Atopic dermatitis: epidemiology & off-label therapy
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1

GENERAL INTRODUCTION AND AIMS OF THE THESIS
INTRODUCTION

The hallmark of atopic dermatitis/eczema (AD) is that it is a chronic and relapsing inflammatory skin disorder associated with IgE-mediated sensitization and impairment of the epidermal-barrier function. Pruritus, visible as excoriations and/or prurigo lesions, is the major symptom of AD. Pruritus is so dominant that AD is also known as ‘the itch that rashes’. As AD is often a significant source of distress to those affected, the impact of AD on the quality of life is considerable.\(^1,2\) Besides the associated symptoms, the appearance of AD affected skin can be stigmatizing.

AD is a very common disease which is known under many different names, such as constitutional eczema, neurodermitis and allergic eczema. The semantics have been thoroughly described in ‘Histoire de la dermatite atopique’ by Wallach, Taïeb and Tilles.\(^3\) The word ‘atopy’ dates from 1922\(^4\), quite well before IgE was recognized.\(^5\) The word ‘Allergie’ (‘allergy’) is over 100 years old and was introduced by Von Pirquet.\(^6\) Presence of IgE on cutaneous mast cells was identified and its binding to Langerhans cells in AD was first described in 1986.\(^7\) Functional subpopulations of human T cells, with the principal role for type 2 T cells in central immune organ IgE production, were first revealed in 1990.\(^8,9\) AD is part of the allergy syndrome, in which patients may develop rhinitis, conjunctivitis, food allergy, allergic contact urticaria, allergic asthma and AD in any order and in any combination over time.

There is no laboratory-test based diagnosis possible today. Histopathology is supportive but not definitive. For clinicians, it is difficult to give a precise definition of this disease that has so many different clinical phenotypes, is characterized by such a large variety in severity and is so unpredictable in its natural course in the individual patient. Thereby, until now, no consensus is achieved on major topics as diagnostic criteria, outcome assessment, pathophysiology and therapy.

CLINICAL PHENOTYPES

AD is characterized by highly pruritic erythematous squamous lesions often associated with pronounced lichenification and excoriations. Variations in localisations of eczema occur with age; infantile, juvenile and adult types are usually, but not always discerned.\(^10-12\) In 45–60% of the children, onset of AD occurs during the first six months of life and this ‘infantile AD’ runs until 2–3 years of age.\(^13\) In this phase, the typical distribution pattern is that of a balaclava\(^14\), with eczematous and highly pruritic lesions on the head and neck,
sparing the periorbital and perioral regions. In many cases, weeping and crusting occur. In ‘juvenile AD’, the flexural phenotype ensues. This childhood phase normally lasts from the age of 2–3 until puberty (13–15 years old). Typically, lesions are localized in the neck and in the elbow and knee folds. In ‘adult AD’, in addition to this juvenile flexural distribution, there is pronounced involvement of wrists and ankles, and facial and neck eczema become common locations. It must be emphasized that these are clinical observations. In addition, there are a substantial number of entities to be considered in a differential diagnosis (Table 1).

Table 1. Flexural and/or cheek eczema: differential diagnosis in patients with AD clinical phenotype

<table>
<thead>
<tr>
<th>Chronic dermatoses</th>
<th>Atopiform dermatitis</th>
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<tr>
<td></td>
<td>Prurigo</td>
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<td>Seborrhoic eczema</td>
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<td>Allergic contact dermatitis</td>
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<td>Irritant contact eczema</td>
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<td>Nummular eczema</td>
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<td>Rosacea</td>
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<td>Couperose</td>
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<td>Essential teleangiectasia</td>
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<td>Ulerythema ophryogenes</td>
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<td></td>
<td>Keratosis pilaris</td>
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<td>Juvenile acne</td>
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<td></td>
<td>Psoriasis</td>
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<td></td>
<td>Ichthyosis</td>
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<td>Infections and infestations</td>
<td>Scabies</td>
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<td></td>
<td>Human immunodeficiency virus</td>
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<td></td>
<td>Dermatophytosis</td>
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<td></td>
<td>Erythema infectiosum</td>
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<td></td>
<td>Other viral exanthema</td>
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<tr>
<td>Malignancies</td>
<td>Cutaneous T-cell lymphoma</td>
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<td></td>
<td>Letterer-Siwe disease</td>
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<td>Immunologic disorders</td>
<td>Juvenile lupus erythematoses</td>
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<td></td>
<td>Dermatitis herpetiformis</td>
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<td></td>
<td>Graft-vs-host disease</td>
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<td></td>
<td>Dermatomyositis</td>
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<tr>
<td>Immunodeficiencies</td>
<td>Wiskott-Aldrich syndrome</td>
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<td></td>
<td>Severe combined immunodeficiency disease</td>
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<td></td>
<td>Hyper-IgE syndrome</td>
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<td></td>
<td>DiGeorge syndrome</td>
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<tr>
<td>Metabolic disorders</td>
<td>Zinc, pyridoxine, or niacin deficiency</td>
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<td></td>
<td>Phenylketonuria</td>
</tr>
</tbody>
</table>

