.A. Middelkamp-Hup, P.I. Spuls and C. Flohr. TREatment of Atopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. *Br. J. Dermatol. 2019; Sep; 181(3):492-50.*

L.C.J. van Delft, W. Woliner-van der Weg, G.E. van der Kraaij, **F.M. Vermeulen**, S.F.K. Lubeek, N.W.J. Kelleners-Smeets, Ph.I. Spuls. Samen beslissen en keuzetools in de dermatologie. *Nederlands Tijdschrift voor Dermatologie en Venereologie. 2019; Mei; 29:54-56.*

M.A. Belfort; L. White, **F.M. Vermeulen**. Association of fetal cranial shape with shoulder dystocia. *Ultrasound Obstet Gynecol. Mar; 39(3):304-9.*

PhD Portfolio

PhD Student: F.M. Vermeulen

PhD period: 01-08-2016 till 30-04-2020

Promotor: Prof. Dr. P.I. Spuls

Copromotor: dr. L.A.A. Gerbens

	Year	Workload (ECTS)
1. PhD training		
General courses		
Basic Course Legislation and Organisation (BROK)	2016	1
Good clinical practice	2016	0.3
Endnote	2017	0.1
Project Management	2017	0.6
Scientific writing in English	2018	1.5
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	2018	0.3
Practical Biostatistics	2019	1.1
Oral presentations at (inter)national conferences / meetings		
Shared decision making in de dermatologie. Klinische wetenschappelijke bespreking. AMC, The Netherlands	2016	0.1
How to measure the what to measure. TREAT Registry Taskforce. London, UK	2016	0.6
How to measure the what to measure. TREAT Registry Taskforce meeting. Amsterdam, The Netherlands	2017	0.6
TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. European Academy of Dermatology and Venereology (EADV), Paris, France	2018	0.6
The European TREatment of ATopic eczema (TREAT)	2019	0.6
Registry Taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. European Academy of Dermatology and Venereology (EADV), Madrid, Spain		
The European TREatment of ATopic eczema (TREAT)	2019	0.2
Registry Taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. Klinische wetenschappelijke bespreking, AMC, The Netherlands		
Off-label use of methotrexate in dermatological practice – a systematic review with GRADE approach. Klinische wetenschappelijke bespreking, AMC, The Netherlands	2019	0.2

	Year	Workload (ECTS)
Poster presentations at (inter)national conferences		
TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. European Academy of Dermatology and Venereology (EADV), Paris, France	2018	0.4
Towards More Shared Decision Making in Dermatology: Development of Evidence-based Decision Cards for Psoriasis and Atopic Eczema Treatments. European Academy of Dermatology and Venereology (EADV), Paris, France	2018	0.3
Towards More Shared Decision Making in Dermatology: Development of Evidence-based Decision Cards for Psoriasis and Atopic Eczema Treatments. Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, The Netherlands	2019	0.4
TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, The Netherlands	2019	0.4
The current extent of and need for shared decision making in atopic dermatitis and psoriasis in the Netherlands: an online survey study amongst patients and physicians. European Academy of Dermatology and Venereology (EADV), Madrid, Spain	2019	0.3
The European TREatment of ATopic eczema (TREAT)	2019	0.3
Registry Taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. World Congress of Dermatology (WCD), Milan, Italy	2019	0.3
International conferences		
TREAT Registry Taskforce consensus meeting, Amsterdam, The Netherlands	2016	0.5
TREAT Registry Taskforce meeting, Paris, France	2018	0.1
European Dermato-Epidemiology Network (EDEN) Berlin, Germany	2018	0.6
International Symposium on Atopic Dermatitis (ISAD), Utrecht, The Netherlands	2018	0.9
European Academy of Dermatology and Venereology (EADV), Paris, France	2018	1.1
Harmosing Outome Measures for Eczema (HOME) VI meeting, Paris, France	2018	0.1
European Academy of Dermatology and Venereology (EADV), Madrid, Spain	2019	1.1
TREAT Registry Taskforce meeting, Madrid, Spain	2019	0.1
National conferences / symposiums		
Samen Beslissen: van onderzoek, naar duurzame toepassing.	2016	0.2
Therapeutic Drug Monitoring in Biologics Symposium. Amsterdam, The Netherlands	2016	0.3
Symposium Samen Beslissen: Van onderzoek, naar duurzame toepassing. Tilburg, The Netherlands	2016	0.2
Symposium Shared Decision Making and the Ageing Patient, VuMC, Amsterdam, The Netherlands	2016	0.1

