Current Treatment Options in Allergy (2014) 1:384–396
DOI 10.1007/s40521-014-0032-y

Atopic Dermatitis (A Wollenberg, Section Editor)

Systemic Treatment of Severe Atopic Dermatitis in Children and Adults

Uffe Nygaard, MD[1]
Christian Vestergaard, MD, PhD, DMSc[1,2,*]
Mette Deleuran, MD, DMSc[1]

Address
[1]Department of Dermatology and Venereology, Aarhus University Hospital, University of Aarhus, Aarhus, Denmark
[*,2]Department of Dermatology and Venerology, Aarhus University Hospital, P.P. Ørumsgade 11, 8000, Aarhus, Denmark
Email: chr-vest@post9.tele.dk

Published online: 17 September 2014
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Key points

1. Systemic therapy can be an effective treatment of severe AD in both children and adults.
2. There is robust evidence supporting the use of cyclosporine A, azathioprine, methotrexate and mycophenolate mofetil.
3. The use of oral glucocorticoids should be reserved for treating an acute exacerbation or for breaking a particularly recalcitrant case; and they should never be used for long periods.
4. All therapies offer various benefits, diverse adverse effects and different needs for clinical follow-up and laboratory analyses, and it is pivotal to monitor the patient accordingly.

Keywords Atopic dermatitis · Atopic eczema · Treatment · Therapy · Systemic treatment · Systemic therapy · Immunosuppressive therapy · Immunomodulation · Biological treatment

Opinion statement

Most patients with atopic dermatitis (AD) can control their skin disease with emollients combined with topical immunosuppressive therapy, ultraviolet (UV) therapy or both. Unfortunately, though, a small group of children and adults is not sufficiently treated with any combination of these therapies. This group includes the patients with the most recalcitrant phenotype who have severe AD, with frequent major exacerbations or chronic localised AD lesions like eyelid eczema. They can be a challenge to treat, and systemic treatment is the next step to induce and maintain disease control. It is crucial when planning systemic therapy that treatment be tailored to the unique patient. Systemic treatment of severe AD in both young and old is a delicate matter, and special care should be taken to monitor possible side effects. Some patients respond well to one medication but not to others, and predicting the effect of a medication for the individual patient is

not possible. Therefore, some patients have to try several systemic immunosuppressants before they obtain sufficient control of the disease.

Introduction

Atopic dermatitis (AD) is a very common, recurrent, pruritic inflammatory disorder of the skin that has reached epidemic proportions in many countries. In the past decades, there has been an increase in the prevalence, and AD now affects 10–20 % of children and 3–10 % of adults in affluent countries, with a similar but delayed rise in the developing world [1]. In most patients, AD is first observed in early childhood, but it may also develop in adolescents and adults. Since approximately one-third does not clear the disease before adulthood, many carry the burden of AD throughout life [2]. Severe AD is not a clearly defined entity and several terms have been used to designate the condition [3]. A physician assessing a specific patient history of obstinate eczema with a string of unsuccessful treatments could come to the diagnosis of severe AD; or the diagnosis could be based on a definite severity criteria like severity SCORing of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA) and Six Area Six Sign Atopic Dermatitis (SASSAD) [4–7]. Either way, severe AD is a debilitating condition with a devastating socioeconomic impact on both the patient and society. These patients often experience accompanying morbidity from pruritus like chronic scratching, restlessness, disturbed sleep and anxiety [8, 9]. In children with severe AD, systemic immunosuppressive intervention should be considered when physical growth, psychological development, and school attendance are impaired, as is a reasonable life quality for both the patient and his or her family. In adults with an established diagnosis of severe AD, the need for systemic immunosuppressive intervention may be supported by certain life circumstances, like a complicated job situation, finishing exams or psychological stress harming interpersonal relationships. In this review, we focus on systemic treatment of severe AD in both children and adults.

Systemic treatment options in severe atopic dermatitis

Before instigating systemic therapy, it is important to establish the right diagnosis. There should be an investigation of any potential triggering factors such as concomitant allergies, either by skin prick testing, specific IgE analyses or provocation tests. Additional diagnostic deliberation comprises an evaluation of *Staphylococcus aureus* infections and completion of any requisite treatment. Finally, these should be an evaluation of whether a reasonable treatment outcome may be expected in light of the patient's ability to strictly adhere to a prescribed regimen of topical treatment and use of emollients.

