Update “Systemic treatment of atopic dermatitis” of the S2k guideline on atopic dermatitis

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Guideline

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Summary

This guideline is an update from August 2020 the S2k-guideline "Atopic dermatitis" published in 2015. The reason for updating this chapter of the guideline were the current developments in the field of systemic therapy of atopic dermatitis. The agreed recommendations for systemic treatment in atopic dermatitis of the present guideline are based on current scientific data. Due to the approval of dupilumab for the treatment of moderate to severe atopic dermatitis, which cannot be treated sufficiently with topical drugs alone, this part of the guideline has now been adapted and newly consented. The indication for systemic therapy and the therapeutic response to topical and systemic treatment should be recorded and documented in a suitable form in clinic and practice. A standardized documentation of the indication for system therapy in atopic dermatitis can be recommended and is also part of the updated chapter of this guideline.

Systemic treatments

This article describes the currently available scientific data and consensus recommendations (Table 1) on systemic treatment of atopic dermatitis (AD). Due to the fact that a new compound (dupilumab) was approved for treating moderate to severe AD, which cannot be treated sufficiently with topical medication alone, this part of the guideline [1] has now been updated (Figure 1). The structured procedure for wording and consensus of recommendations described in the original version of the guideline was again utilized for the updates. The consensus conference for the current amendment on systemic treatment took place on February 13, 2019 with a neutral moderator (Dr. med. R. N. Werner, AWMF guideline consultant) according to the nominal group procedure. The composition of the guideline group as well as the aims and target group of this guideline have also been described in the original version published in 2015 [2]. A disclosure of potential conflicts of interest, their evaluation and how to deal with conflicts of interest in the preparation of recommendations can be found, together with a description of methods, in the online version of this article at www.awmf.org, the webpage of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft medizinisch-wissenschaftlicher Fachgesellschaften). A complete update of the guideline is planned for 2021.

Any indication for systemic treatment, as well as the patient's response to topical and systemic treatment should be documented in both practice and hospital settings. A standardized documentation form of indications for systemic treatment in AD patients (Table 2) can be recommended.

Objective signs can be documented using scores for clinical severity, e.g. oSCORAD (objective-SCORing Atopic Dermatitis) or EASI (Eczema Area and Severity Index). POEM (Patient Oriented Eczema Measure) is an example of scores for subjective symptoms. The barrier function of the skin can be assessed by using a skin function analyzer for detecting transepidermal water loss (TEWL) and stratum corneum (SC) hydration. Quality of life can be measured via the DLQI (Dermatology Life Quality Index). PO-SCORAD (Patient Oriented SCORAD) can be used for documenting severity over time in a practice setting.

Table 1 Wording of the recommendations according to the original version of the guideline [2].

Positive
Is recommended*
Can be recommended
May be considered
Negative
Is not recommended

*Alternatively and in special cases, the term "must" is used for stipulations and measures considered unequivocal and mandatory. This was the consensus among all contributors.

3.10–3.12 Anti-inflammatory systemic medications approved for treating atopic dermatitis

Recommendation	Consensus
Appropriate documentation of the indication for systemic treatment of AD is recommended (for example, in a standardized manner as shown in Table 2).	Strong consensus

3.10 Oral glucocorticosteroids

Controlled clinical trials on efficacy

There are no controlled trials on the short-term or long-term (longer than one week) use of systemic glucocorticosteroids

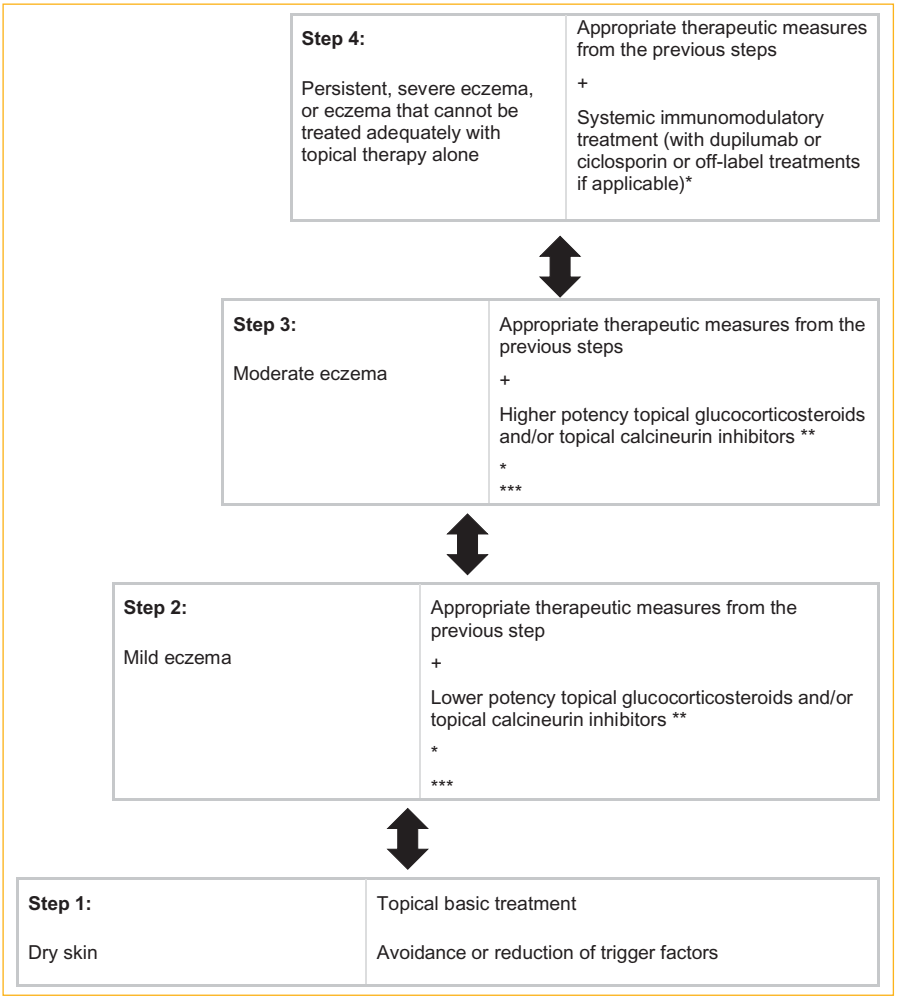

Figure 1 Four-step therapeutic regimen for atopic dermatitis. Depending on the severity of AD and/or diagnostic queries (such as provocation testing with allergens), outpatient, day-care or full-time inpatient treatment is recommended. *UV-therapy is often indicated from level 2 onwards, taking into account the age restriction (not in childhood). Caution: no combination with ciclosporin A and topical calcineurin inhibitors. **First-line therapy: Usually topical glucocorticosteroids, in case of intolerance/non-effectiveness and at special localizations (such as face, intertriginous skin areas, genital area, scalp in infants) topical calcineurin inhibitors. ***The additional use of antipruriginous and antiseptic agents may be considered.
Note: For reasons of clarity, Figure 1 does not include all the procedures discussed in this guideline.

