

REVIEW ARTICLE

Systemic therapy for atopic dermatitis

D. Simon¹ & T. Bieber²

¹Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; ²Department of Dermatology and Allergy, University of Bonn, Bonn, Germany

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Correspondence

Dagmar Simon, MD, Department of Dermatology, Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland.
Tel.: +41-31-632-2278
Fax: +41-31-632-2233
E-mail: dagmar.simon@insel.ch

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Abstract

Systemic therapy for atopic dermatitis (AD) is indicated in patients with severe disease refractory to adequate topical treatment. Currently available drugs aim to decrease inflammation by suppressing and/or modulating immune responses and thus may indirectly improve skin barrier function, resulting in a decrease in clinical signs and symptoms in particular pruritus. Before considering systemic treatment, patient adherence to topical treatment including skin care has to be ensured. The selection of the drug depends on the disease severity, localization, complications, concomitant diseases, and age of the patient, but also on their availability and costs as well as the doctor's experience. Bearing in mind the potential risk of resistance, systemic therapy with antibiotics should be exclusively considered in clinically manifest infections such as in children. Here, we review recently published clinical trials and case reports on systemic therapy of pediatric and adult patients with AD to draw conclusions for clinical practice. Although AD is a common disease, controlled clinical studies investigating the efficacy of systemic drugs are scarce, except for cyclosporine, which has been approved for the therapy of severe AD.

Atopic dermatitis (AD) is the most common skin disease in childhood with an impressive increase in the prevalence over the last decades (1–4). Although AD may disappear over time, 40–60% of pediatric patients with AD continue to have symptoms later on in life (5, 6). Although in approximately 60% of patients AD manifests in childhood, it may also develop in adolescent and adults (6). Fortunately, most of the patients with AD can control their skin disease with topical therapy and skin care. However, there is a considerable group of patients with severe AD who have eczematous skin lesions not responding to the prescribed treatment with moisturizers, topical corticosteroids (TCS), and/or topical calcineurin inhibitors (TCI) or experience immediate flare-ups after tapering topical anti-inflammatory therapy. In cases of refractory AD, it is important to check whether the diagnosis of AD is correct and consider possible differential diagnoses (e.g., allergic or irritant contact dermatitis, psoriasis, cutaneous mycosis, scabies, cutaneous T-cell lymphoma, or even genetic disorders such as Netherton syndrome, hyper-IgE syndrome, and Wiskott–Aldrich syndrome). In particular, contact allergies to ingredients of topical drugs, for example, to preservatives, emollients, fragrances, and corticosteroids, have to be excluded (7, 8). Most importantly, the compliance of the patients or their parents is a real issue.

The success of any, in particular topical dermatological therapy, depends on the patient's adherence. To achieve a maximal effect, the treatment should individually be tailored to the patient's needs, such as skin condition with special focus on severity of skin lesions, affected areas, skin dryness, and preference of vehicles, and consider avoidance of triggering factors, for example, allergens, skin irritants, and psychological stress. In our experience, refractory AD is not always due to ineffectiveness or tachyphylaxis to topical therapy, but rather an issue of compliance. Individual treatment plans, patient education, including basic knowledge on the pathogenesis, practical demonstrations, and written instructions are a prerequisite for improving compliance. By application of wet wraps, the effect of medications or moisturizers can be enhanced and a rapid reduction in pruritus may be achieved (9). Wet wraps are suitable for use at home, for localized and generalized skin lesions in particular for short-term intervention of acute flares in pediatric and adult patients. In our experience, education and practical demonstrations given by an experienced nurse in the eczema clinics significantly increase patient compliance.

When should systemic therapy be considered?

If AD cannot be controlled by topical therapy despite optimizing treatment plan and adherence, systemic therapy

should be considered (10, 11). Patients with severe AD are mainly those with early onset, widespread/generalized skin lesions, and long and continuous disease course. Short-term systemic therapy with immunosuppressive drugs should also be discussed in patients with acute severe exacerbations. In addition, severe localized AD lesions might call for systemic therapy. Atopic lid eczema and blepharoconjunctivitis often require systemic immunosuppressive intervention to prevent secondary alterations of the lids and ectropium. Hand eczema that often follows a chronic disease course has a high impact on patients' quality of life due to inflammation and pruritus as well as restrictions in occupational and private activities. Therefore, in addition to avoiding irritants and contact allergens, the decision on systemic therapy, for example, with alitretinoin for hand eczema, should not be protracted.