In severe AD, the aim of any given systemic therapy is to achieve a swift and efficient improvement and control of inflammation and pruritus, regardless of whether treatment is instituted to alleviate an acute exacerbation or a chronic disease.

Review of current treatment options

Systemic immunosuppressants

Systemic glucocorticoids

Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptor. The activated glucocorticoid receptor complex upregulates the

expression of anti-inflammatory proteins and represses the expression of pro-inflammatory proteins; hence, the immunomodulatory property [10]. Clinical trials in both adults and children are very few; nonetheless, systemic glucocorticosteroids are widely prescribed for AD as a consequence of clinical experience. In studies conducted on children and adults, systemic glucocorticosteroids have shown little ability to control symptoms and reduce inflammation, and they show less efficacy than cyclosporine A in adults with severe AD, and induced stable remission in only one of 21 patients [11, 12]. Systemic glucocorticosteroid toxicity is related to the mean dose, cumulative dose and duration of use. Side effects include skin thinning and purpura, pseudo-Cushing's disease, sleep disturbance, mood changes, and furthermore, hyperglycaemia or new onset diabetes, peptic ulcers and gastritis, osteoporosis, and increased susceptibility to infections [13]. Patients can develop steroid dependency with adrenal suppression and impaired ability to produce natural corticosteroids, and together with a high risk of rebound effect when tapering the treatment, cessation is challenging [14]. Systemic glucocorticosteroids must be avoided as a long-term treatment in adults and children, and should only be used to break severe disease or control exacerbations during other treatments, and for no longer than a few weeks. Even a fairly high dose can simply be stopped, and need not be tapered when used for no longer than two weeks [15].

Cyclosporine A

Cyclosporine A is a calcineurin inhibitor that reduces the activity of the immune system by selectively acting on T cells by interfering with their action and growth [16]. Several controlled trials and meta-analysis have proved cyclosporine A to be superior to placebo, prednisolone, and intravenous immunoglobulin, and equal to mycophenolate sodium in the treatment of AD [17–19, 20•, 21]. The effect is increased and time to response is decreased with higher dosage [22]. The effect is similar in adults and children, although younger patients show higher tolerability with respect to nephrotoxicity. Most patients need no more than short-term therapy for sufficient response, although cyclosporine A can be administered as repeated pulse treatments in recurrent disease [23]. The effective and safe long-term use of cyclosporine A for up to 12 months is documented with a low rate of severe adverse events [20•, 22]. Side effects include hypertrichosis, gingival hypertrophy and headache, but are often minor or absent. Severe side effects are rare but well described, and include renal toxicity, hypertension and hepatotoxicity, which also make regular monitoring of organ specific parameters and blood pressure mandatory. When prolonged treatment is needed, the dosage should be adjusted to the lowest level possible for controlling disease activity [23].

Azathioprine

Azathioprine is a purine analogue that inhibits DNA/RNA synthesis and repair and most strongly affects proliferating cells, such as the T cells and B cells, giving rise to a general class effect as an immunosuppressant. It is a commonly used immunosuppressive drug in the management of severe AD, in both children and adults [3]. Several studies have documented a moderate improvement in disease activity and patient symptoms with an efficacy comparable to

methotrexate and superior to placebo [24, 25•, 26, 27]. In order to achieve adherence to the treatment among patients, it is important to inform them that clinical improvement of their AD can be seen as late as six to eight weeks after therapy is commenced. The slow on-set of action makes the drug a lesser choice in managing acute severe exacerbations. The main side effects include gastrointestinal disturbance, hepatotoxicity, viral infections, impaired liver function, slightly increased risk of cancer, especially non-melanoma skin cancers, and myelosuppression with lymphocytopenia as the most frequent outcome [26]. Myelosuppression can be related to a partial or total lack of thiopurine methyltransferase activity, and pre-treatment thiopurine methyltransferase activity determination or genotyping can be done [28]. A second approach is a low-dose regimen at start-up with weekly laboratory monitoring. Patients with normal levels of thiopurine methyltransferase may also develop these side effects, and should also be followed with measurement of hematologic parameters and liver function tests at adequate intervals. In 2011, the US Food and Drug Administration (FDA) issued a black box warning on azathioprine concerning a potential increased risk of hepatosplenic T cell lymphoma. To date, this specific malignancy has not been registered in any patients with AD [29].

