

# Systemic immunosuppressive treatment in adult patients with atopic dermatitis: current and new treatment options

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## Summary

**Treatment options for severe, difficult to treat atopic dermatitis patients are currently limited. Cyclosporine A is registered for the treatment of atopic dermatitis in many European countries. Alternative off-label treatment options are azathioprine, mycophenolate sodium and methotrexate. Dupilumab® is the first biologic, which is extensively studied in atopic dermatitis. Several other systemic immunosuppressive/immunomodulatory drugs for treatment of moderate to severe atopic dermatitis, including small molecules and other monoclonal antibodies (anti-IL13 and anti-IL31), are currently studied in clinical trials.**

*KEY WORDS: atopic dermatitis; systemic immunosuppressive treatment.*

## Introduction

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 the onset of AD 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 systemic immunosuppressive treatment is required.

Several reviews of oral immunosuppressive drugs that are used in the treatment of AD are published in the past years. These reviews 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. In this RCT, cyclosporine A (CsA) is recommended as first-line treatment, azathioprine (AZA) can be considered as second-line treatment, and methotrexate (MTX) as a third-line treatment option. Other oral immunosuppressive drugs that are regularly used in AD are oral corticosteroids and mycophenolate sodium. Methotrexate is not considered as an oral immunosuppressive drug, but acts as folic acid antagonist.

In the first part of this manuscript current oral immunosuppressive/immunomodulatory treatments for AD are discussed. In the second part, a short overview of new treatment options for AD is provided.

## Current oral immunosuppressive/immunomodulatory drugs in AD (Table 1)

The oral immunosuppressive/immunomodulatory drugs that are used in AD differ with respect to side effect profile, time to response and time to relapse after discontinuation. The choice of drugs depends on several considerations including characteristics of the drug, patient characteristics and treatment indication.

### Cyclosporine A

CsA is the only registered oral immunosuppressive drug for the treatment of AD in many European countries. CsA is usually started at 3-5 mg/kg/day and tapered

Table 1 - Overview of oral immunosuppressive drugs for treatment of severe AD. Adapted from: Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol.* 2016;30:729-747.

	Cyclosporine A	Azathioprine	Methotrexate	Mycophenolic acid
<b>Decrease in clinical score (%)</b>	54-95	26-39	42-52	55-68
<b>Treatment period in trials (weeks)</b>	max 52	max 24	max 24	max 30
<b>Time to respond (weeks)</b>	2	8-12	8-12	8-12
<b>Time to relapse (weeks)</b>	< 2	>12	> 12	> 12
<b>Most important side effects</b>	serum creatinine ↑ blood pressure ↑	hematological liver enzymes ↑ gastro-intestinal	hematological liver enzymes ↑ gastro-intestinal	hematological skin infections gastro-intestinal
<b>Starting dose</b>	5 mg/kg/day	50 mg/day	5 mg/week	MMF 1000-2000 mg/day (EC-MPS 1440 mg/day)
<b>Maintenance dose</b>	2.5-3 mg/kg/day	2-3 mg/kg/day*	increase to max 25 mg/week	MMF 2000 mg/day** (EC-MPS 1440 mg/day)
<b>Pregnancy</b>	possible	conflicting data, possible with strict indication	teratogenic, absolutely contra- indicated	conflicting data, better not to use
<b>Fathering</b>	possible	little information, possible with strict indication	little information, conflicting data, contra-indicated	little information, better not to use

\* TPMT heterozygote 1-1.5 mg/kg/day

MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolic sodium.

after 3 to 6 weeks to a maintenance dose of 2.5-3 mg/kg/day. Increased blood pressure and kidney failure are side effects, therefore monitoring of blood pressure and renal function is indicated during the entire treatment duration.