(continuous or intermittent) compared to placebo or other systemic immunosuppressants for severe AD.

Based on non-controlled observations (experience) and on the basic fact that systemic glucocorticosteroids are potent anti-inflammatories, it can be assumed that they are effective.

However, there is a high risk of relapse of AD after discontinuation of this treatment.

Summarized assessment

Short-term treatment with oral glucocorticosteroids shows a substantial therapeutic effect.

Treatment recommendation	Consensus
Short-term treatment with oral glucocorticosteroids (over a period of a few weeks, dosed at ≤ 0.5 mg/kg body weight [BW] prednisolone equivalent) to interrupt an acute flare-up of AD, may be considered especially for adult patients but in exceptional cases also for children and adolescents in severe cases of AD and combined with a concept for subsequent treatment modalities after discontinuation.	Strong consensus
Because of adverse effects, long-term treatment of AD with systemic glucocorticosteroids is not recommended.	Strong consensus

Table 2 Checklist for the indication of systemic anti-inflammatory treatment of AD in adults as previously published [3].

According to the current AWMF guideline on atopic dermatitis, systemic treatment is indicated for moderate and/or severe atopic dermatitis that cannot be adequately treated with topical treatment alone. The following criteria must be assessed when initiating or continuing systemic treatment:

1.	**General conditions for systemic treatment**		**yes**	**no**
1	**Age**	≥ 18 years	**O**	
2	**Diagnosis**	Clinically proven atopic dermatitis	o	
2.	**Clinical eligibility criteria for systemic treatment**		**yes**	**no**
A	**Relevant objective severity**	Is present, since at least one of the following criteria is fulfilled:	**O**	
		• Physician's global assessment (PGA) of severity is at least 3 on the five-point scale, or	o	o
		• EASI >15 or	o	o
		• SCORAD >40/ oSCORAD >20 or	o	o
		• Treatment-refractory affection of >10 % of body surface area (BSA) or	o	o
		• Treatment-refractory eczema in sensitive/visible areas or	o	o
		• High frequency of relapses (>10/year) with current treatment or	o	o
B	**Relevant subjective burden**	Is present, since at least one of the following criteria is fulfilled:	**O**	
		• DLQI >10 or	o	o
		• Pruritus >6 (on VAS or NRS ranging from 0–10) or	o	o
		◦ Relevant sleep disturbance at night due to eczema/pruritus	o	o
C	**Lack of treatment response**	All other approaches except systemic treatment are insufficient, since at least one of the following criteria is fulfilled:	**O**	
		• No satisfactory response to topical or phototherapy or	o	o
		• No expectation of success with topical measures alone or	o	o
		Patient has already received one indicated systemic treatment unsuccessfully • Contra-indication/no response/loss of efficacy/adverse events	o	o
3.	**Conclusion**			
D	➔ **Systemic treatment is indicated since at least one criterion from each of the sections A, B, and C is fulfilled:**		**O yes**	
E	➔ The following approved systemic drugs are not indicated due to previous adverse events, contra-indications, or expected lack of efficacy: _____			
F	➔ Treatment to be initiated with: _____			
G	Patient's informed consent has been obtained: _____		**O yes**	
	Date, signature (if required)			

3.11 Dupilumab

Dupilumab is a monoclonal antibody approved for treating moderate to severe AD that does not respond sufficiently to topical treatments alone. For use in adults, it was approved in Germany in September 2017 and in Switzerland in April 2019, and for use in adolescents from the age of 12, in August 2019 [4, 5]. It targets the alpha chain of the IL-4 type I receptor and IL4/IL13 type II receptor and thus blocks the action of two key enzymes of atopic inflammation.

Clinical trials on efficacy

The efficacy and tolerability of dupilumab have been proven in several clinical trials. In a Phase IIb dose-finding study, 379 adult patients with AD and an EASI score > 16 were treated over a period of 16 weeks with different dosages resp. dosing intervals, starting at 100 mg every four weeks and increasing up to 300 mg/week [6]. In all four treatment groups, a significant improvement in the severity of AD (EASI) was observed as compared with placebo ($P < 0.0001$). Both in the treatment group and in the placebo group, the most common adverse event was nasopharyngitis (28 % resp. 26 %). In a separate publication, quality of life parameters and pruritus scores from the same cohort were determined and compared [7]. Treatment with dupilumab led to a significant reduction of pruritus and sleep disturbance, while DLQI and other quality of life parametes increased. The results of two parallel Phase III trials [8] showed a response to dupilumab according to the pre-defined endpoint (almost complete or complete healing) in 36 % to 38 % of patients in both studies. A 75 % reduction of the EASI skin score was seen in significantly more patients in the treatment groups than in the placebo groups ($P < 0.001$): In patients treated with dupilumab every other week, the mean reduction of EASI was 72.3 ± 2.6 % after 16 weeks, compared to 72.0 ± 2.6 % in the group with weekly dupilumab administration. In the placebo groups, the EASI mean reduction values were 37.6 ± 3.3 % (SOLO-1 trial) resp. 67.1 ± 2.5 %, 69.1 ± 2.5 %, and 30.9 ± 3.0 % (SOLO-2 trial). Other clinical endpoints such as reduction of pruritus, symptoms of depression or quality of life were also improved in significantly more cases with dupilumab treatment: Reduction of pruritus by ≥ 4 points (Numeric Rating Scale; NRS 0–10) was observed in 36–41 % of patients treated with dupilumab but only in 10 % (SOLO 1) resp. 12 % (SOLO 2) of placebo patients. The mean quality of life improvement measured using the DLQI (0–30 points) was between -9.0 ± 0.4 and -9.5 ± 0.4 points in dupilumab patients compared to -5.3 ± 0.5 (SOLO 1) and -3.6 ± 0.5 points (SOLO 2) in placebo patients.

Injection site reactions (8–19 % in the dupilumab group) and conjunctivitis (3–5 % infectious and non-specific conjunctivitis in the dupilumab group) were the most frequent adverse effects compared to the placebo group (injection site reactions 6 %; rate of infectious and non-specific conjunctivitis ≤ 1 %).