Systemic immunosuppressive therapy for concomitant atopic diseases, for example, bronchial asthma, often results in a simultaneous improvement in AD lesions. In children with severe AD, systemic immunosuppressive therapy should be considered to allow age-appropriate physical and psychic growth and prevent complications such as hypoproteinemia resulting in growth retardation and behavioral deficits as well as improve patients' and their families' quality of life (12–14). In addition to the objective clinical signs of AD, the decision on systemic therapy is strongly dictated by subjective symptoms and the patient's complains, in particular pruritus followed by scratching, secondary restlessness and sleeplessness, anxiety about uncertain disease course, and complications as well as fear of adverse effects of topical drugs, namely TCS (15). Further, individual life situations, for example, customer contact, final examinations, and joblessness (often triggered by AD), might force to initiate more potent therapeutic measures.

Before starting any immunosuppressive or immunomodulatory therapy for AD, a clinical and laboratory work-up of the patient is mandatory. In particular, underlying active infectious diseases including hepatitis B and C or HIV infections have to be ruled out. Necessary organ function tests before and during therapy depend on the drugs prescribed.

Which options are available for the systemic therapy of AD?

Pathogenic background

Recent progress in understanding the pathogenesis of AD revealed its heterogeneity based on the distinct genetic and epigenetic profiles as well as various pathophysiological pathways involved. This heterogeneity results in various endophenotypes and subsequently distinct clinical phenotypes (16). So far, AD phenotypes have mainly been distinguished based on clinical presentation, severity, onset and disease course, IgE sensitization, and concomitant allergic diseases. According to our current knowledge, AD results from complex gene–gene and gene–environment interactions (17–19). Genes relevant for AD pathogenesis have been assigned to genes involved in the epidermal barrier function and genes involved

in the regulation of innate and adaptive immune responses (16, 20, 21). An impaired skin barrier, for example, caused by missing or reduced expression and/or function of filaggrin (22, 23), LEKTI (24) or antimicrobial peptides (25) making the skin susceptible for environmental irritant, microbial and allergenic factors may give rise to an inflammatory reaction involving both innate and adaptive immune responses (26–30). The resulting skin inflammation is dominated by a T-helper 2 response (17), which itself may further impair skin barrier function (31, 32).

Considering these pathogenic events as key factors in AD development implies that the treatment has to focus on the restoration of the impaired skin barrier and the resolution of skin inflammation as well as the avoidance of environmental triggers (33). Even though systemic immunosuppressive therapy may effectively reduce cellular infiltration and cytokine expression, the remaining two therapeutic aims should not be neglected to achieve maximal improvement and avoid exacerbations of AD.

Immunosuppressive and immunomodulatory therapy

Systemic therapy for AD currently stands for immunosuppressive and immunomodulatory therapy as systemic drugs effectively restoring skin barrier function are not available yet. Substances such as cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate reduce disease-relevant inflammatory cell numbers and cytokine expression, but also exert general immunosuppressive effects (34). Alitretinoin, interferon, intravenous immunoglobulins, and biologics can be ascribed to immunomodulatory substances that may restore immune balance (Fig. 1).

Corticosteroids

By binding to regulatory elements of many genes via their receptor, glucocorticosteroids affect the transcription of several mediators involved in the pathogenesis of AD including cytokines, chemokines, and adhesion molecules by inflammatory cells as well as resident cells. This results in an inhibition of cell proliferation, vasoconstriction, and resolution of inflammation (34). Therapy with oral corticosteroids should be restricted to break severe exacerbations of AD and pruritus. Controlled clinical trials in both children and adults are lacking. As a rule, the initial dosage of 0.75–1 mg/kg per day should be tapered in 7–10 days. Methylprednisolone bolus therapy (intravenous; 20 mg/kg per day for 3 days) was reported to achieve a fast and sustained improvement over several weeks in 5 of 7 children (35). In adults with severe AD, oral prednisolone (0.5–0.8 mg/kg per day) for 2 weeks was not able to sufficiently control symptoms (36). Therefore, despite their frequent use in daily praxis, oral corticosteroids are not recommended to induce stable remission of AD or long-term control because of potential side-effects. These include diabetes, hypertension, gastric ulcers, osteoporosis, skin atrophy, glaucoma, Cushing's syndrome, and growth retardation. As patients often develop a rebound effect after tapering, ceasing oral corticosteroids might be challenging.

