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# Systemic Therapy of Atopic Dermatitis in Children

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## Abstract

Atopic dermatitis (AD) is a common disease in childhood that is a serious burden on patients and their families. Most AD is mild and can be managed with the use of emollients and standard therapy consisting of topical corticosteroids or topical calcineurin inhibitors. However, in a subgroup of patients with moderate to severe AD, the disease is recalcitrant to topical therapy and systemic treatments become necessary.

Short courses of systemic corticosteroids are often used in clinical practice, but their use is controversial. International guidelines suggest that in the case of acute flare-ups, patients might benefit from a short course of systemic corticosteroids, but long-term use and use in children should be avoided. Ciclosporin is an immunosuppressant agent that acts directly on cells of the immune system, with an inhibitory effect on T cells. When AD cannot be controlled by standard topical therapies, ciclosporin significantly decreases symptom scores, disease extent, pruritus and sleep deprivation, and improves quality of life. The most frequent adverse effects associated with the use of ciclosporin are hypertension and renal dysfunction, but they are usually reversible after drug discontinuation. Ciclosporin has been found to be safely used, effective and well tolerated in children with severe AD. However, studies to assess the long-term effectiveness and safety of ciclosporin in AD are lacking.

In patients for whom ciclosporin is not suitable, or when there is a lack of response, alternative drugs should be considered, such as azathioprine or interferon-γ. Intravenous immunoglobulins and the monoclonal antibody infliximab only have a place in the systemic therapy of AD when other drugs have failed. Mycophenolate mofetil has recently been introduced in the treatment of recalcitrant AD. Efalizumab and omalizumab are monoclonal antibodies with a possible future role in the treatment of AD, but further studies are needed.

Atopic dermatitis (AD) is the most frequent chronic skin disease of early childhood, with a relapsing remitting course that is responsible for a serious burden on the affected children and their families. AD worldwide prevalence is increasing, being highest in the paediatric population with values of up to 20%.[1,2] Early onset of AD has been associated with an increased risk of asthma, and many authors have indicated AD as the first manifestation of the so called atopic march.[3] Moreover, the disease causes a significant impairment of quality of life (QOL).[4]

Most AD is mild, and patients can be treated with emollients and topical anti-inflammatory agents (i.e. topical corticosteroids and topical calcineurin inhibitors).[5-9] The prevalence of moderate AD is reported to vary between 7% and 33%, and of severe AD between 0% and 13%.[10-14] However, only a few population-based studies report the severity of AD and different severity scales are used; moreover, AD severity might vary in different populations. These factors may explain the discrepancies between the reported percentages.

When a patient does not respond to conventional topical treatment, compliance to therapy should be checked before prescribing systemic medications.[15] Nevertheless, in a subgroup of patients, the disease activity and the concurrent symptoms are recalcitrant and cannot be sufficiently controlled with the conventional topical treatments.[16,17]

The management of AD treatment has been widely discussed in several consensus conferences, and a step-based approach to the disease has been proposed[18] (see table I). Dry skin should be only treated with emollients and avoidance of trigger factors. For mild to moderate and moderate to severe forms of AD, topical corticosteroids of increasing potency and/or topical calcineurin inhibitors are suggested. Systemic therapy should only be considered in case of severe, recalcitrant AD. When symptoms flare repeatedly, physicians may consider several systemic therapies, such as aggressive short-course systemic corticosteroids, immunosuppressants, biologicals, antimicrobials, antihistamines and leukotriene inhibitors.[21]

## 1. Systemic Corticosteroids

Systemic corticosteroids are frequently used for short-term therapy of severe AD, but their use is controversial. In 2003, reports from a consensus conference indicated that they may be associated with significant adverse effects (e.g. suppression

**Table I.** Step-based approach to the therapy of atopic dermatitis (AD) according to the severity score

| Type of AD | Therapy |
|---|---|
| AD in remission | Emollients, skin hydration, avoidance of allergens or other triggers |
| Mild AD (e.g. SCORAD index <25) | Topical corticosteroids of low to mid potency and/or topical calcineurin inhibitors |
| Moderate AD (e.g. SCORAD index 26–50) | Topical corticosteroids of mid to high potency and/or topical calcineurin inhibitors |
| Severe recalcitrant AD (e.g. SCORAD index >50) | Systemic therapy |