In another trial (LIBERTY AD CHRONOS) the antibody was used in patients with moderate to severe AD over a period of one year, with placebo control [9]. Patients (n = 740) were randomized in three groups as described for the SOLO trials. In addition to systemic treatment, this study allowed the combined use of topical glucocorticosteroids and topical calcineurin inhibitors, as needed. The primary clinical endpoints were again (almost) complete healing of the skin lesions, or a 75 % reduction of the EASI score after 16 weeks. In addition, patients were compared and safety aspects assessed again after 52 weeks. The primary endpoint of (almost) complete healing of lesions was achieved by 39 % of patients in the treatment groups and 12 % in the placebo group. A 75 % EASI reduction was seen in 64 % resp. 69 % of the two treatment groups and in 23 % of the placebo group after 16 weeks of treatment; these levels remained unchanged after one year. No abnormal laboratory parameters were observed at any time; injection site reactions (15 % and 19 % in the dupilumab groups and 8 % in the placebo group [9]) as well as conjunctivitis (14 % and 19 % in the dupilumab groups and 8 % in the placebo group [9]) were the most frequent adverse events. In another, monocentric trial, a subgroup of patients treated weekly with dupilumab was analyzed as to their quality of life [10]. The tool *Quality of Life Index of Atopic Dermatitis* (QoLIAD) has been developed especially for measuring quality of life in AD patients and was utilized in this study. Over twelve weeks, the effects of dupilumab were clearly positive (QoLIAD reduction –64.0 ± 6.91 with dupilumab versus –11.1 ± 9.31 with placebo). This correlated with an improved state of the skin and decreased pruritus.

In 2018, a controlled trial was published about a cohort of patients with moderate to severe AD who no longer responded to ciclosporin or in whom this compound was contraindicated [11]. Even in this selected subgroup of AD patients, dupilumab was as effective as in the other Phase III trials.

In the dupilumab trial program, two adverse effects were observed more frequently with dupilumab than with placebo: Injection site reactions, and development or aggravation of non-infectious conjunctivitis. However, the real frequency of this atypical conjunctivitis is assumed to be higher than in some of the studies. Depending on the study protocol, up to 28 % of patients showed atypical conjunctivitis – which in some of the patients was so severe that it necessitated discontinuation of treatment. The pathomechanism of this rosacea-like, non-infectious conjunctivitis is not well understood. According to available studies, this is not the typical

manifestation of atopic/allergic conjunctivitis. Interestingly, this adverse reaction has hitherto not been observed in trials on bronchial asthma, where dupilumab is also very effective. Management of this adverse event consists of moisturizing the eye (artificial tears, lid edge hygiene) [12] and, after exclusion of possible infectious causes in consultation with an ophthalmologist, short-term use of topical glucocorticosteroids (for instance, eye drops with fluorometholone, or if necessary a switch to eye drops with ciclosporin resp. ciclosporin emulsion 1 mg/ml, once a day) [13]. Eye drops with 0.1 % fluorometholone are approved for the indication "allergic inflammation", and in contrast to other glucocorticosteroids they show only low penetration into the aequous humor [14]. Ophthalmic preparations with tacrolimus have been successfully used internationally [15] and are commercially available in Japan, but they are currently not available for use on the eyes in Germany, either as commercial preparations or as quality assured extemporaneous preparations.

In addition to the adverse events described above, oral herpes simplex infection is listed in the Summary of Product Characteristics (SmPC) as a frequent side effect. The study data, however, do not indicate any increased risk of eczema herpeticatum with dupilumab treatment. The pivotal trials with dupilumab actually show a marked decrease in incidence of severe skin infections [16].

With respect to the inhibition of IL-4/IL-13 pathways, the SmPC states that pre-existing helminthic infections need to be treated before initiating dupilumab treatment [17]. With regard to the laboratory values, the SmPC lists transient eosinophilia after initiation of treatment (in < 2 % of patients on dupilumab vs. < 0.5 % in patients on placebo).

In August 2019, dupilumab was approved for adolescents aged 12 years or more with moderate to severe AD in whom systemic treatment is indicated. The design of the Phase III study on dupilumab in adolescents with moderate to severe AD also contained the use of topical glucocorticoids as 'rescue' therapy [18]. In this trial (LIBERTY AD ADOL), patients received either dupilumab every two weeks with a dosage according to body weight (n = 82, 200 mg dupilumab per administration with a body weight of < 60 kg or 300 mg with a body weight of ≥ 60 kg), or 300 mg dupilumab every four weeks (n = 84), or placebo (n = 85) over a period of 16 weeks. The patients were subsequently observed in an open follow-up phase. After 16 weeks of treatment with dupilumab (200 resp. 300 mg) every two weeks, a quarter (24.4 %) of participants showed no or minimal clinical signs of AD (Investigator's Global Assessment [IGA] 0 or 1). The co-primary endpoint of the trial (EASI-75) was achieved by 41.5 % of the patients treated with dupilumab every two weeks, as compared with 8.2 % of those treated with placebo. The patients treated with dupilumab also reported a significant reduction of pruritus. With dupilumab, 48.8 % of patients achieved a clinically relevant reduction of pruritus by ≥ 3 points on the *Peak Pruritus Numerical Rating Scale* (NRS), while this was achieved by only 9.4 % of patients on placebo. This improvement was also reflected in a better quality of life. 61 % of the dupilumab patients and 20 % of the placebo patients reported a clinically relevant improvement of their quality of life by at least six points on the *Children's Dermatology Life Quality Index* (CDLQI). Both the efficacy and the safety profile of dupilumab was comparable with the results in adult AD patients; the most frequent adverse events were injection site reactions, conjunctivitis, and herpes virus infections [19].

Live vaccines and attenuated live vaccines must not be administered simultaneously with dupilumab, wheras inactivated vaccines are permitted [4, 5]. The potential influence of dupilumab on vaccine responses was studied in another placebo-controlled trial with 178 patients receiving dupilumab. Immune responses to tetanus toxoid and meningococcal polysaccharides were compared [20]. More than 80 % of all patients in both study groups developed adequate serological immune responses.

Summarized assessment

Dupilumab, a biological, has been approved as first-line treatment for moderate to severe AD in adults and adolescents from 12 years of age in the EU and Germany since September 2017, and in Switzerland since April 2019. The approved dosage (for subcutaneous injection) is 600 mg as an initial dose for adults and adolescents aged 12–17 with a body weight of ≥ 60 kg, and 400 mg for adolescents aged 12–17 with a body weight of < 60 kg. This is followed by 300 mg (resp. 200 mg for adolescents aged 12–17 with a body weight of < 60 kg) every other week as a maintenance dose. [Child admission > 6 years was not available.]

- The primary goal of the pivotal trials (IGA scores of 0–1 after 16 weeks, corresponding to complete or almost complete healing of AD lesions) was achieved in 36 % to 38 % of adult patients and 24.4 % of adolescent patients.
- In the pivotal trials, only two adverse events occurred more frequently in the treatment groups than in the placebo groups: Injection site reactions, and development or aggravation of non-infectious conjunctivitis. This side effect can be managed by moisturizing the eye (artificial tears, lid rim hygiene), short-term use of topical glucocorticoids (such as eye drops with fluorometholone) after exclusion of infectious causes by consultation with an ophthalmologist, and, if required, ciclosporin-containing eye drops.

- According to the SmPC, patients treated with dupilumab can safely receive inactivated vaccines.