In a meta-analysis by Schmitt et al. randomized controlled trials and uncontrolled studies of CsA treatment in patients with AD were included (9). Fifteen studies including 602 patients were analysed of which 12 studies appeared homogeneous enough to be pooled. A dose related response with a pooled mean decrease in disease severity of 22% (95% confidence interval 8-36%) under low dose CsA ( $\leq 3$  mg/kg) and 40% (95% confidence interval 29-51%) at dosages  $\geq 4$  mg/kg was reported. After 6-8 weeks of CsA treatment the relative effectiveness was 55% (95% confidence interval 48-62%). The use of CsA was limited due to the development of side effects; a significant increase of serum creatinine levels was reported in 11%, hypertension in 6%, and gastrointestinal symptoms in 40% of patient months of active treatment with CsA.

In a retrospectively study by Hijnen et al., 73 patients with AD refractory to conventional therapy treated with CsA in daily practice were analyzed. CsA treatment was successful in 76.7% of the patients. Non-responsiveness of CsA treatment in patients with severe AD was reported in 6.8% and a moderate response in 16.4%. An increase in serum creatinine of more than 30% com-

pared to baseline and hypertension was found in 9.6 and 15.1% of the patients, respectively. A relapse of AD after discontinuation of CsA treatment was observed in 54.8% and a rebound with clinical symptoms more severe than at baseline was reported in 8.2% of the patients (10).

In a drug survival study of CsA treatment in 356 AD patients we recently showed that treatment results in daily practice were less positive in comparison to clinical trials with respect to discontinuation rates due to ineffectiveness (23%) and side effects (28%) (11).

In another daily practice study we analyzed serum creatinine levels during and after treatment with CsA in 150 AD patients. Serum creatinine levels were statistically significant, but not clinically relevant, increased compared to baseline level after 3 weeks of CsA treatment and stabilized during the 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 a 30% increase of serum creatinine. All patients showed serum creatinine levels within 30% compared to baseline during follow-up (12).

#### Azathioprine

The purine antagonist, AZA has a slow onset of action. The maximal clinical efficacy is reached after 8 to 12

weeks of treatment. Reduced enzymatic activity of thiopurine S-methyltransferase (TPMT) is associated with increased 6-thioguanine nucleotide (6-TGN) levels which may cause myelotoxicity. However, TPMT levels do not predict all cases of myelotoxicity, therefore, ongoing hematological monitoring is crucial. Studies indicate that between 50 and 75% of thiopurine-related leucopenia occurs in patients with normal TPMT levels (13, 14). It is recommended to start AZA with a starting 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. As clinical effectiveness of AZA is reached after 8-12 weeks; in daily practice oral corticosteroids are frequently used in a tapering dose to bridge this period. Azathioprine was compared to placebo in two RCTs (15, 16). These RCTs included 37 and 41 patients, respectively, and reported a reduction of AD severity of 26 and 37% after 12 weeks of treatment with AZA. Side effects led to early discontinuation of AZA in 10.8% and 14.6% of the patients. The main side effects were gastrointestinal disturbances, nausea, vomiting and deranged liver enzymes.

A recent daily practice study of Thomsen et al. included 60 patients and reported a less favorable outcome of AZA treatment in comparison with clinical trials (17). Nearly half of the patients discontinued AZA treatment within one year because of insufficient clinical response or side effects. We found comparable results in the drug survival study on daily practice treatment of 94 patients with AD treated with AZA (18). Side effects were a reason for discontinuation of AZA in 38% of the patients and 21% of the patients discontinued due to ineffectiveness.

#### **Methotrexate**

The folic acid antagonist MTX reaches maximal clinical efficacy after 8 to 12 weeks. The recommended dose of MTX varies between 7.5 and 22.5 mg/week. As clinical effectiveness of MTX is reached after 8-12 weeks, oral corticosteroids are frequently used in a tapering dose in daily practice to bridge the period to clinical effectiveness.

One prospective study (n = 12) and one retrospective study (n = 20) showed clinical efficacy and safety of MTX treatment in patients with severe AD (19, 20). The main side effects were nausea and an increase of liver enzymes. In the study of Lyakhovitsky et al. transient discontinuation due to side effects was indicated in 15% of the patients (19).