**SCORAD index** = SCORing AD.[19,20]

of the hypothalamic-pituitary-adrenal axis or growth) and are not routinely recommended.[22]

A recent systematic review of systemic treatments for AD[16] identified only two randomized controlled trials evaluating the efficacy of systemic corticosteroids and including children affected by severe AD. The first study evaluated 4 weeks of daily oral beclometasone (as dipropionate) 0.8 mg/kg plus nasal beclometasone 0.4 mg/kg in 26 children affected by severe refractory AD. Mean severity of AD decreased by 22% and no severe adverse events were reported.[23] In the second study, patients were treated for 2 weeks with flunisolide (age-adjusted dose). Mean clinical severity was reduced by 39% and no relapses were observed for 3 weeks after discontinuation. No severe adverse events were reported.[24]

However, evidence from these trials is insufficient and no data could be identified for prednisolone, which is the standard systemic corticosteroid used in clinical practice. It has also been reported that patients often have severe symptom flares when systemic corticosteroids are tapered or discontinued.[18,21] The 2006 Practical Allergy (PRACTALL) consensus group guidelines suggest that in the case of acute flare-ups, patients might benefit from a short course of systemic corticosteroids, but long-term use and use in children should be avoided.[18]

In 1994, a study was published showing clinical improvement in five of seven children affected by severe AD and treated with intravenous bolus dosages of methylprednisolone (20 mg/kg/day) for 3 days.[25] Improvement was maintained for several months and no severe adverse effects were observed. However, to the best of our knowledge, no other studies have been published confirming the usefulness of intravenous corticosteroids for the treatment of AD.

When short courses of systemic corticosteroids are used, parents should be reassured by the clinician about the possible adverse effects, as suppression of the hypothalamic-pituitary-adrenal axis can be avoided by a correct progressive reduction of dose (table II), and effects on growth or Cushing's syndrome only occur with long-term therapy.

**Table II.** Corticosteroid therapy tapering

| Duration of corticosteroid course | Tapering |
|---|---|
| <1 week | Does not require tapering |
| <1 month | Taper over 7–14 days until the physiological dose,[a] then taper from physiological dose to complete withdrawal |
| >1 month | Taper gradually every 15–30 days until the physiological dose,[a] then taper from physiological dose to complete withdrawal |

a Physiological dose ~10 mg/m$^2$/24 hours.[26,27]

## 2. Ciclosporin

Ciclosporin is an immunosuppressant prodrug that acts directly on cells of the immune system by inhibiting T-cell function.[28,29] Ciclosporin exerts its immunosuppressive action by binding to an intracellular immunophilin (cyclophilin) and forming a complex that inhibits the activity of the enzyme calcineurin phosphatase. This enzyme is involved in an immunological pathway that leads to the transcription of several cytokine genes, particularly interleukin (IL)-2, which is recognized as the major activation factor for T cells in numerous immunological processes. Inhibition of IL-2 production blocks the activation of T helper cells and T regulatory cells, and the activation of natural killer cells and monocytes. AD symptoms respond to ciclosporin because the disease is mediated by activated T cells and thus is sensitive to a reduction in IL-2 expression.

The role of ciclosporin in severe, recalcitrant AD is well established. In patients in whom AD cannot be controlled by standard topical therapies, ciclosporin significantly decreases symptom scores, disease extent, pruritus and sleep deprivation, and has also been shown to improve QOL.[28] A recent meta-analysis considered 15 studies on the use of ciclosporin in AD, with a total of 602 patients, including both children and adults.[17] Consistent evidence was found that short-term use of the drug effectively decreased AD severity. The mean clinical improvement after 6–8 weeks was calculated as being approximately 55%, but after discontinuation

50% of patients relapsed within 2 weeks and 80% within 6 weeks.[17]

The recommended starting dosage, which applies for both children and adults, is 5 mg/kg twice daily for the first 2 weeks, by which time a clinical improvement should be observed. The dosage can then be reduced to 1.5–3 mg/kg/day, according to clinical response and the patient's serum creatinine levels. If a clinical response is observed, the ciclosporin dose can be tapered slowly over the next 2–3 months. The total length of treatment is usually 6–12 months.[29] Some authors suggest that if there is no response after the first 2 weeks of treatment the dosage can be temporarily increased to 7 mg/kg/day.[21]