Treatment recommendation	Consensus
Dupilumab can be recommended for the treatment of chronic, moderate to severe AD in adolescents aged 12 years and older and in adults who cannot be adequately treated with topical medications alone.	Strong consensus
Dupilumab may also be considered for treating children below 12 years of age with treatment-refractory, severe AD. This is an off-label treatment option. Expert recommendations on dosage in children (≥ 6 months of age) are available.	Consensus
In cases of evident eczema, a combination of dupilumab with topical anti-inflammatory medication is recommended.	Strong consensus

3.12 Ciclosporin

Introduction

Ciclosporin is an immunosuppressant that has been approved for treating AD since 1997. Its mechanism of action is analogous to that of the topical macrolides tacrolimus and pimecrolimus: Inhibition of calcineurin-dependent signaling pathways with a resulting suppression of (pro-)inflammatory cyctokines such as IL-2 and interferons, and the associated suppression of T cell activation.

In contrast to tacrolimus or pimecrolimus, ciclosporin must be administered systemically.

A guideline issued by the German Dermatological Society (DDG) in 2009 on the use of ciclosporin in dermatology recommends short-term or interval treatment for severe AD. The aim is to achieve treatment intervals of about four months, whereby the compound can be administered again in cases of relapse [21]. The guideline stresses that relatively frequent adverse effects such as an increase in creatinine or hypertension should not automatically lead to treatment discontinuation but rather that the patient should be closely monitored and the dose reduced, or antihypertensive treatment initiated.

Reference is made to the S1 guideline on the use of ciclosporin in dermatology [21] which covers many practical aspects.

Controlled clinical trials on efficacy

Ciclosporin versus placebo

The data from eight RCT (randomized controlled trials) were pooled for a meta-analysis [22] and showed clear therapeutic effects on the parameters affected area, erythema, sleep disturbance, and reduction in steroid use. The authors of this meta-analysis conclude that ciclosporin is undoubtedly more effective than placebo. However, the effects are not sustained: Eight weeks after discontinuation of treatment, the scores return to baseline levels.

Three additional RCT were published after this meta-analysis:

Ciclosporin versus mycophenolic acid

A randomized, controlled long-term study in Utrecht compared the effects of ciclosporin and mycophenolic acid [23]. 55 patients with AD were initially treated with ciclosporin (5 mg/kg BW) for six weeks. The patients were then divided into two groups and received either ciclosporin (3 mg/kg BW) or 1440 mg mycophenolic acid over a maintenance period of 30 weeks, followed by 12 weeks of follow-up treatment. During the first ten weeks after randomization, the skin scores and the serum levels of the inflammation marker TARC were higher in the group treated with mycophenolic acid. Seven out of 25 patients treated with mycophenolic acid temporarily required additional treatment with oral corticosteroids. In the later observational phase of the study, the effects of ciclosporin and mycophenolic acid did not show any differences. After discontinuation, disease activity was higher in the ciclosporin pretreated group than in the mycophenolic acid pretreated group.

Ciclosporin versus methotrexate

In a rather small multicenter study in Egypt, children with severe AD (n = 40; 8–14 years of age) were randomized to a ciclosporin treatment group (2.5 mg/kg BW/day) or a methotrexate treatment group (7.5 mg/week) [24]. The study period was twelve weeks of treatment plus twelve weeks of follow-up. Both treatment regimens proved safe and effective, with no significant difference regarding skin improvement (SCORAD).

There are comparative data from the Netherlands on 'drug survival' for methotrexate, azathioprine, and ciclosporin in patients with AD, which allows an assessment of efficacy and tolerability. Ciclosporin (approved) shows a lower drug survival than methotrexate (off-label) [25, 26].

Ciclosporin versus prednisolone

In view of the fact that in 'real life', many AD patients do receive oral corticosteroids over extended periods of time, a prospective study directly compared oral prednisolone with ciclosporin. Due to unstable disease progressions, the study was discontinued before the envisaged total number of 66 patients was reached. The evaluable data from 38 patients showed a trend in favor of better clinical efficacy of ciclosporin in AD [27].

Dosage of ciclosporin for AD treatment

An RCT in 106 adult patients with severe AD tested a ciclosporin regimen independent of body weight [28]. Patients received a micro-emulsion of ciclosporin at either 150 mg/day or 300 mg/day; after this, the dose was reduced by 50 % and a follow-up examination was performed after eight weeks. The higher dose was more effective (reduction of the total symptom score [TSS], $P < 0.5$). In both groups, a subgroup of patients showed a response after two weeks. Due to more frequent increases in serum creatinine ($P < 0.1$), however, the authors recommended initiating treatment with the lower dose (150 mg/day corresponded to 2.2 mg/kg BW/Tag, 300 mg/day corresponded to 4.2 mg/kg BW/day).

Continuous versus intermittent treatment of AD in children and adolescents aged 2–16 years

Repeated short-term treatment was compared with continuous treatment in a cohort of 40 children aged 2 to 16 years [29]. Both groups showed a significant improvement of clinical scores and quality of life, with no significant differences. Continuous treatment with ciclosporin, however, resulted in a more sustained improvement. Since repeated short-term treatment, which entails a lower cumulative dose of ciclosporin, was sufficiently successful in a number of patients, an individual approach was proposed.

A study from South Korea treated more than 60 patients (children and adults, age 9–68 years) over more than six months and carefully observed any adverse events with ciclosporin. The mean initial dose was 2.7 ± 0.9 mg/kg BW/day. This treatment proved very effective with a reduction of the SCORAD skin score by more than 60 %; only one patient discontinued treatment because of renal dysfunction. Eight patients developed arterial hypertension which, however, was easily treated. The authors conclude that long-term treatment with ciclosporin is effective and safe [30].

Study data on drug survival indicate that reduced drug survival with ciclosporin is associated with a higher patient age, and increased drug survival is associated with medium to high initial doses (> 3.5–5.0 mg/kg BW/day) [26].

Ciclosporin versus UV therapy

An open, ramdomized multicenter study compared two parallel groups with 36 patients each [31]. Patients received eight-week treatment cycles with either ciclosporin or UVA (up to 16 J/cm^2)/UVB (up to 0.26 J/cm^2) treatment (two to three sessions per week). Over a period of one year, patients in the ciclosporin group experienced significantly more days of remission than those in the UVA/UVB group.

Galenics of ciclosporin

One study [32] compared ciclosporin micro-emulsion with an older galenic formulation. Initially, the micro-emulsion acted faster and showed higher efficacy. After eight weeks, both formulations were equally effective.

Adverse events, safety profile

Careful monitoring of blood pressure and renal function parameters are essential for patients taking ciclosporin, since this drug may cause both structural and functional kidney damage. The risk of nephrotoxicity is increased if dosage exceeds 5 mg/kg BW, in cases of increased serum creatinine, in older patients, and with long-term treatment.

