# Management of difficult to treat atopic dermatitis

Jorien van der Schaft

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# Management of difficult to treat atopic dermatitis

## Het beleid bij moeilijk behandelbaar constitutioneel eczeem

*(met een samenvatting in het Nederlands)*

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# Chapter 1

General introduction

# GENERAL INTRODUCTION

## ATOPIC DERMATITIS: PREVALENCE AND TREATMENT OPTIONS

Atopic dermatitis (AD) is a chronic pruritic and relapsing inflammatory skin disease affecting an increasing number of patients.[1] The lifetime prevalence of AD is estimated between 15-30% in children and 2-10% in adults. The incidence has increased 2- to 3-fold during the past 3 decades in industrialized countries with the highest prevalence found in Northern Europe.[2, 3] The onset of AD occurs during the first 6 months of life in 45% of children and before the age of 5 years in at least 85% of the affected patients. Children with onset before the age of 2 years will have persisting manifestations of the disease in 20%. An additional 17% will have intermittent symptoms by the age of 7 years. The onset of AD after adolescence is only 16.8% in adult patients with AD.[1]

Health-related quality of life can be worsened by AD because of its detrimental influence on work, self-confidence, sport, sleep, and social interaction. This results in impairments of social functioning and psychological wellbeing.[4, 5] In the majority of patients, long-term adequate disease control can be reached after education and instruction with respect to optimal skin care, and the correct use of topical corticosteroids, topical immunomodulators and/or UV-light therapy.[6, 7] However, in patients with difficult to treat AD, controlled disease cannot be reached with topical corticosteroids in safe amounts, adequate instructions and self-management training. In these patients treatment with oral immunosuppressive drugs is required. Various immunosuppressive drugs are used in AD, including cyclosporin A, mycophenolate mofetil, enteric-coated mycophenolate sodium, methotrexate, azathioprine, and oral corticosteroids. In many countries, cyclosporin A is the only registered oral immunosuppressive drug in the treatment of AD and other oral immunosuppressive drugs are used off label. The mode of action of the different compounds is presented in Table 1. Methotrexate is not considered as an oral immunosuppressive drug, but acts as folic acid antagonist.

## EFFICACY AND SAFETY OF ORAL IMMUNOSUPPRESSIVE DRUGS FOR ATOPIC DERMATITIS IN CLINICAL TRIALS

Several overviews of oral immunosuppressive drugs used in the treatment of AD are published the past years. These overviews are based on data gathered from clinical trials and case reports. Roekevisch *et al*.[8] performed a systematic review on the efficacy and safety of systemic treatments for moderate-to-severe AD in randomized controlled trials (RCT). Thirty-four RCTs with 12 different systemic treatments in 1653 patients were

included. Based on these RCTs, cyclosporin A is recommended as first-line treatment, azathioprine can be considered as second-line treatment, and methotrexate as a third-line treatment option.

**Table 1** – Mode of action of different oral immunosuppressive drugs.

| group | compound | mode of action |
|---|---|---|
| calcineurin inhibitors | cyclosporin A | - inhibition T-cell activation by interfering with calcium-dependent signaling events involved in cytokine transcription |
| purine antagonists | azathioprine | - interference with purine base production and DNA/RNA synthesis<br>- depression of cell-mediated immunity |
| inosine monophosphate-dehydrogenase (IMPDH) inhibitors | enteric-coated mycophenolate sodium/ mycophenolate mofetil | - inhibition de novo synthesis of guanosinenucleotide, needed for DNA/RNA synthesis<br>- inhibition of T- and B-lymphocyte activation and proliferation<br>- induction of apoptosis of activated T-lymphocytes |
| folic acid antagonist | methotrexate | - anti-inflammatory effects through augmenting concentrations of adenosine, which acts as an endogenous anti-inflammatory agent<br>- modulating cytokine release and adhesion molecule expression |
| oral corticosteroids | predniso(lo)ne | - various immunosuppressive and anti-inflammatory effects<br>- effects on cell migration and phagocytosis by leucocytes and monocytes |

Schmitt *et al.*[9] described a meta-analysis of controlled and uncontrolled trials of cyclosporin A treatment in patients with AD. Fifteen studies including 602 patients were analysed. All studies reported a decrease in the mean severity of AD with a relative effectiveness of 55% (95% confidence interval 48-62%) after 6 to 8 weeks of cyclosporin A treatment. The use of cyclosporin A was limited due to the development of side effects; significant increase of serum creatinine levels were reported in 11%, hypertension in 6%, and gastrointestinal symptoms in 40% of patient months of active treatment with cyclosporin A.

The inosine monophosphate-dehydrogenase (IMPDH) inhibitors mycophenolate mofetil and enteric-coated mycophenolate sodium have been evaluated in various studies. Several open pilot studies demonstrated clinical efficacy and safety of mycophenolate mofetil in patients with moderate-to-severe AD.[10-15] Van Velsen *et al.*[16] described the results of enteric-coated mycophenolate sodium treatment in 10 adult patients with severe AD during a 6-month observational period. AD improved in all patients in the course of 4-8 weeks of treatment and this improvement remained stable

over the 6-month treatment period. None of the patients discontinued enteric-coated mycophenolate sodium use and only mild side effects were reported.

Haeck *et al*.[17] performed a comparative study between cyclosporin A and enteric-coated mycophenolate sodium. Adult patients with severe AD received cyclosporin A (5 mg/kg/day) during a 6-week period and were consecutively randomized to compare enteric-coated mycophenolate sodium (1440 mg/day) (n = 26) and cyclosporin A (3 mg/kg/day) (n = 24) during 30 weeks of maintenance treatment. An increase of AD severity was reported after randomization in both groups; this increase was larger in the enteric-coated mycophenolate sodium study group in which more rescue medication was used. After 10 weeks of maintenance treatment the AD severity was comparable in both groups until the end of the maintenance phase. However, the side effect profile of enteric-coated mycophenolate sodium was more favorable and no relapse after stopping enteric-coated mycophenolate sodium was observed during 12 weeks of follow-up in contrast to the cyclosporin A treated patients.

The purine antagonist, azathioprine was compared to placebo in two RCTs.[18, 19] These RCTs including 37 and 41 patients, respectively, reported a reduction of AD severity of 26% and 37% after 12 weeks. Side effects led to early discontinuation of azathioprine in 10.8% and 14.6% of the patients.

One prospective study (n = 12) and one retrospective study (n = 20) showed clinical efficacy and safety of methotrexate treatment in patients with severe AD.[20-21]

A RCT of Schram *et al.*[22] compared azathioprine (n = 22) and methotrexate (n = 20) during a 12-week period. Patients were treated with methotrexate varying between 10-22.5 mg/week or azathioprine 1.5-2.5 mg/kg/day. The clinical skin severity score was comparable in both groups after 12 weeks of treatment (patients treated with methotrexate reduction of 42% compared with 39% reduction in the azathioprine group). There was no significant difference in the number and severity of side effects (side effects leading to early discontinuation methotrexate 5% versus 9% in the azathioprine group) and the use of rescue medication was comparable in both groups.

There is a lack of efficacy studies of oral corticosteroids in the treatment of AD. However, treatment with oral corticosteroids should generally be avoided because of short-term and long-term side effects.

## OUTCOME PARAMETERS FOR ATOPIC DERMATITIS

There is a wide variety of clinical scoring systems used in clinical trials to describe the efficacy of oral immunosuppressive drugs in patients with AD. A systematic review identified 20 named instruments to assess the severity of AD of which most have not been tested properly or do not perform adequately when tested.[23] The use of a uniform and

simple clinical scoring system in both clinical trials and daily practice would improve the external validity of trial data concerning efficacy of oral immunosuppressive drugs in AD. The Harmonising Outcome Measures for Eczema (HOME) initiative agreed in an international consensus study that the Eczema Area and Severity Index (EASI) is the preferred core instrument to measure clinical signs in all future trials on the treatment of AD.[24] Ideally the EASI score should also be used in daily practice, however if this score is too time consuming the Investigator Global Assessment (6-point scale) seems to be a good alternative, as the IGA has a very good correlation with clinical skin scores.[25, 26] Despite all attempts to optimize clinical severity scores for AD, scoring of the AD remains subjective. Frequent training of all staff members involved in clinical scoring increases the reliability, but intra- and inter-individual differences remain.[27]

Disease specific biomarkers can overcome this problem and can be used as an objective measure of disease activity. Several biomarkers have been found to correlate with disease severity of AD. The most reported are eosinophilic cationic protein (ECP), total IgE, soluble interleukin-2 receptor (sIL-2R), and thymus and activation-regulated chemokine (TARC/CCL17).[28-31] In a systematic review was found that TARC showed the best correlation with disease severity, with weighted mean r-values of 0.60 and 0.64 in longitudinal and cross-sectional studies, respectively.[32] However, a recent study reported that in AD a combination of biomarkers showed a better correlation with disease severity compared to a single biomarker, which might be attributed to the heterogeneity of the disease.[33]

Clinical scoring systems and biomarkers describe disease severity and extent, but do not measure the impact of the skin disease experienced by the patient. The interest for Patient Reported Outcome Measures (PROMs), like the Patient Oriented Eczema Score (POEM) and Dermatology Life Quality Index (DLQI) has increased in the past years.[34, 35]

## DRUG SURVIVAL

In clinical trials the efficacy of a specific oral immunosuppressive drug is often presented as a mean decrease of the clinical score in the total patient group. Some trials present the percentage of patients reaching 50% decrease of the clinical severity score. This presentation gives a better impression of the individual response to the oral immunosuppressive drug. However, a clear definition of a responder and a non-responder to treatment is lacking.

Drug survival is a real life reflection of daily practice and measures the length of time a patient continues to take a particular drug: it is a well-recognized measure, which encompasses factors such as effectiveness, safety, and patients' and doctors' preferences.[36-38]

Drug survival analysis is based on the reason for discontinuation of the drug, which reflects the real life situation in daily practice without intervening of a fixed research protocol. Clinical decisions made by the physician and patient together determine the outcome instead of clinical skin scores. The reason for discontinuation of a drug in daily practice reflects the balance between effectiveness and side effects. Measurement of clinical skin scores may provide additional information on clinical efficacy at a fixed time point, but are not sufficient to reflect the performance of a drug in a real life situation.

The concept of drug survival analysis origins from oncology, in which the fraction of patients living for a certain amount of time after treatment is measured. Apart from oncology drug survival analysis has frequently been used to describe daily practice treatment results with biologics in rheumatoid arthritis.[39, 40] More recent, literature about drug survival of patients with psoriasis treated with biologics was published.[41, 42]

Kaplan-Meier survival analysis, which is the underlying statistical model of drug survival, examines and models the time it takes for events to occur. Besides death, events could be recurrence of disease or discontinuation of a drug. An example of a survival curve is shown in Figure 1.

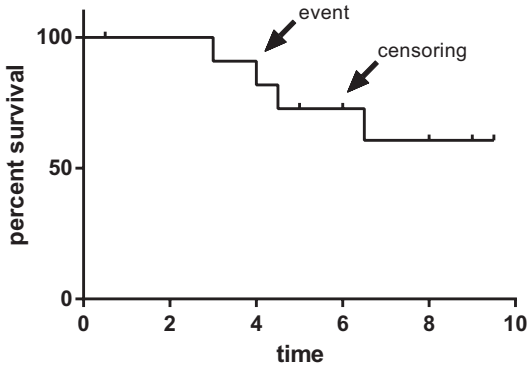


**Figure 1 –** Example of a drug survival curve.
At time point zero the group consists of 100%. The survival curve reflects each event at the appropriate point with a step down. Each tick mark represents the time one patient was censored. Patients may have censored survival times if the event has not yet occurred (or there is no evidence to show that either has occurred). This could happen when patients drop-out of the follow-up or the study has a fixed time-line and the event occurs after the cut-off.

## OUTLINE OF THIS THESIS

In this thesis about the challenges in the management of difficult to treat atopic dermatitis in adults two topics are discussed. The characteristics of difficult to treat AD are addressed in *chapter 2* and *3*.

The performance of oral immunosuppressive drugs in daily practice is investigated in *chapter 4-9*. We analyzed the drug survival of cyclosporin A in 356 adult patients with atopic dermatitis in *chapter 4*. The long-term effect of cyclosporin A treatment on serum creatinine levels is described in 150 patients with AD in *chapter 5*. In *chapter 6* the first experience with extended release tacrolimus, an alternative calcineurin inhibitor, in the treatment of patients with severe AD is discussed. *Chapter 7* describes the drug survival of azathioprine and enteric-coated mycophenolate sodium, two oral immunosuppressive drugs that are used off-label in the treatment of AD, in 94 and 84 patients, respectively. The importance of attention to concomitant medication use in patients treated with azathioprine and liver enzyme disturbances is addressed in *chapter 8*. *Chapter 9* describes the drug survival of 89 patients with AD treated with methotrexate. Finally, all findings will be discussed in *chapter 10* in the context of potential clinical implications. The outline of this thesis is depicted in Table 2.

**Table 2** – Outline of the topics in this thesis and the corresponding chapters.

| | |
|---|---|
| **Characteristics of difficult to treat AD** | |
| Chapter 2: | Serum vitamin D levels in adult patients with atopic dermatitis: recommendations for daily practice |
| Chapter 3: | Is there an additional value of in-patient treatment for patients with difficult to treat atopic dermatitis? |
| **What is the performance of oral immunosuppressive drugs in daily practice?** | |
| Chapter 4: | Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis |
| Chapter 5: | Serum creatinine levels during and after long-term treatment with cyclosporin A in patients with severe atopic dermatitis |
| Chapter 6: | First experience with extended release tacrolimus in the treatment of adult patients with severe, difficult to treat atopic dermatitis: clinical efficacy, safety and dose finding |
| Chapter 7: | Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis |
| Chapter 8: | Increased liver enzyme levels during azathioprine treatment; beware of concomitant use of proton pump inhibitors |
| Chapter 9: | Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis |

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# Chapter 2

## Serum vitamin D levels in adult patients with atopic dermatitis: recommendations for daily practice

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*Submitted*

## ABSTRACT

Literature on serum 25-hydroxyvitamin D3 (25(OH)D) levels in patients with atopic dermatitis (AD) in relation to severity based on clinical eczema score shows contradictory results. This may be due to the fact that a single clinical eczema score do not reflect long-term disease severity. Studies in asthma express disease severity based on "treatment need", such as frequency and dosage of asthma medication, which better reflects long-term disease severity.

In the present study, AD severity was also based on treatment need and patients were classified as difficult to treat when the eczema was uncontrolled by potent topical corticosteroids. Their serum 25(OH)D levels were compared to a group of patients with adequate response to topical corticosteroids. The serum 25(OH)D status was insufficient/deficient in 69.5% of the total number of patients. Patients with difficult to treat AD had a higher risk to be 25(OH)D deficient than patients with an adequate response to topical corticosteroids (adjusted OR 1.92; 95% CI 1.01-3.66). These data recommend serum 25(OH)D screening in AD patients, in particular in patients with difficult to treat AD.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a high prevalence in children and adults. The pathogenesis is complex and probably due to a combination of various factors like genetic predisposition, environmental factors as well as barrier disruption or hyper-reactivity of the immune system.[1]

Vitamin D status is assessed by serum 25-hydroxyvitamin D3 (25(OH)D) levels. The function of 25(OH)D, known to regulate calcium and phosphate homeostasis, is thought to be highly complex. A deficient serum 25(OH)D level leads to osteomalacia and therefore needs to be supplemented.[2]

Several studies have also associated insufficient/deficient serum 25(OH)D levels with many other conditions such as heart disease, asthma, diabetes mellitus, rheumatoid arthritis and cancer.[2] The past years, a number of trials have been established to examine the effects of vitamin D supplementation on non-musculoskeletal diseases. Most trials failed to demonstrate benefits of vitamin D supplementation. Ongoing trials have to clarify if vitamin D deficiency does play an etiological role in these diseases.[3]

Previous data on serum 25(OH)D levels in patients with AD were mainly collected from small numbers of patients and mainly in children. The results were contradictory on an association between AD severity and serum 25(OH)D levels.[4-8] In these studies AD severity is expressed by means of a single clinical eczema score at a fixed time point. Since AD is a chronic disease with remissions and exacerbations, a single measurement does not reflect disease severity.

In allergic asthma (AA) higher serum 25(OH)D levels are associated with a reduced risk of asthma exacerbations.[9] In addition, Confino-Cohen *et al.* found that in a large adult population-based study in asthma, serum 25(OH)D deficiency was associated with a higher risk of exacerbations (OR 1.22 95%CI 1.07-1.39).[10] Other studies in AA report that patients with low serum 25(OH)D levels have increased corticosteroid requirements, indicating more difficult to treat AA.[9] Interestingly, in these studies disease severity was based on "treatment need", such as frequency and dosage of asthma controller medications or hospital emergency department visits.

In the present daily practice cross-sectional study AD patients were classified as difficult to treat if their eczema was uncontrolled by high amounts of (very) potent topical corticosteroids. Their 25(OH)D status was defined by measuring serum 25(OH)D levels. These results were compared to the 25(OH)D status of AD patients with an adequate response to topical corticosteroids.

## PATIENTS AND METHODS

### Patients

All new adults with AD visiting the specialized eczema outpatient clinic of the Dermatology and Allergology department of the University Medical Center Utrecht between March 2013 and August 2014, were included. Patients were identified using the electronic patient file database with a selection filter on the diagnosis of AD and the determination of a serum 25(OH)D level.

The diagnosis of AD was confirmed by the criteria of Hanifin and Rajka and the criteria of Williams.[11,12]

To classify AD severity based on treatment need, patients were categorized as difficult to treat when oral immunosuppressive drugs (cyclosporin A, enteric-coated mycophenolate sodium, azathioprine, methotrexate or prednisolone >3 months) were used at the moment of serum 25(OH)D measurement or within one year before or thereafter. Patients had an indication for treatment with oral immunosuppressive drugs when daily treatment with potent to very potent topical corticosteroids in maximum amounts were not effective or could not be tapered to a safe maintenance scheme. Serum 25(OH)D levels in this group were compared to those of a group of AD patients with controlled AD using a maintenance dose of topical corticosteroids (maximum 100 g/week of potent topical corticosteroids).

The following additional information was recorded: age, sex, and the season at blood sampling. Photosensitive AD, phototherapy <3 months before serum 25(OH)D level determination or the use of vitamin D supplements at the moment of determination of serum 25(OH)D level were exclusion criteria.

### Serum 25-hydroxyvitamin D3 levels

Serum 25(OH)D level was used as a continuous and categorized variable. The categories were defined as sufficient (≥75 nmol/L), insufficient (50-74.9 nmol/L) and deficient (<50 nmol/L) based on international recommendations.[13]

### Statistical analysis

Descriptive statistics were used to describe patient characteristics relative to the two AD severity groups (patients with difficult to treat AD and patients with an adequate response to topical corticosteroid treatment). Unadjusted comparisons between AD severity groups and mean serum 25(OH)D levels were made with the independent sample T-test. A one-way between-groups analysis of covariance was conducted to adjust for age, sex, and season at blood sampling. To express the risk on a deficient 25(OH)D status for patients with difficult to treat AD, the odds ratio (OR) and 95% confidence interval (CI) was calculated. A logistic regression analysis was conducted to calculate the adjusted

OR for age, sex and season at blood sampling. P-values of <0.05 were considered as statistically significant. Statistical analyses were performed in SPSS (IBM SPSS Statistics 21, windows version).



## RESULTS

Two hundred and ten patients meeting the inclusion criteria were identified. The mean age was 36.5 (SD 14.5) years and 106 (50.5%) patients were male. Mean serum 25(OH)D level was 61.0 (SD 30.7) nmol/L. The serum 25(OH)D status was sufficient in 64 (30.5%), insufficient in 57 (27.1%) and deficient in 89 (42.4%) patients.

AD was classified as difficult to treat in 71 (33.8%) patients; 139 (66.2%) patients had an adequate response to topical corticosteroids (Table 1). There was no significant difference of mean serum 25(OH)D level in patients with difficult to treat AD (55.7 (SD 33.8) nmol/L) compared to patients with an adequate response to topical corticosteroids (63.6 (SD 28.8) nmol/L) (p=0.076) (Figure 1). Differences between AD severity groups after adjustment for age, sex and season at blood sampling were not significant (adequate response to topical corticosteroids mean serum 25(OH)D 62.2 (SD 2.6) nmol/L; difficult to treat AD mean serum 25(OH)D 58.6 (SD 3.7) nmol/L; p=0.439).

**Table 1** – Patient characteristics and 25(OH)D levels and status for the total group, patients with difficult to treat AD and patients with an adequate response to topical corticosteroids.

| | **total group (n = 210)** | **difficult to treat AD (n = 71)** | **AD with adequate response to topical corticosteroids (n = 139)** | **p-value** |
|---|---|---|---|---|
| age, mean (SD) | 36.5 (14.5) | 41.0 (14.0) | 34.1 (14.2) | 0.001 |
| sex, n (%) | | | | |
| male (%) | 106 (50.5%) | 50 (70.4%) | 56 (40.3%) | 0.001 |
| female (%) | 104 (49.5%) | 21 (29.6%) | 83 (59.7%) | |
| season at blood sampling, n (%) | | | | |
| winter (%) | 37 (17.6%) | 13 (18.3%) | 24 (17.3%) | 0.354 |
| spring (%) | 82 (39.0%) | 23 (32.4%) | 59 (42.4%) | |
| summer (%) | 58 27.6%) | 20 (28.2%) | 38 (27.3%) | |
| autumn (%) | 33 (15.7%) | 15 (21.1%) | 18 (12.9%) | |
| serum 25(OH)D level (nmol/L), mean (SD) | 61.0 (30.7) | 55.7 (33.8) | 63.6 (28.8) | 0.076 |
| serum 25(OH)D status, n (%) | | | | |
| deficient (<50 nmol/L) | 89 (42.4%) | 39 (54.9%) | 50 (36.0%) | 0.031 |
| insufficient (50-74.9 nmol/L | 57 (27.1%) | 15 (21.1%) | 42 (30.2%) | |
| sufficient (≥75 nmol/L) | 64 (30.5%) | 17 (23.9%) | 47 (33.8%) | |

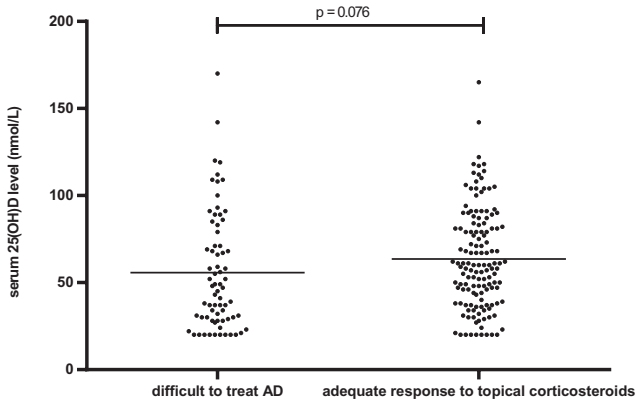


**Figure 1** – Serum 25(OH)D levels in relation to AD severity (patients with difficult to treat AD and patients with an adequate response to topical corticosteroids). Horizontal lines indicate mean values. Adjustment for age, sex and season at blood sampling (p=0.439).

The distribution of serum 25(OH)D status was significantly different between patients with difficult to treat AD and patients with an adequate response to topical corticosteroids (p=0.031). Patients with difficult to treat AD had a higher risk to be 25(OH)D deficient than patients with an adequate response to topical corticosteroids (OR 2.17; 95% CI 1.21-3.88). The OR adjusted for age, sex, and season at blood sampling was 1.92 (95%CI 1.01-3.66).

## DISCUSSION

The results of the present study illustrate that only 30.5% of the total group of AD patients (n=210) had a sufficient serum 25(OH)D status. A high percentage (42.4%) of patients showed a deficient serum 25(OH)D status. Patients with AD were classified in two severity groups based on their treatment requirements. Although there was no significant difference in mean serum 25(OH)D levels between both severity groups, the percentage of AD patients with a deficient serum 25(OH)D status was significantly higher in the group classified as difficult to treat AD compared to patients with adequate response to topical corticosteroids. This was independent from age, sex, and season at blood sampling.

Classification of AD severity based on treatment response in daily practice is new and may give a better reflection of AD severity over time than a single clinical eczema score. All AD patients included in this study needed maintenance treatment with topical corticosteroids to control their eczema. However, patients with difficult to treat AD had

high clinical eczema scores over time, despite adequate use of (very) potent topical corticosteroids and therefore being in need for systemic immunosuppressants. The results of this study show that 54.9% of these patients have deficient serum 25(OH)D levels.

Previous case-control and cross-sectional studies were performed in small numbers of AD patients, mainly being children. AD severity was based on a single clinical eczema score. In the case-control study of El Taieb *et al.*[4] the mean serum 25(OH)D level was significantly lower in 29 children with AD compared to 30 controls. Children with mild AD (SCORAD <25) had a significantly higher mean serum 25(OH)D level compared to children with moderate (SCORAD 25-50) and severe AD (SCORAD >50); severity classification was based on SCORAD (Scoring Atopic Dermatitis). Wang *et al.*[5] reported another case-control study; the mean serum 25(OH)D level was significantly lower in 498 children with AD compared to 328 non-allergic controls. Serum 25(OH)D levels showed an association with AD severity based on SCORAD and on the Nottingham Eczema Severity Score (NESS). A cross-sectional study in 97 children with AD of Chiu *et al.*[6] reported no significant difference between mean serum 25(OH)D level in patients with mild AD compared to patients with moderate and severe AD (based on SCORAD). Peroni *et al.*[7] reported a significantly higher mean serum 25(OH)D level in patients with mild AD compared to patients with moderate and severe AD in a cross-sectional study in 37 children (based on SCORAD). Akan *et al.*[8] performed a cross-sectional study, which showed a negative correlation between individual SCORAD values and serum 25(OH)D levels in 73 children with AD.

Although the importance of a sufficient serum 25(OH)D level is demonstrated in osteomalacia, there is no evidence that vitamin D supplementation has positive effects on disease severity or improves the response to topical corticosteroids in AD. Hata *et al.*[14] performed a double-blind study in 30 adult patients with AD and 30 non-atopic controls. After randomization patients received active vitamin D (4000 IU/day) or placebo for 21 days. Serum 25(OH)D levels increased, but AD severity based on clinical eczema score (Eczema Area and Severity Index (EASI)) did not change significantly. Camargo *et al.*[15] performed a randomized, double-blind, study on vitamin D supplementation for winter-related AD in 107 children. After randomization patients received active vitamin D (1000 IU/day) or placebo for one month. The vitamin D supplemented group showed a significant improvement of AD severity based on EASI score compared to the placebo group (p=0.04). Interpretation of these studies results is difficult, because there is only limited information on topical AD treatment during the study.

In general, vitamin D supplementation is recommended in case of 25(OH)D insufficiency/deficiency to prevent osteomalacia. A recent study showed that patients with AD are more prone to develop osteopenia and osteoporosis.[16] In the total group, 69.5% had

an insufficient/deficient vitamin D status and should use vitamin D supplementation. Therefore, screening serum of 25(OH)D level is recommended in all patients with AD needing maintenance treatment with topical corticosteroids to control their eczema. Since patients with difficult to treat AD have the highest risk for insufficiency/deficiency (76.0%), vitamin D screening in this subgroup is strongly recommended.

A limitation of this study is the selection of patients treated in a tertiary center. Patients with mild eczema, controlled by occasional or intermittent use of topical corticosteroids or topical immunomodulators are not included in this study. Therefore, the results of the present study are only applicable to patients needing maintenance treatment with topical corticosteroids or oral immunosuppressive drugs to control eczema. Another limitation is the unavailability of data on clinical factors such as physical activity, sunlight exposure and dietary intake that regulate vitamin D homeostasis.

In summary, the serum 25(OH)D status of the total group of AD patients was insufficient/deficient in 69.5% of the patients. As only 30.5% of the patients had a sufficient vitamin D status, we recommend serum 25(OH)D screening in all patients with AD needing maintenance treatment with topical corticosteroids to control their eczema. Patients with difficult to treat AD have the highest risk for deficient serum 25(OH)D levels; in this subgroup vitamin D screening is strongly recommended. Vitamin D supplementation should be considered in case of 25(OH)D levels <75 nmol/L.