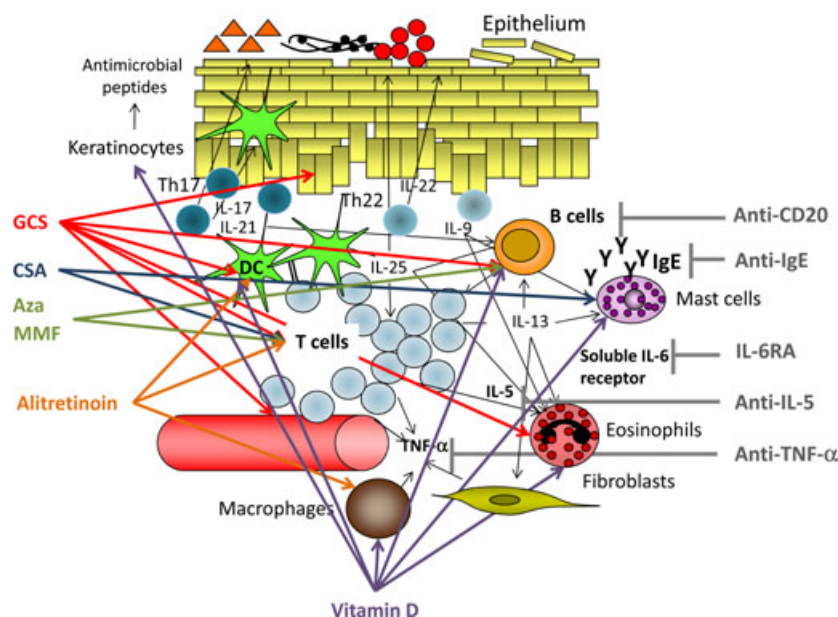


Figure 1 Targets of substances that have been used for systemic therapy of AD. Conventional strategies (left) reduce inflammatory cell proliferation and activation and thus cytokine production. Biologics (right) target specific cytokines and mediators involved in

inflammation. Because inflammatory as well as resident cells express the vitamin D receptor, vitamin D therapy may exert a broad spectrum of action. CSA, cyclosporine; MMF, mycophenolate; GCS, corticosteroids; IL-6RA, IL-6 receptor antagonist.

Cyclosporine

Cyclosporine inhibits T-cell activation and proliferation by blocking nuclear factor of activated T cells (NFAT)-dependent cytokine production (34). In randomized placebo-controlled trials, cyclosporine has been demonstrated to have significant beneficial effects in improving skin lesions, pruritus, and thus quality of life in adult and pediatric patients with AD (37–39).

A meta-analysis of 15 studies, including over 600 patients, revealed 55% improvement in disease severity after 6–8 weeks of cyclosporine treatment (40). Cyclosporine is licensed for the treatment of severe AD in some European countries. Doses of 3–5 mg/kg body weight per day are recommended for initial therapy, which can be tapered after achieving improvement of AD. In most patients, a short-term therapy is sufficient. It can be repeated in patients with recurrent flare-ups (interval therapy) (41). Patients with chronic severe AD and frequent exacerbations might require long-term therapy with an individually adjusted maintenance dose at lowest levels controlling the disease (41).

In any cases, concomitant topical corticosteroid therapy may be needed, but is well tolerated and might decrease the minimum effective dose of cyclosporine (40). Due to potential adverse effects, in particular renal toxicity and hypertension, monitoring of renal function parameters and blood pressure is mandatory (41). Adverse events appeared more likely in patients treated with higher doses (40). Because of an increased risk for skin cancer, cyclosporine therapy should not be combined with phototherapy.

Azathioprine

Azathioprine, which blocks the synthesis of RNA and DNA and thus inhibits the proliferation of T and B cells, has been used for treatment of severe AD for years in particular in the UK and USA (34). Studies in children and adults supplied evidence for its efficacy in improving skin symptoms, reducing pruritus and sleep loss, decreasing *Staphylococci* colonization (42–46). Azathioprine may cause severe side-effects including gastrointestinal disturbances, liver dysfunction, and leukopenia (45). The underlying cause for myelosuppressive effects of azathioprine is a partial or total deficiency in thiopurine methyltransferase (TPMT) activity. Patients at risk can be identified by determining TPMT activity and/or genotyping. In children screened for normal TPMT levels before therapy, no myelosuppression was observed under treatment with 2.5–3.5 mg/kg azathioprine for severe AD (47). Adult patients with AD, in whom the azathioprine dose was adapted to TPMT activity, showed similar disease improvement compared with patients with normal TPMT activity receiving 2.5 mg/kg azathioprine (48).