A RCT of Schram et al. compared AZA (n = 22) and MTX (n = 20) during a 12-week period. Patients were treated with MTX varying between 10-22.5 mg/week or AZA 1.5-2.5 mg/kg/day (21). The clinical skin severity score was comparable in both groups after 12 weeks of treatment (patients treated with MTX showed a reduction of 42% in severity, compared with 39% reduction in the AZA group). There was no significant difference in the number and severity of side effects (side effects led to early discontinuation in 5% of the patients treated with MTX versus 9% in the AZA group), and the use of rescue medication was comparable in both groups.

A drug survival study on MTX treatment in daily practice

in 89 patients with AD reported that half of the patients benefits from this treatment. After one year of MTX treatment discontinuation due to subjective side effects was uncommon. However, at the moment of data analysis the median duration of treatment was only 223 days (22).

#### **Mycophenolate acid**

The inosine monophosphate-dehydrogenase inhibitors mycophenolate mofetil and enteric-coated mycophenolate sodium (EC-MPS) have a slow onset of action with a maximal clinical efficacy that is reached after 8-12 weeks. Therefore, in daily practice oral corticosteroids are frequently used to bridge this period. The recommended dosages for mycophenolate sodium is 2 g/day and for EC-MPS 1440 mg/day.

Mycophenolate mofetil and EC-MPS 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 (23-29). Van Velsen et al. (29) described the results of EC-MPS 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 a 6-month treatment period. None of the patients discontinued EC-MPS use and only mild side effects were reported.

Haecck et al. (30) performed a comparative study between CsA and EC-MPS. Adult patients with severe AD received CsA (5 mg/kg/day) during a 6-week period and were consecutively randomized to compare EC-MPS (1440 mg/day) (n = 26) and CsA (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 EC-MPS study group in which more rescue medication was used. After 10 weeks of maintenance treatment AD severity was comparable in both groups until the end of the maintenance phase. However, the side effect profile of EC-MPS was favorable and after stopping EC-MPS the relapse-free period was longer compared with CsA. In a recent drug survival study including 84 patients with AD treated with EC-MPS in daily practice showed less favorable results compared to previous clinical trials (18). Side effects were a reason for discontinuation of EC-MPS in 18% of the patients and 42% of the patients discontinued due to ineffectiveness.

Thijs et al. recently showed that there is a large inter-individual variability in mycophenolate acid blood levels. The presence of UGT1A9 polymorphisms correlates with low MPA exposure and increased enzyme activity. In this retrospective study a significant higher number of UGT1A9 polymorphisms was found in the group that did not respond to treatment with mycophenolate acid. These patients might benefit from a higher mycophenolate acid dose (31).

#### **Systemic corticosteroids**

Clinical effectiveness of treatment with systemic corticosteroids is reached fast. However, systemic corticosteroids are not advised for long-term treatment in most guidelines because of the severe side effects. In addi-

tion, short courses of systemic corticosteroids may lead to a rebound phenomenon in AD patients. Systemic corticosteroids in a tapering dose can be considered in patients starting another systemic treatment (bridging treatment).

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

### **Practical aspects concerning oral immunosuppressive drug use in AD**

Before oral immunosuppressive 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, MTX and preferably not with AZA in case of a wish for pregnancy and should take appropriate contraceptive measures for at least 3 months after discontinuation. The use of CsA and prednisone should be restricted during pregnancy for women. CsA and prednisone do not influence male fertility outcome (32). 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 in consultation with their oncologist.

Lack of experience of the dermatologist 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.

### **Treatment indication**

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. This will be clarified with two examples from our daily practice (Figure 1). In Figure 1a the patient suffers from severe, difficult to treat AD (IGA 4-5 on a 6 point scale), despite adequate daily treatment with potent topical corticosteroids (>100 grams/week) for several weeks. 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 temporarily needed. 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. 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 1b, the eczema is more or less adequately controlled using daily treatment with topical corticosteroids, resulting in an IGA of <3. However, in this patient tapering topical corticosteroids to an intermittent use results in an exacerbation of AD. Since long-term daily treatment with high amounts of topical corticosteroids (>100 grams/week) should be avoided to prevent side effects, oral immunosuppressive drugs are used to enable tapering of topical corticosteroids. 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.