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# Chapter 3

## Is there an additional value of inpatient treatment for difficult to control atopic dermatitis?

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*Under review*

## ABSTRACT

An inpatient treatment and education program has been developed for patients with difficult to control atopic dermatitis (AD), with the aim to reach adequate self-management and long-term disease control. This observational study included adult patients diagnosed with difficult to control AD, admitted for a structured inpatient treatment and education program. The primary outcome was the Six Area, Six Sign Atopic Dermatitis (SASSAD) score. In total, 79 patients (mean age 38.8 (SD17.1) were included. The median duration of hospitalization was 11 days (IQR8-14). The mean percentage decrease in SASSAD score between admission and discharge was 60.7%, of which 64 (81.0%) patients reached SASSAD50. The mean percentage decrease in SASSAD score was 69.0% during follow-up, of which 63 (79.7%) patients still had a SASSAD50. In the majority of these difficult to control AD patients the admission resulted in sustained disease control. This could be achieved by optimization of treatment with topical corticosteroids.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic and relapsing skin disease resulting from complex interactions between genetic and environmental factors.[1-3] Health-related quality of life is worsened because its negative influence on work, self-confidence, sport, sleep and social interaction. This may result in loss of social functioning and psychological wellbeing.[4-6]



In the majority of patients, AD can be adequately controlled with topical corticosteroids, topical immunomodulators, coal tar preparations, and/or ultraviolet phototherapy. Despite these therapeutic options, a subgroup of patients with difficult to control AD remains; in this group treatment with oral immunosuppressive drugs to reach disease control is sometimes required.

Education to enhance disease knowledge, psychological improvement in disease perception and scratch control behavior modification, together with regular daily treatment, will lead to better skin care. Previous studies showed an improvement in disease control and quality of life resulting from education about AD; especially time spent with the patient and the qualification of the trainer are important to reach a positive outcome.[7-9]

The department of Dermatology at the University Medical Center Utrecht (UMCU) has a multidisciplinary team consisting of dermatologists, dermatological nurses, social workers, dieticians and other specialists, to instruct and support patients with AD at the outpatient clinic. All patients are informed about the chronicity of the disease, the use of topical corticosteroids, how to cope with exacerbations, itch, and if necessary psychosocial care.[10] The majority of the patients is able to control their eczema after adequate instruction and further support by dermatological nurses in an outpatient setting, face-to-face or online. However, in patients with more severe and extensive eczema, this treatment requires a lot of effort and motivation. Treatment may fail due to inability to combine time spent to treatment with work, family activities and social activities. Sometimes patients are too exhausted due to sleep deprivation and therefore unable to deal with intensive topical therapy. Other factors responsible for outpatient treatment failure are psychosocial factors, for instance depression or lack of social support.

To improve therapy outcome for difficult to control AD patients, a standardized inpatient treatment and education program has been developed. The aim of the present observational study was to evaluate the efficacy of an inpatient treatment and education program for patients with difficult to control AD.

## METHODS

### Patient selection and intervention

This observational study included patients with difficult to control AD in an outpatient setting admitted to the clinical department of Dermatology at the UMCU between March 2010 and data lock in January 2014. Inclusion criteria were the availability of the Six Area, Six Sign Atopic Dermatitis (SASSAD) score at admission, discharge and follow-up (until 3 months after discharge).[11] All patients were diagnosed with AD according to the criteria of Hanifin and Rajka and the criteria of Williams.[12-13] Only the first admission of patients with more than one admission in this period was evaluated.

During admission, all patients received a structured treatment and education program according to the protocol for inpatient treatment (Figure 1). Patients were treated with topical corticosteroids class III (potent corticosteroids). Some patients received additional treatment with oral immunosuppressive drugs, antihistamines and antibiotics. After inpatient treatment, a visit at the multidisciplinary outpatient clinic was scheduled (<3 months after discharge) to monitor disease activity and to evaluate self-management and reintegration. During follow-up the use of topical corticosteroids was tapered to a safe maintenance scheme.

Thereafter, visits at the outpatient clinic were only performed if indicated. A personal digital eczema portal to communicate with the dermatological nurse remained available for all patients.[14]

### Outcome measures and data analysis

The primary outcome was the SASSAD score. Secondary outcome parameters included serum thymus and activation-regulated chemokine (sTARC) level and need for oral immunosuppressive treatment to reach controlled AD.[15, 16]

Statistical analysis of the data was performed using SPSS 21.0 (SPSS inc. Chicago IL, USA). Descriptive statistics were used to describe patient characteristics. Data description was based on means (standard deviation (SD)) and median (inter quartile range (IQR)) for continuous endpoints and on frequencies for categorical variables. SASSAD50 (score reduction of 50% or more) and SASSAD75 (score reduction of 75% or more) were calculated for admission – discharge and admission – follow-up. Mean SASSAD scores were compared with the paired sample t-test. sTARC and need for oral immunosuppressive treatment were compared between admission and discharge, and discharge and follow-up using the Wilcoxon signed rank test and McNemar test. P-values of <0.05 were considered as statistically significant.

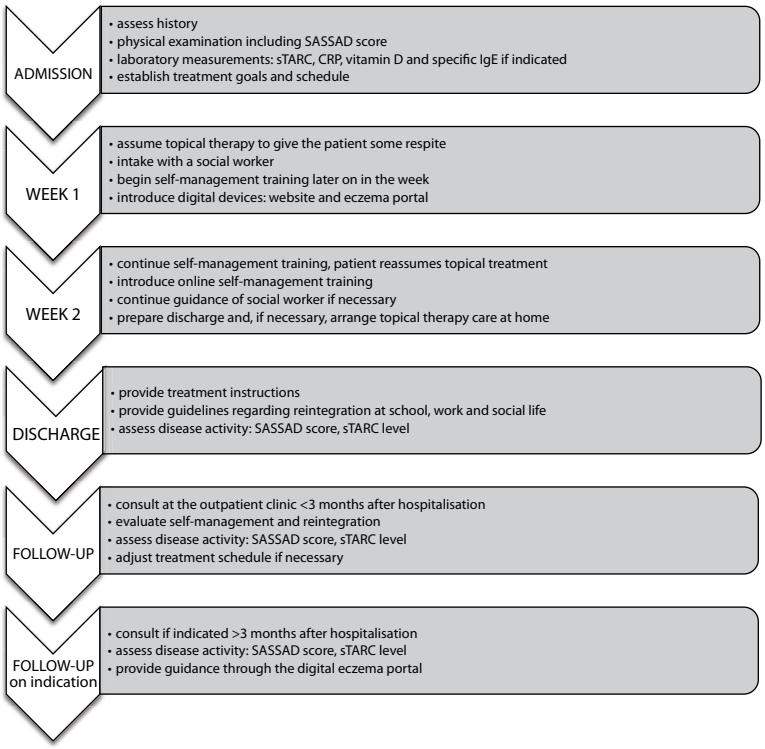


**Figure 1** – Clinical treatment and education program for patients with difficult to control AD in the UMCU.

## RESULTS

### Patient characteristics

In total, 79 patients with a mean age of 38.8 (SD 17.1) were included of which 38 (48.1%) were male. The indication for admission in all patients was failure or expected failure of treatment in an outpatient setting. Forty-three patients (54.4%) were admitted at their first outpatient consultation. Table 1 shows the therapeutic history of the patients; 51 (64.6%) patients had used oral immunosuppressive drugs in the past; 19 patients (24.1%) had admissions for AD in the past.

### Hospitalization period

The median duration of hospitalization was 11 days (IQR 8-14). At discharge, 64 (81.0%) patients reached SASSAD50. Thirty-four (43.0%) patients reached SASSAD75. The mean percentage decrease in SASSAD score between admission and discharge was 60.7%; the mean SASSAD decreased significantly from 34 (SD 13.2) at admission to 11 (SD 6.7) at discharge ($p<0.001$). The individual course of SASSAD scores between admission and discharge for all patients is shown in Figure 2.

Median sTARC was significantly lower at discharge (892 pg/mL; IQR 507-1919) compared to admission (5717 pg/ml; IQR 2061-10615) ($p<0.001$) (sTARC missing in 25 patients).

In fifty-nine (74.7%) patients controlled AD was achieved using only topical corticosteroids. In six (7.6%) patients, admitted with uncontrolled AD despite the use of oral immunosuppressive drugs, AD control was reached by optimizing additional topical treatment with corticosteroids. In one (1.3%) patient AD was insufficiently controlled with topical corticosteroids during hospitalization and therefore treatment with an oral immunosuppressive drug was added. In 13 (16.5%) patients it was possible to discontinue treatment with an oral immunosuppressive drug, and to reach adequate disease control using only topical corticosteroids.

**Table 1** – Therapeutic history.

| **therapeutic history** | **n[a] (%)** |
|---|---|
| topical treatment only | 11 (13.9%) |
| oral immunosuppressive drugs | 17 (21.5%) |
| oral immunosuppressive drugs and phototherapy | 22 (27.8%) |
| oral immunosuppressive drugs and previous admission[b] | 3 (3.8%) |
| oral immunosuppressive drugs, phototherapy and previous admission[b] | 9 (11.4%) |
| phototherapy | 10 (12.7%) |
| phototherapy and previous admission | 5 (6.3%) |
| previous admission[b] | 2 (2.5%) |

[a]all patients used topical corticosteroids
[b]previous admission before March 1, 2010

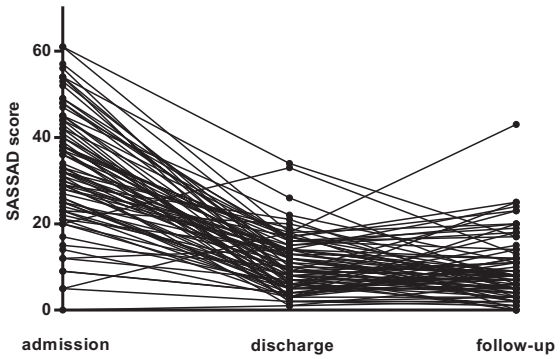


**Figure 2** – Course of SASSAD score at admission, discharge and follow-up.

There was a significant decrease between admission and discharge in the number of patients needing oral immunosuppressive drugs to reach controlled AD (p=0.002) (Table 2).

**Table 2** – SASSAD and treatment need at admission, discharge and follow-up.

| | admission | discharge | follow-up | p-value admission – discharge | p-value discharge – follow-up |
|---|---|---|---|---|---|
| **SASSAD** | | | | | |
| mean (SD) | 34 (13.2) | 11 (6.7) | 9 (7.4) | 0.001[a] | 0.154[a] |
| **SASSAD50** | | | | | |
| n, (%) | | 64 (81.0%) | 63 (79.7%) | | |
| **SASSAD75** | | | | | |
| n, (%) | | 34 (43.0%) | 44 (55.7%) | | |
| **treatment need, n (%)** | | | | | |
| topical corticosteroids monotherapy, n (%) | 60 (75.9%) | 72(91.1%) | 70 (88.6%) | 0.002[b] | 0.500[b] |
| oral immunosuppressive drugs, n (%) | 19 (24.1%) | 7 (8.9%) | 9 (11.4%) | | |

[a]paired sample t-test
[b]McNemar Test

### Follow-up (< 3 months)

At the moment of follow-up visit in the outpatient clinic, 63 (79.7%) patients still had reached a SASSAD50. Forty-four (55.7%) patients had reached a SASSAD75. The mean SASSAD at follow-up (9 (SD 7.4)) was not significantly different compared to the mean SASSAD at discharge (11 (SD 6.7)) (p=0.154). The mean percentage decrease in SASSAD score at follow-up was 69.0% compared to admission. The individual course of SASSAD score between discharge and follow-up for all patients is shown in Figure 2.

sTARC levels were not significantly different between discharge (1133 pg/ml; IQR 528-2065) and follow-up (911 pg/ml; IQR 555-1623) (p=0.674) (sTARC missing in 37 patients). There was no significant difference in the need for oral immunosuppressive drugs to reach controlled AD during follow-up compared to discharge (p=0.500). In three (3.1%) patients a readmission <3 months after discharge was indicated.

### Long-term follow-up (>9 months-<12 months)

Twenty-eight patients still visited the outpatient clinic >9 months after discharge. At follow-up (>9 months-<12 months), 21 (75.0%) patients still had a SASSAD50 and 8 (27.6%) patients a SASSAD75. The mean percentage decrease in SASSAD score was 52.4% during long-term follow-up compared to admission. Five (17.9%) patients started oral immunosuppressive drugs because insufficient disease control with topical treatment.

Twenty-three (82.1%) patients had sufficient control of AD with topical corticosteroids. In another six (6.1%) patients a readmission <12 months after discharge was indicated.

## DISCUSSION

The present study shows a significant and sustained clinical effect of an inpatient treatment and education program in a large group of patients with difficult to control AD. This study showed that patients with difficult to control AD were not always difficult to treat. Although, more than 60% of the patients in this study had a history of oral immunosuppressive drug use for AD, suggesting difficult to treat AD, disease control with topical treatment was reached with an inpatient treatment and education program and psychosocial support in the majority of patients.

All patients had difficult to control AD in an outpatient setting. In half of the patients, multidisciplinary care in our outpatient clinic, sometimes in combination with oral immunosuppressive drugs, was insufficient. In the other half of the patients exhaustion, psychological and psychosocial disturbance/disruption were a reason for admission at the first presentation in our center. An alternative treatment option for these patients would be starting oral immunosuppressive drugs or an increase of the dose of the oral immunosuppressant already used. The results of this study show that controlled AD was reached by optimizing topical treatment with corticosteroids in the majority of these patients. Treatment with oral immunosuppressive drugs was no longer indicated or was discontinued. The fact that at admission 19 (24.1%) of 79 patients were treated with oral immunosuppressive drugs and at follow-up this were only nine (11.4%) patients, underlines the additional value of the clinical treatment and education program.

In the first week of the inpatient program, the main treatment goals were optimizing topical treatment including topical corticosteroids and emollients and to identify the barriers for adequate treatment at home. In the second week the patient was actively involved in application of topical treatment with much emphasis on self-management and coping with AD exacerbations. Much attention was paid to acquire skills to incorporate skin treatment in daily life at home. Relatives or community care were involved in the treatment and education program if indicated.

Previous studies on the effect of inpatient treatment of AD show comparable results in smaller patient groups.[6, 17-19] Quality of life before and after hospitalization was the outcome in the majority of these studies. Only two studies determined clinical skin scores and sTARC levels and one study reported follow-up data. The type of treatment and structure of the program of the hospitalization period was often not discussed.

Improvement in disease control and quality of life can also be reached after education and training in outpatient settings, such as outpatient clinics, day care units and eczema

schools.[7-9] Although the majority of AD patients benefit from these training programs, there is a subgroup of patients who are still not capable to control their eczema. This was the situation in half of the patients in our study. In the other half of the patients in our study admission was indicated because of exhaustion, psychological and psychosocial disturbance/disruption.

Time to rest and getting out of the daily routine are major advantages of an inpatient treatment and education program. Also the support from the dermatological nurse during nocturnal itch attacks and 100% focus on the skin are factors that are also responsible for the success.



The present study showed a rapid improvement of AD severity in the majority of the patients between admission and discharge and a sustained improvement during follow-up. The long-term effect of the clinical treatment and education program is difficult to measure in a daily practice setting. The primary aim of the program is to improve self-management. Therefore, follow-up visits >3 months after discharge were only performed when indicated, for instance in case of exacerbations, need for psychosocial support or safety monitoring of oral immunosuppressive treatment. Therefore, SASSAD scores of patients with follow-up >9 months represent a selection of patients with probably more severe disease (17.9% of the patients (with follow-up >9 months) were treated with oral immunosuppressive drugs).

Some patients were admitted despite low SASSAD scores. The indications for hospitalization in these patients were severe eczema around the eyes, exhaustion caused by the AD and psychosocial problems. In two patients the SASSAD score was increased at discharge compared to admission. In the first patient treatment with extended release tacrolimus had to be tapered due to side effects during admission. In the second patient an improvement of AD during hospitalization is described in the medical records. This anomalous result might be attributed to the inter-observer variability of the SASSAD score.[20]

The clinical treatment and education program was not successful for all patients. In three (3.1%) patients a readmission <3 months after discharge was indicated. In another six (6.1%) patients a readmission <12 months after discharge was indicated due to non-compliance, significant psychosocial problems and co-morbidity. In the majority of these patients controlled AD was reached after a readmission.

Our study has several limitations. As this was an observational daily practice study, no control group was included. For further studies it would be interesting to compare our inpatient program to a 2-3 weeks intervention with fast acting oral immunosuppressive drugs combined with education and self-management training in an outpatient setting. Another limitation of our study is that no Patient Reported Outcomes Measures (PROMSs) were included. In the current program the Patient Oriented Eczema Measure (POEM) is used in the follow-up of all patients, including the patients who do not have scheduled visits.

In conclusion, a structured inpatient treatment and education program for adult patients with uncontrolled AD in an outpatient setting is effective in the majority of patients and

therefore may prevent or delay systemic immunosuppressive treatment. To assess long-term efficacy PROMs, such as POEM should be included in further studies.

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# Chapter 4

## Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis

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## ABSTRACT

### Background

Long-term data of cyclosporin A (CsA) treatment in patients with severe atopic dermatitis (AD) in daily practice is lacking.

### Objectives

The primary objective was to perform a detailed analysis of drug survival, which is the length of time a patient continues to take a drug, for CsA in a long-term daily practice cohort of patients with AD. The secondary objective was to identify determinants of drug survival.

### Methods

Data was extracted from a retrospective cohort of patients treated with CsA for AD. Drug survival was analyzed by Kaplan-Meier survival curves. Determinants of drug survival were analyzed using a univariate and a multivariate Cox regression analysis with backward selection.

### Results

In total, 356 adult patients were analysed (386 patient-years). The overall drug survival rates were 34%, 18%, 12% and 4% after 1, 2, 3 and 6 years, respectively. Reasons for discontinuation were controlled AD (26.4%), side effects (22.2%), ineffectiveness (16.3%), both side effects and ineffectiveness (6.2%) or other reasons (11.0%). Older age was associated with a decreased drug survival related to controlled AD (HR 0.91). Older age was associated with a decreased drug survival related to side effects (HR 1.14). An intermediate-high starting dose (> 3.5-5 mg/kg/day) was associated with an increased drug survival related to ineffectiveness (HR 0.63).

### Conclusions

This is the first study on drug survival for CsA treatment in AD. Older age was associated with decreased drug survival related to controlled AD and side effects. An intermediate-high starting dose was associated with an increased drug survival related to ineffectiveness.

## INTRODUCTION

Atopic dermatitis (AD) is a very common chronic inflammatory skin disease with a high prevalence in children and adults. Most patients with AD can be adequately treated with topical corticosteroids, topical immunomodulators or UV-light therapy. However, in patients with severe AD with insufficient control of their eczema with topical treatment and/or UV-light, oral immunosuppressive therapy is required.

Cyclosporin A (CsA) is a potent inhibitor of T lymphocyte-dependent immune responses and in many European countries the only registered oral immunosuppressive drug in the treatment of AD.[1] Schmitt *et al*.[2] 2 performed a meta-analysis of controlled and uncontrolled trials of CsA treatment in patients with AD. Fifteen studies including 602 patients were analysed. All studies reported a decrease in the mean severity of AD with a relative effectiveness of 55% (95% confidence interval (95%CI) 48-62%) after 6 to 8 weeks of CsA treatment. The use of CsA was limited due to the development of side effects; significant increase of serum creatinine levels were reported in 11%, hypertension in 6% and gastrointestinal symptoms in 40% of patient months of active treatment with CsA. Results from controlled and uncontrolled trials indicate that CsA is a safe and potent drug in the treatment of AD.[2] However, data on the generalizability of these data into daily practice in a large unselected patient group are lacking.[3] In addition, the identification of determinants of influence on treatment success could further improve individual patient care.

Drug survival is a reflection of daily practice and measures the length of time a patient continues to take a particular drug: it is a well-recognized measure, which encompasses factors such as side effects, ineffectiveness, non-compliance and others.[4, 5]

To our knowledge, this is the first study on drug survival for CsA treatment in adult patients with AD. The primary objective of our study was to perform a detailed analysis of drug survival for CsA in a long-term daily practice cohort of patients with severe AD. The secondary objective was to identify determinants of CsA drug survival separately for discontinuation due to controlled AD, side effects and ineffectiveness.

## PATIENTS AND METHODS

### Patient selection and treatment

The data was collected in two tertiary referral centers in the Netherlands (University Medical Center Groningen and University Medical Center Utrecht) with a lot of expertise in the field of diagnoses and treatment of AD. All physicians were well experienced and familiar with the criteria of Hanifin and Rajka[6] and the criteria of Williams[7]; these criteria were always used for the diagnosis AD. All adult patients with moderate to severe AD treated with CsA were retrospectively included to form a daily practice cohort. Patients

had failed topical therapies and/or UV-light therapy. Patients treated in the period from 1991 until data lock in December 2013 were included. The first episode of treatment with CsA in the academic center was included for drug survival analysis. Treatment interruptions of less than 2 weeks were considered as a continuous episode as patients sometimes need to discontinue CsA due to infections or (dental) surgery. A next episode of CsA treatment in the observation period was excluded. The following information was recorded: gender, age, history of oral immunosuppressive drug use, starting dose of CsA, duration of CsA treatment and reason for discontinuation of CsA.

Patients were treated according to the standard follow-up protocol to minimize differences between physicians (Table 1). Two different dose schemes were used: an intermediate-high starting dose (>3.5-5 mg/kg) with tapering of the dose after 3 to 6 weeks or a low starting dose (≤3.5 mg/kg/day) with increase of the dose in case of insufficient response according to the opinion of the treating physician. In patients with controlled AD defined as relief of AD symptoms mentioned by the patient and a satisfactory result reported by the physician, the CsA dose was gradually reduced and treatment was finally discontinued. When the dermatologist considered CsA as ineffective and/or that it led to side effects, the dose was adjusted or CsA was discontinued.

**Table 1** – Standard treatment protocol of cyclosporin A.

| | |
|---|---|
| **dosage** | starting dose cyclosporin A (3 to 6 weeks) |
| | low dose ≤3.5 mg/kg/day. |
| | intermediate-high dose: >3.5-5 mg/kg/day. |
| | maintenance dose cyclosporin A |
| | ≤3.5 mg/kg/day. |
| | dose adjustment in case of low disease activity or side effects. |
| **co-medication** | application of topical steroids class 3, maximum 100 grams per week. |
| | patients were instructed to avoid NSAIDs. |
| **laboratory assessments** | start: blood count, kidney and liver function tests, cholesterol and triglycerides. |
| | follow-up: kidney function, cholesterol and triglycerides (only after 3 months). |
| **visit frequency** | initial phase: after 3, 6 and 12 weeks. |
| | maintenance phase: every 3 months. |

NSAIDs: non-steroidal anti-inflammatory drugs.

## Drug survival and statistical analysis

Drug survival was analysed using Kaplan-Meier survival curves. Four events for drug survival were defined and analysed separately: discontinuation overall (a), discontinuation due to controlled AD (b), discontinuation due to side effects (c) and discontinuation due to ineffectiveness (d).

Patients were censored when still active at the moment of data lock, lost to follow-up or

discontinued due to an event other than the event of interest. When patients discontinued for other reasons (eg. non-compliance, pregnancy), they were considered to have an event in the overall drug survival analysis (a), but were censored in the sub analyses (b, c and d). Patients that discontinued CsA due to both side effects and ineffectiveness were considered to have an event in both sub analyses (c and d). Patients treated for more than 6 years were censored. All side effects leading to discontinuation of CsA were collected.

The following possible determinants of drug survival were formulated: age, gender, treatment with oral immunosuppressive drugs in the past and the starting dose of CsA. In a univariate Cox regression model patients were compared on each potential predictor and determinants of drug survival were selected. Determinants that differed between the two groups with a p-value <0.2 were imported in a multivariate Cox regression model and a full model was built by backward selection. Hazard ratios (HRs) of age were categorized in a 5-year interval. In the multivariate analysis p-values of <0.05 were considered as statistically significant. Missing data was excluded from the analyses. Statistical analyses were performed in SPSS (for Windows version 20, SPSS Inc).



## RESULTS

### Patient and treatment characteristics

In total 356 patients (mean age 37.6 (SD 14.2) and 189 (53.1%) male) were analysed with a total of 386 patient-years. The median duration of treatment was 356 (range 3 - 2190) days, 287 (80.6%) patients were naïve for oral immunosuppressive drugs. CsA starting dose was >3.5-5 mg/kg/day in 195 (54.8%) of the patients (Table 2).

Phototherapy, azathioprine and methotrexate were not prescribed during CsA treatment, as both centers consider these treatments combined with CsA as contra-indicated. Nine (2.5%) patients continued using CsA in the first weeks of treatment with enteric-coated mycophenolate sodium as a bridging treatment.

### Reasons for discontinuation of treatment

In December 2013, the moment of data lock, 44 (12.4%) patients were still actively treated with CsA and 312 (87.6%) patients had discontinued treatment. Ninety-four (26.4%) patients had discontinued treatment due to controlled AD. Side effects were a reason for discontinuation of CsA in 79 (22.2%) patients. Hypertension (7.3%), gastrointestinal symptoms (6.4%) and headache (4.2%) were the most reported side effects leading to discontinuation of treatment (Table 3). Ineffectiveness was a reason for discontinuation in 58 (16.3%) of the patients. Twenty-two patients (6.2%) discontinued CsA because of both side effects as ineffectiveness. Twenty (5.6%) patients were lost to follow-up and 39 (11.0%) patients stopped CsA due to other reasons (Table 2).

**Table 2** – Patient and treatment characteristics.

| | n = 356 | |
|---|---|---|
| **patient characteristics** | | |
| mean age, SD | 37.6 | 14.2 |
| male | 189 | 53.1% |
| **oral immunosuppressive drugs history** | | |
| prior immunosuppressive drugs | 69 | 19.4% |
| naïve for immunosuppressive drugs | 287 | 80.6% |
| **starting dose** | | |
| ≤3.5 mg/kg/day | 160 | 44.9% |
| >3.5-5 mg/kg/day | 195 | 54.8% |
| missing | 1 | 0.3% |
| **status of cyclosporin A use at the moment of data lock**[a] | | |
| active | 44 | 12.4% |
| discontinued | 312 | 87.6% |
| **reason for discontinuation** | | |
| controlled atopic dermatitis | 94 | 26.4% |
| side effects | 79 | 22.2% |
| ineffectiveness | 58 | 16.3% |
| both side effects and ineffectiveness | 22 | 6.2% |
| other (non-compliance, pregnancy) | 39 | 11.0% |
| lost to follow-up | 20 | 5.6% |

[a] data lock: December, 2013
SD: standard deviation

## Drug survival analysis

Figure 1a shows the overall drug survival for CsA in patients with AD. The median overall drug survival was 256 days. The percentage of patients still using CsA was 34%, 18%, 12% and 4% after 1, 2, 3 and 6 years, respectively.

The drug survival split by reason for discontinuation is shown in Figure 1b, c, and d. The median drug survival for controlled AD was 861 days (Figure 1b). Controlled AD was a reason for discontinuation in 28%, 48%, 52% and 68% of the patients after 1, 2, 3 and 6 years, respectively.

The median drug survival of patients that discontinued CsA due to side effects was 1203 days and 1373 days for patients that discontinued due to ineffectiveness (Figure 1c and d). A total of 28%, 39%, 48% and 56% of the patients discontinued treatment due to side effects after 1, 2, 3 and 6 years, respectively. Ineffectiveness was a reason for discontinuation in 24%, 38%, 44% and 56% of the patients after 1, 2, 3 and 6 years, respectively.