Mycophenolic acid

The efficacy of mycophenolate mofetil (MMF) in the treatment for severe AD has been shown in several cases and small studies (49–54). Monotherapy with MMF with initial doses of 1 g twice daily over 4 weeks followed by 4 weeks with 0.5 g twice daily lead to a significant reduction in disease severity with a sustained improvement during the follow-up until week 20 (49). The percentage of patients responding to MMF therapy can be estimated with 70–80%

(50, 51). Successful long-term treatment in three patients with MMF 1–2 g daily over 12 to 29 months has been reported (52). After inducing remission with high-dose cyclosporine, maintenance therapy with mycophenolate sodium (1440 mg/day) was as effective as low-dose cyclosporine in improving signs and symptoms of AD (55). Main adverse events reported under mycophenolic acid therapy in patients with AD were nausea, fatigue, flu-like symptoms, liver enzyme abnormalities, and infections such as herpes zoster, herpes simplex, and staphylococcal infection (50, 51, 55, 56).

Methotrexate

Methotrexate is an analogue of folic acid interfering with folic acid metabolism, resulting in a reduced production of pyrimidine and purine nucleotides required for DNA and RNA synthesis. Thus, methotrexate may reduce chemotaxis of and cytokine production by lymphocytes or induce cell death (34). Methotrexate was shown to be effective in moderate-to-severe AD. The application of a median dose of 15 mg per week resulted in a decrease in disease activity by 52% from baseline after 24 weeks with a persistent improvement in 8 of 12 patients over 12 weeks after stopping therapy (57). A retrospective study reported an improvement of >70% as assessed by the physician in 75% of patients treated with weekly doses of 7.5 to 25 mg methotrexate intramuscularly over 3 months (58). Similar results were achieved by low-dose methotrexate therapy with 10–25 mg weekly for 8 to 12 weeks (59). Note that, it takes approximately 2 weeks to 3 months after initiating therapy until symptoms improve (57–59). Patients not responding to 15 mg methotrexate per week after three months failed to improve with further dose escalation (57). A recent study reported that methotrexate 7.5 mg per week is as effective and safe as cyclosporine 2.5 mg/day in children with severe AD at age 7–14 years (60). Before starting methotrexate therapy, liver toxicity and teratogenicity have to be considered. Nausea and increase in liver enzymes were the main adverse events observed that eventually caused transient or total discontinuation of methotrexate therapy (58–60).

Alitretinoin

Alitretinoin, 9-cis retinoic acid, is an antagonist vitamin A derivative that binds to both retinoic acid receptors RAR and RXR. Alitretinoin has been shown to be effective in the treatment for severe hand eczema, including atopic hand eczema (61). Best responses were observed in hyperkeratotic forms and fingertip eczema (61, 62). Recently, it has been reported that alitretinoin at a standard dose of 30 mg daily significantly improved extra-palmar AD lesions in six patients treated for severe atopic hand eczema (63). As hand eczema severely affects patients' quality of life, treatment with alitretinoin should be considered in AD patients with involvement of the hands not responding to topical corticosteroids and/or calcineurin inhibitors. Most frequent adverse effects reported were headache, increase in serum cholesterol and triglyceride levels, and decrease in thyroid-stimulating hormone (61). As all retinoids are teratogenic, alitretinoin is not indicated in pregnant women, and treatment of women at childbearing age should be avoided or given under strict contraception.

Intravenous immunoglobulins

Because of their immunomodulatory potential, intravenous immunoglobulins (IVIg) have been used for the treatment of severe autoimmune and inflammatory skin diseases including severe AD (34). First observations on an improvement in AD skin symptoms were made in patients treated with intravenous gamma-globulins for Kawasaki disease or idiopathic thrombocytopenic purpura, who had AD in addition (64). Adjunctive therapy with IVIg (six cycles with high-dose IVIg 2 g/kg per month) significantly improved skin symptoms in four of six patients with AD (65). Moreover, IVIg therapy allowed the reduction in concomitant systemic drugs in patients on long-term corticosteroid therapy (66). The benefit of IVIg therapy for patients with severe AD has controversially been discussed, as some reports revealed no or just slight improvement (67, 68). IVIGs have also been used in children with severe AD (three cycles of 2 g/kg IVIg per month), resulting in a significant decrease in disease activity and inflammatory markers, for example, serum eosinophil cationic protein levels (69). In a recent case series, a decrease in blood eosinophilia and IgE levels in parallel with an alleviation of skin symptoms has been reported following IVIg (70). In children with AD refractory to systemic immunosuppressive therapy, IVIg should be considered (71).