### **New systemic immunosuppressive/immunomodulating treatment options in AD**

#### ***Aprelimast***

Aprelimast is an oral phosphodiesterase 4 (PDE4) inhibitor, which is registered for the treatment of psoriasis in Europe.

An open-label pilot study on aprelimast treatment of 16 patients with AD showed significant reduction of the eczema severity score after 3 and 6 months (33).

#### ***Janus kinase inhibitors***

The role of the janus kinase (JAK) signal transducer and activator of transcription pathway in Th2 immunity, activating eosinophils, and suppressing regulatory T cells is reported in several studies (34). Tofacitinib citrate is an oral JAK 1/3 inhibitor approved for the treatment of moderate to severe rheumatoid arthritis.

A small pilot study in 6 patients with moderate to severe AD treated with tofacitinib showed a significant decrease of the eczema severity score during 8 to 29 weeks of treatment. No adverse events were reported (35). The effect of baricitinib, a JAK 1/2 inhibitor is evaluated in an ongoing randomized, double-blind, placebo-controlled phase 2 trial (36).

### **Antibody-based treatments in AD: early studies (Table 2)**

Several monoclonal antibodies, licensed for other indications, have been studied in patients with AD. Most of these studies were relatively small, proof of principle studies.

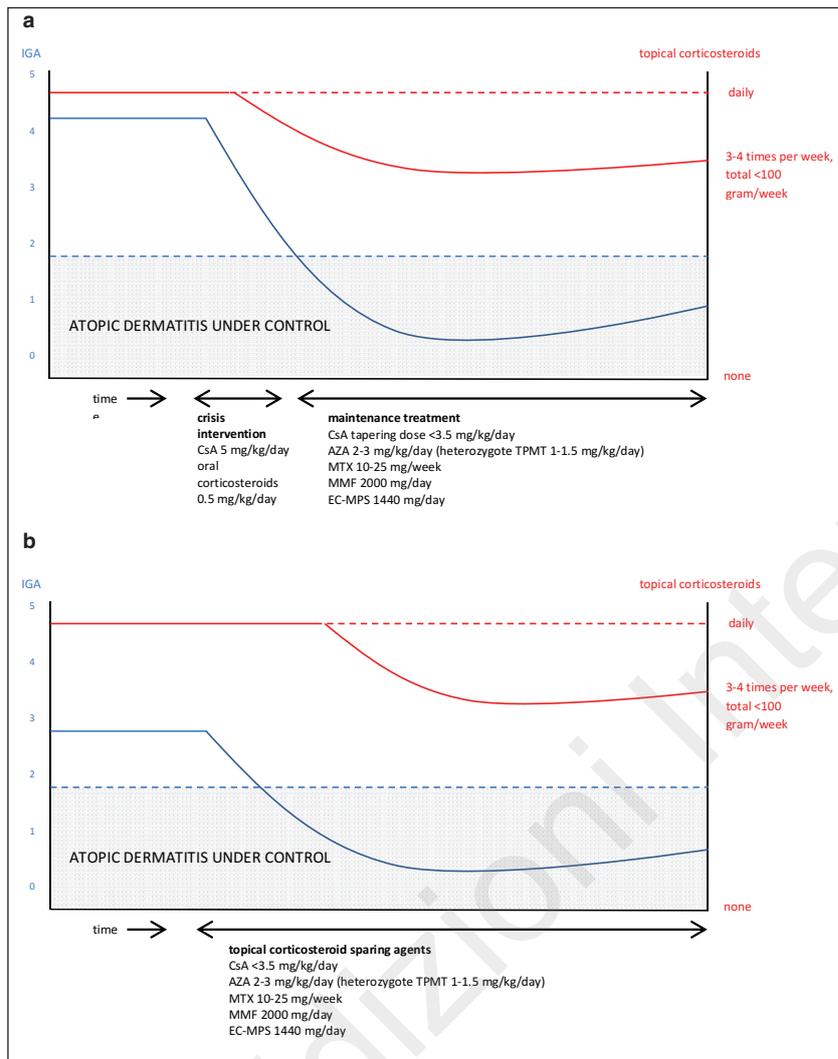


Figure 1a, b - Two different situations in which systemic immunosuppressive drugs can be added to treatment with topical corticosteroids. a) (Exacerbation protocol): the patient suffers from very severe AD (IGA 4-5). Blue line: course of IGA score. Red line: frequency of topical corticosteroid use. b) (Steroid sparing protocol): AD is relatively under control by using daily application of topical corticosteroids, resulting in an IGA of 3 or lower. However, tapering topical corticosteroids to intermittent use results in an exacerbation of AD. Blue line: course of IGA score. Red line: frequency of topical corticosteroid use.

### Ustekinumab

Ustekinumab is a monoclonal antibody that binds to the P40 subunit of IL-12 and IL-23, this suppresses Th1, Th17 and Th22 activation. Case reports reported varied responses (37, 38). In a recently published phase 2, double-blind, placebo-controlled study, 33 patients with moderate-to-severe AD were randomized to either ustekinumab (n=16) or placebo (n=17), with subsequent crossover at 16 weeks and last dose at 32 weeks. Dosing was 45 and 90 mg per injection