**Table 3** – Side effects which were reported as reasons for discontinuation of cyclosporin A.

| | side effect | number of patients (%) | | median duration of cyclosporin A treatment (IQR) |
|---|---|---|---|---|
| **side effect as reason for discontinuation** | hypertension | 26 | (7.3%) | 244 (145-527) |
| | gastrointestinal symptoms | 24 | (6.7%) | 63 (17-103) |
| | headache | 15 | (4.2%) | 54 (14-159) |
| | serum creatinine increase | 12 | (3.4%) | 294 (112-588) |
| | tiredness | 10 | (2.8%) | 100 (51-200) |
| | flu like symptoms | 9 | (2.5%) | 108 (41-197) |
| | tremor/tingling | 7 | (2.0%) | 104 (13-261) |
| | muscle pain/weakness | 7 | (2.0%) | 104 (70-329) |
| | shortness of breath | 5 | (1.4%) | 39 (19-81) |
| | edema | 4 | (1.1%) | 63 (17-180) |
| | physical condition loss | 4 | (1.1%) | 147 (67-299) |
| | vision changes | 4 | (1.1%) | 84 (35-104) |
| | dizziness | 3 | (0.8%) | 21 (14-329)[a] |
| | concentration problems | 2 | (0.6%) | 41 (6-75)[a] |
| | gum hyperplasia | 2 | (0.6%) | 116 (104-127)[a] |
| | low Hb | 2 | (0.6%) | 513 (207-818)[a] |
| | conjunctivitis | 1 | (0.3%) | 33 |
| | erysipelas | 1 | (0.3%) | 238 |
| | hairloss | 1 | (0.3%) | 109 |
| | hypertrichosis | 1 | (0.3%) | 98 |
| | mood changes | 1 | (0.3%) | 101 |
| | palpitations | 1 | (0.3%) | 261 |
| **side effect, but also ineffectiveness as reason for discontinuation** | hypertension | 8 | (2.2%) | 348 (124-647) |
| | serum creatinine increase | 7 | (2.0%) | 467 (244-700) |
| | gastrointestinal symptoms | 4 | (1.1%) | 168 (101-336) |
| | headache | 3 | (0.8%) | 108 (62-372)[a] |
| | tiredness | 3 | (0.8%) | 338 (228-372)[a] |
| | hypertrichosis | 2 | (0.6%) | 466 (189-742)[a] |
| | eczema herpeticum | 1 | (0.3%) | 22 |
| | herpes simplex infection | 1 | (0.3%) | 99 |
| | muscle pain/weakness | 1 | (0.3%) | 700 |
| | palpitations | 1 | (0.3%) | 707 |
| | physical condition loss | 1 | (0.3%) | 338 |
| | tingling | 1 | (0.3%) | 372 |

Discontinuation of cyclosporin A due to side effects could be caused by multiple reasons; therefore the sum of patients exceeds 100%.
IQR: interquartile range
[a]median and range

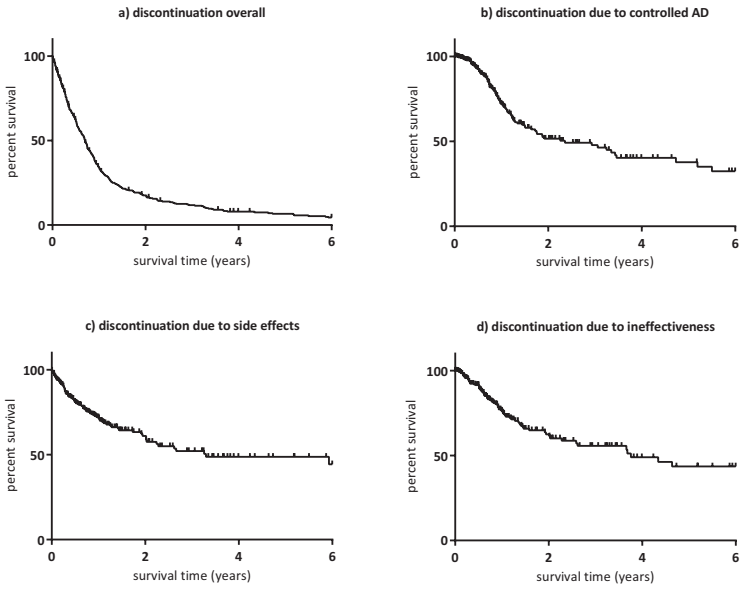


**Figure 1** – Cyclosporin A drug survival split for reasons of discontinuation.
The median drug survival overall (discontinuation due to controlled AD, side effects, ineffectiveness and other reasons) was 256 days. The median drug survival related to discontinuation due to controlled AD was 861 days. The median drug survival related to side effects was 1203 days. The median drug survival related to ineffectiveness was 1373 days. The sample size consisted of 356, 53, 19 and 10 patients at start and after 2, 4 and 6 years, respectively.

## Determinants of drug survival

Table 4 shows the determinants for longer and shorter drug survival as determined by a univariate Cox regression analysis. In contrast to other studies, in which an event in the drug survival analysis indicates that the drug is no longer successful, CsA treatment can also be discontinued due to controlled AD. This requires the interpretation of data from another view as this event favours the effectiveness of CsA. Older age and male gender was associated with a decreased drug survival related to controlled AD. A starting dose of >3.5-5 mg/kg/day was associated with an increased drug survival related to AD. Multivariate Cox regression analysis showed that older age was associated with a decreased drug survival related to controlled AD (HR 0.91, 95%CI 0.84-0.99) (Figure 2). In other words, discontinuation due to controlled AD was decreased for patients with older age.

Older age was associated with a decreased drug survival related to side effects. Patients naïve for oral immunosuppressive drugs and a starting dose of >3.5-5 mg/kg/day were associated with an increased drug survival related to side effects. Multivariate Cox regression analysis identified that older age was associated with a decreased drug survival related to side effects (HR 1.14, 95%CI 1.06-1.22). Meaning that discontinuation

**Table 4** – Determinants of drug survival as determined by univariate Cox regression analysis.

| | **drug survival, event =** | | |
|---|---|---|---|
| | **discontinuation due to controlled atopic dermatitis** | **discontinuation due to side effects** | **discontinuation due to ineffectiveness** |
| older age[a] | **0.92 (0.84-0.99)** | **1.14 (1.06-1.22)** | 0.97 (0.89-1.05) |
| male sex | **0.78 (0.52-1.16)** | 0.85 (0.58-1.26) | 1.16 (0.74-1.82) |
| naïve for oral immunosuppressive drugs | 1.18 (0.67-2.08) | **0.68 (0.44-1.08)** | 1.11 (0.61-2.02) |
| starting dose >3.5-5 mg/kg/day | **1.27 (0.83-1.93)** | **0.74 (0.50-1.10)** | **0.63 (0.41-0.98)** |

Data are presented as hazard ratio (95% confidence interval). Bold numbers indicate hazard ratios with a p-value <0.2.
[a]age in 5-year intervals.



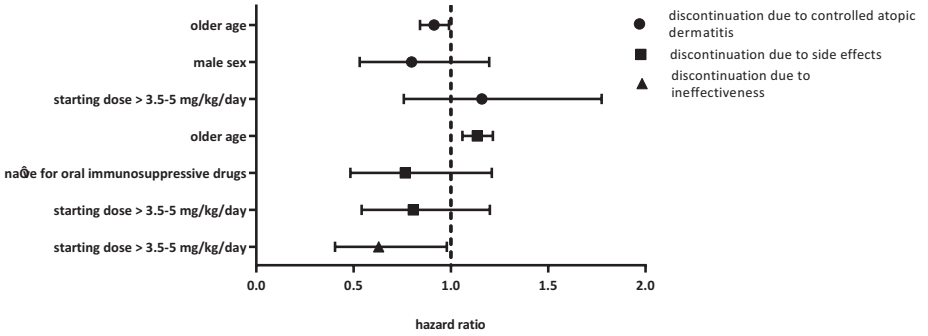


**Figure 2** – Determinants of drug survival, split for reason of discontinuation (hazard ratios and 95% confidence intervals). All hazard ratios were calculated by multivariate Cox regression analysis. Hazard ratios based on age in 5-year intervals.

due to side effects was increased for patients with older age. Additional multivariate Cox regression analysis to find the age at which drug survival with respect to side effects decreased showed a HR of 1.71 (95%CI 1.15-2.54) for patients with an age of 45 year or older compared to younger patients.

An intermediate-high starting dose (> 3.5-5 mg/kg/day) was associated with an increased drug survival related to ineffectiveness (HR 0.63, 95%CI 0.41-0.98). In other words, discontinuation due to ineffectiveness was decreased for patients with an intermediate-high starting dose.

## DISCUSSION

Drug survival analysis has frequently been used to describe daily practice treatment results of rheumatoid arthritis with biologics.[8, 9] More recent, literature about drug survival of patients with psoriasis treated with biologics is published.[10, 11] To the best of our knowledge, this is the first study on drug survival in patients with AD treated with CsA in daily practice.

This drug survival analysis showed that CsA is important and valuable in the daily practice treatment of adult patients with AD. CsA treatment was discontinued due to controlled AD in a significant group of patients. The drug survival rates for CsA were 34%, 18%, 12% and 4% after 1, 2, 3 and 6 years, respectively, with a median drug survival duration of 256 days. The reasons for discontinuation of CsA were controlled AD (26.4%), side effects (22.2%), ineffectiveness (16.3%), both side effects and ineffectiveness (6.2%) and other reasons (11.0%). Older age was associated with a decreased drug survival related to controlled AD. Older age was associated with a decreased drug survival related to side effects (increased risk for patient > 45 years). An intermediate-high starting dose (> 3.5-5 mg/kg/day) was associated with an increased drug survival related to ineffectiveness.

Previous clinical studies have demonstrated that CsA is a safe and potent drug in the maintenance treatment of severe AD.[2] However, to be clinically useful, these results must also be generalizable to patients in a daily practice setting. In the literature there are several examples of low generalizability of trial results into daily practice. For example with respect to the treatment with biologics, lower response rates in daily practice than in RCTs were reported in both psoriasis and rheumatoid arthritis.[12-14] The external validity of clinical study results is also investigated in the treatment of depression with antidepressants and psychotherapy. The outcome of treatment for mild to moderate depression in daily practice was shown to be less effective compared to results from RCTs.[15]

There are several possible explanations for the difference between daily practice and trial results. First there is a difference in patient selection. In clinical trials only patients who fulfil strict inclusion criteria are included. Patients' characteristics, such as comorbidity, susceptibility to side effects and earlier treatment failure may influence treatment success. In most RCTs these characteristics are reported incomplete, which limits the generalizability of the outcome.

The external validity of a randomized clinical trial (RCT) also depends on whether the outcomes are clinically relevant. The main outcome in clinical trials in AD is often the mean/median decrease in eczema score in the total group compared to before or the difference in mean/median decrease in eczema score between 2 treatment groups at fixed time points. However, mean scores give no information on individual response

rates. Another factor influencing external validity of RCTs is the limited duration of treatment. Whether initial response is a good predictor of long-term benefit is unknown.

In our daily practice cohort 79/356 patients (22.2%) discontinued CsA treatment due to side effects. This percentage is much higher than mentioned in earlier clinical trials. For instance in the RCT of Haeck *et al.*[16] only 3/26 patients (11.5%) discontinued CsA due to adverse events. Higher rates of discontinuation of treatment due to adverse events in clinical practice compared to RCTs is also described in other diseases, such as cardio-vascular disorders.[17, 18] In the present study a significant number of patients who stopped treatment due to side effects were treated for longer periods compared to most trials. Another explanation might be that patients who choose to participate in clinical trials are often very motivated to fulfill the trial period, despite of the occurrence of side effects.



In our study, discontinuation due to ineffectiveness was registered in 58/356 patients (16.3%). This percentage is also much higher compared to clinical trials. Due to the short duration of most clinical trials, patients are frequently motivated to continue treatment until the end of the trial, despite ineffectiveness. In the present study, a starting dose of >3.5-5 mg/kg/day was associated with an increased drug survival related to ineffectiveness. This strengthens the decision to start CsA treatment with an intermediate-high dose and tapering of the dose after 3 to 6 weeks, especially because the risk on discontinuation due to side effects did not increase.

Older age was associated with a decreased drug survival related to controlled AD. Older age was also associated with a decreased drug survival related to side effects, especially for patients aged 45 years and older. This supports the fact that CsA is less suitable for patients with older age.

The determinants in the Cox regression model do not fully explain the outcome. Many other factors for example disease severity, physicians' preferences and adherence to treatment influence the outcome as well. In a daily practice study patients are less compliant than in clinical trials. However, with this drug survival study, we wanted to give a reflection of the daily practice use of CsA. Less compliant patients are part of daily practice.[19] A limitation of this study might be the low explained variance of the results of the Cox regression analysis.

Drug survival analysis is not a study of efficacy, but a reflection of the situation in daily practice. Clinical decisions made by physician and patient together, based on the balance between efficacy and tolerability, determine the outcome. Therefore retrospective data, especially when clear monitor protocols are used in daily practice, are very suitable for drug survival analysis, as they are not primarily collected with a research purpose. The CsA dosing regimen was determined by the physician. Deciding factors that might have influenced the dosing regimen were in particular the severity of the AD

and co-morbidity. Unfortunately, it is not possible to determine the influence of these factors on the chosen dosing regimen retrospectively.

Drug survival is influenced by various factors such as drug effectiveness, treatment or patient satisfaction, the availability of other treatment options and the occurrence of side effects.[3, 4] Treatment will be more often continued despite side effects or moderate response, when no other treatment options are left. In the present study, CsA was the first oral immunosuppressive drug in 80.6% of the patients. Drug survival might be lower in this patient group due to the availability of off-label second choice oral immunosuppressive drugs such as azathioprine, mycophenolic acid and methotrexate. Selection bias is unavoidable in daily practice as patients receive a treatment based on the physicians' and patients' preferences. This is one of the strengths of daily practice studies as well.

Drug survival is determined by the occurrence of events. An event indicates that a drug is no longer successful. However, CsA treatment can also be discontinued due to controlled AD. This requires the interpretation of data from another view because discontinuation of treatment due to controlled AD is an event that favours the effectiveness of CsA. Therefore, in assessing the effectiveness of CsA by drug survival, the reason for discontinuation of treatment is very important.

A limitation of this study is the retrospective design, which brings dependency on quality of medical records. Drug survival analysis might describe reality better than a clinical score. Reasons for discontinuation are more about the real use of medication with a combination of different influences, while a clinical score is a more artificial measurement of effectiveness. In addition, start and stop dates of medication and reason for discontinuation of treatment are retrospective assessable. However, clear definitions of individual responders and non-responders are important and clinical trials should report the number of non-responders.

In conclusion, we present the first analysis of drug survival for CsA in the treatment of severe AD to date. Discontinuation of CsA due to side effects was increased for patients with older age (increased risk for patient > 45 years) and discontinuation due to controlled AD was decreased for patients with older age. Discontinuation due to ineffectiveness was decreased for patients with an intermediate-high starting dose (>3.5-5 mg/kg/day).

More drug survival studies of other oral immunosuppressive drugs used in patients with AD in daily practice would further improve individual patient care.

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# Chapter 5

## Serum creatinine levels during and after long-term treatment with cyclosporin A in patients with severe atopic dermatitis

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## ABSTRACT

Safety data with respect to kidney function during long-term cyclosporin A (CsA) treatment in patients with atopic dermatitis (AD) is limited. Serum creatinine levels before, during and after CsA were collected in a retrospective cohort of adult patients with AD. The median duration of treatment of 150 patients was 280 days (IQR 203-528). There was a significant, but not clinically relevant, increase of serum creatinine compared to baseline level after 3 weeks CsA and stabilization during maintenance phase on group level. Twenty-two (14.7%) patients had more than 30% increase of serum creatinine (cut off point for clinically relevant change) compared to baseline level. These patients were significantly older than patients without 30% increase (mean age 41.4(SD15.6) versus 33.8(SD11.7) (p=0.01)). During follow-up, all patients showed serum creatinine levels within 30% compared to baseline. Serum creatinine levels during follow-up were not significantly different compared to baseline on group level.

## BACKGROUND

Atopic dermatitis (AD) is a chronic inflammatory skin disease with exacerbations and (partial) remission. Although most patients with AD can be treated adequately with topical corticosteroids, topical immunomodulators or UV-light therapy, a subgroup of patients with moderate to severe AD is in need for oral immunosuppressive treatment.

Cyclosporin A (CsA) is a potent inhibitor of T lymphocyte-dependent immune responses and used in the treatment of moderate to severe AD. Several controlled and uncontrolled trials showed the clinical efficacy of CsA.[1]

CsA causes an increased vascular resistance, which may lead to decreased renal plasma flow and decreased clearance of endogenous creatinine.[2] Therefore, kidney function during CsA treatment needs to be carefully monitored. While the population variation of serum creatinine is large, the within-individual variation of serial measurements is much smaller (10%) and can detect a change in renal function.[3] In acute kidney injury a serum creatinine rise of 50% is considered relevant according to the Rifle criteria. For chronic use of CsA a rise of 30% can be considered as a cut off to predict kidney dysfunction. In patients with persistent serum creatinine increase after discontinuation of CsA therapy, structural kidney damage may occur.[4]

In patients with severe AD, maintenance treatment with CsA for several years is sometimes necessary to achieve adequate disease control and improvement in quality of life. Therefore there is need for information on the long-term effect of CsA on kidney function in patients with AD.

Long-term CsA treatment is used in patients with organ transplantation as immunosuppressive treatment to prevent rejection. However, this patient group is not comparable to patients with AD because of differences in baseline renal function, co-morbidity, concomitant medication, CsA dosing and the confounding effect of rejection in case of renal transplantation. Fear of irreversible kidney damage after long-term use of CsA by dermatologists is mostly based on publications about patients with psoriasis.[5] The guideline on psoriasis of the European Dermatology Forum recommends a maximum duration of CsA maintenance treatment of two years based on expert opinion.[6] However, a recent population-based cohort study demonstrates that moderate to severe psoriasis itself is associated with an increased risk of chronic kidney disease (based on diagnostic code in general practitioner medical records, GFR or both), independent of traditional risk factors and medication such as CsA.[7] As there is no evidence for intrinsic kidney disease in patients with AD, data concerning kidney function during CsA treatment in psoriasis patients cannot be extrapolated to patients with AD. At this moment safety data with respect to kidney function during long-term (> 1 year) CsA treatment in patients with moderate to severe AD is limited.

The aim of the present study was to investigate serum creatinine levels during and after long-term maintenance treatment with CsA in a non-selected group of patients with moderate to severe AD in daily practice.

## METHODS

### Patients, study design and outcomes

The medical records of all patients with moderate to severe AD (diagnosed according to the criteria of Hanifin and Rajka)[8] treated with CsA from November 1994 until data lock in December 2013 at the Department of Dermatology of the University Medical Center Utrecht were analyzed with respect to serum creatinine levels during and after CsA treatment. Patients eligible for inclusion were treated with CsA according to the standard treatment and monitoring protocol used in the outpatient clinic (Table 1). Missing serum creatinine level at baseline due to starting CsA in another hospital was an exclusion criterion. Treatment periods with CsA less than 6 weeks were also excluded from the analyses as in clinical trials significant serum creatinine increase was not a reason for discontinuation of treatment during high dose early in the treatment with CsA.[9]

Information about patient characteristics, duration of CsA treatment and follow-up was extracted from medical records. The following data with respect to kidney function was recorded *a)* serum creatinine level at baseline, *b)* serum creatinine after three weeks of CsA treatment (high dose 3.5 – 5 mg/kg/day) and *c)* mean serum creatinine level during the maintenance phase (intermediate dose ≤ 3.5 mg/kg/day).

**Table 1** – Standard treatment and monitoring protocol of cyclosporin A treatment for patients with atopic dermatitis.

| | | |
|---|---|---|
| **dosage** | - | starting dose 3.5 – 5 mg/kg/day. |
| | - | maintenance phase ≤ 3.5 mg/kg/day. |
| | - | dose reduction in case of low disease activity or side effects. |
| | - | dose reduction or stop if serum creatinine increase of >30% above baseline level on two consecutive occasions. |
| **co-medication** | - | application of topical steroids class 3. |
| | - | patients were instructed to avoid NSAIDs[a] |
| **laboratory assessments** | - | start: blood count, kidney function, liver enzymes, cholesterol and triglycerides. |
| | - | follow-up: kidney function, cholesterol and triglycerides (only after 3 months). |
| **visit frequency** | - | initial phase: after 3, 6 and 12 weeks. |
| | - | maintenance phase: every 3 months. |

[a]NSAIDs: non-steroidal anti-inflammatory drugs

Patients with serum creatinine increase >30% compared to baseline level were further examined with respect to the presence of clinical symptoms (eg. edema), age, intercurrent causes of the increase (age-related increase of serum creatinine (more than 5 years compared to baseline[10], co-morbidity, medication use influencing kidney function) and serum creatinine levels after dose adjustment.

In patients who stopped CsA treatment, the most recent serum creatinine value from the medical record was registered. In patients who restarted CsA or another oral calcineurin inhibitor, the serum creatinine value before the restart was registered.

### Data analysis

Statistical analyses were performed in SPSS (for Windows version 20, SPSS Inc). Skewed distribution in treatment duration and duration of follow-up were observed, therefore median and interquartile ranges (IQR) were described. Differences in serum creatinine at the different time points during treatment were compared with a paired t-test. Differences between patient groups were compared with an one-way ANOVA for continuous variables and with the chi-square test for categorical variables. Probability levels of 0.05 and below were considered as statistically significant.



## RESULTS

One hundred and fifty patients meeting the inclusion criteria were identified. At the moment of data analysis, ten (6.7%) patients were still using CsA and 140 (93.3%) patients had discontinued treatment. Follow-up data was available of 92 (65.7%) out of 140 patients. Starting treatment in another hospital was an exclusion criterion for 52 patients and 24 patients were excluded because the duration of CsA treatment was less than 6 weeks.

### Serum creatinine during CsA treatment (n = 150)

The median duration of CsA treatment of the 150 patients was 280 days (IQR 203-528). Fifty-three (35.3%) episodes run one year or longer of which 24 (16.0%) episodes run longer than two years (Table 2).

The mean (SD) serum creatinine level at baseline was 79.0 (SD 12.8) µmol/L, this level increased to 83.8 (SD 14.3) µmol/L after three weeks of CsA treatment (high dose 3.5 - 5 mg/kg/day) and to a mean level of 82.9 (SD 13.1) µmol/L during the maintenance phase (intermediate dose ≤ 3.5 mg/kg/day). Although increases of serum creatinine levels were small in individual patients (Figure 1), in the total group of patients CsA treatment during high dose and intermediate dose resulted in a significant increase of serum creatinine compared to baseline levels (p=0.000). Serum creatinine levels were not significantly different with respect to treatment duration.

**Table 2** – Serum creatinine level during cyclosporin A treatment and a subdivision in the duration of treatment.

| | | | mean (SD) serum creatinine (µmol/L) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **n (%)** | **median duration of treatment (IQR) in days** | **baseline** | **3 weeks (3.5 – 5 mg/kg)** | **p-value baseline – 3 weeks** | **mean during maintenance (≤ 3.5 mg/kg)** | **p-value baseline – mean during maintenance** | **mean age (SD)** | **M : F** |
| **total patient group** | 150 | 280 (203-528) | 79.0 (12.8) | 83.8 (14.3) | 0.000 | 82.9 (13.1) | 0.000 | 34.9 (12.5) | 79 : 71 |
| **duration of treatment** | | | | | | | | | |
| < 6 months | 32 (21.3%) | 110 (70-167) | 76.7 (11.9) | 82.6 (16.8) | *0.001* | 82.3 (15.2) | *0.003* | 33.0 (12.9) | 20 : 12 |
| 6-12 months | 65 (43.3%) | 269 (244-293) | 79.5 (12.4) | 83.6 (14.0) | *0.000* | 82.3 (12.9) | *0.013* | 33.1 (11.6) | 34 : 31 |
| 12-24 months | 29 (19.3%) | 520 (443-652) | 78.9 (13.5) | 85.1 (14.6) | *0.007* | 83.6 (13.9) | *0.031* | 39.1 (15.2) | 14 : 15 |
| > 24 months | 24 (16.0%) | 1309 (832-1865) | 80.8 (14.6) | 84.3 (12.0) | *0.159* | 84.7 (10.3) | *0.051* | 37.4 (9.8) | 11 : 13 |
| one-way ANOVA | | | *p = 0.661* | *p = 0.992* | | *p = 0.867* | | | |

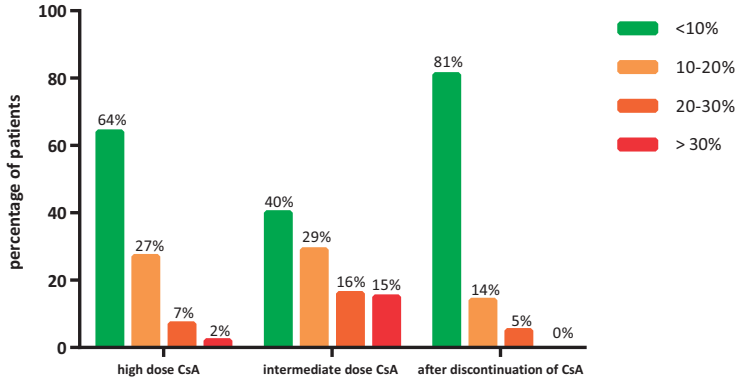


**Figure 1** – Percentage increase of serum creatinine in individual patients during and after cyclosporin A treatment determined at 3 weeks (high dose 3.5 – 5 mg/kg/day), during maintenance phase (intermediate dose ≤ 3.5 mg/kg/day) and after discontinuation compared to baseline level.
Serum creatinine levels were available for 150 patients during high dose CsA and intermediate dose CsA; in 92 out of 150 patients serum creatinine levels after discontinuation of CsA were available.



## Follow-up: serum creatinine after discontinuation of CsA treatment (n = 92/140)

Follow-up data was available of 92 (65.7%) of the 140 patients that had discontinued CsA treatment (Table 3). The median duration of follow-up was 357 days (IQR 87-1005). The mean serum creatinine at baseline of 80.8 (SD 12.9) µmol/L was not significantly different from the latest mean level after CsA discontinuation, being 80.5 (SD 12.9) µmol/L. Serum creatinine levels were not significantly different during follow-up with respect to treatment duration and duration of follow-up (except for patients with a follow up >2 years and a treatment duration of <1 year).

The percentage serum creatinine increase compared to baseline after discontinuation of CsA treatment per patient is shown in Figure 1. Overall, serum creatinine level was within the normal variation of 10% compared to baseline in 74 patients, increased from 10% to 20% compared to baseline in 13 patients and between 20% and 30% in 5 patients. Possible intercurrent causes of more than 10% variation of serum creatinine level (the within-individual variation of serial measurements) during follow-up were: 4 patients recently discontinued CsA (<1.5 month) (4 patients 10-20% increase), in 3 patients age had increased more than 5 years compared to baseline (2 patients 10-20% increase; one patient 20-30% increase), 2 patients were using medication influencing kidney function (ACE inhibitor and diuretic) (2 patients 20-30% increase) and in 9 patients no intercurrent cause was found (7 patient 10-20% increase; 2 patients 20-30% increase).

### Patients with >30% serum creatinine increase compared to baseline level during CsA treatment (n = 22/150)

Twenty-two (14.7%) patients had more than 30% increase of serum creatinine compared to baseline level during CsA treatment. In 3/22 patients this increase developed during high dose CsA and continued during the maintenance phase, in 19/22 patients the increase developed during the maintenance phase of treatment. Clinical symptoms were not reported. Patients with > 30% increase of serum creatinine level were significantly older than patients without 30% increase of serum creatinine (mean age 41.4 (SD 15.6) versus 33.8 (SD 11.7) (*p=0.01*)). Gender and duration of CsA use were not of influence on the occurrence of clinically relevant serum creatinine increase. No intercurrent causes of serum creatinine increase were found in these patients (co-morbidity, other medication use influencing kidney function or interactions with co-medication).

In Figure 2 a flowchart with adjustments in the management of the 22 patients with clinically relevant serum creatinine increase is depicted. One patient discontinued CsA immediately and 14 patients had a dose adjustment. Successful dose reduction, defined as normalization of serum creatinine with controlled AD was reported in 7 patients. In 7 patients dose reduction was not successful due to uncontrolled AD in 4 patients and insufficient decrease of serum creatinine level in 3 patients; subsequently CsA treatment was discontinued in these patients. In the remaining 7 patients CsA dose was not adjusted and serum creatinine levels were further monitored.