(based in part on Leung et al 2004)
NOMENCLATURE

In general, the requirements of a disease definition are that it should result in an optimum discrimination; it should be easy to remember and to use, correspond to the current clinical concept of the disease and be acceptable as an accurate tool for studies.\textsuperscript{15} The clinical phenotype of AD, but without allergen-specific IgE, is the focus of an ongoing debate. A major step was made by introducing the terms intrinsic and extrinsic AD.\textsuperscript{16} The term ‘Intrinsic AD’ was probably first coined by Wüthrich for patients having the phenotype of AD but without detectable allergen-specific IgE.\textsuperscript{17} In ‘extrinsic AD’, external allergens are assumed to sensitize the patient by penetration of a disturbed epidermal barrier. However, the term atopiform dermatitis (AFD) for ‘intrinsic AD’ as proposed by J.D. Bos, might be more clear since it indicates that it has the clinical phenotype of AD, but without atopy.\textsuperscript{18} The percentage of AFD (intrinsic AD) in patients primarily diagnosed as AD varies from 6.9\% to 55.6\%.\textsuperscript{19} A systematic review on this subject showed that the proportion of IgE sensitisation among phenotypic AD was more frequent in hospital than in population based studies.\textsuperscript{20}

PATHOFYSIOLOGY

AD is a multitrait disorder. Two major hypotheses concerning the mechanisms of AD have been proposed; the inside (immunocentric) and the outside (corneocentric) paradigm. The first hypothesis postulates a primary defect in immunological processes (T-cells) that causes IgE sensitisation and a secondary epithelial-barrier dysfunction due to skin inflammation. In the second hypothesis, AD is primarily seen as a disorder of the skin barrier, characterized by malfunction of the corneal layer, enhanced penetration of allergens and secondary sensitisation.

A major development in understanding the pathophysiology was the recognition of functional subsets of T cells, which by their cytokine production profile, could be divided into Th1 cells (mainly producing IFN-$\gamma$) and Th2 cells (mainly producing IL-4, IL-5 and IL-13). Langerhans’ cells of the skin are believed to contribute to Th2 polarization.\textsuperscript{21,22} Th2 cells have been implicated in stimulating B cells to become IgE producing plasma cells. Atopy thus may be seen as a syndrome in which there is central immune dysregulation for yet unexplained reasons. Recent work indeed shows that myeloid and plasmacytoid dendritic cells isolated from peripheral blood of AD patients have an aberrant function compared to healthy controls, as they have a significantly decreased
capacity to produce cytokines (IL-12). This may favour a Th2 cell response (Figure 1).\textsuperscript{23,24}

A concordance rate among monozygotic twins of 77% compared to 15% in dizygotic twins, suggests a strong genetic role in AD.\textsuperscript{25} Genes encoding for proteins involved in skin barrier function and innate immunity are thought to be

\textbf{Figure 1.} Pathogenesis. AD may be seen as a vicious circle of pathogenetic events in which it is as yet uncertain where it starts. Central is the immunological background of atopy in which a systemic abnormality may be present, perhaps at the level of plasmacytoid dendritic cells (pDCs) which by their abnormal cytokine production profile preferentially induce type 2 T cells (Th2) in the secondary immune organs such as lymph nodes. Pruritus, to begin with, leads to stress and vice versa, and the resulting skin excoriations add to an already existing skin barrier defect. The damage to epithelial cells leads to the production of pro-inflammatory mediators that recruit leukocytes, such as monocytes, eosinophils and T cells, into the lesions. These T cells are activated by dendritic cells that are supposed to present allergens and superantigens to them. The route by which these antigens reach the skin is as yet undetermined but many assume they directly enter the skin through the damaged skin barrier. The activation of type 2 T cells, for which there may be a role for abnormal pDCs, is of particular importance as their production of IL-31 seems to be a major mediator of the pruritus.
important in the genetic susceptibility for AD. Genome wide scans have revealed potential AD associated loci. Several candidate genes have been identified on chromosome 5q31-33.26 Those genes encode for cytokines involved in the regulation of IgE synthesis and may contribute to the imbalance of Th1 and Th2 immune response.