Methotrexate

Methotrexate is a folic acid antagonist that inhibits cell division, DNA/RNA synthesis and repair and protein synthesis, altogether suppressing the activity of the immune system. Methotrexate has been used for decades in the treatment of severe AD, but only a few non-randomised controlled trial (RCT) studies have investigated the effect and treatment regimens. Thus recommendations have been based on open non-controlled case series and individual experiences [30–32]. A controlled study that compared methotrexate with azathioprine in adults showed that methotrexate significantly lowered AD severity and improved life quality [25•]. An open-label multi-centre study concluded that methotrexate in low doses can be considered as effective, relatively safe, and well-tolerated treatments for severe AD in children [33•], and this finding is supported by a recent retrospective study [34]. The efficacy of methotrexate was comparable to both cyclosporine A and azathioprine [25•, 33•]. As methotrexate is a very common drug in dermatology, the safety profile is well recognized, with nausea and increased liver enzymes as principal side effects, while cytopenia is of primary concern. Only very rarely, acute idiopathic pulmonary fibrosis is seen.

Any noteworthy impact on liver or bone marrow function should give cause to dose reduction or transient or total discontinuation of treatment. Relevant co-administration of 5 mg folic acid two days after the weekly dose of methotrexate can reduce subjective symptoms [35]. Subcutaneous administration can increase bioavailability and tolerability in most patients who do not respond to oral treatment or suffer from intolerable gastrointestinal side effects. As for azathioprine, patients should be informed that onset of action takes between two weeks and three months [30–32]. One study suggests that patients who do not benefit from a moderate weekly dose (10–15 mg) of methotrexate over a three-month treatment period will probably not benefit from an increased dosage [30]. Methotrexate is generally well tolerated and is considered very safe for long-term treatment, based on experience and multiple studies including both adults and children suffering

from psoriasis or rheumatologic disease [36, 37]. Methotrexate is teratogenic and fertile women should use adequate contraception. The same is recommended for men treated with methotrexate living with a woman of childbearing potential.

Mycophenolate derivates

Mycophenolic acid reversibly inhibits inosine monophosphate dehydrogenase, leading to decreased B cell and T cell proliferation and immunosuppression. Mycophenolic acid may lead to immunosuppression through other mechanisms as well, by the induction of apoptosis of activated T lymphocytes and through inhibition of adhesion molecule expression and lymphocyte recruitment [38]. Mycophenolate mofetil is shown to effectively reduce disease severity and have patients with severe AD have a sustained improvement during follow-up [39–41]. Up to 80 % of patients respond to treatment, and successful long-term treatment for up to 29 months has been reported [42–44]. One small open-label trial showed that enteric coated mycophenolate sodium was also effective in decreasing the severity of AD with few and tolerable adverse events [45]. Mycophenolate mofetil was equally effective compared to low-dose cyclosporine A in controlling symptoms of AD after inducing quick remission with high-dose cyclosporine A [20•]. This RCT also showed a prolonged improvement of AD treated with mycophenolate sodium compared to cyclosporine A, although patients receiving mycophenolate sodium required more frequent rescue therapy for flare ups during the treatment period. Only a few side effects were reported and no serious adverse events occurred. One small case series reported no significant effect of mycophenolate mofetil in an especially refractory subgroup of patients with severe AD [46]. Key side effects from treatment with mycophenolate derivates are gastrointestinal symptoms, including nausea, diarrhoea, and abdominal cramping—these decrease with the use of enteric-coated mycophenolate sodium and most patients will tolerate treatment if the daily dose is divided in two. Cytopenias are of major potential concern and patients undergoing treatment require regular monitoring [20•, 42, 43]. Lastly, an increased susceptibility to infections and liver enzyme abnormalities has been reported [47]. This drug is teratogenic and should be used accordingly.

Biologics

Interferon-gamma

Interferon-gamma is a dimerised, soluble cytokine whose action in AD is poorly understood, but stems in part from its immunostimulatory and immunomodulatory effects [48]. Interferon-gamma has shown varying results in the treatment of severe AD [49]. Several studies, including two RCTs, demonstrated a reduction in both signs and symptoms of AD [50–54]. Response rates were low in an open-label study, only showing an effect in patients having IgE levels below 1,500 IU/ml [55]. Differences in study designs make conclusions regarding the most optimal treatment strategy difficult. Side effects include granulocytopenia, fever, chills, myalgias, headache, and pain at the injection site; the flu-like

symptoms can be prevented with administration of acetaminophen at bedtime the day prior to treatment [50]. The data suggest that interferon-gamma has only a limited role in the treatment of severe AD.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody that in a small, open uncontrolled study indicated a positive effect on the severity of AD. Six adults with severe AD all experienced significant improvement of disease activity and tolerated the treatment well [56]. This positive effect was not seen in a subsequent case report on two patients [57]. Side effects comprise fever, infusion reactions, and increased rates of infection.