Another study documented new infections in 101 AD patients treated with ciclosporin and compared them with a control group of the same size. Surprisingly, the incidence of infections tended to be lower in the ciclosporin group. Eczema herpeticatum as the most frequent infectious disease was not increased in the ciclosporin group [33].

Treatment with ciclosporin for severe AD is relatively safe. However, according to the guidelines, regular monitoring of renal function and hypertension as well as other parameters is essential. The original version of the S2k guideline on AD recommends induction treatment with an effective dose of 2.5–5 mg/kg BW/day until good overall improvement of the dermatosis has been achieved (strongest positive recommendation [1]), followed by a step-wise dose reduction. After therapeutic response, the dose can be reduced to the individual maintenance dose every two weeks (around 0.5–1.0 mg/kg BW/day). Even though long-term treatment is basically safe, intermittent treatment is recommended if the skin disease responds well to minimise the risk of adverse events with this immunosuppressant. Abrupt discontinuation is possible without the risk of rebound effects, but for practical reasons, the AWMF-S1 guideline [21] recommends a step-wise dose reduction.

Summarized assessment

Randomized controlled trials (RCT) with ciclosporin versus placebo show a clear therapeutic effect of ciclosporin.

Treatment duration depends on success and tolerability. Short-term intermittent therapy is an option where ciclosporin doses are reduced in a step-wise manner once sufficient improvement has been achieved. If long-term treatment is indicated (especially in cases of increased relapse frequency) continuous treatment should be administered with the lowest individually effective dose.

Due to the spectrum of adverse events, long-term treatment with ciclosporin is not helpful in AD. If the therapeutic response is good, interruption of treatment after 4–6 months is recommended. Tentative discontinuation should be performed after two years at most [21].

Attempting to increase long-term safety by reducing the dose will compromise efficacy and is not recommended.

Ciclosporin micro-emulsion offers the benefits of faster initiation of effects and increased initial efficacy which may be an advantage in short-term treatments.

Ciclosporin is also effective in children and adolescents with AD. Short-term intermittent treatment is associated with lower cumulative ciclosporin doses and is sufficiently effective in many patients, thus an individual regimen is recommended for this (off label) indication.

Intermittent ciclosporin treatment over a period of one year is more effective than intermittent UVA/UVB therapy with two to three sessions per week.

Regular monitoring of renal function is essential, especially with long-term treatment. Up to 50 % of patients on long-term ciclosporin therapy will show an increase in serum creatinine of > 30 %; this is usually dose-dependent and reversible after discontinuation. Ciclosporin treatment can be discontinued abruptly without the risk of rebound effects. In some cases, however, step-wise reduction (tapering off) may delay a rapid relapse.

The results presented by Haeck et al. [23] indicate a basically equal efficacy of mycophenolic acid and ciclosporin. Mycophenolic acid displays slower but more sustained action; it has, however, not been approved for treatment of AD (or other dermatoses).

Based on its approval status, ciclosporin can be used as a first line treatment for AD if systemic treatment is indicated.

According to our current state of knowledge, the risk-benefit ratio for ciclosporin is inferior to dupilumab, due to its well-known nephrotoxicity, hypertensive side effects, increased risk of infection, and risk of carcinogenicity in long-term treatment.

When treating AD with ciclosporin, determination of ciclosporin trough levels is unnecessary and is thus not recommended. Vaccination with live attenuated vaccines should be avoided during ciclosporin treatment (SmPC Ciclosporin dura soft capsules, updated July 2019).

Treatment recommendation	Consensus
Ciclosporin may be considered for short to medium-term treatment of chronic, severe AD in adults.	Strong consensus
When using ciclosporin for AD, the individual, expected risk-benefit ratio needs to be evaluated in comparison to possible therapeutic alternatives.	Strong consensus
An initial dose of 2.5–5 mg/kg BW/day in two single doses is recommended.	Strong consensus
Induction treatment is recommended for AD. The effective dose between 2.5–5 mg/kg BW/day should be maintained until a marked improvement has been achieved. Subsequently, step-wise dose reduction is recommended. After response, dose reduction every two weeks (by 0.5–1.0 mg/kg BW/day) can be recommended until the individual maintenance dose has been reached.	Strong consensus
Before initiation of treatment, the patient must be examined especially with regard to blood pressure and renal function.	Strong consensus
If the response is good, treatment interruption after 4–6 months is recommended.	Strong consensus
For severe AD, treatment over a period of more than six months may be considered if well tolerated.	Strong consensus
Ciclosporin may also be considered as a treatment option for children and adolescents with treatment refractory, severe AD (off-label use < 16 years of age).	Strong consensus
Due to the increased risk of skin cancer, ciclosporin treatment for AD should not be combined with phototherapy.	Consensus
Optimum UV protection is recommended during ciclosporin treatment.	Strong consensus

3.13–3.16 Anti-inflammatory drugs that have not been approved for AD treatment

3.13 Azathioprine

Azathioprine has been used for many years in Anglo-American countries to treat AD in adult patients.

(Controlled) clinical trials on efficacy

37 patients aged 17 to 73 years were studied in a randomized clinical trial with crossover design [34]. The drop-out rate was high (16 patients), with 12 patients dropping out during azathioprine treatment and four during placebo treatment. Each of the study periods lasted for three months; azathioprine dosage was 2.5 mg/kg BW/day. The '*Six Area, Six Sign Atopic Dermatitis*' skin score (SASSAD) decreased by 26 % during azathioprine treatment and by 3 % during placebo treatment ($P < 0.01$). Pruritus, sleep disturbances, and fatigue showed significant improvement during active treatment but not during placebo treatment.

In another double-blind, placebo-controlled study in an outpatient setting [35], 63 patients with active AD were studied in parallel groups. 42 patients received azathioprine and 21 patients received placebo over a period of twelve weeks. After the initiation phase, the maintenance dose depended on the existence of a thiopurin methyltransferase (TPMT) polymorphism. This key factor serves for the identification of azathioprine-induced myelotoxicity. Patients with normal TPMT activity received a maintenance dose of 2.5 mg/kg BW azathioprine, while patients with reduced TPMT activity (heterozygous phenotype) received a maintenance dose of 1.0 mg/kg BW. In general, this study found a clear therapeutic effect of azathioprine in both patient subgroups (decrease of disease activity over a period of twelve weeks by 37 % in the treatment group versus 20 % in the placebo group). None of the patients displayed any signs of myelotoxicity.

A retrospective study in a total of 48 children and adolescents (age 6–16) with severe AD found a very good response in 28 patients and a good response in 13 patients treated over a period of three months. Seven children showed no or hardly any response. None of the patients developed neutropenia during the treatment period. TPMT activity had been investigated in all patients before initiation of treatment. The initial therapeutic dose was 2 mg/kg BW/day; in 14 patients this was increased to 3 mg/kg BW/day during the treatment phase due to insufficient therapeutic response. The mean duration until a treatment response occurred was four weeks [36].