Susceptibility loci (ATOD1-6) as well as single nucleotide polymorphisms (SNPs) have been described. Within the past 3 years, it has become apparent that of these susceptibility loci, ATOD2 is localized in the ‘epidermal differentiation complex’ on chromosome 1q21. It harbours the filaggrin gene for which null mutations have been found. Filaggrin has a role in keratin cytoskeleton aggregation during epidermal differentiation and corneocyte formation, when cells of the granular layer collapse into corneal layer scales. Mutations resulting in loss of filaggrin production, both rare and prevalent forms, have been identified in approximately 25% of AD patients in Western, mainly white Europeans.26-35

Till now, these mutations explain only a small proportion of the genetic heritability.

EPIDEMIOLOGY

Epidemiology can be defined as a scientific discipline that studies the (environmental) factors determining the causes, frequency and distribution of diseases in a community or specified population. Considerable efforts are being made to investigate the epidemiology of AD. In this introduction we focus on the prevalence, diagnostic criteria and outcome measures of AD.

Prevalence

Prevalence studies have been conducted to both assess the magnitude of this health care problem as to try to identify the environmental factors associated with its development. In order to identify affected patients it is of vital importance to have a clear disease definition and to have reliable and validated diagnostics.

Prevalence can be established as lifetime prevalence, 1-year prevalence or point prevalence. As AD has a fluctuating course, the 1-year prevalence is often used.36 In order to diagnose AD, diagnostic questionnaires, diagnostic criteria and/or clinical examination have been introduced and used. The choice for one of those diagnostic measures depends on the setting (population versus hospital-based), the available resources (finance, medical staff, time) and on the purpose (estimation of an international prevalence or to establish an accurate diagnosis for inclusion of a clinical trial).
The most commonly used and validated questionnaire is the International Study of Asthma and Allergies in Childhood (ISAAC). The ISAAC provides a standardized method for estimation of prevalences of all atopic diseases within and between countries over the world. In 1998, the prevalence of AD in 56 countries was measured using the ISAAC questionnaire; prevalences ranged from 0.3% to 20.5%. Using ISAAC on large scale contributes to comparable prevalence outcomes worldwide.

Table 2 shows a summary of 1-year period prevalences from different epidemiological studies in different age groups and countries worldwide. From these data, it may be concluded that AD is a very common disease in the infantile and juvenile age periods. Probably at least one to every 30 adults has one or more periods of AD. There is hardly any doubt that during the second half of the 20th century, there has been an increase of the prevalence of AD in western countries for which various explanations have been put forward. As genetics alone cannot explain why AD has reached epidemic proportions, environmental factors clearly have a major role in the expression of the disease and thus, in the genotype-phenotype switch. A major theory explaining the increased prevalence and incidence of AD and atopy in general is the ‘hygiene hypothesis’. In summary, that view indicates that lack of microbial stimulation in the newborns’ immune system due to hygienic environments in modern societies has resulted in lack of signals diverting type 2 responses to regulatory and type 1 T cell responses. Western lifestyle and urban over rural residency are thought to result in a rise in allergic diseases, e.g. by less exposure to parasites, better housing and diet. The increase of the prevalence of atopy has come to a standstill now in some western countries, while it is on the increase in developing nations. Reasons for this need to be further explored (urban/rural residency, migration, pollution, etc.) for a better understanding of these factors. This could open up to new preventive and treatment strategies.

### Table 2

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Europe</th>
<th>North America</th>
<th>South America</th>
<th>Asia</th>
<th>Australia</th>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>infant (0-4)</td>
<td>7.275 - 25.676</td>
<td>6.977 - 20.378</td>
<td>30.879</td>
<td>1.880 - 4.480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adult (&gt;16)</td>
<td>0.292 – 8.493</td>
<td>7.194</td>
<td>3.095</td>
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</table>
Diagnostic criteria

Various lists of diagnostic criteria for AD have been proposed during the last decades. A proportion of these criteria were validated against clinical examination. Clinical examination is regarded the gold standard for diagnosis of AD, although it is hard to standardize and accuracy will depend on the expertise of the examiner. Unluckily, uniformity in the use of diagnostic criteria for AD is lacking. Nevertheless, agreement about the definition of AD and widely accepted diagnostic criteria are needed to conduct future valuable studies and to be able to compare and if applicable pool the results of studies.