Mepolizumab

This humanized monoclonal antibody that recognizes interleukin-5 was investigated in a randomized trial including 40 adults with moderate to severe AD [58]. Two single doses of 750 mg mepolizumab did not result in significant improvement in patients with AD, despite a significant decrease in peripheral blood eosinophils. Only mild and temporary side effects were registered.

Omalizumab

Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that specifically binds to free human immunoglobulin E in the blood and interstitial fluid [59]. A number of case series describe a beneficial effect of omalizumab in patients with moderate to severe AD [60–62]. Two studies revealed a drastic effect of omalizumab in combination with either intravenous immunoglobulin or rituximab [63, 64]. In contrast, an RCT study including 20 patients did not show superior effect of omalizumab compared to placebo in patients suffering from chronic AD [65]. Side effects include injection site reactions, anaphylaxis, and possible increased risk of cancer.

Infliximab

Infliximab is a chimeric monoclonal antibody against tumour necrosis factor alpha (TNF-α). The effect of anti-TNFα treatment has been investigated in an open-label study including nine patients [66]. It was reported to significantly reduce severity and symptoms of AD during induction therapy in all patients, but failed to sustain this effect during long-term maintenance therapy. In addition there have been reports on poor effect and even exacerbations of AD linked to anti-TNFα treatment, and furthermore, patients with psoriasis have shown AD-like eruptions upon treatment with infliximab [67–70]. Infliximab therapy is associated with risks of infusion reactions, infections, and malignancy.

Alefacept

Alefacept is a fusion protein that binds CD2, and selectively inhibits T cell activation, and induces apoptosis of memory T cells. In two pilot studies of ten and nine adult patients with moderate to severe AD [71, 72], alefacept

decreased severity by 78 % in the first study, while in the second study only two patients experienced significant reduction in AD severity, and in one patient there was increased disease activity. Importantly, two of the participants withdrew as a result of AD exacerbation.

Tocilizumab

Tocilizumab is an interleukin-6 receptor antagonist investigated in a case series including three adult AD patients with disease refractory to topical treatment [73]. Two of these had failed cyclosporine A therapy, but no other systemic treatment had been tried in any of the patients. All experienced declining disease activity and could taper topical treatment; however, treatment led to severe infections.

Dupilumab

An antibody directed against the interleukin-4 receptor has shown promising results, with significant dose-related declines of AD severity and both reduction of body surface area affected and EASI score compared to placebo [74, 75]. The drug is currently being tested in phase III studies.

Intravenous immunoglobulin

Intravenous immunoglobulin contains the pooled, polyvalent, IgG antibodies extracted from plasma of blood donors. The mode of action of intravenous immunoglobulin is not fully elucidated but is believed to involve the inhibitory Fc receptor [76]. There are a number of cases and small studies showing a beneficial effect of intravenous immunoglobulin on severe recalcitrant AD [77, 78]; however, these are opposed by reports showing little or no improvement [79, 80]. A single RCT from 2011 including 40 paediatric patients documented a significant reduction in disease severity compared to placebo. Relapse of the disease occurred around six months after discontinuing treatment [81]. Consistent with other literature evaluating the use of intravenous immunoglobulin in patients with immunodeficiencies, hematologic disease or Kawasaki syndrome, the best response is seen in children [78, 82, 83]. Side effects are seen in up to 20 % of infusions of intravenous immunoglobulin, but most are mild and transient, and serious adverse events are uncommon. Common side effects are malaise, fever, chills, headache, dyspnoea, and urticaria. These reactions often respond to temporary discontinuation of the infusion and NSAIDs, antihistamines, or glucocorticoids can be helpful in some cases.

Extracorporeal photopheresis

Extracorporeal photopheresis involves the collection of white blood cells with subsequent exposure to a photosensitizer, 8-methoxypsoralen, and ultraviolet A radiation. It is speculated that the immunosuppressive action of the procedure may derive from preferential apoptosis of activated or abnormal T cells [84]. Treatment with extracorporeal photopheresis suggests a beneficial effect in patients suffering from severe refractory AD, but has only been investigated in eight small studies [85–91]. In the largest study of 35 patients with severe, refractory AD, extracorporeal photopheresis led to a significant decrease in the

disease severity score [88]. There is some indication that the use of extracorporeal photopheresis has a bigger impact on subject symptoms like pruritus than on objective signs of disease activity [92].