A systematic review published in 2011 [37] evaluated 43 articles investigating the effects of azathioprine in AD. The authors conclude that there is substantial evidence in support of a moderate therapeutic effect of azathioprine in AD. Assessment of thiopurin methyltransferase (TPMT) activity is recommended to predict azathioprine myelotoxicity.

One case report describes life-threatening myelotoxicity after azathioprine treatment of AD in a patient with normal TPMT activity [38].

Hon et al. published a retrospective analysis of 17 cases where azathioprine (mean dose 1.2–3.5 mg/kg BW/day) had been used in children and young adults (age 9.3 to 22.1 years) for treatment of refractory AD [39]. Significant improvement of the skin was observed after both three months and six months. In one female patient, azathioprine treatment did not result in sufficient treatment success and was discontinued after four months. In this study, female patients showed better efficacy after six months of treatment.

In a more recent study, twelve children with severe AD were treated with azathioprine and followed-up prospectively [40]. The children and adolescents were between two and 18 years of age and had moderate to severe AD with a SCORAD index of > 25. Patients with normal TPMT activity received 2.5 mg/kg BW/day. Eleven out of twelve patients showed a marked clinical improvement.

Azathioprine versus mycophenolate mofetil

A retrospective analysis of 28 pediatric patients with AD from North Carolina, USA, compared the treatment effects and adverse effects of azathioprine and mycophenolate mofetil using structured telephone interviews. Altogether, 28 patients were treated with azathioprine, and 12 patients with mycophenolate mofetil. In both groups, more than 60 % reported a clear improvement. The proportion of cutaneous infections was the same in both groups, but abnormal laboratory values were more frequently observed in patients treated with azathioprine [41].

Azathioprine versus methotrexate and ciclosporin

Comparative data from the Netherlands are available on drug survival in AD patients with methotrexate, azathioprine, and ciclosporin; this allows an evaluation of efficacy and tolerability. Azathioprine (not approved) and ciclosporin (approved) have lower drug survival than methotrexate (not approved) [25, 26].

Adverse events, safety profile

Berth-Jones et al. concluded that azathioprine is an effective and useful compound for treating severe AD but that the rate of adverse events is comparatively high [34]. Especially leukocytes and hepatic enzymes need to be monitored during treatment. The list of adverse events states that especially the high dose resulted in gastrointestinal problems in 14 patients; leukopenia was observed in two patients, and altered hepatic enzymes in eight patients.

Summary assessment

Azathioprine is appropriate for treating severe AD.

Treatment recommendation	Consensus
Azathioprine (off-label) may be considered for treating chronic, severe AD if dupilumab or ciclosporin are ineffective or contraindicated.	Majority consensus*
Assessment of the enzyme thiopurin methyltransferase (TPMT) before initiation of treatment is recommended so the dose can be reduced to decrease the risk of bone marrow toxicity. Doses of 1–3 mg/kg BW/day are recommended depending on TPMT activity.	Consensus
Regardless, the dose of azathioprine must be reduced to one-quarter of the normal dose if the patient receives concomitant medication with xanthine oxidase inhibitors such as allopurinol, oxipurinol, or thiopurinol.	Strong consensus
Phototherapy during azathioprine treatment is not recommended.	Strong consensus
Optimal UV protection is recommended during azathioprine treatment.	Strong consensus

*Some dissenters stated that using azathioprine (off-label) was equivalent to ciclosporin (approved).

3.14 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressant approved for treating nephritis associated with systemic lupus erythematosus and in the context of transplantation.

Controlled clinical trials on efficacy

There are no randomized, controlled clinical trials on mycophenolate mofetil treatment for AD.

There are, however, a number of positive case reports as well as positive clinical studies with open-label designs:

- Benez et al. [42]: MMF dosage 2 g/day for month 1–5, 1 g/day month 6–16 resp. 2 g/day for twelve months,
- Grundmann-Kollmann et al. [43]: MMF dosage 2 g/day for two and four weeks, respectively,
- Grundmann-Kollmann et al. [44]: MMF dosage 2 × 1 g/day for week 1–4, 2 × 500 mg/day for week 5–8,
- Hansen et al. [45]: MMF dosage 2 × 1 g/day for twelve weeks,
- Neuber et al. [46]: MMF dosage 1 g/day in week 1, 2 g/day for week 2–12.

A number of open-label observational studies have found mycophenolate mofetil to be effective for AD in adult patients. A retrospective analysis from New York described 14 children who were treated with mycophenolate mofetil [47]. Eight of these children showed a complete or more than 95 % healing of eczematous lesions during the treatment period, while another five showed marked improvement. The maximum effects developed slowly (after a treatment duration of nine weeks on average). The doses used were generally low (between 30 and 50 mg/kg BW), and the patients showed no severe adverse events.

In a case series published in 2009, adult patients (n = 10) with severe AD received 720 mg mycophenolic acid twice a day over a period of six months. Mycophenolic acid is the active substance of mycophenolate mofetil, which is hydrolyzed into the active compound mycophenolic acid in the stomach. All patients had previously been treated with other oral immunosuppressants which had been discontinued due to adverse events or lack of effect. Mycophenolic acid proved to be effective in reducing eczema scores and in improving in-vitro parameters indicative of allergic inflammation. However, use of topical glucocorticosteroids could not be reduced during the six month course of the study. No drop-outs were documented, and there were no relevant adverse events [48].

In an investigator-blinded, randomized, controlled trial, mycophenolate mofetil (enteric-coated mycophenolate sodium, EC-MPS) was compared with ciclosporin in fifty-five adult patients with severe AD [23]. After a six-week initiation phase with ciclosporin (5 mg/kg BW), patients received either ciclosporin (3 mg/kg BW) or EC-MPS (1440 mg) over a maintenance period of 30 weeks. This was followed by a twelve-week follow-up period. Both compounds showed equal efficacy during the maintenance phase, even though clinical improvement was observed comparatively later in the EC-MPS group. After discontinuation of treatment, the effect of EC-MPS was sustained for a longer period of time [23].

Other study data

Blood levels of mycophenolic acid vary greatly. Low blood levels and increased enzyme activity are correlated with the presence of UGT1A9 polymorphisms. In a retrospective study from Utrecht, 65 adult patients with AD who had been treated with mycophenolic acid were classified as 'responders' or 'non-responders' to mycophenolic acid treatment [49]. UGT1A9 polymorphisms were investigated via PCR. The 'non-responder' group comprised a significantly higher

proportion of patients with UGT1A9- polymorphism, and vice versa, 86 % of all patients with UGT1A9 polymorphisms were 'non-responders'. Binary logistic regression analysis showed odds ratios of 8.65 (95 % confidence interval [CI] 0.93–80.17) for the risk 'Non-responder to mycophenolic acid'.