for patients weighting ≤ 100 or > 100 kg, respectively. The ustekinumab group achieved better clinical scores, but the difference between groups was not significant (39). A small study showed a significant decrease in degree of epidermal hyperplasia/proliferation and the number of infiltrating dermal T cells, dendritic cells and mast cells after treatment. Quantitative real-time polymerase chain reaction of lesional skin showed a reduction of T-helper 2-/22-associated molecules after therapy. Therefore it is

Table 2 - Antibody-based treatments in AD (February 2017).

Early studies	Phase 2 studies	Phase 3 studies
anti-IL-12/23 (ustekinumab®)	anti-IL-13 (lebrikuzimab®)	anti-IL4-receptor antagonist (Dupilumab®)
anti-IL-5 (mepolizumab®)	anti-IL-13 (tralokinumab®)	
anti-CD20 (rituximab®)	anti-IL-31 (nemolizumab®)	
anti-IgE (omalizumab®)		

conceivable that at least a subgroup of patients with predominant severely infiltrated disease characteristics might benefit from ustekinumab (40).

#### **Mepolizumab**

Mepolizumab is a monoclonal antibody directed against IL-5, which is essential for eosinophil growth, differentiation and migration. In a randomized double-blind, placebo-controlled study 18 patients received mepolizumab and 22 patients placebo. Two single doses of mepolizumab of 750 mg each given 1 week apart did not lead to clinical difference after 14 days, despite a significant decrease in peripheral blood eosinophils (41).

#### **Rituximab**

Rituximab is a monoclonal anti-CD20 antibody that eliminates B cells. As also B cells play a role in AD pathogenesis a pilot study including 6 patients with severe AD was performed. These patients were treated with 2 intravenous applications of rituximab of 1000 mg each, 2 weeks apart. All 6 patients showed an improvement of AD within 4 to 8 weeks. One patient developed a flare in week 12. At 16 and 24 weeks all patients had low eczema severity scores (42). In another study in which 2 patients with severe AD were treated with rituximab 500 mg each, 2 weeks apart, only temporary improvement of AD was found. Furthermore, partial improvement only lasted until the tenth week after start (43).

#### **Omalizumab**

Omalizumab is a monoclonal anti-IgE antibody approved for the treatment of asthma and chronic spontaneous urticaria. Studies reported both improvement as failure of treatment with respect to efficacy in patients with AD. A systematic review and meta-analysis of 2 RCTs and 13 case series with 3 or more cases reported that less than half of the patients with AD had achieved marked clinical improvement after receiving omalizumab. The majority of patients was treated with 600 mg or more omalizumab per month. Patients with lower serum concentrations of IgE might have a therapeutic benefit as IgE serum concentrations of lower than 700 IU/mL were significantly associated with an excellent clinical response compared to patients with IgE concentrations of 700 to 5000 IU/mL (44).