The most frequently used sets of clinical criteria for the diagnosis of AD are that of Hanifin and Rajka (H&R) and the UK Working Party criteria. The H&R criteria that were published after a meeting in 1980, have been used in genetic, biological, immunological, epidemiological and clinical studies ever since.47 The UK Working Party has tried to further identify and validate sets of clinical criteria.48-50 They went through the various stages of developing criteria, starting with a hospital based population study and ending with community oriented studies.51,52

In the Millennium Criteria (MC) proposed by J.D. Bos, there is one mandatory criterium which is biological and immunological in nature.53 Presence of allergen-specific IgE in a given patient is a prerequisite for using the word atopy. A diagnosis of AD thus can only be made when there is allergen-specific IgE. The MC have been validated and refined in a case-control study.54 Overall accuracy of the MC was 88.6%. Out of the MC, the best discriminatory principal and additional criteria of the Millennium Criteria were identified using tree analysis. However, the MC need to be further validated in a trial setting that better resembles clinical practice.

Outcome measurement

Outcome measurement can be performed for e.g. disease severity, symptoms, safety and quality of life. Severity outcome measures are needed for valid, reliable and applicable reporting in prospective studies and clinical practice and can serve different purposes: (1) to measure disease severity at a certain point of time and thereby discriminate between patients; (2) to measure changes in disease severity over a period of time (e.g. in an efficacy trial); and (3) to predict disease severity in the future (in prognostic models). To assess disease severity in AD mostly clinical severity outcomes are used. Clinical severity outcome measures can be physician or patients based or both and are designed to assess signs and/or symptoms of the target disease. Charman et al. reviewed all the randomized controlled trials (RCT’s) of therapeutic intervention published
between 1994 and 2001 and showed that 91% included an assessment of clinical signs, of which only 27% used a clinical severity outcome measure that was published before. Until now, 20 clinical severity outcome measures were proposed for AD, but only three of these measures were recommended in a recently published systematic review by Schmitt et al.: severity Scoring of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI) and Patient-Oriented Eczema Measurement (POEM).

To incorporate outcome measures in daily practice and clinical trials, outcome measures should achieve good clinimetric quality. Besides, validity and reliability, essential features for outcome measures are the responsiveness and the minimal clinically important difference. The responsiveness ensures the ability to detect meaningful changes in disease activity and the minimal clinically important difference can identify changes in clinical severity outcome measurements as clinically relevant or not.

The use of unvalidated outcome measures can provoke bias and inaccuracy. Thereby, the variety in outcome methodology is hindering comparison between RCT’s. Currently, attempts are being made on an international level to Harmonise Outcome Measures for Eczema (HOME) by identifying core outcome domains, which are aimed to be widely accepted among dermatologists.

In addition to clinical severity outcome measures, biomarkers are of growing interest for severity outcome assessment. The benefits of biomarkers are that objective read-out is guaranteed and treatment effect can be easily compared between studies. Multiple markers for AD have been proposed, but unfortunately a lot of these could not comply with the requirements for being a reliable biomarker. Requirements are 1) to be disease specific among other diseases of the allergy syndrome, 2) to correlate with other (clinical) severity measurements and 3) to have a sustained effect under different therapeutic strategies.

Thymus and activation-regulated chemokine (TARC), a chemokine that attracts CC chemokine receptor 4 or 8-positive cells, was found to correlate with disease severity of AD and was disease specific among the allergy syndrome.

THERAPY

Treatment of AD can target several aspects of the disease. The first target encompasses the skin-barrier-dysfunction and the decreased synthesis of skin proteins in AD patients. In this light, moisturization of the skin is a priority in restoring the skin barrier function and for this purpose emollients are widely used. Avoiding irritants is advised as AD patients are at risk for developing hand
eczema and irritant contact dermatitis. A new treatment strategy in this area is aimed at acidification of the skin. As neutralization of the stratum corneum adversely impacts epidermal functions including permeability and integrity of the skin, it is thought that acidification of stratum corneum improves these functions in inflammatory skin.60

The second target for treating AD is the Staphylococcal aureus colonization of the skin as AD patients have a higher rate of bacterial adhesion and decreased capacity to produce antimicrobial peptides.61 Thereby, it was shown that Staphylococcal aureus colonization can promote inflammation through superantigen activation.62,63 Nevertheless, a recent Cochrane review failed to show any evidence that antistaphylococcal intervention is clinically helpful in AD patients with clinically non-infected skin.64 However, chronic use of dilute bleach baths decreased the clinical severity of AD in patients with clinical signs of secondary bacterial infections.65 A study by Hata et al. showed that oral vitamin D significantly increased the levels of cathelicidin, a antimicrobial peptide.66 The impact of increasing the production of antimicrobial peptides on clinical disease severity is a new field to explore.