Adverse events, safety profile

"Dear healthcare provider" letters (DHCP) for both mycophenolic acid and mycophenolate mofetil state that the compounds are strongly teratogenic in humans and thus increase the rates of miscarriage and congenital malformation when used during pregnancy. The compounds are contraindicated for women of reproductive age who are not using a highly effective method of contraception. Treatment should not be initiated in this population without a pregnancy test, so inadvertent use during pregnancy can be avoided. The compound is also contraindicated during lactation. Effective contraception must be used not only during treatment but also for six weeks after discontinuation. As a precaution, sexually active men are advised to use condoms during treatment and for at least 90 days after discontinuation. It is also recommended that female partners of men who are treated with the compound should use effective contraception during treatment and for 90 days after the last dose.

Gastrointestinal complaints, especially nausea and diarrhea, are the most common adverse events with MMF. Leukocyte and thrombocyte counts may also decrease. However, the gastrointestinal complaints usually occur at an early stage of treatment and often subsides over the course of therapy.

Summarized assessment

Positive clinical case reports and positive open-label clinical studies suggest that MMF may be effective in AD.

Similar to methotrexate, off-label use of mycophenolate mofetil is a therapeutic alternative for severe AD.

Treatment recommendation	Consensus
Mycophenolate mofetil may be considered in individual (off-label) cases for treating chronic, severe AD, especially for maintenance therapy.	Consensus
Mycophenolate mofetil is contraindicated in women and men who desire to have a child. The SmPC should be consulted for recommendations on contraception also beyond 90 days after treatment discontinuation.	Strong consensus

3.15 Methotrexate

Methotrexate (MTX) is an immunosuppressant and is frequently used for treating psoriasis. Its use has not been established for AD.

(Controlled) clinical trials on efficacy

Methotrexate in adults

In an open-label study, Weatherhead et al. investigated twelve adult patients over a period of 24 weeks. MTX was administered in increasing doses, starting at 10 mg per week and increasing by 2.5 mg per week until clinical efficacy was achieved [50]. After 24 weeks, the SASSAD skin score had improved by 52 %. The median dose was 15 mg MTX per week. Nine patients showed sustained improvement even twelve weeks after discontinuation.

An open-label study published in 2008 was the first to report on the efficacy of methotrexate in a case series. In a subsequent study in Israel, nine patients with AD or 'idiopathic eczema' were treated with once-weekly oral doses of 10–20 mg methotrexate [51]. Skin improvement was observed in all patients after only three to seven days. Six out of nine patients showed complete remission after three months of treatment, the other three patients showed a strong improvement.

A retrospective analysis assessed the data of 20 adult patients with moderate to severe AD who were treated with oral (10–25 mg) or intramuscular methotrexate (plus folic acid, 5 mg once a week) over a period of 8–12 weeks. These patients had previously shown no response to topical glucocorticosteroids, antihistamines, and 'second line' treatments [52]. After two weeks to three months, 16 out of 20 patients showed an improvement in both their skin (SCORAD score) and quality of life (DLQI). Three out of five patients who had developed increased liver enzymes during therapy had to discontinue treatment. One patient developed peripheral neuropathy which resolved after discontinuation.

Methotrexate in children

A retrospective study analyzed data from 47 Irish children who received methotrexate for AD [53]. After a single challenge application with 5 mg MTX, the children received 0.3–0.5 mg/kg BW once a week. Due to the slow onset of effects, only children who had been treated with MTX for at least three months were included in the evaluation. The global skin score IGA decreased from 4.25 to 2.8 points after 3–5 months of treatment, and further to 1.9 points in patients who were treated for more than ten months. Along with the skin scores, indicators for quality of life also improved

over time. Treatment was well tolerated, and thus the authors conclude that MTX constitutes a safe and effective treatment option for children with severe AD.

Methotrexate versus azathioprine

In a randomized study, 42 adult patients with severe AD were treated with either methotrexate (10–22.5 mg/week) or with azathioprine (1.5–2.5 mg/kg BW/day) for 12 weeks, with a follow-up period of another twelve weeks. Investigators assessing the skin scores were 'blinded' as to the treatment used. Clinical effects were comparable: After twelve weeks, the skin score had improved by 42 % on average with methotrexate and by 39 % with azathioprine. There was also no difference in the rates of adverse events [54].

There are comparative data from the Netherlands on drug survival for methotrexate, azathioprine, and ciclosporin in AD patients; this allows an evaluation of efficacy and tolerability. Methotrexate (not approved) shows better drug survival than ciclosporin (approved) and azathioprine (not approved) [25, 26].

Summarized assessment

An open-label study indicated that MTX may be effective for AD. The SmPC should be consulted for contra-indications (especially pregnancy; desire for having children [also in men], kidney and liver damage).

Treatment recommendation	Consensus
The use of methotrexate (off-label) may be considered for long-term treatment of chronic, severe AD.	Strong consensus

3.16 Alitretinoin

Alitretinoin is approved for treating chronic hand eczema and is particularly effective in hyperkeratotic forms. In a case series, six adult patients with AD were treated with 30 mg alitretinoin over a period of twelve weeks, in addition to topical treatments such as prednicarbate, mometasone, or tacrolimus, which had not been sufficiently effective when used alone [55]. This treatment resulted in a marked improvement of both palmar and extrapalmar lesions. Skin scores improved by > 50 % altogether; none of the patients complained of dry skin. Three out of six patients reported headaches. In this open-label case series with six patients, alitretinoin was well tolerated. It has potential value in treatment of atopic hand eczema, based on previously conducted controlled trials and on this observational study. Controlled trials will be required to exclude a placebo effect regarding the improvement of extrapalmar skin lesions.

Treatment recommendation	Consensus
Treatment of hand eczema with altretinoin (off-label) within the framework of the approved indication may also be considered in cases of concomitant AD.	Strong consensus
In cases of atopic hand eczema, alitretinoin may be considered as systemic treatment.	Strong consensus

3.17 Available biologicals not approved for treating atopic dermatitis

Monoclonal anti-IgE antibodies

Anti-IgE (omalizumab) is approved for treating allergic bronchial asthma and severe urticaria.

Controlled clinical trials on efficacy

Krathen et al. (2005) treated three patients with omalizumab over a period of four months. In this case series, no effect on AD was observed [56].

In a case series of five patients, Vigo et al. (2006) did observe clinical effects, some quite marked, on AD [57].

At this point in time, it is unclear whether the therapeutic effect in the latter case series may be connected to the overall somewhat lower levels of total IgE. In both case series, the dose of omalizumab was much lower than the dose recommended for allergic bronchial asthma. The total IgE concentration in serum of the AD patients was so high that dose-adapted use of omalizumab was impossible.

Belloni et al. have published another case series with eleven patients treated with the anti-IgE antibody omalizumab [58]. About half of the patients showed an improvement, in some cases very marked, when treated with this antibody at doses below those recommended for allergic bronchial asthma. Predictive parameters for a possible response of AD patients to omalizumab could not be determined.