Interferon-gamma

Although mentioned in certain guidelines and reviews, interferon (rIFN)-gamma therapy became less important, most likely because of alternative drugs with better benefit–risk profiles.

Treatment with recombinant interferon (rIFN)-gamma leads to a normalization of the cytokine dysbalance in AD by decreasing IL-4 and IL-6 (72). Best results in controlling AD symptoms have been achieved with an induction of remission followed by a maintenance therapy with IFN-gamma up to 2 years (73–75). Long-term IFN-gamma therapy has successfully been administered to children (76). The main adverse effects reported were flu-like symptoms (74).

Biologics

Biologics have widely been used in dermatology, in particular for the treatment of psoriasis and autoimmune diseases. So far, none of the biologics available has been approved for AD therapy. Several biologics that have the potential to target cytokines or mediators known to play a role in the pathogenesis of AD have been used in individual patients and small clinical trials. Some of these reports were summarized here.

Anti-CD20

The depletion of B cells, known to act as antigen-presenting cells, promote T-cell activation and produce proinflammatory cytokines and IgE, with rituximab (anti-CD20 antibody) resulted in a rapid reduction in skin inflammation in all patients with a sustained effect over 5 months in five of six patients, although specific IgE levels were not affected (77). In two cases affected by very severe AD, rituximab showed limited effects (78).

Anti-IL-5

Skin inflammation of AD is associated with eosinophilic infiltration. Therefore, depletion of eosinophils seems a promising approach for AD treatment. Upon short-term therapy with an anti-IL-5 antibody (mepolizumab; 2×750 mg), a moderate improvement in clinical symptoms was observed, although a rapid depletion of eosinophils in the peripheral blood was noted (79). Studies investigating a reduction in exacerbations and steroid-sparing effect of anti-IL-5 antibody therapy in AD analogous to those performed in patients with bronchial asthma (80, 81) have not been performed so far.

Anti-IgE

Based on the observations that approximately 80% of patients with AD have increased IgE levels in blood, anti-IgE antibody therapy has been applied. Upon low-dose anti-IgE antibody therapy (omalizumab, 10 cycles of 150 mg), SCORAD levels decreased by 50% in two and by 25–50% in four of 11 patients with AD (82). A significant improvement in skin symptoms has been reported in patients with concomitant AD and bronchial asthma receiving omalizumab because of severe airway disease (83). Interestingly, a randomized placebo-controlled double-blind study revealed no significant effect of omalizumab on clinical signs of AD, although a decrease in serum IgE levels, surface IgE, and FcεRI receptor expression on blood cells as well as a reduction in IgE+ cells but not FcεRI+ cells in the skin was observed (84). A recent study identified AD patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines as responders to omalizumab therapy (85). Meanwhile, omalizumab therapy in combination with IVIg and rituximab has been applied to patients with severe AD resulting in drastic clinical improvement and long-term effects (86, 87).

Anti-TNF- α and other strategies

Anti-TNF- α therapy has been reported to significantly decrease AD signs and symptoms including pruritus during induction therapy, but failed to achieve a long-term maintenance effect (88). However, inadequate effects or even severe exacerbations of AD upon anti-TNF- α therapy have been reported (89, 90). Therefore, we would not recommend this treatment for AD.

Blocking the IL-6 receptor pathway resulted in a marked improvement in AD in severely affected patients, however, led to adverse severe infections (91).

Considering the pathogenesis of AD, there are a number of interesting mediators and receptors that might serve as potential therapeutic targets, for example, IL-4, IL-13, and their receptors, as well as IL-25, IL-31, histamine, and histamine receptors 1 and 4 (92, 93).