Anti-inflammatory therapy is the third target for treatment of AD. Mainstay of anti-inflammatory therapy is the use of topical corticosteroids. However, while having an anti-inflammatory effect, topical steroids also decrease epidermal proliferation and differentiation and the synthesis of lipids. This is probably the main reason for a rebound effect after discontinuation.67 Other topical drugs include tar products and the relatively new calcineurin inhibitors.68,69 These therapies can be applied in the acute phase or as maintenance treatment.

For severe cases of AD, systemic anti-inflammatory treatment is indicated. Registered systemic treatment options for AD are cyclosporin and oral glucocorticosteroids, of which cyclosporin is first choice.70,71 While proven to be effective, some of the patients have a contra-indication for or have to discontinue cyclosporin due to ineffectiveness or side effects. Moreover, long-term use of cyclosporin raises concerns over (nephro)toxicity. Systemic glucocorticosteroids are used frequently to suppress exacerbations, although clinical data are lacking. A recent RCT comparing short term cyclosporin versus prednisolone was interrupted because of an unsuspected high proportion of withdrawals due to severe exacerbations in the prednisolone group.71 Long-term treatment with glucocorticosteroids is relatively contra-indicated due to the cumulative effect of the side effects.72 This illustrates the need for novel medium-to-long term treatment options for patients with severe AD.
OFF-LABEL THERAPY

Currently, there are no new systemic drugs for AD to be expected. This results from the fact that therapeutics can only be registered by pharmaceutical companies after expensive development and clinical trials. It appears that the commercial interest is too small for these investments. In the light of increasing health-care costs however, awareness starts to come that there are valuable old and cheap drugs within reach. Those drugs are not registered for use in AD, thus treatment is off-label. Many drugs in daily practice are prescribed off-label, approaching 50% of prescriptions in dermatology.

The list of off-label tested and prescribed drugs for AD is long and includes the use of mycofenolate mofetil, azathioprine, methotrexate, interferon-γ, oral pimecrolimus and intravenous immunoglobulines. The strength of evidence of the first three is generally low but supports their use in AD.

With the introduction of biologic treatment in dermatology, evidence appears about its efficacy in AD. In general, biologics have the property to deplete specific cells and mediators. Mainly case reports and pilot studies have been performed testing the effectiveness of biologics such as infliximab, efalizumab, adalimumab, omalizumab and etanercept. Though some of these biologics have shown to be effective in some patients, their immune modulating properties predispose to skin infection and the potential risk of malignancies in long-term use is of concern.

With admission of drugs in unregistered indications, there is an unknown balance between dose, efficacy and safety pattern. As international and national regulatory agencies are currently applying new rules and regulations concerning off-label drug use, guidelines are needed to provide evidence for or against a given therapy, to overcome legal issues involved and to indicate new research areas.
AIMS OF THE THESIS

Atopic dermatitis is one of the most common forms of dermatitis and much research is directed at its epidemiology and therapy. Nevertheless, there are aspects of AD that need some further attention.

As part of the ‘hygiene hypothesis’ it is thought that eczema is more common in urban than in rural communities. However, such a notion was never assessed systematically. Chapter 2 is a systematic review that shows the available evidence by summarizing all the relevant primary studies on this subject.

Over the years many criteria were introduced to diagnose AD. However, not all of these diagnostic criteria are validated and show to have good diagnostic properties. Chapter 3.1 is a systematic review that summarizes the evidence concerning the validity of diagnostic criteria for AD.

The Millennium Criteria are diagnostic criteria that were developed to accurately diagnose true atopic AD and are aimed to ensure homogenous populations to facilitate clinical research. In Chapter 3.2 the Millennium Criteria are further validated and refined by conducting a hospital-based cohort study.

Severity outcome assessment is conditional for evaluating treatment response or to compare different therapeutic options for efficacy/effectiveness. Thereby, the possibility to pool results from different clinical trials is of vital importance to ensure meta-analysis and thereby to generate a high level of evidence in favour of or against the use of a given therapy.

Chapter 4 is a validation study in which two clinimetric properties of four severity outcome measures are analysed.

Since therapeutic options are scarce, management of patients with severe AD can be challenging. Cyclosporin and oral corticosteroids are the only systemic treatments that are officially registered for AD in the Netherlands. However treatment can fail or can be contra-indicated. Chapter 5.1 is a RCT in which two off-label drugs, methotrexate and azathioprine, are compared for efficacy and safety in patients with severe AD. Chapter 5.2 & 5.3 are systematic reviews that encompass the off-label use of azathioprine and efalizumab in dermatological patients.
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