A controlled trial published in Vienna compared omalizumab to placebo over a period of 16 weeks in 20 patients with extrinsic AD [59]. Immunological parameters showed that omalizumab has effects on IgE receptors in both blood and skin. Clinically, however, administration of this antibody did not result in improvement of eczema scores but only to occasional improvements of atopy patch test reactions. The authors drew the tentative conclusion that therapeutic effects may be possible in delayed reactions.

In a case series, four patients were treated with omalizumab in combination with intravenous immunoglobulins

(IVIG). 300 mg omalizumab were administered subcutaneously together with 10 g IVIG i.v. After only six weeks, the skin condition in three out of four patients had improved by more than 50 % [60].

Summarized assessment

Omalizumab does not have any proven effect on AD; positive effects derive from case reports.

Treatment recommendation	Consensus
Treatment of AD with omalizumab is not recommended.	Strong consensus

Ustekinumab

Ustekinumab is approved for treating psoriasis, psoriasis arthritis, and chronic inflammatory bowel disease. "Ustekinumab is recommended for induction therapy of moderate to severe psoriasis vulgaris if other treatment options have not resulted in sufficient therapeutic success, are not tolerated or are contraindicated" [61].

Eyerich et al. examined three patients who had simultaneous diagnoses of both AD and psoriasis [62]. Treating psoriatiform skin lesions with a TNFα inhibitor resulted in a resolution of the psoriatiform skin lesions while at the same time exacerbating eczema. However, treatment with ustekinumab, an anti-IL-12/IL-23 antibody, resulted in improvement of both the psoriasiform and the eczematous skin lesions.

A case series from Ireland reported on ten patients with severe AD, four of whom showed complete or near-complete healing with ustekinumab treatment [63].

In a larger, placebo-controlled trial from Japan, a total of 79 adult patients with AD were randomized into three groups: ustekinumab 45 mg, ustekinumab 90 mg, or placebo [64]. Changes in the EASI skin score after twelve weeks constituted the primary endpoint. The mean reduction of the skin scores in the three treatment arms was between 37.5 % and 39.8 % with no significant differences between the treatment groups and the placebo group. Other study parameters such as pruritus reduction, changes in quality of life, and changes in a global assessment score also showed no significant differences after twelve weeks.

A Phase II study in the USA treated 33 patients with moderate to severe AD with either ustekinumab or placebo [65]. A cross-over of treatment modalities was performed after 16 weeks; the last dose was administered after 20 weeks. Topical treatment with glucocorticoids was permitted. In this study, the proportion of patients who achieved a 50 % SCORAD reduction after 12, 16, and 20 weeks was higher in the treatment group than in the placebo group. However, this difference was not statistically significant. The profiles of inflammatory patterns determined during the treatment period did show a marked therapeutic effect of ustekinumab treatment on Th17 and Th2 cytokines. No clinically relevant adverse events were observed.

Treatment recommendation	Consensus
Ustekinumab is not recommended for treating AD as the sole indication. If additional diagnoses such as psoriasis, psoriasis arthritis, rheumatoid arthritis, or chronic-inflammatory bowel disease are present as well, treatment with ustekinumab may be considered.	Strong consensus

Other biologicals

Positive case reports have provided limited experience with rituximab, and tocilizumab in the treatment of AD.

Rituximab

In a pilot study with six patients, two intravenous applications of rituximab with an interval of two weeks resulted in a marked improvement of AD [66]. However, the mean skin score at baseline was only 30 (out of 107) SCORAD points in these patients, so it remains to be seen whether the treatment is also effective in severe AD. The small number of patients and the lack of a placebo group further limit the significance of this study. A case report published in 2010 described the successful treatment of a severely affected patient with this antibody [67]: After only one infusion, the lesions shrank from 80 % of the body surface to 5 % and she had no more relapses. Pregnancy was confirmed before the second planned infusion, 14 days after the first, resulting in the birth of twins by cesarean section at 36 weeks of an uncomplicated gravidity. At the time of publication, the two boys were eight months old and appeared healthy.

Tocilizumab

Tocilizumab is an anti-IL-6 receptor antagonist that is approved (in combination with methotrexate) as third-line therapy for adult patients with moderate to severe active rheumatoid arthritis.

Tocilizumab was used successfully at a dose of 8 mg/kg BW once a month in three patients with severe, treatment refractory AD [68]. Within three to six months, the skin score improved by more than 80 % in two patients, and by 51 % in one patient. However, two out of three patients developed bacterial superinfection.

Treatment recommendation	Consensus
Treatment of AD with rituximab or tocilizumab is not recommended.	Strong consensus

3.18 Apremilast

A topical phosphodiesterase (PDE)-4 inhibitor for treating AD is available in the USA but not in Europe. This summary only covers the data on systemic use of the PDE4 inhibitor, which is approved for treating psoriasis and psoriatic arthritis.

A case series published data on five patients treated off-label with apremilast, a PDE4 inhibitor approved for psoriasis. Four patients had chronic, severe AD, and one patient had atopy with severe eczema on the hands and feet [70]. The AD patients had previously been treated with other systemic drugs. Apremilast was dosed according to the recommendations for psoriasis. All patients reported a marked improvement in erythema, scaling, and dryness around the skin lesions within the first two to four weeks. The associated pruritus also improved, and the skin scores as determined by the investigator were reduced by about 75 %. The fifth patient (with hand and foot eczema) showed the best treatment success with healing of about 90 % of his skin lesions.

One case report was published on the use of apremilast in an eight-year-old boy [71]. His total IgE was 11 769 U/ml, with a relative proportion of eosinophils of 8 %. The patient had previously been treated with topical glucocorticosteroids, topical calcineurin inhibitors, systemic glucocorticosteroids, and mycophenolate mofetil, all without satisfactory improvement of his skin lesions. Treatment with omalizumab (used for concomitant severe bronchial asthma) also had not improved his skin lesions. Apremilast was dosed at 30 mg/day. The compound led to a rapid and marked reduction of pruritus within two weeks and to improvement of the inflammatory lesions on his trunk.

A prospective trial investigated the use of apremilast in comparison with placebo in AD (https://clinicialtrials.gov), but the results have not yet been published.

Treatment recommendation	Consensus
Treatment of AD with apremilast is not recommended.	Strong consensus

Note

Parts of the previous version of this guideline, from August 2020 published in 2008 [1, 69], were used in this update. Developments in system therapy for AD are currently progressing rapidly. Substances that are approved for the indication of atopic dermatitis after the consensus of this guideline chapter will be taken into account in a new update. New sections on scope, concept, case numbers, and results of published clinical studies were partially adapted from written versions of oral presentations (Werfel, Tagungshandbücher Derma Update 2009–2019).

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Conflict of interest

Potential conflicts of interest are disclosed in the online version of this article on www.awmf.org, the webpage of the working group of medical-scientific professional societies (Arbeitsgemeinschaft medizinisch-wissenschaftlicher Fachgesellschaften).

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