At the moment of data analysis 3/22 patients were still using CsA. Serum creatinine values of these patients were increased 0%, 3% and 36% compared to baseline level, respectively at the moment of data lock. The patient with 36% increase in serum creatinine had a very low starting value (47 µmol/L), probably due to hyperfiltration. During follow-up serum creatinine values stabilized, so no dose adjustments were done.

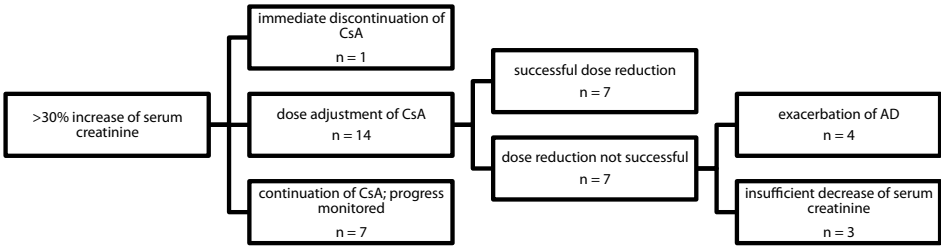


**Figure 2** – Flowchart with the adjustments in the management of patients with clinically relevant serum creatinine increase.

**Table 3** – Serum creatinine after discontinuation of cyclosporin A treatment and a subdivision in the duration of follow-up and duration of treatment.

| | | | | | mean (SD) serum creatinine (µmol/L) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **n** | **median duration of treatment (IQR)** | **median duration of follow-up (IQR)** | **baseline** | **3 weeks (3.5 – 5 mg/kg)** | **p-value baseline – 3 weeks** | **mean during maintenance (≤ 3.5 mg/kg)** | **p-value baseline – mean during maintenance** | **latest after discontinuation** | **p-value baseline – latest after discontinuation** |
| **total patient group** | | 92 | 269 (188-423) | 357 (87-1005) | 80.8 (12.9) | 85.0 (14.5) | 0.000 | 84.8 (13.0) | 0.000 | 80.5 (12.9) | 0.832 |
| follow-up < 2 years | | 61 | 274 (177-432) | 112 (50-357) | 80.7 (12.2) | 85.3 (14.6) | 0.001 | 84.3 (12.9) | 0.006 | 79.5 (12.1) | 0.391 |
| duration of treatment | 0 – 12 months | 42 | 253 (152-276) | 94 (48-369) | 81.0 (13.1) | 86.2 (15.4) | 0.003 | 84.3 (13.6) | 0.039 | 79.7 (12.3) | 0.433 |
| | > 12 months | 19 | 575 (437-742) | 229 (57-353) | 80.1 (10.2) | 83.3 (12.9) | 0.214 | 84.3 (11.4) | 0.074 | 79.2 (11.7) | 0.726 |
| follow-up > 2 years | | 31 | 260 (203-407) | 1730 (899-2528) | 80.9 (14.4) | 84.6 (14.5) | 0.059 | 85.9 (13.3) | 0.017 | 82.5 (14.3) | 0.368 |
| duration of treatment | 0 – 12 months | 22 | 244 (164-267) | 1628 (879-2109) | 79.3 (12.1) | 84.7 (14.4) | 0.005 | 86.4 (13.8) | 0.001 | 83.8 (14.5) | 0.013 |
| | > 12 months | 9 | 702 (464-1051) | 2493 (1971-3111) | 84.9 (19.3) | 84.4 (15.5) | 0.929 | 84.6 (12.9) | 0.948 | 79.3 (14.2) | 0.166 |
| one-way ANOVA | | | | | *p = 0.940* | *p = 0.840* | | *p = 0.582* | | *p = 0.294* | |

### Follow-up of patients with >30% serum creatinine increase compared to baseline level during CsA treatment (n = 22)

Follow-up of serum creatinine levels of 19/22 patients that had discontinued CsA showed 7 patients with serum creatinine levels within 10% compared to baseline, 4 patients with an increase of 10 to 20% and another 4 patients with an increase of 20 to 30%. Follow-up of serum creatinine levels was missing in 4 patients. However, in these patients serum creatinine levels decreased to 103%, 107%, 109% and 117% compared to baseline already during CsA treatment.

## DISCUSSION

In the present study, serum creatinine levels during long-term CsA treatment in a large group of unselected AD patients treated in daily practice were retrospectively analyzed.

There was a significant, but not clinically relevant, increase of serum creatinine compared to baseline level after 3 weeks CsA (high dose 3.5 – 5 mg/kg/day) and stabilization during maintenance phase (intermediate dose ≤ 3.5 mg/kg/day) on group level.

The significant increase of serum creatinine during CsA treatment compared to baseline could be explained by an increased vascular resistance due to CsA, which may cause decreased renal plasma flow and decreased clearance of endogenous creatinine.[2] However, in most cases, the rate of increase falls within the normal variation of 10% in individual patients and is therefore not clinically relevant.

There are few data available on kidney function during CsA treatment in patients with AD. Schmitt *et al*.[1] reported the effect of CsA on serum creatinine levels in patients with AD in a meta-analysis of clinical trials. Serum creatinine increase of more than 30% compared to baseline level was an adverse event in up to 10.9% of patient months of active treatment with CsA. The duration of CsA treatment ranged from six weeks to one year and the initial dose of CsA ranged from 2.5 to 5 mg/kg/day. An increased serum creatinine level was one of the main side effects resulting in discontinuation of CsA treatment. In a retrospective study of Hijnen *et al*.[11] 73 patients with severe AD were treated with CsA doses varying between 2.5 and 5 mg/kg/day in daily practice. A mean peak rise of serum creatinine level of 15.8% compared to baseline was reported after a mean treatment duration of 192.9 (SD 252.7) days. Serum creatinine increase of more than 30% compared to baseline level was reported in 9.6% of the patients. In 5.5% of the patients dose reduction was successful and in 4.1% of the patients serum creatinine increase was followed by discontinuation of treatment. No information on the reversibility of serum creatinine levels during follow-up was reported.

In our median observation period of 280 days (IQR 203-528), 22 (14.7%) patients had more than 30% increase of serum creatinine compared to baseline level. This relative

high percentage compared to earlier studies can be explained by differences in patient population. In our study non-selected patients treated in daily practice were included and most patients were treated for longer periods compared to most clinical trials.

There was no significant difference in duration of CsA treatment between patients with and without increase of serum creatinine of more than 30% compared to baseline level. This result suggests that the occurrence of clinically relevant serum creatinine increase is independent of the duration of CsA treatment. This is in contrast to patients with psoriasis in which longer duration of treatment seemed to be a risk factor for kidney dysfunction.[5] The mean age of the 22 patients with clinically relevant serum creatinine increase in our study was significantly higher compared to patients without this serum creatinine increase. In patients with psoriasis treated with CsA higher age was reported as a risk factor as well.[5] In the retrospective study of Hijnen *et al*.[11], no correlation between age and serum creatinine levels was observed.



Although the treatment protocol prescribes dose reduction or discontinuation of CsA treatment in case of serum creatinine increase of more than 30% compared to baseline level, this was not always complied to by the dermatologist. This might be attributed to the fact that there is a large inter-individual variation in the range of normal serum creatinine levels. A clinically relevant increase of serum creatinine may still fall within the normal range and for this reason unnoticed. Especially when serum creatinine level before start of CsA is very low, as was observed in one patient in this study (47 µmol/L). Although our treatment and monitoring protocol advices dose reduction in case of 2 consecutive measurements of >30% serum creatinine increase, dose adjustments in many patients were based on a single measurement (11 out of 22 patients had an adjustment based on a single measurement). This may have led to an overestimation of patients with clinical relevant serum creatinine increase.

In the second part of our study serum creatinine levels after stopping CsA were analyzed. These follow-up data are very important because a persistent elevated serum creatinine compared to baseline after cessation is an indication of structural kidney damage.[5] Like Maza *et al*.[5] we decided to consider an increase of more than 30% as clinically relevant.

Follow-up data were not always available, as the treatment and monitoring protocol does not advise measurement of serum creatinine level after discontinuation of CsA. The most frequent reasons for measuring serum creatinine levels in the follow-up were the start of a new oral immunosuppressive drug or monitoring recovery in patients with increased serum creatinine levels during CsA treatment. Therefore, the follow-up data consist of a selection of patients with difficult to treat AD (multiple oral immunosuppressive drugs necessary) and patients with elevated serum creatinine during CsA treatment.

In 48/140 patients follow-up was not available. However, these patients had no clinically relevant increase of serum creatinine level during CsA treatment.

The 92 patients showed serum creatinine levels within 30% compared to baseline in all patients, indicating no clinically relevant serum creatinine increase after discontinuation of CsA. Treatment duration and duration of follow-up had no effect on serum creatinine levels.

Eighteen patients however maintained a moderately elevated serum creatinine level between 10 and 30% compared to baseline of which the clinical relevance is unclear. We do recommend additional monitoring of kidney function and blood pressure at set intervals (e.g. yearly via a general practitioner) to evaluate the course of this elevation over time.

A limitation of this study is the retrospective design. Although laboratory results are reliable other information in medical records may be of lower quality. For this reason no estimate on cumulative dose of CsA and other possible influencing factors (co-morbidity, obesity and co-medication) could be made.

In this study kidney function is reflected by serum creatinine levels and not by GFR or proteinuria, which are used more often prevalent today to assess renal function. Although estimated GFR (eGFR) is considered more reliable to assess kidney function than serum creatinine, there were several reasons to report creatinine values. First of all changes in creatinine can be interpreted just as easy by the use of creatinine values as with eGFR (a 30% rise in creatinine will inadvertently result in a 30% reduction of eGFR) since race and gender are fixed and a change of age of only one or two years influences the results of these formulas only very modestly. Moreover most frequently used formulas tend to underestimate kidney function particularly when eGFR is over 60 ml/min/1.73m$^2$, which is more or less the norm for patients with AD. Thirdly to accurately apply these formulas race has to be entered in the formula and this is not regularly available in the (our) hospital records.[12, 13]

Proteinuria and microalbuminuria are a known sign of calcineurin inhibitor nephrotoxicity and also associated with a worse renal prognosis.[4, 14] However, measurement of proteinuria and microalbuminuria are not in the current monitoring protocol of CsA treatment for patients with AD, therefore we could not use these parameters.

In conclusion, in contrast to previous studies in other patient groups, long-term treatment with CsA was not associated with clinically relevant serum creatinine increase during treatment and during follow-up. The consequent monitoring of serum creatinine levels and CsA dose adjustment if creatinine levels increase in our study population may explain the lack of irreversible serum creatinine increase. Therefore, close monitoring of serum creatinine levels during CsA treatment remains strictly recommended. Patients with increased age are at higher risk to develop clinically relevant serum creatinine in-

crease. In patients with more than 10% serum creatinine increase compared to baseline after discontinuation of CsA, additional monitoring of kidney function and blood pressure at set intervals is recommended.

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# Chapter 6

## First experience with extended release tacrolimus in the treatment of adult patients with severe, difficult to treat atopic dermatitis: clinical efficacy, safety and dose finding

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*Under review*

## ABSTRACT

### Background

Extended release tacrolimus (ERT) is a potential treatment for patients with atopic dermatitis (AD).

### Objective

To evaluate the clinical efficacy and safety of ERT in adult patients with severe, difficult to treat AD with side effects and/or insufficient response to cyclosporin A.

### Methods

Nine patients with severe AD were treated with ERT (starting dose 0.15-0.2 mg/kg/day) for 6 months. Disease activity was monitored using the Six Area, Six Sign Atopic Dermatitis (SASSAD) score. Plasma tacrolimus concentrations were measured and pharmacogenetics to assess CYP3A4/CYP3A5 metabolizing potential was performed.

### Results

SASSAD scores (mean, SD) decreased from 31.4 (9.8) to 15.2 (7.2) ($p<0.05$) after 2 weeks treatment. Two patients discontinued ERT within 6 months due to side effects. After 6 months treatment, disease activity was stable in the remaining seven patients. Based on CYP3A4/CYP3A5 genotype cluster classification, four patients were classified as 'extensive metabolizers' of ERT and five as 'intermediate metabolizers'. In two 'intermediate metabolizers' plasma tacrolimus concentrations were above safety level.

### Conclusion

Treatment with ERT was effective in the majority of patients. ERT should not be started above 0.1 mg/kg/day to prevent plasma tacrolimus concentrations above safety levels; plasma tacrolimus concentrations should be monitored.

## INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases among children and adults.[1] Most patients can be treated adequately with topical corticosteroids, topical immunomodulators, coal tar preparations, and/or ultraviolet phototherapy. However, in patients with insufficient disease control with topical treatment or in patients needing daily treatment with large amounts of potent topical corticosteroids for longer periods, oral immunosuppressive drugs are indicated. Cyclosporin A (CsA), azathioprine, mycophenolic acid, methotrexate (MTX) and oral corticosteroids are commonly used in the treatment of moderate to severe AD. CsA and oral corticosteroids generally reduce disease activity within 2-3 weeks, while the other drugs take 2-3 months.[2-5] This is a major drawback in daily practice.

CsA is the only oral immunosuppressive drug registered for the treatment of severe AD in most European countries. However, there is a group of patients in which CsA treatment is inappropriate due to insufficient response, contra-indications or side effects and an alternative fast acting drug is required. Oral corticosteroids can be used as short-term treatment, but the long-term use is limited because of side effects.



Like CsA, tacrolimus is a calcineurin inhibitor, but has higher potency *in vitro*. Studies in healthy subjects have demonstrated that tacrolimus has a more favorable safety profile compared to CsA, especially regarding blood pressure and renal function.[6] Extended release tacrolimus (ERT, Advagraf®, Astellas Pharma, Tokyo, Japan) has the advantage of a more consistent plasma concentration over time and a reduced peak concentration compared to the original formulation of tacrolimus. In addition, the once daily dosing may increase the adherence to therapy.[7, 8] Therefore, ERT may be an interesting second choice treatment for patients with severe AD, in which CsA treatment failed.

Tacrolimus is extensively metabolized by CYP3A4 and CYP3A5. Besides tacrolimus, CYP3A4/CYP3A5 is involved in the metabolism of many other drugs, such as CsA, nifedipine and olanzapine. Tacrolimus pharmokinetics is characterized by a wide inter-individual variability, which may be partly explained by single nucleotide polymorphisms (SNPs) in the genes coding for CYP3A4 and CYP3A5. The presence of a CYP3A4 intron 6 C>T SNP is associated with an intermediate or poor tacrolimus metabolism (Table 1), which can result in high plasma tacrolimus levels. However, variation in the CYP3A5 genotype explains the major portion of the inter-individual variation in tacrolimus pharmacogenetics: carriers of two *CYP3A5*3* nonfunctional alleles (*CYP3A5*3/*3* (GG)*;* non-expressers of CYP3A5) require substantially less tacrolimus (about 50% less) to reach an similar concentration than patients carrying a *CYP3A5*1* active allele (*CYP3A5*1/*3* (GA) or *CYP3A5*1/*1* (AA); expressers of CYP3A5). The influence of CYP3A4/CYP3A5 genotype on tacrolimus metabolism is depicted in Table 1.[9]

**Table 1** – *CYP3A4/CYP3A5* genotype cluster classification.[9]

| | **CYP3A4 intron 6 CT or TT (SNP)** | **CYP3A4 intron 6 CC (wild type)** |
|---|---|---|
| *CYP3A5*1* noncarriers (*CYP3A5*3/*3* (GG); non-expressers of CYP3A5) | poor metabolizers | intermediate metabolizers |
| *CYP3A5*1* carriers (*CYP3A5*1/*3* (GA) or *CYP3A5*1/*1* (AA); expressers of CYP3A5) | intermediate metabolizers | extensive metabolizers |

The objective of this observational study was to evaluate the clinical efficacy and safety of 6 months ERT treatment in adult patients with severe, difficult to treat AD, that previously had side effects and/or insufficient response to CsA treatment. In addition, we investigated plasma tacrolimus concentration, including analysis of metabolizing potential based on pharmacogenotype.

## METHODS

### Patients and study design

Adult patients with severe, difficult to treat AD and side effects and/or insufficient response of prior CsA treatment were included in an investigator-initiated, open-label single center proof of concept study. Patients were treated for 6 months with ERT according to a standard protocol. Patients concomitantly used emollients and potent topical corticosteroids (class III, European classification system) (maximum 100 grams/week).

### Parameters of disease activity

Primary outcomes were disease severity measured by SASSAD score (Six Area, Six Sign Atopic Dermatitis) and the extend of eczema measured as body surface area (BSA).[10] Secondary outcomes were the sTARC (serum thymus and activation-regulated chemokine) level and POEM (Patient-Oriented Eczema Measure).[11, 12] Measurements were performed at start of ERT, after 2, 4 weeks and subsequently every month.

### Safety

At each visit patients were asked if they had experienced any subjective side effects. Laboratory parameters, including full blood count, lymphocyte subsets, liver enzymes, electrolytes, urea, creatinine, total cholesterol, HDL and LDL cholesterol, triglycerides, and blood pressure, were evaluated.

### ERT dosing, plasma tacrolimus concentration and CYP3A4/CYP3A5 pharmacogenotype analysis

ERT was started at 0.15-0.2 mg/kg once daily; after 2 weeks the dose was adjusted based on the clinical response and/or the occurrence of side effects. At each visit plasma tacrolimus concentrations were measured (24 hours after intake). ERT dose was reduced in case of plasma tacrolimus concentrations >15.0 µg/L.

The MagnaPure LC System (Roche diagnostics GmbH, Mannheim, Germany) was used to isolate genomic DNA from serum. SNPs in the genes coding for CYP3A4 and CYP3A5 were analysed as described previously.[9]

### Statistical analysis

Statistical analysis was performed in SPSS for windows (IBM SPSS Statistics 20). Nonparametric tests were used because data were not normally distributed. Changes in SASSAD, BSA, sTARC and POEM during ERT treatment were compared with baseline using the Wilcoxon signed rank test. Probability levels of 0.05 and below were considered as statistically significant.



## RESULTS

Nine patients, four men and five women (mean age 42.5 (range 18–68 years)) with severe AD were treated with ERT for 6 months between September 2011 and December 2013. All patients discontinued prior CsA treatment due to side effects and/or insufficient response, and in seven (78%) out of nine patients treatment with other oral immunosuppressive drugs had also failed due to side effects and/or insufficient response (Table 2).

Two (22%) out of nine patients discontinued ERT treatment within 6 months. One patient because of nausea (after 44 days of treatment), and another patient due to increased serum creatinine levels (>30% compared to baseline on day 62 of treatment) (Table 2). These side effects resolved after discontinuation of ERT in both patients.

### Parameters of disease activity

After 2 weeks of ERT treatment, the mean SASSAD score (SD) decreased from 31.4 (9.8) to 15.2 (7.2) ($p<0.05$), mean BSA (SD) from 62 (14) to 43 (21) ($p<0.05$) and mean sTARC (SD) from 3088 (1460) pg/mL to 1079 (863) pg/mL ($p<0.05$) (Figure 1). The POEM score (SD) decreased from 20 (6) to 14 (10) ($p<0.05$). After 3 and 6 months disease activity remained stable in the seven patients that fulfilled 6 months of ERT treatment.

**Table 2** – Use of oral immunosuppressive therapy before start of ERT and if applicable reason for discontinuation of ERT within 6 months.

| patient | age (years) | gender | previous oral immunosuppressive treatment before start of ERT | reason for discontinuation of CsA | discontinuation of ERT within 6 months (reason) |
|---|---|---|---|---|---|
| 1 | 46 | male | AZA, CsA, mycophenolic acid, oral corticosteroids[a] | insufficient response | no |
| 2 | 37 | female | CsA | hypertension, hypertrichosis | no |
| 3 | 68 | female | CsA, mycophenolic acid, oral corticosteroids[a] | insufficient response, serum creatinine increase | yes (nausea) |
| 4 | 52 | female | AZA, CsA, mycophenolic acid, oral corticosteroids[a] | headache, hypertension, serum creatinine increase, tiredness | yes (serum creatinine increase) |
| 5 | 40 | male | AZA, CsA, oral corticosteroids[a] | insufficient response | no |
| 6 | 19 | female | CsA | flu like symptoms, tingling | no |
| 7 | 56 | male | CsA, MTX, mycophenolic acid | insufficient response | no |
| 8 | 18 | female | CsA, mycophenolic acid, oral corticosteroids[a] | serum creatinine increase | no |
| 9 | 44 | male | CsA, mycophenolic acid, oral corticosteroids[a], prograf[c] | gastro-intestinal symptoms | no |

AZA, azathioprine; CsA, cyclosporin A; MTX, methotrexate

[a] oral corticosteroids were used > 3 months

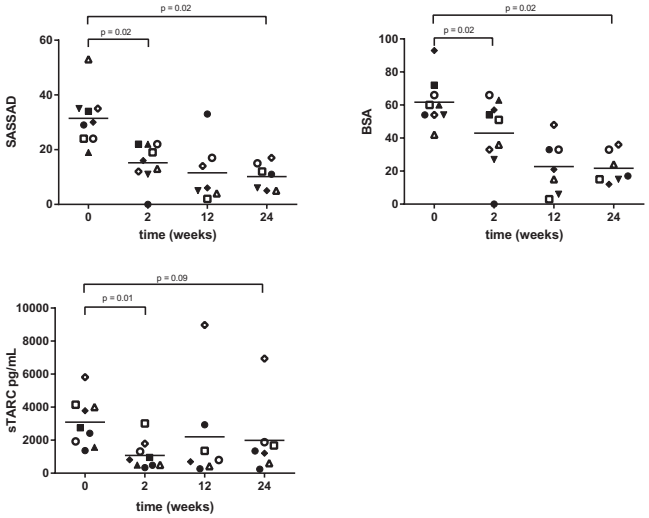


**Figure 1** – SASSAD, BSA and sTARC at baseline and during treatment with ERT. Scatter plots show mean and distribution of data.

## Safety

*Subjective side effects*

Table 3 shows the subjective side effects, which were reported during ERT treatment. In one patient ERT treatment was discontinued because of severe nausea (plasma tacrolimus concentration 9.7 µg/L).

**Table 3** – Number of patients with side effects during ERT use and dose reduction due to side effects.

| side effect | number of patients (%) with side effect | number of patients with dose reduction due to side effect |
|---|---|---|
| diarrhea | 3 (33%) | 0 |
| muscle pain | 3 (33%) | 1 |
| nausea | 3 (33%) | 2 (1 discontinuation of ERT) |
| dizziness | 2 (22%) | 1 |
| headache | 2 (22%) | 1 |
| increased frequency of micturition | 2 (22%) | 1 |
| tremor | 2 (22%) | 1 |
| edema | 1 (11%) | 0 |
| obstipation | 1 (11%) | 0 |
| tiredness | 1 (11%) | 0 |



*Laboratory examination and blood pressure*

During 6 months of ERT treatment, serum creatinine increased >30% compared to baseline in two (22%) patients (plasma tacrolimus concentration 8.2 µg/L and 6.5 µg/L). In one patient ERT dose reduction (12 to 5 mg/day; 0.18 to 0.08 mg/kg/day) and addition of a calcium antagonist did not normalise serum creatinine. After discontinuation serum creatinine level normalised within 6 weeks. In the second patient, ERT dose was reduced from 10 to 7 mg/day (0.16 to 0.11 mg/kg/day). This resulted in a normalization of serum creatinine level within 4 weeks, and the AD remained under control. No clinically relevant changes were found in the laboratory results and blood pressure of the other patients.

*ERT dosing, plasma tacrolimus concentrations and CYP3A4/CYP3A5 pharmacogenotype analysis*

The ERT starting dose ranged from 0.15 to 0.19 mg/kg/day (mean 0.17 mg/kg/day), resulting in a wide range of plasma tacrolimus concentrations, varying from 4.4 to 23.4 µg/L (mean 10.8 µg/L) at 2 weeks. The clinical response, measured as the percentage decrease in SASSAD score, was independent of plasma tacrolimus concentrations (Table 4). During the maintenance phase, ERT doses varied between 0.09 and 0.19 mg/kg/day (mean 0.15 mg/kg/day); plasma tacrolimus concentrations varied between 2.0-

10.9 µg/L (mean 6.8 µg/L) at 12 weeks in seven patients. At 12 weeks, clinical response was independent of plasma tacrolimus concentrations.

Genotype analysis showed that all nine patients were homozygous for the CYP3A4 intron 6 wild type (*CYP3A4* intron 6 CC). Four patients (44%) were carriers of a *CYP3A5**1 active allele (all *CYP3A5*1/*3* (GA)): these patients were classified as 'extensive metabolizers' of ERT. Five patients (56%) were carriers of two *CYP3A5*3* nonfunctional alleles (*CYP3A5*3/*3* (GG)): these patients were classified as 'intermediate metabolizers' of ERT. No 'poor metabolizers' were included in this study. In the 'extensive metabolizers', a mean starting dose of 0.18 mg/kg/day resulted in a mean plasma concentration of 6.4 µg/L after 2 weeks of treatment (concentration/dose ratio 35.6). In the 'intermediate metabolizers' a mean starting dose of 0.16 mg/kg/day resulted in higher mean plasma tacrolimus concentrations of 14.0 µg/L after 2 weeks of treatment (concentration/dose ratio 87.5 µg/L/mg/kg/day) (Table 4 and Figure 2).

**Table 4** - Percentage decrease of SASSAD, ERT dose and plasma concentration in the initial phase (2 weeks) of ERT treatment for 4 (44%) 'extensive metabolizers' and 5 (56%) 'intermediate metabolizers' of TAC.

| CYP3A4 intron 6 CT, TT (SNP) or CC (wild type) | CYP3A5*1/*3 (GA) CYP3A5*1/*1 (AA) or CYP3A5*3/*3 (GG) | CYP3A4/ CYP3A5 genotype cluster classification | | % decrease SASSAD | tacrolimus dose (mg/ day) | normalised tacrolimus dose (mg/ kg/day) | plasma tacrolimus concentration (µg/L) | dose corrected plasma tacrolimus concentration (µg/L per mg/ kg/day) |
|---|---|---|---|---|---|---|---|---|
| CC | GA | extensive | | 15.8 | 9 | 0.16 | 9.7 | 60.6 |
| CC | GA | metabolizers | | 8.3 | 12 | 0.17 | 4.4 | 25.9 |
| CC | GA | | | 100 | 12 | 0.18 | 4.4 | 24.4 |
| CC | GA | | | 75.5 | 12 | 0.19 | 6.9 | 36.3 |
| | | | mean (SD) | 49.9 (44.9) | 11.3 (1.5) | 0.18 (0.01) | 6.4 (2.5) | 36.8 (16.7) |
| CC | GG | intermediate | | 65.7 | 15 | 0.19 | 23.4 | 123.2 |
| CC | GG | metabolizers | | 35.3 | 10 | 0.15 | 11.8 | 78.7 |
| CC | GG | | | 46.7 | 10 | 0.15 | 8.0 | 53.3 |
| CC | GG | | | 20.8 | 9 | 0.16 | 9.0 | 56.3 |
| CC | GG | | | 68.6 | 12 | 0.16 | 17.6 | 110.0 |
| | | | mean (SD) | 47.4 (20.2) | 11.2 (2.4) | 0.16 (0.02) | 14.0 (6.5) | 84.3 (31.4) |

SASSAD Six Area, Six Sign Atopic Dermatitis, SD standard deviation

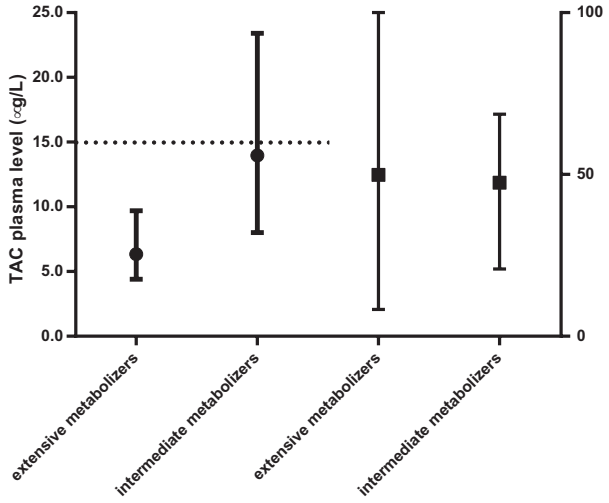


**Figure 2** – Mean plasma tacrolimus concentration higher in 'intermediate metabolizers' compared to 'extensive metabolizers' of TAC. No difference in mean percentage decrease of SASSAD between 'intermediate' and 'extensive metabolizers' of TAC.