Allergen-specific immunotherapy

The use of allergen-specific immunotherapy in allergic rhinitis is well documented, and as patients suffering from severe AD often have concomitant type I allergies causing allergic rhinitis and/or asthma, the use of allergen-specific immunotherapy in AD is meaningful [93]. One RCT investigated the efficacy of allergen-specific immunotherapy in patients with AD and allergy to house dust mites [94]. During a one-year treatment period, AD severity significantly decreased in a dose-dependent manner. This is supported by two other studies showing beneficial effect on AD severity when concomitant mite or pollen allergy was treated with either house dust mite or birch pollen extract, respectively. It should be noted that allergen-specific immunotherapy was of no benefit to AD patients without type I allergy [95, 96]. Side effects are related to administration route, and are mild and transient, including local reactions like oral pruritus or redness, pruritus and swelling.

Immunoadsorption

Immunoadsorption has been established as an effective and specific tool to remove immunoglobulin and immune complexes from the blood [97]. One open-label pilot study enrolled 12 adults with severe AD [98]. A total of ten immunoadsorptions were applied on five consecutive days in week 1 and week 5. All patients completing therapy (two drop-outs) experienced very significant reduction in both SCORAD and pruritus at week 13. One patient had a severe adverse event in the form of *Staphylococcus aureus* septicaemia. RCTs and larger studies on both adults and children are needed.

Discussion and conclusion

The high prevalence of AD implies that dermatologists frequently encounter severe cases of AD, even if it is only a small subset of the total number of AD cases. AD is caused by a complex interaction of both an inborn and an acquired barrier and immune dysfunction. No matter which systemic therapy is chosen, it should therefore never be unaccompanied. Systemic therapy should be accompanied by use of relevant skin emollients, avoidance of triggering factors, written and/or oral patient education, practical demonstration by an educated nurse, and very often, a topical treatment like corticosteroids or calcineurin inhibitors [14]. No registered systemic treatment option fulfils every need; and both patients and dermatologist are regularly faced with an absent or poor response to a given systemic therapy. This should not lead to the conclusion that any systemic treatment option will fail; rather, it should motivate the expert to collaborate with the patient to find a second, third or even fourth alternative. Systemic non-steroidal treatment options with grade A or B evidence include cyclosporine A, azathioprine, methotrexate and mycophenolate mofetil [99••, 100••]; yet, as this review demonstrates, several other therapies, including newcomers in the field of biologics, look promising. When a patient is suitable

for systemic therapy, the choice of agent will depend not only on a possible licensing in the given country, but also on what is feasible in the given clinical setting, and most importantly, on the patient's sex, age, medical history, AD phenotype, comorbidities and expected level of adherence. The aim of the present review is to allow the clinician to make an informed choice about approach and systemic agent appropriate to the clinical situation at hand, rather than to claim which approach and systemic agent is correct in a given case. Clinicians are encouraged to go even further when standard regimens fail and to explore the literature in their search for productive therapeutic approaches. Lastly, we believe that a brighter future is in store for all AD patients, because basic research discoveries like the loss of function mutations in the filaggrin gene and new insights into the complex interaction between a skewed immunological response and a disrupted skin barrier function cast light over key factors in AD and have the potential to accelerate development of impending new drugs. An indication of how this may already be underway is verified by accessing clinicaltrials.gov, which on 16 June 2014 had no less than 19 open studies testing systemic treatment in AD patients, many of which involve new biologics.

Compliance with Ethics Guidelines

Conflict of Interest
Uffe Nygaard declares no conflict of interest. Christian Vestergaard is an investigator/speaker/advisor for Astellas, Leo Pharma, Abbvie, MSD, MEDA pharma, GSK. Mette Søndergaard Deleuran is a speaker and/or advisor for AbbVie A/S, MSD, Pierre fabre Dermo-cosmetique, Meda Pharma, Leo Pharma and Regenero.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Funding Sources
None.

Author Contributions
All authors have participated sufficiently in the work to take public responsibility for its contents as stated at http://www.publicationethics.org.uk

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One of the three most important RCTs on comparative efficacy and safety of systemic immunosupressives.

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