Immunoabsorption

Based on the observation that a subgroup of patients with severe AD has extremely increased total serum IgE levels,

immunoabsorption was applied. A pilot study investigating 12 patients with AD refractory to systemic treatment showed a 24% to 82% individual SCORAD reduction upon ten immunoabsorptions (94). In parallel, skin-bound IgE and inflammatory cell numbers decreased, whereas only a short-term depletion of serum IgE was observed (94). So far, randomized trials on immunoabsorption are not available and long-term effects are not known.

Allergen-specific immunotherapy

Although allergen-specific immunotherapy (ASIT) has widely been applied for other atopic diseases such as allergic rhinitis and asthma, the number of studies in AD is limited. ASIT has mainly been studied in patients with AD sensitized to house dust mites and birch pollen. Both subcutaneous and sublingual applications have been applied. After 1 year of ASIT to house dust mites, a decrease in AD severity and concomitant topical corticosteroid use in a dose-dependent manner was observed (95). In particular, patients with severe AD were reported to profit from ASIT to house dust mites (96). Also, SLIT results in a significant improvement in AD as assessed by SCORAD in patients with AD sensitized to house dust mites (97). Some patients with AD allergic to pollen experience acute exacerbations during pollen seasons. ASIT with birch pollen extract for 12 weeks was shown to significantly reduce skin symptoms and improve quality of life despite strong birch pollen exposure (98). Although a recent systematic review on ASIT for AD stated a significant positive effect (99), current data do not allow a broad recommendation so far.

Antimicrobial treatment

Antibiotics

The impaired skin barrier predisposes for microbial colonization on lesional as well as nonlesional skin, for example, with *Staphylococcus aureus* in over 90% of patients with AD. *S. aureus* can trigger exacerbations and promote persistence of AD lesions by releasing toxins that function as superantigens and induce extensive T-cell activation. They further destroy the skin barrier as well as induce IgE antibodies, with subsequent degranulation of basophils and mast cells resulting in flare-ups and pruritus (100, 101). Therefore, reducing *S. aureus* colonization by controlling inflammation and improving barrier function are supposed to improve AD. Restoring the epithelial barrier using skin protective measures and anti-inflammatory therapy also results in reduced colonization with *S. aureus* (102, 103). Upon application of emollients and wet wraps with antiseptics, a rapid resolution of acute AD exacerbations in parallel with a decreased *S. aureus* colonization was observed (104). Furthermore, bathing with disinfectants has been shown to reduce *S. aureus* on the skin resulting in a significant reduction in AD severity (105). Both topical therapy and systemic antibiotic therapy are not necessary and therefore should not be recommended to achieve a reduction in bacterial colonization. In particular, the continuous use of antibiotics

Table 1 Summary of pharmacological systemic therapy for atopic dermatitis. Note that, all immunosuppressive and immunomodulatory regimens listed here are not approved for AD except cyclosporine in some European countries

Therapeutic approach	Substances	Comments	References
Immunomodulation immunosuppression	Corticosteroids	Short-term therapy to coup acute exacerbations, 0.75–1 mg/kg/ day, tapering to 0 in 7–10 days, no long-term therapy recommended	35, 36
	Cyclosporine	Approved for AD therapy Initial dose 3–5 mg/kg/day, tapering to lowest sufficient dose for long-term therapy	37–41
	Azathioprine	Studies in pediatric and adult patients with AD, adapt dose to TPMT activity,	42–48
	Mycophenolate mofetil	Initial dose 2 g/day, maintenance dose 1 g/day	49–56
	Methotrexate	7.5–25 mg per week, studies in pediatric and adult patients	57–60
	Alitretinoin	Approved for therapy of severe hand eczema, 10–30 mg/day, teratogenic	61–63
	Intravenous immunoglobulins	Controversial results on efficacy in AD	64–71
Biologics	Anti-CD20, rituximab	Effect in moderate-to-severe AD, open-labeled study	77, 78
	Anti-IL-5, mepolizumab	Moderate effect upon 2 × 750 mg	79
	Anti-IgE, omalizumab	Controversial results, minimal effect despite reduced serum and tissue IgE	82–88
	Anti-TNF-alpha	Not recommended because severe AD exacerbations may occur	89–91
	Anti-IL-6 receptor antagonist	Effective, high risk of severe infections	92
Immunoabsorption		Significant reduction in severity and pruritus in severe AD, pilot study	94
Allergen-specific immunotherapy	Subcutaneous	Effect in patients with AD sensitized to house dust mites or birch pollen	95–99
Antimicrobials	Antibiotics	In severe bacterial superinfection	100–106
	Antivirals	For eczema herpeticum	10, 11
	Antimycotics	Severe head-and-neck dermatitis	108–110
Vitamins	Vitamin D	Controversial results	115–121

whether topical or systemic should be avoided to reduce the risk of bacterial resistance. In our opinion, exclusively severe bacterial superinfection of eczematous skin with oozing and yellow crusted lesions, which are more typical for AD in childhood, may require systemic antibiotic therapy. In addition to *S. aureus*, *Streptococcus pyogenes* was found to cause superinfection of eczematous lesions, in particular in patients with uncontrolled AD (106).