## DISCUSSION

This is the first study on the efficacy and safety of ERT in patients with severe, difficult to treat AD. We found that after 2 weeks of ERT treatment, disease severity parameters decreased significantly and remained stable after 3 and 6 months of treatment. All patients were previously treated with CsA, but discontinued CsA treatment due to side effects and/or insufficient response. Seven out of nine patients (78%) also failed on other oral immunosuppressive drugs. Surprisingly, in these extremely - difficult to treat - AD patients, ERT treatment was successful in 7 (78%) out of nine patients, and resulted in less side effects compared to CsA.

Although CsA has proven to be effective in various controlled and uncontrolled studies, side effects may limit its use. In a systematic review, Schmitt *et al.*, reported a significant increase of serum creatinine levels in 11% of patient months of active treatment with CsA.[2] Furthermore, hypertension was reported in 6% of patient months and gastrointestinal symptoms in 40% of patient months. Although CsA is the only registered oral immunosuppressive drug for the treatment of AD, several oral immunosuppressive drugs are being used 'off-label' including azathioprine, mycophenolic acid and MTX. These drugs need 2-3 months to achieve clinical efficacy; therefore combinations with oral corticosteroids are often necessary resulting in an increased risk of side effects.[13]

Oral tacrolimus might be an alternative fast acting treatment in patients with severe AD, due to its close relationship to CsA (both calcineurin inhibitors) together with a more

favorable safety profile.[6] Also in the current study, patients reported less side effects during ERT treatment compared to previous treatment episodes with CsA. Only one out of three patients that stopped CsA treatment because of serum creatinine increase also discontinued ERT for this reason.

Literature concerning the efficacy and safety of oral tacrolimus in AD is scarce. In 2003 Schroer *et al*. reported successful treatment of a patient with severe, therapy resistant AD with the original formulation of oral tacrolimus 5 mg twice daily.[14] Lee *et al*. recently described a small case series of patients with severe, therapy resistant AD in which treatment with oral tacrolimus 5 mg twice daily failed in three out of four patients.[15] In an open-label study in twelve patients with severe AD, Keaney *et al.* studied sequential treatment with oral tacrolimus (0.08 mg/kg/day, twice daily) for 6 weeks, followed by topical tacrolimus over a 14-week treatment period.[16] In this study, topical tacrolimus 0.1% ointment was added from week 4. Keaney *et al.* showed a 67% improvement of EASI, a 45% improvement of the Physician Global Assessment and a 69% reduction in the pruritus score after 14 weeks compared to baseline. The effect of monotherapy with oral tacrolimus in the first 3 weeks was less impressive compared to our study. Major differences between earlier studies and our study are the longer treatment duration and the use of the extended release formulation of oral tacrolimus. ERT has the advantage of more consistent plasma concentrations and reduced peak concentrations. Another advantage of ERT is the once daily dosing, resulting in better adherence to therapy.[7, 8]

The variations in clinical outcomes during treatment with oral tacrolimus in the above mentioned studies in patients with AD might be attributed to the large differences in the doses that were used. The recommendations for oral tacrolimus dosing in organ transplant patients is based on body mass. The recommended dose in these patients ranges from 0.1-0.4 mg/kg/day in order to achieve plasma tacrolimus concentrations between 10-15 µg/L, which is thought to be the optimal concentration to prevent organ transplant rejection. Earlier studies in psoriasis patients describe starting doses from 0.1-0.15 mg/kg/day to 0.3 mg/kg/day.[17, 18]

In organ transplant patients, the plasma tacrolimus concentration has to be in a particular range to prevent rejection. Therefore, the ERT dose is adjusted according to the plasma tacrolimus concentration. This is in contrast to patients with AD, in which the ERT dose is based on clinical effectiveness. However, in order to avoid high and potential toxic drug concentrations, drug monitoring of plasma tacrolimus concentrations is necessary. Plasma tacrolimus concentrations should not exceed 15.0 µg/L, as toxic plasma tacrolimus concentrations can cause neurotoxicity and nefrotoxicity.[19]

In this study, plasma tacrolimus levels and farmacogenetics were used to search for an optimal ERT starting dose in daily practice. Remarkably, a small range in starting dose (0.15 to 0.19 mg/kg/day) resulted in a wide range of plasma tacrolimus concentrations (4.4 to 23.4 µg/L) after 2 weeks of treatment. In two patients plasma tacrolimus concentrations were above safety level.

Tacrolimus pharmokinetics is characterized by a wide inter-individual variability, which may be partly explained by polymorphisms in the genes coding for CYP3A4 and CYP3A5 (Table 1).[9] Based on CYP3A4/CYP3A5 genotype cluster classification, the present study showed four 'extensive metabolizers' of ERT and five 'intermediate metabolizers'. In the 'extensive metabolizers', plasma tacrolimus concentrations were 50% lower compared to the 'intermediate metabolizers' using the same mean starting dose of ERT. The clinical relevance of the low plasma tacrolimus concentrations in the 'extensive metabolizers' in our study is unclear, because clinical efficacy was not related to the plasma tacrolimus concentration in this small patient group. However, in two 'intermediate metabolizers', starting doses of 0.16 and 0.19 mg/kg/day resulted in high plasma tacrolimus concentrations above safety level after two weeks of treatment (17.6 µg/L and 23.4 µg/L, respectively). One of these patients had severe subjective side effects, which decreased after dose reduction. To avoid such severe side effects in the early treatment phase, a starting dose of ≤0.1 mg/kg/day in these patients would have been safer. Therefore, an ERT starting dose of ≤0.1 mg/kg/day is recommended for daily practice when CYP3A4/CYP3A5 farmacogenetics are not performed before treatment. The ERT starting dose has to be adjusted based on clinical effectiveness and plasma tacrolimus concentration. An advantage of farmacogenetics is that 'poor metabolizers' of tacrolimus can be identified (5.4% of the patients according to literature).

Limitations of the present study are the open design and the small sample size.

In conclusion, in a population of difficult to treat, severe AD patients, treatment with ERT was found effective and safe in the majority of patients. ERT had a favorable side effect profile compared to CsA. A starting dose of maximal 0.1 mg/kg/day is recommended to avoid toxic plasma levels and severe side effects in the early treatment phase. A drug survival study in a large group of patients with long-term follow-up is needed for a reflection of daily practice results of ERT treatment.

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# Chapter 7

## Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis

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*Under review*

## ABSTRACT

### Background

Long-term data of azathioprine and enteric-coated mycophenolate sodium (EC-MPS) in the treatment of adult patients with severe atopic dermatitis (AD) in daily practice is lacking.

### Objective

The primary objective was to perform an analysis of drug survival, which is the length of time a patient continues to take a drug, for azathioprine and EC-MPS in a long-term daily practice cohort of patients with AD. The secondary objective was to identify determinants of drug survival.

### Methods

Data was extracted from a retrospective cohort of adult patients with AD treated with azathioprine or EC-MPS. Drug survival was analyzed by Kaplan-Meier survival curves. Determinants of drug survival were selected using a univariate Cox regression analysis and analyzed with a multivariate Cox regression analysis with backward selection.

### Results

In total, 94 patients treated with azathioprine and 84 patient treated with EC-MPS were analysed. The overall drug survival rates were 43%, 26% and 14% for azathioprine and 44%, 33% and 25% for EC-MPS after 1, 2 and 3 years, respectively. Reasons for discontinuation of azathioprine were controlled AD (10.6%), side effects (36.2%), ineffectiveness (19.1%), both side effects and ineffectiveness (2.1%) and other reasons (6.4%). Reasons for discontinuation of EC-MPS were controlled AD (10.7%), side effects (14.3%), ineffectiveness (38.1%), both side effects and ineffectiveness (3.6%) and other reasons (3.6%).

### Conclusion

The overall drug survival of azathioprine and EC-MPS was comparable. Drug survival of aza course of thioprine was mainly limited by discontinuation due to side effects, while drug survival of EC-MPS was mainly limited by discontinuation due to ineffectiveness.

## INTRODUCTION

Atopic dermatitis (AD) can be treated with oral immunosuppressive drugs, in case of insufficient control with topical treatment and/or UV-light therapy. Cyclosporin A (CsA) is the only oral immunosuppressive drug registered for the treatment of severe AD in many European countries. Side effects, ineffectiveness and the risk of a rebound after discontinuation of treatment are the main reasons for searching alternative immunosuppressive treatment options.[1, 2]

Results from clinical studies indicate that azathioprine and enteric-coated mycophenolate sodium (EC-MPS) are safe and potent second line drugs in the treatment of AD.[3-7] However, data on the generalizability of these results into daily practice in a large unselected patient group are lacking. In addition, head-to-head trials in which azathioprine and EC-MPS are compared, have never been performed. The choice of a compound is based on the experience and preference of the dermatologist.

Drug survival is the length of time a patient continues to take a particular drug. It is a well-recognized measure, which encompasses factors such as side effects, ineffectiveness, non-compliance and others.[8, 9] Drug survival analysis is not a study of efficacy, but a reflection of the situation in daily practice. Clinical decisions made by physician and patient together, based on the balance between effectiveness and tolerability, determine the outcome. Data derived from daily practice are very suitable for drug survival analysis.

The primary objective of this study was to perform a detailed analysis of drug survival for azathioprine and EC-MPS in a long-term daily practice cohort of adult patients with severe AD. The secondary objective was to identify determinants of drug survival.



## PATIENTS AND METHODS

### Patient selection

The data was collected in two tertiary referral centers in the Netherlands (University Medical Center Groningen and University Medical Center Utrecht) with expertise in diagnosis and treatment of AD. All adult patients with moderate to severe AD treated with azathioprine and/or EC-MPS were retrospectively included to form a daily practice cohort. Patients had failed topical therapies and/or UV-light therapy and had a contraindication for CsA treatment or had failed CsA treatment due to side effects and/or ineffectiveness. Patients treated in the period from October 1995 (azathioprine) and November 2004 (EC-MPS) until data lock in December 2013 were included. Only the first episode of azathioprine or EC-MPS treatment was analysed. Treatment interruptions of less than 2 weeks were considered as a continuous episode as patients sometimes need

to discontinue oral immunosuppressive drugs temporary due to infections or (dental) surgery. The following information was recorded: gender, age, history of oral immunosuppressive drug use, concomitant use of CsA or oral corticosteroids, maintenance dose of azathioprine, duration of treatment and reason for discontinuation of treatment.

In both centers patients were treated according to the standard follow-up protocol to minimize differences between physicians (Table 1). In patients with controlled AD defined as relief of AD symptoms mentioned by the patient and a satisfactory result reported by the physician, treatment was discontinued after gradually reducing the dose. In case of lack of efficacy or side effects, the dose was adjusted or the treatment was discontinued.

**Table 1** – Standard treatment protocol of azathioprine and enteric-coated mycophenolate sodium.

| | **azathioprine** | **enteric-coated mycophenolate sodium** |
|---|---|---|
| **dosage** | starting dose (2 weeks) | starting and maintenance dose |
| | 50 mg/day | 720 mg twice daily |
| | maintenance dose | dose adjustment in case of low disease activity or side effects. |
| | 150-200 mg/day | |
| | dose adjustment in case of low disease activity or side effects. | |
| **co-medication** | concomitant therapy with oral corticosteroids (maximum 0.5 mg/kg/day) (cyclosporin A (maximum 3.0 mg/kg/day) in case of EC-MPS) in tapering dose allowed. | |
| | application of topical corticosteroids class 3, maximum 100 grams per week. | |
| **laboratory assessments** | blood count, kidney and liver function tests. | |
| **visit frequency** | initial phase: after 2, 4, 6, 8 and 12 weeks. | initial phase: after 3, 6 and 12 weeks. |
| | maintenance phase: every 3 months. | maintenance phase: every 3 months. |

## Drug survival and statistical analysis

Drug survival was analysed using Kaplan-Meier survival curves. Four events for drug survival were defined and analysed separately: discontinuation overall (a), discontinuation due to controlled AD (b), discontinuation due to side effects (c) and discontinuation due to ineffectiveness (d).

Patients were censored when still active at the moment of data lock, lost to follow-up or discontinued due to an event other than the event of interest. When patients discontinued treatment for other reasons (eg. non-compliance, pregnancy), they were considered to have an event in the overall drug survival analysis (a), but were censored in the sub analyses (b, c and d). Patients that discontinued treatment due to both side effects and ineffectiveness were considered to have an event in both sub analyses (c

and d). Patients treated for more than 3 years were censored after 3 years. All side effects leading to discontinuation of treatment were collected.

Potential determinants of drug survival were formulated: age, gender, oral corticosteroids concomitantly used at the moment of discontinuation and the azathioprine maintenance dose. Determinants of drug survival were selected by comparing patients on each potential predictor in a univariate Cox regression model. Determinants that differed between the two groups with a p-value <0.2 were entered in a multivariate Cox regression model. By backward selection, a full model was built. Hazard ratios (HRs) of age were categorized in a 5-year interval. In the multivariate analysis p-values of <0.05 were considered as statistically significant. Missing data was excluded from the analyses. To compare the drug survival distributions of azathioprine and EC-MPS treatment, the log rank test was performed or described when the curves crossed. Statistical analyses were performed in SPSS (for Windows version 21, SPSS Inc).

## RESULTS

### Patient and treatment characteristics

The drug survival of 94 patients (mean age 42.9 (SD 13.9), 54 (57.4%) male) treated with azathioprine was analysed. The median duration of treatment was 180 (range 4 - 1095) days with a total of 82 patient-years. Eleven (11.7%) patients were naïve for oral immunosuppressive drugs as they had a contra-indication for treatment with CsA. Fifty-five (58.5%) patients concomitantly used oral corticosteroids during treatment with azathioprine. At the moment of discontinuation of azathioprine 23 (24.5%) patients were treated with oral corticosteroids (Table 2).

In the EC-MPS treatment group, drug survival of 84 patients (mean age 43.7 (SD 13.3), 50 (59.5%) male) was analysed. The median duration of treatment was 324 (range 14 - 1095) days with a total of 110 patient-years. Six (7.1%) patients were naïve for oral immunosuppressive drugs as treatment with CsA was contraindicated. Forty-six (54.8%) patients concomitantly used oral corticosteroids. At the moment of discontinuation of EC-MPS 17 (20.2%) patients were using oral corticosteroids as concomitant medication. Twenty-one (25.0%) patients concomitantly used CsA. At the moment of discontinuation of EC-MPS 3 (3.6%) patients were treated with CsA (Table 2).

### Reasons for discontinuation of treatment

In the azathioprine treatment group, 24 (25.5%) patients were still actively treated at the moment of data lock. Ten (10.6%) patients had discontinued treatment due to controlled AD, of which 3 patients concomitantly used oral corticosteroids at the moment of discontinuation (Table 3). Side effects were the most frequent reason for discontinuation

of azathioprine in 34 (36.2%) patients. Gastro-intestinal symptoms (19.1%), increased transaminases (7.4%) and tiredness (5.3%) were the most reported side effects leading to discontinuation of treatment (Table 4). Ineffectiveness was a reason for discontinuation in 18 (19.1%) patients. Two patients (2.1%) discontinued azathioprine due to both side effects and ineffectiveness. Six (6.4%) patients stopped azathioprine due to another event.

Twenty-two (26.2%) patients were still actively treated with EC-MPS at the moment of data lock and 3 (3.6%) patients were lost to follow-up (continuation of treatment in another hospital). Nine (10.7%) patients had discontinued due to controlled AD, none of them concomitantly used oral corticosteroids or CsA at the moment of stopping (Table 3). Ineffectiveness was the most frequent reason for discontinuation of EC-MPS in 32 (38.1%) patients. Side effects were the reason for discontinuation in 12 (14.3%) patients. Respiratory symptoms (6.0%), gastro-intestinal symptoms (4.8%) and flu like symptoms (4.8%) were reported most frequent (Table 4). Three (3.6%) patients stopped EC-MPS due to both side effects and ineffectiveness and 3 (3.6%) patients stopped due to another event.

**Table 2** – Patient and treatment characteristics.

| | **azathioprine (n = 94)** | **enteric-coated mycophenolate sodium (n = 84)** | **p-value** |
|---|---|---|---|
| **patient characteristics** | | | |
| mean age (SD) | 42.9 (13.9) | 43.7 (13.3) | 0.68[a] |
| male (%) | 54 (57.4%) | 50 (59.5%) | 0.88[b] |
| **oral immunosuppressive drugs history** | | | |
| prior oral immunosuppressive drugs | 83 (88.3%) | 78 (92.9%) | 0.32[b] |
| naïve for oral immunosuppressive drugs | 11 (11.7%) | 6 (7.1%) | |
| **concomitant use of** | | | |
| **oral corticosteroids** | 55 (58.5%) | 46 (54.8%) | 0.65[b] |
| median % of total treatment episode[c] | 82.8 (3.2-100.0%) | 41.4 (0.5-100.0%) | 0.04[d] |
| used at moment of discontinuation | 23 (24.5%) | 17 (20.2%) | 0.59[b] |
| cyclosporin A | - | 21 (25.0%) | na |
| median % of total treatment episode[c] | - | 25.6 (1.6-100.0%) | na |
| used at moment of discontinuation | - | 3 (3.6%) | na |
| **status of use at the moment of data lock[e]** | | | |
| active | 24 (25.5%) | 22 (26.2%) | 0.18[b] |
| discontinued | 70 (74.5%) | 59 (70.2%) | |
| lost to follow-up | 0 (0.0%) | 3 (3.6%) | |

[a] independent sample t-test, [b] Pearson chi-square test, [c] the percentage of total treatment episode is the duration of concomitant therapy divided by the duration of total azathioprine/EC-MPS episode, [d] Mann-Whitney U, [e] data lock: December, 2013.

**Table 3** – Reasons for discontinuation of treatment and the number of patients with concomitant use of oral corticosteroids and cyclosporin A at the moment of discontinuation.

| | azathioprine (n = 94) | | enteric-coated mycophenolate sodium (n = 84) | | |
|---|---|---|---|---|---|
| reason for discontinuation | number of patients (%) | oral corticosteroids used at moment of discontinuation, n (%) | number of patients (%) | oral corticosteroids used at moment of discontinuation, n (%) | cyclosporin A used at moment of discontinuation, n (%) |
| controlled AD | 10 (10.6%) | 3 (3.2%) | 9 (10.7%) | 0 (0.0%) | 0 (0.0%) |
| side effects | 34 (36.2%) | 10 (10.6%) | 12 (14.3%) | 5 (6.0%) | 1 (1.2%) |
| ineffectiveness | 18 (19.1%) | 4 (4.3%) | 32 (38.1%) | 8 (9.5%) | 2 (2.4%) |
| both side effects and ineffectiveness | 2 (2.1%) | 2 (2.1%) | 3 (3.6%) | 1 (1.2%) | 0 (0.0%) |
| other (non-compliance, pregnancy) | 6 (6.4%) | 4 (4.3%) | 3 (3.6%) | 3 (3.6%) | 0 (0.0%) |

## Drug survival analysis

Figure 1a shows the overall drug survival for azathioprine and EC-MPS in patients with AD. The median overall drug survival for azathioprine was 201 days. The percentage of patients still using azathioprine was 44%, 26% and 14% after 1, 2 and 3 years, respectively. The median overall drug survival for EC-MPS was 322 days. The percentage of patients still using EC-MPS was 45%, 36% and 27% after 1, 2 and 3 years, respectively. The drug survival split by reason for discontinuation is shown in Figure 1b, c and 1d. Six percent, 21% and 44% discontinued azathioprine and 6%, 15% and 28% discontinued EC-MPS due to controlled AD after 1, 2 and 3 years, respectively. Forty percent, 44% and 47% discontinued azathioprine and 20%, 20% and 23% discontinued EC-MPS due to side effects after 1, 2 and 3 years, respectively. Twenty-three percent, 36% and 41% discontinued azathioprine and 40%, 47% and 51% discontinued EC-MPS due to ineffectiveness after 1, 2 and 3 years, respectively. The median drug survival of azathioprine and EC-MPS with respect to controlled AD, side effects and ineffectiveness could not be estimated, as more than 50% of the patients still used the drug after 3 years.

The log rank test showed that the overall drug survival (p=0.04) and drug survival related to side effects (p=0.01) of EC-MPS was significantly better compared to azathioprine. The drug survival curves related to ineffectiveness cross; a trend towards better drug survival for azathioprine compared to EC-MPS is seen. No significant difference between the drug survival distributions of both drugs was found with respect to controlled AD.

**Table 4** – Side effects which were reported as reasons for discontinuation of treatment and the concomitant use of oral corticosteroids.

| | | azathioprine | | enteric-coated mycophenolate sodium | | |
|---|---|---|---|---|---|---|
| | **side effects** | **number of patients (%)** | **oral corticosteroids used at moment of discontinuation** | **number of patients (%)** | **oral corticosteroids used at moment of discontinuation** | **cyclosporin A ued at moment of discontinuation** |
| **side effects** | gastro-intestinal symptoms | 18 (19.1%) | 4 (4.3%) | 4 (4.8%) | 2 (2.4%) | - |
| **as reason** | increased transaminases | 7 (7.4%) | 3 (3.2%) | - | - | - |
| **for** | tiredness | 5 (5.3%) | - | 1 (1.2%) | 1 (1.2%) | - |
| **discontinuation** | flu like symptoms | 4 (4.3%) | 1 (1.1%) | 4 (4.8%) | 1 (1.2%) | - |
| | myalgia | 3 (3.2%) | - | 2 (2.4%) | - | - |
| | respiratory symptoms | 3 (3.2%) | 1 (1.1%) | 5 (6.0%) | 3 (3.6%) | - |
| | mood changes/concentration | 2 (2.1%) | - | 1 (1.2%) | - | - |
| | myelosuppression | 2 (2.1%) | 1 (1.1%) | - | - | - |
| | drug allergy | 1 (1.1%) | 1 (1.1%) | 1 (1.2%) | - | 1 (1.2%) |
| | edema | 1 (1.1%) | - | - | - | - |
| | erysipelas | - | - | 1 (1.2%) | - | - |
| | hair loss | 1 (1.1%) | - | - | - | - |
| | headache | 1 (1.1%) | 1 (1.1%) | 2 (2.4%) | 1 (1.2%) | - |
| | joint pain | 1 (1.1%) | 1 (1.1%) | - | - | - |
| | palpitations | - | - | 1 (1.2%) | - | - |
| | sinusitis | - | - | 1 (1.2%) | - | - |
| **side effects,** | gastro-intestinal symptoms | 2 (2.1%) | 2 (2.1%) | 1 (1.2%) | - | - |
| **and** | dizziness | 1 (1.1%) | 1 (1.1%) | - | - | - |
| **ineffectiveness** | headache | - | - | 1 (1.2%) | 1 (1.2%) | - |
| **as reason for** | myalgia | 1 (1.1%) | 1 (1.1%) | 1 (1.2%) | 1 (1.2%) | - |
| **discontinuation** | tiredness | - | - | 1 (1.2%) | - | - |

Discontinuation of treatment due to side effects may be due to >1 reason; therefore the sum of patients exceeds 100%.

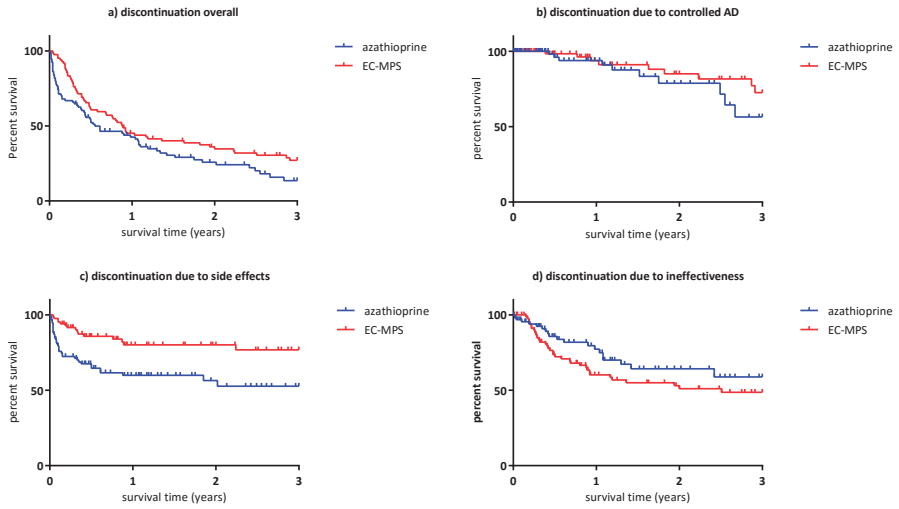


**Figure 1** – Azathioprine and enteric-coated mycophenolate sodium drug survival split for reasons of discontinuation.

## Determinants of drug survival

Table 5 shows the determinants for longer or shorter drug survival for azathioprine and EC-MPS as determined by univariate Cox regression analysis. Multivariate Cox regression analysis for azathioprine showed that concomitant oral corticosteroids at the moment of discontinuation was associated with a decreased drug survival related to side effects (HR 2.16, 95% CI 1.07-0.94). Older age was associated with an increased drug survival related to ineffectiveness (HR 0.81, 95% CI 0.69-0.95) (Table 6).

Multivariate Cox regression analysis for EC-MPS showed that concomitant oral corticosteroids at moment of discontinuation was associated with a decreased drug survival related to side effects (HR 3.82, 95% CI 1.33-10.97) and a decreased drug survival related to ineffectiveness (HR 2.22, 95% CI 1.02-4.80). Male sex was associated with an increased drug survival related to ineffectiveness (HR 0.48, 95% CI 0.25-0.94) (Table 6).

## DISCUSSION

The results of this study show that the overall drug survival of azathioprine and EC-MPS was almost identical. Drug survival of azathioprine was mainly limited by discontinuation due to side effects, while drug survival of EC-MPS was mainly limited by discontinuation due to ineffectiveness.

**Table 5** – Determinants of drug survival as determined by univariate Cox regression analysis.

| | **drug survival, event = discontinuation due to side effects** | **discontinuation due to ineffectiveness** |
|---|---|---|
| **azathioprine** | | |
| older age[a] | 1.1 [0.9-1.2] | **0.8 [0.7-1.0]** |
| male sex | 0.9 [0.5-1.7] | 1.2 [0.5-3.1] |
| concomitant oral corticosteroids at moment of discontinuation | **2.2 [1.1-4.3]** | **2.3 [0.9-6.1]** |
| maintenance dose azathioprine <150 mg/day | 0.9 [0.3-3.2] | 1.0 [0.4-2.9] |
| **enteric-coated mycophenolate sodium** | | |
| older age[a] | 1.1 [0.9-1.3] | 1.0 [0.9-1.1] |
| male sex | **0.4 [0.1-1.1]** | **0.5 [0.2-0.9]** |
| concomitant oral corticosteroids at moment of discontinuation | **3.8 [1.3-11.0]** | **2.2 [1.0-4.7]** |

Data are presented as hazard ratio [95% confidence interval]. Bold numbers indicate hazard ratios with a p-value <0.2. [a]age in 5-year intervals

**Table 6** – Determinants of drug survival as determined by multivariate Cox regression analysis. P-values of <0.05 were considered as statistically significant.

| | **drug survival, event = discontinuation due to side effects** | **discontinuation due to ineffectiveness** |
|---|---|---|
| azathioprine | | |
| older age[a] | - | **0.81 [0.69-0.95]** |
| concomitant oral corticosteroids at moment of discontinuation | **2.16 [1.07-4.34]** | 2.01 [0.76-5.32] |
| enteric-coated mycophenolate sodium | | |
| male sex | 0.40 [0.14-1.15] | **0.48 [0.25-0.94]** |
| concomitant oral corticosteroids at moment of discontinuation | **3.82 [1.33-10.97]** | **2.22 [1.02-4.80]** |

Data are presented as hazard ratio [95% confidence interval]. Bold numbers indicate hazard ratios with a p-value <0.05. [a]age in 5-year intervals

Several previous clinical trials on azathioprine or EC-MPS have reported the clinical efficacy and safety of both agents. Three randomized controlled clinical trials on azathioprine in adult patients with severe AD reported a reduction of clinical score of 26-37% after 12 weeks compared to baseline.[3-5] Side effects led to early discontinuation of azathioprine in 9.1% to 14.6% of the patients. Similar clinical efficacy of EC-MPS was reported in a small open prospective study (6 months) and in a randomized controlled trial (30 weeks treatment).[6, 7] Both studies reported only mild side effects; none of the patients in the open prospective study and 12.5% of the patients in the randomized controlled trial discontinued due to side effects.