### **New antibody-based treatments for AD (Table 2)**

#### **Anti-IL4-receptor antagonist (Dupilumab®)**

Dupilumab®, a fully human monoclonal antibody directed against interleukin (IL)-4 receptor- $\alpha$ , inhibits activity of two key Th2 cytokines, IL-4 and IL-13, reducing expression of type 2 inflammatory markers and skin barrier dysfunction markers in AD (45, 46). Dupilumab® was evaluated in two randomized, double-blind, placebo-controlled phase 3 trials including 671 and 708 patients, respectively (SOLO 1 and SOLO 2). Dupilumab® monotherapy for 16 weeks, in adults with moderate-to-severe AD and inadequate response to topical medications significantly improved clinical signs and symptoms

of AD, including pruritus and impact on sleep, symptoms of anxiety or depression, and quality of life, compared to placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 on the Investigator's Global Assessment (IGA) (clear, almost clear) and a reduction of 2 points or more in that score from baseline at week 16. In 36-38% of the patients who received dupilumab® 300 mg monotherapy every other week and in 36-37% who received dupilumab® 300 mg monotherapy weekly compared with 8-10% who received placebo the primary outcome was reached ( $p < 0.001$  for both) (47).

The least-squares mean percent change in the Eczema Area and Severity Index (EASI) score from baseline to week 16 varied from 67.1% to 72.3% in the dupilumab® groups compared to 30.9% to 37.6% in the placebo groups. The primary end-point EASI 75 (an improvement from baseline to week 16 of at least 75% in the EASI score) was reached in 44-52% in the dupilumab® groups compared to 12-15% in the placebo groups. Injection site reactions and conjunctivitis were more frequently reported in the dupilumab® groups than in the placebo groups (47).

At short notice, the results of a long-term phase 3 study assessing the safety and efficacy of 52 weeks of continuous treatment with 2 dose regimens of dupilumab® with daily concomitant low-/medium-potency topical corticosteroids versus placebo in 740 adults with moderate-to-severe AD will be published.

Approval of dupilumab® for AD treatment is expected in 2017 in the United States and in 2018 in Europe.

#### **Anti-IL-13**

Phase 2 studies with monoclonal antibodies directed against IL-13 (lebrikizumab® and tralokinumab®) have been performed recently (clinicaltrials.gov).

#### **Anti-IL-31**

The humanized antihuman IL-31 receptor A (IL-31RA) monoclonal antibody binds to IL-31RA to inhibit subsequent IL-31 signaling. IL-31 is associated with itch in patients with AD. Anti-IL-31RA was assessed in a randomized, double-blind, placebo-controlled phase 1/1b study. After a single dose of anti-IL-31RA the pruritus visual analogue scale score was reduced by 50% ( $n = 27$  patients) at week 4 compared to 20% in the placebo group ( $n = 9$ ) (48).

### **Conclusion**

Treatment options for severe, difficult to treat AD patients are currently limited. Although CsA is registered for the treatment of AD in many European countries, solid data on long-term effectiveness and safety is lacking. Alternative treatment options such as off-label use of AZA, mycophenolate sodium and MTX have many disadvantages, such as the long time to response (8-12 weeks), and up to 50% treatment failure in daily practice.

Dupilumab® is the first biologic, which is extensively studied in AD. In a large phase 3 study program includ-

ing short-term and long-term treatment, several hundreds of patients were included. Most of these patients also participate the open label extension study, which will provide important additional long-term efficacy and safety data of this new interesting treatment option in AD.

Several other systemic immunosuppressive/immunomodulatory drugs for treatment of moderate to severe AD, including small molecules and other monoclonal antibodies (anti-IL13 and anti-IL31), are currently studied in clinical trials.

We are facing an exciting era concerning the management of moderate to severe, difficult to treat AD patients.

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