Antiviral therapy

Eczema herpeticum is a widespread herpes simplex infection of inflamed skin in patients with AD associated with severe systemic symptoms. Patients with severe AD, untreated skin lesions, early disease onset, and high total serum IgE levels are at high risk to develop eczema herpeticum (107). Patients present with an eruption of dome-shaped blisters and pustules, fever, malaise, and lymphadenopathy. Therefore, eczema herpeticum should be treated without delay using systemic antiviral therapy, such as acyclovir (10, 11).

Antimycotics

In a subset of patients with AD, IgE- as well as T-cell-mediated autoimmune reactions to manganese superoxide dismutase (MnSOD) have been identified as trigger (108). Patients

sensitized to human MnSOD were found to cross-react with structurally related fungal MnSOD derived from *Malassezia* species (109). Systemic ketoconazole has been shown to be effective in the treatment for atopic dermatitis with IgE-mediated hypersensitivity to yeasts (110). However, in most cases of yeast-triggered AD, mainly in the head-and-neck area, a topical antimycotic therapy seems sufficient as it has been demonstrated for ciclopiroxolamine cream (110).

Vitamin D

Vitamin D deficiency has been associated with an increased risk to develop atopic diseases including AD (111–113). Vitamin D was shown to affect both the innate and the adaptive immune system (114), and thus, low vitamin D levels might contribute to the main features of AD such as defective skin barrier and chronic skin inflammation. Vitamin D stimulates antimicrobial peptide expression by endothelial cells; inhibits dendritic cell activation, antigen presentation, and cytokine production; and supports macrophages defending opportunistic infections (114). As most cells of the adaptive immune system express the vitamin D receptor, vitamin D exhibits broad effects, for example, it may inhibit T-cell proliferation, suppress Th17 cell, but increase regulatory T-cell functions, and blocks B-cell proliferation and immunoglobulin production (Fig. 1). Interestingly, the cathelicidin gene is directly regulated

by vitamin D binding to the vitamin D response element in the promotor region (115). Indeed, low vitamin D levels correlated with low serum cathelicidin levels in patients with AD (116), and supplementation with 4000 IU per day vitamin D for 21 days was reported to increase the expression of antimicrobial peptides in lesional AD skin (117), although vitamin D therapy failed to significantly change cathelicidin, human beta-defensin 3, IL-13 blood levels, and AD severity (118).

The results on vitamin D status and therapeutic effects of supplementation are controversial. Recent studies found similar blood vitamin D levels in patients with AD and age- and sex-matching controls and an inverse correlation between eczema and vitamin D in the pediatric population (119, 120). However, AD patients with very low 25 (OH) D3 levels (4 and 15 ng/ml) profited from vitamin D supplementation for 3 months as assessed by a significant decrease in objective and subjective SCORAD (119). Note that, pediatric patients with AD treated with vitamin D were found to have an increased risk of developing food allergy (120). As it is not clear whether vitamin D has a beneficial effect on AD and controlled multicenter studies are missing, we would not recommend general vitamin D therapy for patients with AD.

Conclusion

The management of some moderate to severe forms of AD (SCORAD 18–40) resistant to topical treatment as well as that of severe forms (SCORAD >40) requires the use of systemic drug application. Unfortunately, besides cyclosporine, which is only approved in some European countries for this indication, none of the systemic immunosuppressive or immunomodulatory regimens suggested in national and international guidelines is currently approved (Table 1). As the progress in our understanding of the genetics and pathophysiology of AD is significantly growing in the last decade, the scientific community and the affected patients and their families are expecting some substantial new developments that may be driven by the emerging era of personalized medicine. Considering the substantial socioeconomic burden of AD, there is clear, unmet medical need which needs to be addressed in the future by the pharmaceutical industry.

Conflicts of interest

None.

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