Remarkably, discontinuation of treatment due to side effects and/or ineffectiveness for both azathioprine and EC-MPS is higher in our drug survival study compared to earlier clinical trials. A recent study of Thomsen *et al.*[10] also report a less favorable outcome of 60 patients treated with azathioprine in daily practice compared to those in clinical trials. Nearly half of the patients discontinued azathioprine treatment within one year because of insufficient clinical response or side effects, which is comparable with our results. An explanation might be that patients who participate in clinical trials are often very motivated to fulfill the trial period, despite ineffectiveness or the occurrence of side effects.[11] In addition, the longer treatment duration in daily practice may account for a higher discontinuation rate. In the present study, the concomitant use of CsA and oral corticosteroids may also affect discontinuation due to side effects in both treatment groups. Therefore, the use of CsA and oral corticosteroids in patients who stopped due to side effects was presented (Table 4).

From clinical trials and expert opinion, it is known that clinical efficacy of azathioprine and EC-MPS is reached after 8 to 12 weeks. In 35% of the patients treated with azathioprine and 14% of the patients treated with EC-MPS, who discontinued treatment due to ineffectiveness, the duration of treatment was less than 12 weeks. This period might have been too short to judge about the clinical effectiveness of the oral immunosuppressive drug.



There are differences between clinical trials and drug survival studies. First, drug survival analysis is not a study of efficacy, but a reflection of daily practice. Clinical decisions made by physician and patient together taking into account effectiveness and side effects determine the outcome instead of clinical skin scores at fixed time points. Furthermore, clinical trials use strict inclusion and exclusion criteria, while in daily practice studies all patients are included. Patients' characteristics such as comorbidity, susceptibility to side effects and earlier treatment failure, may influence treatment success. In the present study, 88.3% of the patients in the azathioprine group and 92.9% of the patients in the EC-MPS group were treated with different oral immunosuppressive drugs in the past and stopped therapy because of side effects or treatment failure.

Drug survival analysis in the present study is interfered by the concomitant use of CsA and oral corticosteroids. This reflects the situation in daily practice. Twenty-one (25.0%) patients in the EC-MPS group concomitantly used CsA. These patients were already using CsA at start of EC-MPS treatment. The intention was to use CsA only in the initial phase of EC-MPS treatment for gradual transition from CsA to EC-MPS. However, three patients were still using CsA at the moment of stopping EC-MPS due to controlled AD, suggesting insufficient effectiveness of EC-MPS monotherapy in these patients.

More than half of the patients in both groups used concomitant oral corticosteroids especially in the first weeks of treatment. As clinical efficacy of azathioprine and EC-MPS

is reached after 8 to 12 weeks; in daily practice oral corticosteroids are frequently used to bridge this period. Ideally oral corticosteroids should be tapered after 12 weeks. In this daily practice cohort a considerable number of patients used oral corticosteroids for longer periods or as rescue medication, indicating insufficient effectiveness of azathioprine and EC-MPS monotherapy in a subgroup of patients.

Oral corticosteroids at the moment of discontinuation of azathioprine or EC-MPS treatment may influence the reason for stopping therapy. Therefore oral corticosteroid concomitantly used at the moment of discontinuation was formulated as a determinant of drug survival. The number of patients using concomitantly oral corticosteroids at the moment of discontinuation was comparable in both groups, 23/94 (24.5%) patients in the azathioprine group and 17/84 (20.2%) of the patients in the EC-MPS group (p=0.59). Concomitant oral corticosteroids at the moment of discontinuation was associated with a decreased drug survival related to side effects and ineffectiveness in both treatment groups in the univariate Cox regression analysis. A significant effect on drug survival in the multivariate Cox regression analysis was found for the azathioprine group that discontinued due to side effects and for the EC-MPS groups with respect to discontinuation due to side effects and due to ineffectiveness. So, it seems that concomitantly use of oral corticosteroids in the more advanced phase of treatment has a negative effect on drug survival.

For azathioprine, multivariate Cox regression analysis showed that older age was associated with an increased drug survival related to ineffectiveness. This might be attributed to the fact that older patients have more patience to wait for the clinical effectiveness of azathioprine. The more extensive history of other oral immunosuppressive drugs used and limited availability of alternative treatment options may also cause that patients with older age have a longer drug survival.

Multivariate Cox regression analysis showed that male sex was associated with an increased drug survival related to ineffectiveness for patients treated with EC-MPS. We cannot find an explanation for the difference in drug survival between gender.

The determinants in the Cox regression model do not fully explain the outcome. Other factors for example disease severity, physicians' preferences, adherence to treatment and the availability of other treatment options may influence the outcome as well. A limitation of this study might be the low explained variance of the results of the Cox regression analysis.

In conclusion, overall drug survival of azathioprine and EC-MPS is comparable. Drug survival of azathioprine is mainly limited by discontinuation due to side effects, while drug survival of EC-MPS is mainly limited by discontinuation due to ineffectiveness. Concomitant use of oral corticosteroids in the more advanced phase of treatment has a negative effect on drug survival. Drug survival studies from daily practice data provide important additional information to the results of short-term clinical trials performed in selected patient groups.

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# Chapter 8

## Increased liver enzyme levels during azathioprine treatment; beware of concomitant use of proton pump inhibitors

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*To the Editor,*

Azathioprine (AZA) is a purine antagonist, which is frequently used off label in chronic inflammatory skin diseases. Genetic polymorphisms in thiopurine S-methyltransferase (TPMT) influence the metabolism of AZA. A reduced enzymatic activity of TMPT is associated with increased 6-thioguaninie nucleotide (6-TGN) levels which may cause severe leukopenia. High TPMT activity is associated with increased 6-methylmercaptopurine (6-MMP) levels (toxic 6-MMP >5700 pmol/8x$10^8$ RBCs), which is associated with liver toxicity.[1] Alanine transaminase (ALT) >3 upper limits of normal has been identified as a sensitive, but not necessarily specific signal of liver toxicity.[2] In daily practice AZA is often started with a test dose of 50 mg/day for 1-2 weeks. If laboratory tests show no abnormalities, the dose is increased to up to 150-200 mg/day.

Recently, three female patients (aged 45, 52 and 65) with atopic dermatitis and severe dyshidrotic hand/foot eczema were treated with AZA. After laboratory evaluation, all patients started with a test dose AZA of 50 mg/day, combined with oral prednisolone (20-30 mg/day in a tapering dose). Laboratory testing (total blood count, serum creatinine and liver enzymes) showed no abnormalities and after one week the AZA dose was increased to 100 mg/day and subsequently to 150 mg/day one week later. Laboratory assessments remained stable in all patients. All three patients experienced gastrointestinal side effects, for which a proton pump inhibitor (PPI) was started after several weeks [two patients pantoprazole; one patient omeprazole] (Table 1). The PPI was prescribed by the dermatologist in one patient, and the other two patients started the PPI on their own initiative. Surprisingly, the first laboratory assessment after the start of the PPI showed an increase of liver enzymes in all patients (Table 1). As these patients were already treated with AZA for several weeks without laboratory abnormalities, the physician suspected the addition of the PPI as the potential cause of the liver enzyme disturbances. Therefore, the PPI was discontinued, whilst the treatment with AZA (150 mg/day) was maintained. After discontinuation of the PPI, liver enzyme values gradually normalized, under maintenance of the treatment with AZA. All the three patients were not on any other hepatotoxic medication and did not give history of excessive alcohol consumption.

The onset of action of AZA takes a few weeks and hence prednisolone is often used as a bridging therapy during the first stage of treatment. Both AZA and prednisolone can induce gastrointestinal side effects, which are regularly treated with a PPI. Liver enzyme disturbances are frequently described during treatment with AZA, whereas liver enzyme disturbances due to PPIs are only reported in 0.1-1% of the patients.[3-7] The increased liver enzyme levels in our patients could have been due to AZA. Although TPMT genotyping showed a genotype associated with normal TMPT activity in all patients, a normal/intermediate TPMT activity does not rule out the possibility of AZA-induced liver toxicity.[1]

**Table 1** – ALT and gamma-GT before, during and after the use of a proton pump inhibitor during the treatment with azathioprine.

| | **before start of AZA** | | **AZA 150 mg/ day, before PPI** | | **AZA 150 mg/day combined with PPI** | | | | **after discontinuation of PPI, maintenance of AZA 150 mg/day** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *ALT* | *gamma-GT* | *ALT* | *gamma-GT* | *type of PPI and dose* | *duration of combination* | *ALT* | *gamma-GT* | *ALT* | *gamma-GT* | *time until normalization* |
| case 1 | 10 | 16 | 14 | 25 | pantoprazole, 20 mg/day | 3 weeks | 60 | 614 | 8 | 28 | 11 weeks |
| case 2 | 25 | 16 | 25 | na | pantoprazole, 20 mg/day | 5 weeks | 42 | 100 | 7 | 21 | 5 weeks |
| case 3 | 14 | 22 | 23 | 20 | omeprazole, 20 mg/day | 2 weeks | 254 | 545 | 50 | 27 | 6 months |

AZA: azathioprine; ALT: alanine transaminase in U/L; gamma-GT: gamma-glutamyl transferase in U/L; PPI: proton pump inhibitor; na: not available.

However, the 6-MMP levels were not above the expected value for liver toxicity, which made the contribution of AZA to the liver toxicity less likely. In addition, in all the three cases we observed the normalizing of the deranged liver enzymes upon discontinuation of the PPI without stopping AZA and hence we strongly believe that the liver injury has got an association with concomitant AZA administration with the PPI in these patients.

in all three cases described, liver enzymes gradually normalized after discontinuation of the PPI, while treatment with AZA was maintained, indicating that there was indeed a relation between the PPI use and the increased liver enzymes in these AZA treated patients.

Since PPIs are metabolized by CYP2C19, patients were also genotyped for *CYP2C19*2, *3* and **17* to estimate if there was a contribution of the genotype to the observed side effect. Higher PPI plasma concentrations due to aberrant CYP2C19 activity could potentially cause side effects. However, pharmacogenetic analysis did not show genetic evidence for aberrant CYP2C19 activity in any of the patients.

In the literature, no information on a kinetic interaction between AZA and PPIs was found.[8-10] We therefore estimate that a pharmacodynamic interaction is more likely. The simultaneous use of two drugs that are both capable of increasing liver enzymes might be the explanation for the observations in these patients.

To evaluate the effect of PPI monotherapy on the liver enzymes, the patients would have to discontinue AZA treatment for several weeks. As AZA treatment was successful in all three patients and discontinuation of AZA would probably result in a flare of eczema, we did not investigate the effect of PPI monotherapy on the liver enzymes in our patients.

Therefore, the question whether the use of PPI monotherapy in these patients should be discouraged, cannot be answered completely, which is indeed a limitation of our observation and it calls for more detailed research and large studies. It is advised to monitor liver enzymes in case these patients need to be treated with a PPI in the future. In general, concomitant treatment with a PPI during AZA treatment should not be avoided. However, extra control of the liver enzymes for example after 3-4 weeks after starting this combination in addition to the regular three monthly monitoring is recommended.

In conclusion, in case of liver enzyme disturbances during treatment with AZA, one should be aware of concomitant use of a PPI. The effect of discontinuation of the PPI on the liver enzymes should first be evaluated before AZA is reduced or discontinued. In patients with liver enzyme disturbances when AZA is combined with a PPI, the use of antacids or H2-receptor antagonists should be considered to suppress gastrointestinal side effects.

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# Chapter 9

## Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis

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*DEAR EDITOR*, Methotrexate is prescribed off-label for atopic dermatitis. Some clinical studies of methotrexate treatment in atopic dermatitis demonstrated effectiveness, although the number of patients was small and the treatment and follow-up period were relatively short.[1-5]

Therefore, we conducted an analysis of drug survival for methotrexate in a long-term daily practice cohort of patients with severe atopic dermatitis.

This retrospective study was performed at the Dermatology departments of the University Medical Center Groningen and the University Medical Center Utrecht. In both centers all patients are registered according to the 10th edition of the International Statistical classification of Diseases and Related Health Problems (ICD-10).[6]

The patients for the study were identified by the morbidity atopic dermatitis (XII-L20) and lab monitoring in the same period. Laboratory monitoring is mandatory during treatment with systemic therapy and liver function parameters were used to identify subjects treated with methotrexate.

Patients aged ≥ 18 years with atopic dermatitis according to the U.K. Working Party's Diagnostic Criteria[7], treated between 1997 until data lock in February 2015, were included. Data were retrieved from medical charts, which were prespecified for atopic dermatitis.

Treatment with methotrexate was initiated with 5 to 10 mg per week and gradually increased based on clinical signs with a maximum of 5 mg per visit (maximum total dose 25 mg/week), according to a standard follow-up protocol in both centers. Some patients received concomitant prednisolone (10-30 mg/day); during the startup phase, for crisis intervention or a low maintenance dose (5 mg/day) during their complete methotrexate treatment. A physician global assessment (PGA) score was used to measure retrospectively an overall treatment response at the moment of discontinuation or data lock. The improvement of lesions relative to the baseline (before start of methotrexate) were divided into three groups; PGA1: good effect of treatment, PGA2: moderate effect, PGA3: failure of treatment (no improvement or worse).[8] Treatment episodes less than 8 weeks were excluded for a PGA score.

Only the first methotrexate treatment episodes were analyzed, treatment interruptions up to 14 days were considered as a continuous treatment episode. Drug survival rates of methotrexate were analyzed by Kaplan-Meier survival curves.[9-11] Three 'events' for drug survival were analyzed separately: discontinuation overall (1), discontinuation due to side effects (2) and discontinuation due to ineffectiveness (3). Patients were censored in case of lost to follow-up, active user at the moment of data lock or discontinued due

**Table 1** – Patient, treatment characteristics and side effects reported as reason for discontinuation of methotrexate treatment.

| | n=89 | |
|---|---|---|
| age (years), mean ± SD | 50.7 | ± 17.3 |
| male gender, n (%) | 53 | (59.6) |
| maintenance dose (mg/week), mean ± SD | 13.6 | ± 3.7 |
| subcutaneous administration, n (%) | 10 | (11.2) |
| late onset atopic dermatitis (> 17 years), n (%) (2 missing) | 34 | (38.2) |
| history of other oral immunosuppressive drugs, n (%) | 62 | (69.7) |
| concomitant use of: | | |
| oral corticosteroids (OC), n (%) | 26 | (29.2) |
| median duration of total treatment episode[a], % (range) | 27 | (1-100) |
| (2 missing) | | |
| used OC at moment of discontinuation MTX, n (%) | 7 | (7.9) |
| reasons for discontinuation MTX (combination of OC) | | |
| ineffectiveness, n (%) | 4 | (4.5) |
| side effects, n (%) | 3 | (3.4) |
| used OC at the moment of data lock | 2 | (2.2) |
| status of use at the moment of data lock[b], n (%) | | |
| active | 35 | (39.3) |
| discontinued | 46 | (51.7) |
| lost to follow-up | 8 | (9.0) |
| reasons for discontinuation, n (%) | | |
| ineffectiveness | 13 | (14.6) |
| side effects | 22 | (24.7) |
| controlled AD | 5 | (5.6) |
| other (non-compliance, malignancy, pregnancy) | 6 | (6.7) |
| effectiveness at moment of discontinuation or data lock[b], n (%) | | |
| PGA1 | 38 | (48.7) |
| PGA2 | 28 | (35.9) |
| PGA3 | 12 | (15.4) |
| excluded < 8 weeks | 11 | |
| side effect as reason for MTX discontinuation[c], n (%) | | |
| gastro-intestinal complaints | 6 | (6.7) |
| fatigue | 4 | (4.5) |
| headache | 3 | (3.4) |
| increased liver enzymes | 2 | (2.2) |
| erysipelas, dizziness, aphtae | 2 | (2.2) |
| flu like symptoms, pneumonia, vision changes , shortness of breath, concentration problems, condylomata acuminata, folliculitis, alopecia, depressive symptoms, aggravation of rosacea | 1 | (1.1) |

SD = standard deviation, MTX = methotrexate, PGA = physician global assessment

[a] The percentage of total treatment episode is the duration of concomitant therapy divided by the duration of total MTX treatment episode

[b] Data lock: February 15, 2015

[c] One person might have more than one side effects as reason for discontinuation.

to an event other than the event of interest. Possible determinants of drug survival for the events of interest (side effects or ineffectiveness) were analysed by a univariate Cox regression model, assumptions of proportional hazards were checked and met. Determinants with a p-value less than 0.2 were entered in a multivariate Cox-regression model. By backward selection, a full model was created and p-values less than 0.05 were considered as statistically significant. Data analyses were performed with IBM SPSS Statistics 22.0.

A total of 89 patients were included. The baseline characteristics are displayed in Table 1. The median treatment duration was 223.0 days (range: 11 days – 3.8 years) with a total of 69.3 patient years. At the moment of data lock 35 patients (39.3%) still used methotrexate; 2 of them used concomitant prednisolone. In Table 1, 48.7% of the patients showed a good response to methotrexate treatment (PGA1) at the moment of discontinuation or data lock. In 20 patients who used methotrexate for more than one year, a total of 16 patients (80%) had a PGA1 score. Side effects and ineffectiveness were the main reasons for discontinuation of methotrexate, in 24.7% and 14.6% of the patients, respectively. In case of treatment failure, patients discontinued treatment due to side effects or ineffectiveness in the first year, not later on in the treatment.

The overall drug survival showed that 72.6%, 41.2% and 34.4% of the patients still used methotrexate after 6 months, one year and two years, respectively (Figure 1). The median drug survival was 9.8 (95%CI: 7.7-11.9) months. After six months, one year and two years, the treatment was discontinued in 9.8%, 24.4% and 24.4% of the patients due to ineffectiveness and in 17.1%, 33.4% and 33.4% due to side effects. Univariate Cox regression analysis demonstrated that a higher maintenance dose (dose in 5 mg/kg intervals) was associated with a decreased drug survival related to ineffectiveness (HR: 2.84, 95%CI 1.28-6.31, p=0.01) and an increased drug survival related to side effects (HR



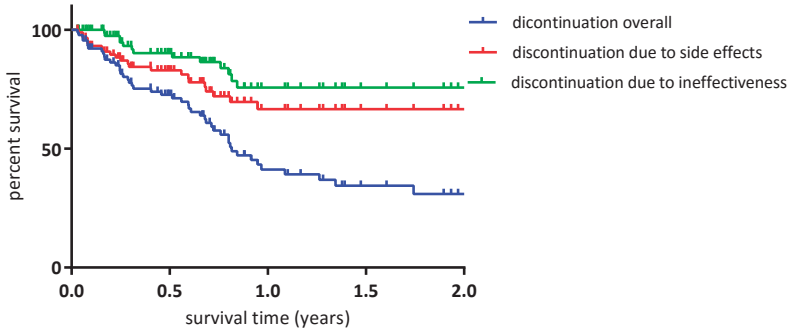


**Figure 1** – Overall drug survival rate for methotrexate in atopic dermatitis patients with separate curves for discontinuation due to side effects and ineffectiveness.

0.42, 95%CI 0.22-0.82, p=0.01). Male gender, older age (age in 5-year intervals), late onset atopic dermatitis, history of other oral immunosuppressive drugs and concomitant prednisolone did not influence the drug survival. No determinants could be selected for the multivariate analyses.

A good response to treatment was found in about half of the patients, which is comparable to the effectiveness of methotrexate treatment in other studies.[1,2] When a patient is treated with an oral immunosuppressive drug in daily practice there is no fixed endpoint, which is in contrast to clinical trials. The PGA score in the current study represented in most cases a long-term effectiveness score; a substantial part of the patients continued treatment for a long period (1 - 3.8 years) with a good long-term effect. Overall 14.6% of the patients discontinued methotrexate because of ineffectiveness. Those patients used a significant higher maintenance treatment dose during the whole treatment period. This suggests that an increased dose was not beneficial in these patients.

Ten patients used methotrexate subcutaneously; three of them changed from oral to subcutaneous administration because of gastro-intestinal complaints. Six patients with oral administration discontinued treatment due to gastro-intestinal complaints; changing the administration route, might have prevented discontinuation.

In conclusion, we present a large daily practice cohort of methotrexate treatment in patients with severe atopic dermatitis in which half of the patients benefit from this treatment. After one year of methotrexate treatment, discontinuation due to subjective side effects is uncommon and treatment appears to be long-lasting effective.

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# Chapter 10

General discussion

## OUTLINE OF THE GENERAL DISCUSSION

In this general discussion, two different topics will be addressed. Firstly, the indication for starting systemic immunosuppressive treatment in patients with atopic dermatitis (AD) is discussed based on a new AD severity classification. Secondly, the performance of oral immunosuppressive drugs in daily practice will be addressed based on the data in chapter 4-9. Finally, a proposal for the daily practice management of difficult to treat AD and recommendations for future research are discussed (Figure 1).

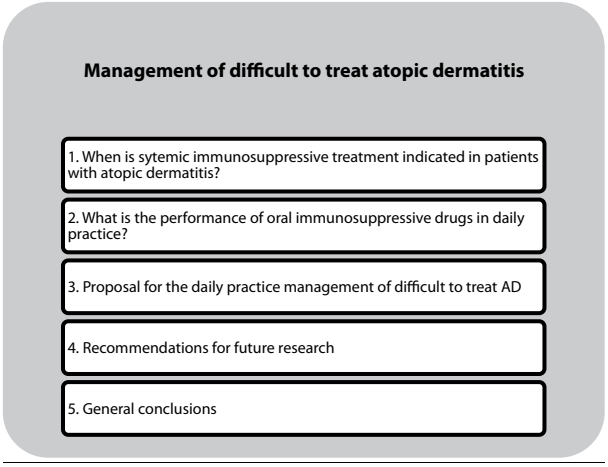


**Figure 1 –** Outline of the general discussion.

## 1. FOR WHICH PATIENTS WITH ATOPIC DERMATITIS IS SYSTEMIC IMMUNOSUPPRESSIVE TREATMENT INDICATED?

### Introduction

AD is a chronic inflammatory skin disease with a course of exacerbations and remissions. In the management of AD, stabilization of the disease by prevention of exacerbations is the major treatment goal; therefore long-term treatment is often indicated. The balance between effectiveness and safety is important in the treatment of chronic diseases such as AD.

The management of AD includes several treatment steps. The majority of patients with AD can be adequately treated with topical treatment. Sometimes UV-light therapy is indicated, however, this is not a long-term treatment option.[1] Long-term treatment with topical corticosteroids can be limited with respect to safety (maximum 100 grams/week, topical corticosteroids with short half-life time).[2] Systemic immunosuppressive drugs are the second step in the treatment of AD. However, there are no clear criteria on

the eligibility of patients for systemic immunosuppressive drugs. In general, systemic immunosuppressive treatment is indicated in patients with severe AD. But what is severe AD? Two different ways to define AD severity are discussed in the following sections.

### AD severity based on clinical skin scores

A recent study evaluated the interpretation of the eczema area and severity index (EASI) for daily practice use. EASI scores were stratified according to the Investigator's Global Assessment (IGA). The severity strata displaying the highest kappa coefficient of agreement were then selected as the recommended EASI band. The following severity strata for the EASI were suggested: 0 = clear; 0.1-1.0 = almost clear; 1.1-7.0 = mild; 7.1-21.0 = moderate; 21.1-50.0 = severe; 50.1-72.0 = very severe (kappa = 0.75).[3] This enables translation of the EASI numerical output into an AD global severity state that should be more meaningful to caregivers and patients. The European Task Force on Atopic Dermatitis (ETFAD) recommends to use the objective scoring atopic dermatitis index (SCORAD) to determine AD severity and considers an objective SCORAD <15 as mild, 15-40 as moderate and >40 as severe AD.[4] In the study of Landheer *et al.* AD severity was categorized based on the six area, six sign atopic dermatitis score (SASSAD) in mild (SASSAD <20), moderate (SASSAD 20-40), and severe (SASSAD >40).[5] Only the categorization of EASI was based on IGA, whereas, the categorization of the SCORAD and SASSAD were based on clinical expert opinion. The patient-oriented eczema measure (POEM) is a validated, patient-derived assessment measure for monitoring AD severity. A study determined the relationship between POEM and two Global Questions concerning patients'/parents' views of the overall severity of their/their child's eczema in order to stratify POEM into five severity brands. The proposed branding for POEM scores were: 0-2 = clear/almost clear; 3-7 = mild; 8-16 = moderate; 17-24 = severe; 25-28 = very severe (kappa = 0.46).[6]

The terms mild, moderate and severe AD cannot be used uniformly because they are dependent on the clinical scoring system that was used.

Classification of AD severity based on a single measurement of a clinical skin score is meaningless. A single measurement could easily over- or underestimate the severity of AD, as AD has a course of exacerbations and remissions. AD severity is also dependent on the prescribed therapy and the extent to which the therapy is correctly applied. This is illustrated by the following example. A patient with an EASI score of 30, which corresponds to severe AD according to the stratification by IGA, presented at the outpatient clinic.[3] The patient already used potent topical corticosteroids; the referring physician asked whether systematic immunosuppressive treatment was indicated. Comprehensive instruction about how to use topical corticosteroids adequately and training in self-management resulted in a rapid decrease to an EASI score of 12 in 6 weeks. The AD of this patient remained adequately controlled with topical treatment in safe amounts

(maximum 100 grams/week, topical corticosteroids with short half-life time) during long-term follow-up in the outpatient clinic (EASI 2). The patient was classified as severe based on the EASI score. However, after treatment instructions and self-management training, he could be classified as having a mild eczema.

On the other hand, patients with low clinical skin scores may have a severe eczema. Most clinical skin scores consist of a composite score for the severity and the extensiveness. A high score for severity, but a low score for extensiveness results in a low composite score. This can lead to a misjudgment of the severity of the disease, which is illustrated by the following case. A patient with severe periorbital AD with a maximal local EASI score for the severity and no eczema on the rest of his skin had an EASI score of 2.4 (out of 72) (head/neck region: severity score 6, area score 2: 10-29%). The EASI score in this patient corresponds to mild AD according to the stratification by IGA.[3] However, adequate disease control was not reached with intensive treatment with topical corticosteroids and self-management training. This example illustrates that a low clinical skin score does not always correlate with mild disease.

**Conclusion 1: The severity of AD cannot be based on a single measurement of the clinical skin score. In addition, the terms mild, moderate and severe AD cannot be used uniformly, because they are dependent on the clinical scoring system that was used.**

## AD severity based on treatment response: difficult to control AD and difficult to treat AD

*From difficult to control AD to controlled AD*

Patients with an unstable course of AD due to exacerbations despite the maintenance use of topical corticosteroids can be defined as difficult to control. In these patients much attention must be paid to adherence to topical treatment and evaluation of self-management. It is important to emphasize the need of continuous treatment and to taper, but not to stop topical treatment when the eczema is controlled. The use of topical corticosteroids with a short half-life time with a maximum of 100 grams/week is considered in daily practice as a safe maintenance scheme.