	Year	Workload (ECTS)
Nederlandse vereniging voor dermatologie en venereologie (NVDV) dermatologendagen. Arnhem, The Netherlands	2017	0.6
Big Data Symposium, AMC, Amsterdam, The Netherlands	2017	0.1
Masterdialogue vitality, AMC, Amsterdam, The Netherlands	2017	0.1
Chanfleury symposium, department of dermatology, Amsterdam, The Netherlands	2017	0.3
Sympsium promoveren zonder stress, AMC, Amsterdam, The Netherlands	2017	0.1
Refereeravond AMC, Amsterdam, The Netherlands	2018	0.1
Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, The Netherlands	2019	0.6
Refereeravond LUMC; Tropische dermatologie . Leiden, The Netherlands	2017	0.4
Healthy living as a life-saving medicine, Joep Lange Institute, Amsterdam, The Netherlands	2018	0.1
2. Teaching		
Scientific internship, Astrid van Huizen (master student). November 2017 – July 2018.	2017 -2018	2
Onderwijs aios dupilumab in AE	2019	0.1
3. Other		
Clinical scientific meeting (weekly), Department of Dermatology AMC, Amsterdam	2016 -2019	2.1
Conducting phase II, III and IV studies as trial doctor (approximately 1-2 days a week), Department of Dermatology, AMC, Amsterdam	2016 -2020	68
Amsterdam Public Health (APH) meeting; quality of care: Ontsluiten van EPIC data voor onderzoek. Amsterdam, The Netherlands	2017	0.1
Amsterdam Public Health (APH) methodology tutorial: how to make a decision aid. AMC, Amsterdam, The Netherlands	2018	0.1
Amc PROmovendi- VEreniging (APROVE) career event. Amsterdam, The Netherlands	2018	0.3
Member of the environmental advisory committee, AMC, Amsterdam, The Netherlands	2019	0.3

Dankwoord

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Graag wil ik een paar mensen in het bijzonder nog bedanken.

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Geen avontuur is ons te gek, ook het nieuwe avontuur waar we nu aan begonnen zijn. Zolang we het samen doen, kunnen we alles aan. Ik hou van je.

Curriculum Vitae

Francisca Maria Vermeulen, genaamd Mariëlle, werd op 23 april 1987 geboren te Leeuwarden. Ze ging naar het Stellingwerf College waar zij in 2005 haar Atheneum diploma behaalde met het profiel Natuur & Gezondheid + economie 1&2. Na een half jaar Biomedische Wetenschappen in Utrecht te hebben gestudeerd besloot ze mee te loten voor de studie Geneeskunde. Hier werd zij het jaar daarop voor ingeloot. Tijdens haar studie was Mariëlle de voorzitter van de galacommissie, werkte Mariëlle onder andere voor PRA Health services - een wereldwijde, onafhankelijke research organisatie - en stuurde ze haar roeiploeg op wedstrijdniveau bij GSR Aegir. Haar wetenschappelijke stage bij de Gynaecologie liep zij in Salt Lake City te Utah in de USA. Niet lang daarna vertrok ze opnieuw naar het buitenland, ditmaal om de coschappen van haar 5e studiejaar in Curaçao door te brengen. Haar semi-arts stage bracht ze door op de afdeling Cardiologie en Longziekten, waarna ze opnieuw naar Curaçao vertrok om daar een jaar op de Gynaecologie afdeling te werken. Bij terugkomst in Nederland startte ze haar promotietraject op de Dermatologie. Het resultaat hiervan zal zij op 7 juli 2021 in de Aula van de Universiteit van Amsterdam verdedigen.