Nearly half of the patients described in *chapter 3* had high clinical skin scores over a long time period despite the use of potent topical corticosteroids. However, an inpatient treatment and education program and psychosocial support led to stabilization of AD, which remained stable during follow-up in the majority of patients using topical corticosteroids in a safe maintenance scheme. This improvement of AD severity was measured as a 50% reduction of SASSAD score (SASSAD50). The inpatient treatment led

to a SASSAD50 in 81.0% of the patients and during follow-up 79.7% patients still had a SASSAD50. Therefore, these patients were difficult to control, but not difficult to treat.

**Conclusion 2: In patients with difficult to control AD therapy adherence should be optimized.**

*From difficult to control AD to difficult to treat AD*

In patients with difficult to treat AD it is not possible to reach adequate long-term disease control despite the different topical treatment options, including adequate (repeated) instructions and training in self-management. These patients have the most appropriate indication for treatment with systemic immunosuppressive drugs (Figure 2).

Patients with difficult to treat AD can be divided in different subgroups such as:

1. Patients with high disease activity over time (signs and/or symptoms), despite daily treatment with high amounts of potent topical corticosteroids including adequate instructions and self-management training.
2. Patients in which reduction of topical treatment to a safe maintenance treatment scheme, for instance 3-4 times/week, topical corticosteroids with short half-life time (maximum 100 grams/week) lead to high disease activity. Patients with side effects of topical corticosteroids, in which treatment with topical immunomodulators, tar or UV-light (comparable with mid potent corticosteroids) leads to high disease activity.
3. Patients with severe eczema periorbital inadequately controlled by topical immunomodulators and/or intermittent use of maximal class 3 topical corticosteroids. Patients with severe eczema periorbital are at risk for developing atopic keratoconjunctivitis (AKC).
4. Patients in which adherence to topical treatment could not be optimized due to severe psychosocial disturbances, for instance resulting in absence from school/work and/or social isolation despite much attention being paid to these problems.

**Conclusion 3: Difficult to treat AD is the most appropriate indication for long-term systemic immunosuppressive treatment.**

Patients with very difficult to treat AD could be classified as patients with treatment failure on one or more systemic immunosuppressive drugs. In the future, this patient group would have the most appropriate indication for treatment with biologicals.

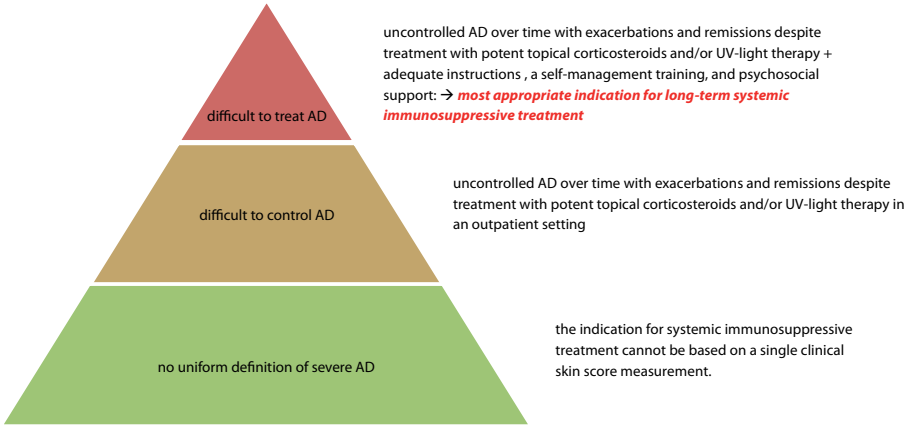


**Figure 2 –** Overview of the subsequent steps in the classification of AD severity.

## 2. WHAT IS THE PERFORMANCE OF ORAL IMMUNOSUPPRESSIVE DRUGS IN DAILY PRACTICE?

### Clinical trials versus daily practice

Cyclosporin A (CsA) is the only registered oral immunosuppressive drug in the treatment of AD. Several second line oral immunosuppressive drugs such as azathioprine (AZA), enteric-coated mycophenolate sodium (EC-MPS), mycophenolate mofetil (MMF) and methotrexate (MTX) are frequently used in daily practice in patients with difficult to treat AD. The clinical efficacy and safety of these compounds has been shown in several clinical trials.[7-20]

Roekevisch *et al*.[21] performed a systematic review on the efficacy and safety of systemic treatments for moderate-to-severe AD in randomized controlled trials (RCT). Thirty-four RCTs with 12 different systemic treatments in 1653 patients were included. Based on these RCTs, CsA is recommended as first-line treatment, AZA can be considered as second-line treatment, and MTX as a third-line treatment option. Recommendations for EC-MPS and MMF were not possible because of limited evidence. A summary of clinical trials also including open studies is provided in Table 1.

Most guidelines concerning the use of oral immunosuppressive drugs in severe AD are based on clinical trials. However, the results of clinical trials are not always generalizable to daily practice for several reasons. First, there is a difference in patient selection. In clinical trials only small groups of patients who fulfill strict inclusion criteria are included. Patients' characteristics, such as comorbidity, susceptibility to side effects and earlier

treatment failure may influence treatment success. In most RCTs these characteristics are reported incomplete, which limits the generalizability of the outcome. The external validity of a clinical trial also depends on whether the outcomes are clinically relevant. The main outcome in clinical trials in AD is often the mean/median decrease in clinical skin score in the total group compared to before or the difference in mean/median decrease in clinical skin score between two treatment groups at fixed time points. However, mean scores give no information on individual response rates. Treatment duration in most clinical trials is short (12-30 weeks); long-term effectiveness and safety data from clinical trials up to one year are only available for CsA and not for AZA, EC-MPS, MMF and MTX. Whether initial response is a good predictor of long-term benefit is unknown. When a patient is treated with an oral immunosuppressive drug in daily practice, there is no fixed endpoint of treatment, which is in contrast to clinical trials. Finally, from literature it is known that participation in a clinical trial improves the adherence to therapy, perhaps leading to more favorable results in clinical trials compared to effectiveness and safety experienced in daily practice.[22]

**Table 1** – The most important characteristics of the different oral immunosuppressive drugs based on trials and open studies.

| compound | number of patients | decrease clinical score | time to respond | treatment period | time to relapse | most important side effects |
|---|---|---|---|---|---|---|
| cyclosporin A | 602 patients | 53-95% | 2 weeks | maximum 1 year | <2 weeks | serum creatinine increase (>30% increase compared to baseline) |
| azathioprine | 91 patients | 26-39% | 8-12 weeks | maximum 24 weeks | >3 months | hematological abnormalities<br>gastro-intestinal side effects<br>increased liver enzymes |
| methotrexate | 71 patients | 42-52% | 8-12 weeks | maximum 24 weeks | >3 months | hematological abnormalities<br>gastro-intestinal side effects<br>increased liver enzymes |
| enteric-coated mycophenolate sodium/ mycophenolate mofetil | 36 patients (EC-MPS); 56 patients (MMF) | 55-68% | 8-12 weeks | maximum 30 weeks | >3 months | hematological abnormalities<br>gastro-intestinal side effects<br>skin infections |

Real life data from patients with AD, treated with systemic immunosuppressive drugs in daily practice provides important and essential information in addition to existing clinical trial data, as the data reports long-term treatment in large unselected patient groups. However, interpretation of daily practice data is not always easy due to several reasons.

In clinical trials usually the same trial doctor performs all visits, while in daily practice patients often visit different doctors over time. Therefore, the quality of daily practice data depends for a large extent on protocols including dose schemes, visit frequency and safety monitoring of the different drugs. The data collected for our drug survival studies at the University Medical Center Utrecht and the University Medical Center Groningen was from patients who were treated according to strict treatment protocols.

Another important issue for daily practice research is the search for realistic outcome measures. In a real life situation the balance between effectiveness and side effects determines whether treatment with the drug will be continued or not. Other factors that determine treatment success in daily practice are for instance the compliance of the patient and the availability of alternative treatment options. In general, patients might accept more side effects when no alternative treatment options are left.

A relatively new tool for the interpretation of real life data from daily practice is drug survival analysis.[23] Drug survival is the length of time a patient continues to take a particular drug: it is a well-recognized measure, which encompasses factors such as effectiveness, safety, and patients' and doctors' preferences. Drug survival analysis is based on the reason for discontinuation of the drug, which is a reflection of the balance between effectiveness and side effects. Predictors associated with drug survival can be identified with additional Cox regression analysis.[23]

**Conclusion 4: Guidelines concerning the use of oral immunosuppressive drugs in severe AD are based on clinical trials. However, clinical trial data does not reflect a real life situation and for that reason is not always generalizable to daily practice.**

**Conclusion 5: Drug survival analysis is a new tool for the interpretation of data from daily practice and reflects the performance of a systemic immunosuppressive drug and is a composite measure of treatment success.**

### What is the performance of oral immunosuppressive drugs in daily practice?

In *Chapters 4*, *7*, and *9* drug survival analyses of the four most frequently used drugs in the treatment of AD, CsA, AZA, EC-MPS and MTX, are described. Based on the study results, the performance of these drugs in daily practice will be discussed in the following section.

An overview of drug survival results is depicted in Table 2. In the search for the systemic immunosuppressive drug with the best daily practice performance, the drug survival of the different compounds needs to be compared. The drug with the best performance has the most optimal balance between effectiveness and side effects. Drug survival analysis revealed that CsA has the best overall performance as discontinuation owing to both side effects and ineffectiveness was relatively low. In addition, in the CsA group, the highest percentage of patients with discontinuation owing to controlled AD was found. EC-MPS treated patients showed the lowest rate of discontinuation due to side effects, however discontinuation owing to ineffectiveness was the highest in this group. The performance of AZA was mainly limited owing to side effects. Discontinuation owing to controlled AD was low in the AZA, EC-MPS and MTX group; this can partly be explained

**Table 2 –** Table 2a shows the number of patients per reason for discontinuation. Table 2b shows the percentage of drug survival per reason for discontinuation after 3 years (after 2 years for MTX).

| | | | | | discontinuation owing to | | | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **discontinued n, (%)** | **age, mean (SD)** | **first compound, n (%)** | **controlled AD n, (%)** | **ineffectiveness n, (%)** | **side effects n, (%)** | **concomitant medication at discontinuation n, (%)** |
| **CsA** | 356 | 312 (87.6%) | 37.6 (14.2) | 287 (80.6%) | 94 (26.4%) | 58 (16.3%) | 79 (22.2%) | - |
| **AZA** | 91 | 70 (74.5%) | 42.9 (13.9) | 11 (11.7%) | 10 (10.6%) | 18 (19.1%) | 34 (36.2%) | 23 (24.5%) |
| **EC-MPS** | 84 | 59 (70.2%) | 43.7 (13.3) | 6 (7.1%) | 9 (10.7%) | 32 (38.1%) | 12 (14.3%) | 20 (23.8%) |
| **MTX** | 89 | 46 (51.7%) | 50.7 (17.3) | 27 (30.3%) | 5 (5.6%) | 13 (14.6%) | 22 (24.7%) | 7 (7.9%) |

| | | | | | discontinuation owing to | | | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **discontinued n, (%)** | **age, mean (SD)** | **first compound, n (%)** | **controlled AD** | **ineffectiveness** | **side effects** | **concomitant medication at discontinuation n, (%)** |
| **CsA** | 356 | 312 (87.6%) | 37.6 (14.2) | 287 (80.6%) | 52% | 44% | 48% | - |
| **AZA** | 91 | 70 (74.5%) | 42.9 (13.9) | 11 (11.7%) | 44% | 41% | 47% | 23 (24.5%) |
| **EC-MPS** | 84 | 59 (70.2%) | 43.7 (13.3) | 6 (7.1%) | 28% | 51% | 23% | 20 (23.8%) |
| **MTX** | 89 | 46 (51.7%) | 50.7 (17.3) | 27 (30.3%) | 32%[a] | 24%[a] | 33%[a] | 7 (7.9%) |

[a] drug survival at 2 years

by the fact that a higher percentage of patients were still using the drug at the moment of evaluation, especially for MTX.

The comparison of the performance of the different compounds has several limitations. First, these studies are retrospective and therefore dependent on the quality of medical records. Secondly, there was no correction for the different baseline characteristics, such as age, gender and use of concomitant medication. In addition, CsA is often used as first choice systemic immunosuppressive drug. The other compounds are used as second, third or sometimes fourth choice. This can both positively as well as negatively influence drug survival. When a compound is used as second or subsequent choice this can indicate more difficult to treat AD, which has a negative effect on the drug survival. On the other hand, patients that used a third or sometimes fourth choice drug probably realize that there are no alternative treatment options available, and therefore might accept more side effects, which has a positive effect on the drug survival. This could also be applicable for the treating physicians. In the drug survival analysis of the different compounds, there was a difference in the number of patients that had discontinued treatment. Patients that were still using the compound probably experienced a good performance of the drug or were not treated long enough to evaluate the effectiveness and side effects, especially for MTX. The performance of the second choice systemic immunosuppressive drugs can be influenced by the use of concomitant medication (oral corticosteroids). Only patients treated with CsA were treated with monotherapy. Finally, patients treated with a second choice systemic immunosuppressive drug were older than patients treated with CsA. A higher age might possibly influence the occurrence of side effects.

**Conclusion 6: CsA has the best performance in the daily practice management of difficult to treat AD based on drug survival analysis. The performance of AZA and MTX is mainly limited owing to side effects, while the performance of EC-MPS is mainly limited owing to ineffectiveness.**



Many dermatologists have been reluctant in prescribing CsA for longer periods because of a fear for kidney damage. The drug survival study on CsA, discussed in *chapter 4*, has shown that CsA treatment duration was not associated with an increase of side effects. In addition, the use of an intermediate-high starting dose (>3.5-5 mg/kg/day) did not lead to an increased discontinuation rate owing to side effects in comparison to patients treated with a low starting dose (≤3.5 mg/kg/day).

The daily practice performance of CsA with respect to kidney function is discussed in detail in *chapter 5*. The majority of patients (85%) did not experience kidney problems during and after CsA treatment. The serum creatinine levels increased >30% compared to baseline level in 15% of the patients during treatment with CsA. This result is com-

parable to percentages reported in previous literature.[7, 24] These patients are in need of treatment with an alternative systemic immunosuppressive drug as treatment with CsA should not be continued in this patient group. The duration of treatment was not associated with the occurrence of >30% serum creatinine increase compared to baseline level. Patients with higher age were more at risk as patients with a >30% serum creatinine increase were significantly older than patients without impaired kidney function (mean age (standard deviation) 41.4 (15.6) vs. 33.8 (11.7) years (p = 0.01)). No other predictors of impaired kidney function were identified.

These results support that one should not be reluctant in prescribing CsA for longer periods in patients with difficult to treat AD. However, close monitoring of serum creatinine levels during the entire CsA treatment period remains strictly recommended.

**Conclusion 7: Impaired kidney function, measured as >30% increase of serum creatinine, is observed in 15% of the patients treated with CsA in daily practice. Higher age, but not longer treatment duration, is associated with an increased risk on impaired kidney function.**

A less frequently used alternative in the treatment of patients with CsA failure is oral tacrolimus. A major advantage above other second choice systemic immunosuppressive drugs is the fast onset of action. Although CsA and tacrolimus are closely related, tacrolimus has demonstrated a more favourable safety profile compared to CsA in healthy subjects, especially regarding blood pressure and renal function. Glomerular filtration rate, effective renal plasma flow, mean arterial pressure and renal vascular resistance were negatively influenced by CsA, but not by tacrolimus.[25] Therefore, tacrolimus might also be an interesting alternative in patients with renal impairment during treatment with CsA.

Extended release tacrolimus (ERT) has the advantage of a more consistent plasma concentration over time and a reduced peak concentration compared to the original formulation of tacrolimus. Studies on the use of oral tacrolimus in inflammatory skin diseases such as AD are scarce.[26-28]

In the observational study in *chapter 6* it is shown that ERT is effective and safe in the majority of patients despite the extensive therapeutic history and/or previous side effects to CsA. Only one out of three patients that discontinued CsA treatment because of serum creatinine increase also discontinued ERT for this reason. Therefore, ERT can be an attractive alternative treatment for patients with difficult to treat AD, who had to discontinue CsA. A drug survival study in a large group of patients with long-term follow-up is needed for a reflection of daily practice performance of ERT treatment.

**Conclusion 8: ERT should be considered as second choice treatment in patients with failure of CsA treatment.**

## 3. PROPOSAL FOR THE DAILY PRACTICE MANAGEMENT OF DIFFICULT TO TREAT AD

### Introduction

Lack of experience may increase the threshold for prescribing systemic immunosuppressive drugs in patients with difficult to treat AD. Unfamiliarity with treatment protocols, uncertainty of how to cope with side effects and fear for irreversible side effects may result in inadequate treatment of patients with severe AD. Although CsA is registered for AD in most countries, it is not always the first choice treatment in daily practice. For example, if a dermatologist regularly treats patients with bullous diseases with AZA, the threshold to use AZA in a patient with severe AD might be lower than starting CsA. Also the familiarity with MTX in the treatment of psoriasis may account for the preferred use of MTX in patients with severe AD.

In the following section a proposal for daily practice management of patients with difficult to treat AD is described based on additional data derived from daily practice studies discussed in this thesis.

### Considerations before starting systemic immunosuppressive treatment

Patients classified with difficult to treat AD are eligible for treatment with systemic immunosuppressive drugs. Before treatment is started, an estimation about the compliance of the patient to use the drug in a secure manner needs to be made. Regular monitoring of safety parameters (laboratory assessment, blood pressure) continue to be necessary for the entire treatment duration. Also personal circumstances of the patient, such as a wish for pregnancy have to be taken into account. Both men and women should not be treated with EC-MPS and MTX in case of a wish for pregnancy and should take appropriate contraceptive measures for at least 3 months after discontinuation. Women with a wish for pregnancy should not be treated with AZA and should take contraceptive measures for at least 3 months thereafter. The use of CsA and prednisone should be restrained during pregnancy for women. CsA and prednisone do not influence male fertility outcome.[29]

In patients with a medical history of a malignancy, except for basal cell carcinoma, the eligibility for treatment with systemic immunosuppressive drugs should be evaluated per patient in consultation with the oncologist.

### Choice of the systemic immunosuppressive drug

The choice between the different systemic immunosuppressive drugs depends on several considerations including characteristics of the drug, patient characteristics and treatment indication.

*Characteristics of the drug*

CsA is the only registered systemic immunosuppressive drug in the treatment of AD. The clinical effectiveness of CsA is fast. Based on drug survival results, CsA is recommended as first choice oral immunosuppressive drug. This is in accordance with the recommendations in the systematic review of Roekevisch *et al*.[21] New information can be derived from the multivariate cox regression analysis in the drug survival study; the effectiveness of CsA is better, when an intermediate-high (>3.5 mg/kg/day) starting dose is used.

In patients with contraindications for the use of CsA and in patients with side effects and/or ineffectiveness of CsA treatment, second line systemic immunosuppressive drugs such as AZA, EC-MPS, ERT, MMF and MTX are indicated.

The choice which particular second line drug should be used is not easy. Based on a systematic review of RCTs AZA was recommended as second line treatment, MTX as a third line treatment option. No recommendations for EC-MPS could be given.[21] Our drug survival analysis shows that the overall performance of AZA and EC-MPS is more or less equal in daily practice, suggesting also a considerable role of EC-MPS as second line treatment. More detailed information showed that the risk of discontinuation owing to side effects was lower during treatment with EC-MPS than during AZA treatment, while EC-MPS treatment was associated with a higher risk of discontinuation owing to ineffectiveness. MTX seemed to be more effective than EC-MPS, but had a higher discontinuation rate owing to side effects.

The effectiveness of MMF in patients with AD has been shown in several case reports.[12-17] In previous studies in patients with AD, the performance of EC-MPS and MMF has not been not compared. The effectiveness in transplantation patients of both drugs is comparable (MMF 2000 mg/day versus EC-MPS 1440 mg/day).[30-32] EC-MPS potentially has less gastrointestinal side effects.[33, 34]

It is possible, as a result of this data on drug survival, to inform the patient more adequately on the performance of the drug. Dependent on the preference of the physician and patient, a choice between a drug with a higher chance of effectiveness (AZA, MTX) or a drug with less chance on side effects (EC-MPS) can be made.

Furthermore, a disadvantage of AZA, EC-MPS, MMF and MTX, is their greater time (3-4 months) before clinical effectiveness is reached.[11, 20] Therefore, bridging treatment with oral corticosteroids is often indicated.

Nevertheless, in the case of CsA failure, treatment with AZA, EC-MPS or MTX should be considered before ERT as these drugs have been studied more extensively compared to our pilot study on ERT in *chapter 6*.[8-20] Due to the limited data and the high costs, ERT should provisionally only be reserved for a selected group of patients with failure to other second line drugs. The start of treatment with MMF and a switch to EC-MPS in case of gastrointestinal side effects should be considered because of the high costs of EC-MPS compared to MMF.

An estimation of the mean yearly costs per patient (body weight 75 kg) are 5440 euro/year for ERT (0.1 mg/kg/day, Advagraf®), 2270 euro/year for CsA (3 mg/kg/day), 208 euro/year for AZA (150 mg/day, Imuran®), 3180 euro/year for EC-MPS (1440 mg/day, Myfortic®), 350 euro/year for MMF (2000 mg/day, Cellcept®) and 26 euro/year for MTX (7.5 mg/week).[35] Medication costs should be taken into account, but should not be leading factor in the decision as to which systemic immunosuppressive drug is started.

*Patient characteristics*

Besides the characteristics of the drug, individual patient characteristics can be restrictive in the choice between the different treatment options. Therefore, a detailed history is important when treatment with a systemic immunosuppressive drug is considered. For instance co-morbidity, such as uncontrolled hypertension or impaired kidney function are contra-indications for starting CsA, while in patients with impaired liver function MTX and AZA are contra-indicated.[36]

Also the use of concomitant medication, leading to possible interactions with oral immunosuppressive drugs, may influence the choice of the compound. For instance, in the case of the regular use of non-steroid anti-inflammatory drugs (NSAIDs), CsA is not the first choice of treatment because of an increased risk of impaired kidney function.[7] AZA is not recommended in combination with ACE-inhibitors because of an increased risk of myelosuppression.[36]

The age of the patient can also influence the choice of the compound. For instance, the drug survival study showed that the performance of CsA is less in older patients, because of a higher risk of discontinuation due to side effects. The performance of AZA is better in older patients, because of lower risk of discontinuation owing to ineffectiveness.

*Treatment indication*

As was stated in part one of the general discussion, patients with difficult to treat AD have an indication for systemic immunosuppressive treatment. The choice of the compound and dose schemes can be adjusted depending on the subgroup indication discussed in part 1. This will be clarified with two examples from daily practice.

In figure 3a a patient suffers from difficult to treat AD (IGA 5 on a 6 point scale), despite adequate daily treatment with potent topical corticosteroids (>100 grams/week) for several weeks (subgroup 1). In this situation, a compound with a short time to reach clinical effectiveness is indicated, such as a high dose CsA (5 mg/kg/day). A reduction in signs and symptoms may be expected within 2-3 weeks. If long-term treatment with oral immunosuppressive drugs is necessary, the CsA dose is tapered to a maintenance dose of 3-3.5 mg/kg after 6 weeks. In case of a contraindication for CsA, a compound with a longer time to reach clinical effectiveness, such as AZA, EC-MPS, or MTX may

be indicated, since its slow onset of clinical effectiveness additional therapy with oral corticosteroids is temporally needed.[11, 20] Ideally, the oral corticosteroids dose is tapered and stopped within 2-3 months. Meanwhile, topical corticosteroid use must be adjusted to a safe maintenance scheme.[2] The search for an optimal balance between a safe topical treatment scheme and the lowest dose of the oral immunosuppressive drug during the entire treatment period is important.

In the second example in figure 3b, the eczema is more or less adequately controlled using daily treatment with topical corticosteroids, resulting in an IGA of <3. However, tapering topical corticosteroids to an intermittent use results in an exacerbation of AD (subgroup 2). As long-term daily treatment with high amounts of topical corticosteroids (>100 gram/week) should be avoided due to side effects, oral immunosuppressive drugs are used to enable tapering of topical corticosteroids.[2] For this purpose an intermediate dose CsA (3.5 mg/kg/day) or one of the second line immunosuppressive drugs with a slower onset of clinical effectiveness can be used.

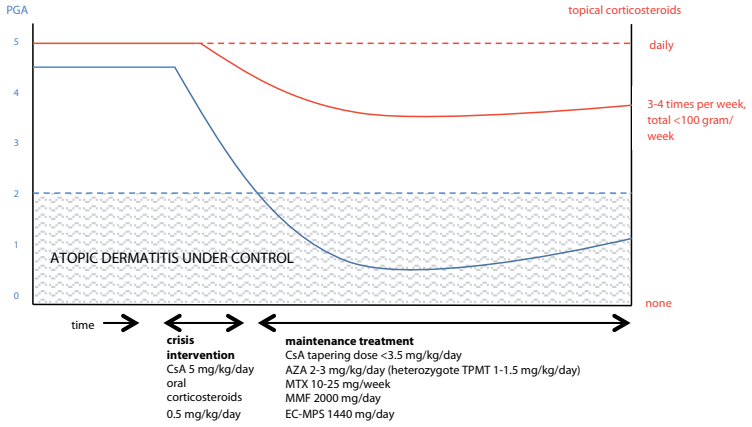


**Figure 3 –** Two different situations in which systemic immunosuppressive drugs can be added to topical treatment. In figure 3a the patient suffers from very severe AD (IGA 4.5). In figure 3b, the AD is more or less suitably managed by using daily treatment with topical corticosteroids, resulting in an IGA of <3. However, tapering topical corticosteroids to an intermittent use results in an exacerbation of AD.

## Practical aspects during treatment with systemic immunosuppressive drugs

CsA should preferably be started with an intermediate-high dose (3.5-5.0 mg/kg/day) to reach fast clinical effectiveness. Our drug survival study did not show an increased risk on discontinuation owing to side effects, when an intermediate-high starting dose was used in comparison to a low starting dose (<3.5 mg/kg/day). In addition,

the discontinuation rate owing to ineffectiveness was lower for patients treated with an intermediate-high starting dose compared to a low starting dose. EC-MPS (and also MMF) can be started with a fixed dose of 720 mg twice daily (MMF 2000 mg twice daily). This is an advantage compared to AZA and MTX, in which a stepwise increase of the dose dependent on laboratory results is indicated. The time before clinical effectiveness of these drugs is thus even longer. Pharmacogenetics enable more individual dosing as described for ERT in *chapter 6*. Recommendations for further research concerning optimization of dose schemes in individual patients will be discussed in part four of the general discussion.

The occurrence of side effects needs to be monitored for the entire treatment duration, as side effects can occur only after long-term treatment as is shown in the drug survival studies in this thesis. During every visit, the patient must be asked for subjective side effects and the skin must be inspected for side effects, such as skin infections and skin malignancies. In addition, blood pressure needs to be monitored in case of CsA use. Safety laboratory assessments are dependent on the type of drug; for instance monitoring of serum creatinine is particularly important during the use of CsA and ERT, while monitoring of liver enzymes and hematological parameters is more important during treatment with AZA, EC-MPS, (MMF), and MTX.

In case of laboratory abnormalities, one must be aware of concomitant medication use as is discussed in *chapter 8*. In three patients the concomitant use of a proton pump inhibitor during treatment with AZA led to liver enzyme disturbances. The proton pump inhibitor was discontinued, whilst the treatment with AZA was maintained. After discontinuation of the proton pump inhibitor, liver enzyme values gradually normalized, under maintenance dose of AZA. In case of kidney problems, the use of NSAIDs should be checked. Also interfering co-medication may cause subjective side effects.

The management of a side effect is dependent on its severity. Ideally dose reduction should result in decreasing severity of side effects with maintenance of clinical effectiveness. In other cases, concomitant medication can be added to reduce side effects, such as nifedipine in case of CsA induced hypertension. It is important to make a conscious consideration whether the drug needs to be discontinued owing to side effects, because only a limited number of treatment options are available for patients with AD.



In daily practice there is no definite outcome to determine effectiveness of a systemic immunosuppressive drug. As was mentioned earlier, the performance of a drug in daily practice is determined by the balance between effectiveness and side effects, which is to a large extent patient dependent.

Monitoring clinical effectiveness is important in daily practice. The present clinical scoring systems (EASI, SCORAD, SASSAD) are time consuming and less reliable in case

of many observers per patient. Therefore, a simple scoring system, such as IGA, which shows a high correlation with the EASI seems to be a good alternative. Alternatives are biomarkers such as TARC, also showing a good correlation with clinical scores.[37-38] Less expensive are patient reported outcomes (PROMs), such as the POEM score.[6] The time point at which the performance an immunosuppressive drug is determined is very important. The effectiveness of an oral immunosuppressive drug with a slow onset of action, such as AZA, EC-MPS and MTX, can only be judged properly after 3-4 months.[11, 20] In case of CsA, most patients have an adequate clinical response on a high dose (5 mg/kg/day), however for long-term treatment the effectiveness on intermediate dose (<3.5 mg/kg/day) should be taken into account. Side effects may occur at the start of treatment with an immunosuppressive drug, but can be reduced by optimization of the dose or co-medication. Therefore the performance of an oral immunosuppressive drug can only be determined after at least 4 months.

## Is there a maximum treatment duration for systemic immunosuppressive drugs?

Due to the chronicity of the disease, long-term treatment of patients with AD is indicated in most cases. However, this does not necessarily mean that all patients with difficult to treat AD, with an indication for systemic immunosuppressive drugs, need to continue this treatment for many years. In the drug survival study on CsA, 26.4% of the patients were able to discontinue treatment owing to controlled AD after a median treatment duration of 319 days (inter quartile range 196-464).

The decision whether to continue or decrease the dose or even stop a systemic immunosuppressant drug should be considered every visit. This decision is based on the balance between many factors including, clinical effectiveness, side effects, patient satisfaction, the availability of other treatment options and so on.

On the other hand, there is a subgroup of difficult to treat AD patients, who have persistent exacerbations of their eczema after several attempts to taper or stop systemic immunosuppressive treatment. These patients need systemic immunosuppressive treatment for many years.

Clinical trials do not provide information concerning long-term safety of these drugs in AD, so this information can only be derived from daily practice registrations. The data of the drug survival studies in this thesis did not show an increase in the frequency of subjective and objective side effects with longer treatment duration.

## 4. RECOMMENDATIONS FOR FUTURE RESEARCH

### Limitations in the current management of difficult to treat atopic dermatitis

Drug survival studies described in this thesis and earlier clinical trials indicate that oral immunosuppressive drugs (CsA, AZA, EC-MPS, MMF and MTX) are very valuable in the management of difficult to treat AD. However, a major limitation is that CsA is the only drug registered for the treatment of AD and for a limited time period (one year). In patients with AD requiring treatment with CsA for more than one year and those with failure of CsA treatment, only off-label treatment options are available. In the near future, it is not to be expected that current systemic immunosuppressive drugs will be registered for treatment of AD. The most important reasons are high costs and the development of new biological agents for the treatment of AD. Therefore, at this moment long-term effectiveness and safety data can only be derived from daily practice.

### Registration of daily practice data

Uniform registration of a limited number of items concerning effectiveness and safety of classical oral immunosuppressive drugs in patients with AD will provide important information concerning the balance between effectiveness and long-term safety. This will lower the threshold of off-label use of oral immunosuppressive drugs in patients with difficult to treat AD. For instance, an important limitation of long-term use of oral immunosuppressive drugs in daily practice is the risk of non-melanoma skin cancer (NMSC) and lymphoma. Although increased NMSC and lymphoma have been reported in patients with psoriasis, inflammatory bowel disease (IBD) and rheumatic diseases, so far there is no evidence for this to occur in patients with AD.[39-42] This needs further investigation in daily practice cohorts of AD patients on long-term treatment with current oral immunosuppressive drugs.

### Optimization of individual dosing using pharmacogenetics and therapeutic drug monitoring

Another limitation in the current management of difficult to treat AD is the lack of indicators to predict individual responses to oral immunosuppressive drugs. Pharmacogenetics enables personalized medicine resulting in a better performance of oral immunosuppressive drugs. This may lower the risk of ineffectiveness and occurrence of side effects. For instance, tacrolimus pharmacokinetics is characterized by a wide inter-individual variability, which may be partly explained by single nucleotide polymorphisms (SNPs) in the genes coding for CYP3A4 and CYP3A5.[43] In the study described in this thesis, four patients were classified as 'extensive metabolizers' of tacrolimus and five patients as 'intermediate metabolizers' based on CYP3A4/CYP3A5 genotype cluster classification. In 'extensive metabolisers' a starting dose of ERT 0.2 mg/kg is safe, while in 'intermedi-

ate metabolizers' a starting dose of 0.1 mg/kg is advised to avoid plasma tacrolimus concentrations above safety level. Another advantage of performing pharmacogenetics before start of treatment with tacrolimus is that 'poor metabolizers' of tacrolimus can be identified (5.4% of the patients according to literature).[43] In these patients treatment with tacrolimus should be avoided. Pharmacogenetics of SNPs for CYP3A4/CYP3A5 genotype may also be helpful in the treatment of patients with CsA.[44]

Pharmacogenetics and therapeutic drug monitoring may also be used to optimize AZA treatment. Earlier studies in other inflammatory diseases such as IBD have demonstrated that thiopurine methyltransferase (TPMT) genotyping prior to AZA treatment followed by personalized dosing significantly reduced the risk of leukopenia due to an increased 6-thioguanine nucleotide (6-TGN) level in the subgroup of patients with a genetic variant.[45] On the other hand, high TPMT activity is associated with increased 6-methylmercaptopurine (6-MMP) levels, which is associated with liver toxicity.[45]

After starting AZA, additional monitoring of thiopurine metabolites 6-TGN and 6-MMP is valuable to further assess the risk of myelotoxicity and liver toxicity. In case of ineffectiveness due low 6-TGN levels, the balance between 6-TGN and 6-MMP could be adjusted with additional treatment with allopurinol.[46-48] Allopurinol allows shunting of AZA metabolites to a more favourable pattern by increasing 6-TGN for immunosuppression (more effectiveness) and decreasing 6-MMP (less liver toxicity).

The pharmacokinetics of mycophenolic acid (MPA) also varies between individuals. This can be explained by the presence of genetic polymorphisms in key enzymes. In transplant patients, UGT1A9 polymorphisms correlate with low MPA levels and acute rejection in MMF/tacrolimus treated kidney transplant patients.[49] Low MPA exposure due to UGT1A9 polymorphisms might partly explain the ineffectiveness in a subpopulation of EC-MPS treated AD patients in our study. Previous studies showed that the pharmacogenetic profile is associated with effectiveness of MTX in patients with rheumatoid arthritis.[50]Therefore, the effectiveness of MTX in the treatment of AD may also be influenced by the pharmacogenetic profile of a patient.

At this moment, pharmacogenetics is applied only on a limited scale in treating inflammatory diseases. It is a new area of personalized disease management, which will become more important in forthcoming years. Currently, pharmacogenetic data is available for only 2% of the approximately 6000 registered drugs.[51]

## Future treatment of atopic dermatitis: is there still room for oral immunosuppressive drugs in the next biological dominated decade?

Several biologicals targeting interleukin (IL) 4, IL-5, IL-12/IL-23, IL-13, IL-22, and IL-31 are in phase 2 trials for AD.[52] Recently, promising phase2/3 results of dupilumab, a fully human monoclonal antibody that blocks IL-4 and IL-13 were published.[53] The blockade

of these key drivers of type 2 helper T-cell mediated inflammation was evaluated in randomized, double-blind, placebo-controlled trials. A 50% reduction of the EASI score was reached in 85% of the patients in the dupilumab arm compared to 35% in the placebo arm ($p<0.001$).

The future costs for biologicals will be high and therefore the requirements for reimbursement will be strict. The requirement for reimbursement will probably include that patients should have been treated before with registered oral immunosuppressive drugs, of which CsA is the only one in the treatment of AD with a limited treatment duration of one year. Daily practice drug survival studies showed that treatment with CsA for more than one year is safe if strict monitoring protocols are followed. In addition, daily practice drug survival studies showed effectiveness and long-term safety of off-label oral immunosuppressive drugs. In future, the routine use of pharmacogenetics and therapeutic drug monitoring could even further improve the performance of oral immunosuppressive drugs. Therefore, a stronger position of oral immunosuppressive drugs in treatment protocols should be appropriate.

Studies in patients with IBD have shown that despite the availability of biologicals, systemic immunosuppressive drugs are still of interest. A recent study in patients with Crohn's disease showed that remission-induction therapy with TNF inhibitors did not result in a better quality of life than a corticosteroid based therapy, but was associated with higher healthcare costs.[54] In a daily practice population of adalimumab users, 27% discontinued therapy. The concomitant use of immunomodulators was independently associated with a decreased risk of discontinuation.[55]

Similar to IBD, it can be expected that oral immunosuppressive drugs will still be used in AD, also after the introduction of biologicals. A randomized controlled trial will reveal whether a biological or an oral immunosuppressive drug will have the best performance in the treatment of AD.



**Vitamin D and atopic dermatitis**

A major part (70%) of patients described in *chapter 2* had a vitamin D insufficiency/deficiency. Data suggests that the risk for vitamin D insufficiency/deficiency is higher in patients with difficult to control AD. Whether the low vitamin D status is a consequence of lifestyle and dietary changes due to AD (for example less time spent outdoors, a diet because of a food allergy as a result of the atopic syndrome) or whether AD severity is negatively influenced by vitamin D deficiency, being independent from AD, is unclear. Randomized placebo-controlled trials on the effect of vitamin D supplementation are difficult to perform because the time before effectiveness of supplementation can be

expected is unknown. Furthermore, treatment of AD needs to be stabilized in both groups for a long period. In addition, it is ethically not acceptable to withhold supplementation from a vitamin D deficient patient.

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# Chapter 11

Summary/Samenvatting

## SUMMARY

In this thesis the management of difficult to treat atopic dermatitis (AD) is discussed. First, the definition of difficult to treat AD is summarized based on a new AD severity classification. Secondly, the performance of oral immunosuppressive drugs in daily practice is discussed. At last, the general conclusions that we have drawn from this thesis are described.

In the management of AD, stabilization of the disease by prevention of exacerbations is the major treatment goal; long-term treatment is often indicated. The balance between effectiveness and safety is important in the treatment of chronic diseases such as AD. The management of AD includes several treatment steps. The majority of patients with AD can be adequately treated with topical therapy. Sometimes UV-light therapy is indicated, however, this is not a long-term treatment option. Long-term treatment with topical corticosteroids can be limited with respect to safety. Although the additional use of topical immunomodulators can reduce the amount of topical corticosteroids, these drugs lack potency in more severe cases of AD. Systemic immunosuppressive drugs are the second step in the treatment of AD. However, there are no clear criteria on the eligibility of patients for systemic immunosuppressive drugs. In general, systemic immunosuppressive treatment is indicated in patients with severe AD. However, the terms mild, moderate and severe AD cannot be used uniformly because they are dependent on the clinical scoring system that was used. Furthermore, classification of AD severity based on a single measurement of a clinical skin score is meaningless. A single measurement could easily over- or underestimate the severity of AD, as AD has a course of exacerbations and remissions. The definition of AD severity should therefore also include treatment need, and the extent to which the therapy is correctly applied.

For instance, the patients described in *chapter 3* had difficult to control eczema, resulting in high eczema scores over time, despite the use of potent topical corticosteroids. The inpatient treatment and education program and psychosocial support led to stabilization of AD in the majority of patients. During follow-up the AD remained stable using topical corticosteroids in a safe maintenance scheme. The AD of this patient group was difficult to control, but not difficult to treat.

Patients with difficult to treat AD have high disease activity over time, despite daily treatment with high amounts of potent topical corticosteroids including adequate instructions and self-management training. Also patients in which reduction of topical treatment to a safe maintenance scheme lead to high disease activity can be classified as difficult to treat AD. Difficult to treat AD is the most appropriate indication for long-term systemic immunosuppressive treatment.

In *chapter 2* we showed that the risk on a vitamin D insufficiency/deficiency is higher for patients with difficult to treat AD. Whether the low vitamin D status is a consequence of lifestyle and dietary changes due to AD or whether AD severity is negatively influenced by vitamin D deficiency, is unknown.

Real life data from patients with AD, treated with systemic immunosuppressive drugs in daily practice provides important and essential information in addition to existing clinical trial data. In contrast to clinical trial data, data from daily practice reports long-term treatment in large unselected patient groups.

The performance of cyclosporin A (CsA), azathioprine, enteric-coated mycophenolate sodium and methotrexate in daily practice is described in *chapter 4, 7, and 9*. The performance of these drugs was analyzed with the use of drug survival analysis. Drug survival is the length of time a patient continues to take a particular drug. Drug survival analysis is based on the reason for discontinuation of the drug, which is a reflection of the balance between effectiveness and side effects.

CsA has the best performance in the daily practice management of difficult to treat AD based on drug survival analysis. The performance of azathioprine and methotrexate is mainly limited owing to side effects, while the performance of EC-MPS is mainly limited owing to ineffectiveness.

Although CsA is registered for the treatment of AD in most European countries, there is reluctance by many dermatologists to use CsA for longer periods due to fear of side effects, especially concerning renal function.

As there is a lack of data on the long-term safety of CsA with respect to renal function, we measured serum creatinine levels before, during and after treatment with CsA (*chapter 5*). There was a significant, but not clinically relevant, increase of serum creatinine compared to baseline levels after three weeks CsA and stabilization during maintenance phase on group level. Twenty-two (14.7%) patients had more than 30% increase of serum creatinine (cut off point for clinically relevant change) compared to baseline level. These patients were significantly older than patients without 30% increase. During follow-up, all patients showed serum creatinine levels within 30% compared to baseline.

In patients with CsA failure due to side effects or ineffectiveness, there is no alternative drug with a comparable fast onset of action. Like CsA, tacrolimus is a calcineurin inhibitor, but has higher potency *in vitro*. Studies in healthy subjects have demonstrated that tacrolimus provides a more favorable safety profile than CsA, especially on blood pressure and renal function. Extended Release Tacrolimus (ERT, Advagraf®) has the advantage of a more consistent plasma level over time and a reduced peak level compared

to the original formulation of tacrolimus. In addition, the once daily dosing may increase the adherence to therapy.

In *chapter 6* the first experience with ERT in the treatment of patients with severe AD is described. Nine patients that were treated with ERT had to discontinue prior CsA treatment due to side effects and/or insufficient response. Surprisingly, treatment with ERT was successful in seven out of nine patients with very difficult to treat AD. In addition, treatment with ERT resulted in less side effects compared to the prior treatment with CsA.

Safety monitoring including laboratory investigations during the use of oral immunosuppressive drugs is very important. In addition, it is important to ask for concomitant medication during every visit as laboratory disturbances can also be caused by the concomitant medication. In *chapter 8,* three patients are described with liver enzyme disturbances during treatment with azathioprine. These patients concomitantly used a proton pump inhibitor because of gastro-intestinal symptoms. After discontinuation of the proton pump inhibitor, under maintenance of azathioprine in the same dose, liver enzyme values gradually normalized.

The following general conclusions can be drawn from this thesis.

- The severity of AD cannot be based on a single measurement of the clinical skin score. In addition, the terms mild, moderate and severe AD cannot be used uniformly, because they are dependent on the clinical scoring system that was used.
- In patients with difficult to control AD therapy adherence should be optimized.
- Difficult to treat AD is the most appropriate indication for long-term systemic immunosuppressive treatment.
- Vitamin D insufficiency/deficiency is very common in patients with AD. Patients with difficult to treat AD are most at risk for vitamin D insufficiency/deficiency.
- Guidelines concerning the use of oral immunosuppressive drugs in severe AD are based on clinical trials. However, clinical trial data does not reflect a real life situation and for that reason is not always generalizable to daily practice.
- Drug survival analysis is a new tool for the interpretation of data from daily practice and reflects the performance of a systemic immunosuppressive drug and is a composite measure of treatment success.
- CsA has the best performance in the daily practice management of difficult to treat AD based on drug survival analysis. The performance of AZA and MTX is mainly limited owing to side effects, while the performance of EC-MPS is mainly limited owing to ineffectiveness.
- Impaired kidney function, measured as >30% increase of serum creatinine, is observed in 15% of the patients treated with CsA in daily practice. Higher age, but not

longer treatment duration, is associated with an increased risk on impaired kidney function.

- ERT should be considered as second choice treatment in patients with failure of CsA treatment.

## SAMENVATTING

In dit proefschrift wordt het beleid bij moeilijk behandelbaar constitutioneel eczeem (CE) besproken. Als eerste wordt de definitie van moeilijk behandelbaar CE samengevat, gebaseerd op een nieuw classificatie systeem voor de ernst van het CE. Als tweede worden de prestaties uit de dagelijkse praktijk van orale immunosuppressiva besproken. Als laatste worden de algemene conclusies van dit proefschrift weergegeven.

Het hoofddoel van de behandeling van CE is stabilisatie van de ziekte door preventie van exacerbaties; langdurige behandeling is vaak geïndiceerd. De balans tussen effectiviteit en veiligheid is belangrijk in de behandeling van chronische ziekten zoals CE. De behandeling van CE bestaat uit verschillende stappen. De meerderheid van de patiënten met CE kan adequaat worden behandeld met topicale therapie. Soms is UV-lichttherapie geïndiceerd, echter, dit is geen behandeloptie voor de lange termijn. Langdurige behandeling met topicale corticosteroïden kan worden beperkt vanwege de veiligheid. Hoewel de toevoeging van topicale immunomodulatoren het gebruik van topicale corticosteroïden kan terugdringen, heeft deze behandeling onvoldoende potentie in de meer ernstige gevallen van CE. Systemische immunosuppressiva zijn de tweede stap in de behandeling van CE. Echter, duidelijke criteria welke patiënten in aanmerking komen voor systemische immunosuppressiva ontbreken. Over het algemeen zijn systemische immunosuppressiva geïndiceerd voor patiënten met ernstig CE. De termen mild, gemiddeld en ernstig eczeem kunnen echter niet uniform worden gebruikt, omdat deze afhankelijk zijn van het gekozen score systeem. Daarnaast is de classificatie van de ernst van het CE op basis van een éénmalige meting van de klinische eczeem score zinloos. Een éénmalige meting kan de ernst van het CE gemakkelijk onder- of overschatten omdat CE in remissies en exacerbaties verloopt. De definitie voor de ernst van het CE moet daarom ook de therapiebehoefte en de mate waarop de therapie correct wordt toegepast bevatten.

Een voorbeeld hiervan zijn de patiënten die in *hoofdstuk 3* worden beschreven. Deze patiënten hadden moeilijk controleerbaar eczeem, resulterend in hoge eczeem scores gedurende langere tijd, ondanks het gebruik van potente topicale corticosteroïden. Het klinische behandel- en educatie programma en psychosociale ondersteuning leidde tot stabilisatie van het CE in de meerderheid van de patiënten. Tijdens follow-up bleef het CE stabiel bij het gebruik van topicale corticosteroïden in een veilig onderhoudsschema. Het eczeem van deze patiëntengroep was moeilijk controleerbaar, maar niet moeilijk behandelbaar.

Patiënten met moeilijk behandelbaar CE hebben gedurende langere tijd hoge ziekteactiviteit, ondanks het dagelijks gebruik van grote hoeveelheden potente topicale

corticosteroïden inclusief adequate instructies en training in zelfmanagement. Ook patiënten waarbij reductie van de topicale therapie naar een veilig onderhoudsschema leidt tot hoge ziekte activiteit kunnen worden geclassificeerd als moeilijk behandelbaar. Moeilijk behandelbaar CE is de meest strikte indicatie voor langdurige behandeling met systemische immunosuppressiva.

In *hoofdstuk 2* hebben we laten zien dat het risico op een vitamine D insufficiëntie/ deficiëntie groter is voor patiënten met moeilijk behandelbaar CE. Of de lage vitamine D status een consequentie van de leefstijl en dieet veranderingen zijn als gevolg van CE, of dat de ernst van het eczeem negatief wordt beïnvloed door het vitamine D gebrek, is onbekend.

Data uit de dagelijkse praktijk van patiënten met CE behandeld met orale immunosuppressiva geeft belangrijke en essentiële informatie in aanvulling op bestaande data uit klinische trials. In tegenstelling tot klinische trial data, bevat data uit de dagelijkse praktijk informatie over de lange termijn behandeling in grote ongeselecteerde patiëntgroepen.

De prestaties van cyclosporin A (CsA), azathioprine, mycofenolzuur en methotrexaat in de dagelijkse praktijk worden beschreven in *hoofdstuk 4, 7 en 9*. De prestaties van deze middelen werden geëvalueerd met behulp van drug survival analyse. Drug survival is de tijdsduur dat een patiënt een bepaald medicament gebruikt. Drug survival analyse is gebaseerd op de reden van stoppen, dit is een reflectie van de balans tussen effectiviteit en bijwerkingen. Behandeling met CsA leidt tot de beste drug survival in de dagelijkse praktijk bij patiënten met moeilijk behandelbaar CE. De prestaties van azathioprine en methotrexaat worden vooral beperkt door bijwerkingen, terwijl de prestaties van mycofenolzuur met name door ineffectiviteit worden beperkt.

Hoewel CsA is geregistreerd voor de behandeling van eczeem in de meeste Europese landen, zijn veel dermatologen terughoudend in het gebruik van CsA voor langere perioden vanwege de angst op bijwerkingen, vooral met betrekking tot de nierfunctie.

Vanwege een tekort aan gegevens over de lange termijn veiligheid van CsA met betrekking tot de nierfunctie, hebben we serum creatinine waarden gemeten voor, tijdens en na behandeling met CsA (*hoofdstuk 5*). Na drie weken CsA behandeling was er een significante, maar geen klinisch relevante toename van het serum creatinine vergeleken met de waarde voor start van de behandeling. Tijdens de onderhoudsfase stabiliseerde de waardes op groepsniveau. Tweeëntwintig patiënten (14.7%) hadden een serum creatinine stijging van meer dan 30% vergeleken met de start van behandeling (afkappunt voor klinisch relevante verandering). Deze patiënten waren significant ouder dan patiënten zonder 30% toename. Na staken van CsA hadden alle patiënten serum creatinine waarden binnen 30% vergeleken met de waarde voor start van behandeling.

Voor patiënten waarbij behandeling met CsA heeft gefaald vanwege bijwerkingen of ineffectiviteit, is er geen geschikt alternatief medicament met een vergelijkbare snelle werking. Tacrolimus is een calcineurine remmer, net zoals CsA, maar heeft een hogere potentie *in vitro*. Studies bij gezonde personen hebben aangetoond dat tacrolimus een gunstiger veiligheidsprofiel heeft dan CsA, vooral voor de bloeddruk en nierfunctie. Extended release tacrolimus (ERT, Advagraf®) heeft het voordeel van een meer constante plasma spiegel gedurende de tijd en een gereduceerde piek spiegel vergeleken met de originele formulering van tacrolimus. Daarnaast wordt de therapietrouw mogelijk vergroot door de eenmaal daagse dosering. In *hoofdstuk 6* wordt de eerste ervaring met ERT in de behandeling van patiënten met ernstig CE beschreven. De negen patiënten die met ERT werden behandeld moesten eerdere behandeling met CsA stoppen vanwege bijwerkingen en/of ineffectiviteit. Opvallend genoeg was behandeling met ERT succesvol in zeven van de negen patiënten met zeer moeilijk behandelbaar eczeem. Daarnaast resulteerde behandeling met ERT in minder bijwerkingen in vergelijking tot de eerdere behandeling met CsA.

Het monitoren van de veiligheid zoals laboratorium onderzoek tijdens het gebruik van orale immunosuppressiva is erg belangrijk. Daarnaast is het navragen van gelijktijdig medicatie gebruik bij ieder bezoek belangrijk omdat verstoringen in laboratoriumwaarden ook kunnen worden veroorzaakt door gelijktijdige medicatie.

In *hoofdstuk 8* worden drie patiënten met afwijkende leverenzymwaarden tijdens het gebruik van azathioprine beschreven. Deze patiënten gebruikten gelijktijdig ook een protonpompremmer vanwege maagklachten. Na het staken van de protonpompremmer, terwijl de azathioprine met dezelfde dosis werd gecontinueerd, normaliseerden de leverenzym waarden geleidelijk.

Op basis van het onderzoek in dit proefschrift kunnen de volgende algemene conclusies worden getrokken.

- De ernst van CE kan niet worden gebaseerd op een éénmalige meeting van een klinische score. Daarnaast kunnen de termen mild, gemiddeld en ernstig niet uniform worden gebruikt, omdat ze afhankelijk zijn van het klinische score systeem dat wordt gebruikt.
- Bij patiënten met moeilijk controleerbaar eczeem moet de therapietrouw geoptimaliseerd worden.
- Moeilijk behandelbaar CE is de meest strikte indicatie voor langdurige behandeling met systemische immunosuppressiva.
- Vitamine D insufficiëntie/deficiëntie komt veel voor bij CE. Patiënten met moeilijk behandelbaar eczeem hebben het meeste risico op een vitamine D insufficiëntie/deficiëntie.

- Richtlijnen over het gebruik van orale immunosuppressiva bij patiënten met ernstig CE zijn gebaseerd op klinische studies. Klinische studies geven niet altijd een goede indruk van de dagelijkse praktijk en zijn daarom niet volledig generaliseerbaar naar de dagelijkse praktijk.
- Drug survival analyse is een nieuwe manier voor de interpretatie van data uit de dagelijkse praktijk en reflecteert de prestaties van een systemisch immunosuppressivum. Drug survival analyse is een samengestelde maat voor behandelsucces.
- CsA presteert het beste in de dagelijkse praktijk behandeling bij moeilijk behandelbaar CE. De prestaties van azathioprine en methotrexaat worden vooral beperkt door bijwerkingen, terwijl de prestaties van mycofenolzuur met name door ineffectiviteit worden beperkt.
- Een gestoorde nierfunctie, gemeten als >30% stijging van het serum creatinine, wordt bij 15% van de patiënten behandeld met CsA in de dagelijkse praktijk gezien. Hogere leeftijd, maar niet langere behandelduur, is geassocieerd met een toegenomen risico op een gestoorde nierfunctie.
- ERT moet worden overwogen als tweede keuze behandeling bij patiënten waarbij behandeling met CsA heeft gefaald.

# Chapter 12

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# Chapter 13

## Appendices

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## LIST OF PUBLICATIONS

### This thesis

**Van der Schaft J**, Ariëns FM, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Serum vitamin D levels in adult patients with atopic dermatitis: recommendations for daily practice. Under review.

**van der Schaft J**, Keijzer WW, Sanders CJ, de Groot AJ, van Os-Medendorp H, Doorn-Op den Akker MM, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Is there an additional value of inpatient treatment for difficult to control atopic dermatitis? Under review.

**van der Schaft J**, Politiek K, van den Reek JM, Christoffers WA, Kievit W, de Jong EM, Bruijnzeel-Koomen CA, Schuttelaar ML, de Bruin-Weller MS. Drug survival for cyclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. Br J Dermatol 2015; 172(6): 1621-7.

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## Other publications

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## CURRICULUM VITAE

Jorien van der Schaft werd geboren op 15 november 1987 te Utrecht. Na haar Gymnasium diploma behaald te hebben in 2006 aan het Stedelijk Gymnasium te 's-Hertogenbosch, begon zij in datzelfde jaar met de opleiding Geneeskunde aan de Universiteit Utrecht. In het laatste jaar van de opleiding heeft zij onder begeleiding van Koos Sanders een bijzondere semi-artsstage Dermatologie gedaan. Vervolgens heeft zij tijdens haar wetenschappelijke stage onderzoek gedaan naar de behandeling van ernstig eczeem met orale immunosuppressiva onder begeleiding van Marjolein de Bruin-Weller. Na het behalen van haar arts-examen in 2012, is zij aansluitend aangenomen als arts-onderzoeker bij de afdeling Dermatologie/Allergologie, hetgeen heeft geleid tot dit proefschrift. In 2015 is zij begonnen met de opleiding tot dermatoloog in het UMC Utrecht met Vigfús Sigurdsson als opleider.