The most common adverse effects are hypertension, renal dysfunction, headache, hypertrichosis, gingival hyperplasia and paraesthesia.[28] Renal toxicity, which is dose- and time-related,[17,28] can be acute or chronic, but usually responds rapidly to either reduction in dose or cessation of the drug.[30] However, the dose should be decreased if serum creatinine levels increase by 30% above the baseline value. Serum creatinine levels should be checked at 2-week intervals for the first 3 months and measured monthly thereafter. If patients are treated for >12 months, creatinine clearance should also be checked annually to estimate glomerular filtration rate.[29] The incidence of mild hypertension has been estimated to vary between 7.8% and 57%, but a dose reduction or the addition of an antihypertensive agent can usually control blood pressure.[28] Blood pressure should be measured at 2, 4 and 8 weeks after beginning ciclosporin and monthly thereafter.[29] An increased risk of lymphoma or internal malignancies was anecdotely reported, but a recent meta-analysis did not highlight an increased risk of lymphoproliferative disorders.[17]

In 2004, Griffiths et al.[31] published comprehensive guidelines about the monitoring of ciclosporin therapy in daily practice for adult patients affected by psoriasis and suggested that it can be applied to dermatological conditions other than psoriasis.[29] In the absence of such guidelines and algorithms for children, we suggest these indications should also be followed for childhood AD.

Paediatric trials indicate that renal toxicity and hypertension are rare in children. Harper et al.[32] evaluated 43 patients aged 2–16 years who received ciclosporin for multiple 12-week courses versus continuous ciclosporin therapy 5 mg/kg/day for up to 1 year. They found no significant difference between the groups, and no overall increase in serum creatinine or blood pressure. Similar safety results were also published by Berth-Jones and colleagues[33] for 27 children aged 2–16 years who were treated for 6 weeks with ciclosporin 5 mg/kg/day. Bunikowski et al.,[34] who treated ten children aged 1–15 years with ciclosporin, found one patient with an increase in creatinine level of >30% from baseline. Nevertheless, these studies do highlight adverse effects such as gastrointestinal symptoms, paraesthesia and headache.

There are no clear indications about the need to check plasma ciclosporin concentrations during therapy in patients with AD. Trough-level monitoring is common but does not necessarily reflect the actual exposure, which is better assessed by measuring ciclosporin concentration 2 hours after intake.[28] Drugs that inhibit the cytochrome P450 system can increase ciclosporin concentrations, whereas inducing drugs can lower it.[31]

Ciclosporin has been found to be safely used, effective and well tolerated in children with severe AD.[33] Overall, the effectiveness of ciclosporin is similar in adults and children, whereas the tolerability might be better in children.[17] However, studies to assess the long-term effectiveness and safety of ciclosporin in AD, mainly addressing the point of possible malignancies, are lacking.

Surprisingly, ciclosporin does not show such effectiveness in paediatric rheumatology, mainly in juvenile idiopathic arthritis,[35] unless associated with methotrexate.[36]

## 3. Azathioprine

Azathioprine is a long-known systemic immunosuppressive agent affecting purine nucleotide synthesis and metabolism, which has been shown to be effective for many dermatological

conditions and can be used, as a non-licenced indication, for AD.[18,37] It has several adverse effects, including myelosuppression, hepatotoxicity and susceptibility for infection, and the recommended dosage (1–3 mg/kg/day) should be determined on the basis of individual thiopurine methyl-transferase (TPMT) levels.[38]

In a randomized, double-blind, crossover, placebo-controlled trial of 37 adults affected by severe AD, a mean reduction of 27% in disease activity after 2 weeks of treatment with azathioprine 2.5 mg/kg was observed.[39] In 2002, a study was published in which 48 children aged 6–16 years who were affected by severe AD and had normal TPMT levels were treated with azathioprine 2–3.5 mg/kg once daily. The response was excellent in 28 of the patients, good in 13 and poor in 7.[40] No patients developed neutropenia, 15 developed transient lymphopenia (always $>1.5\times10^9\times L^{-1}$), 3 a mild microcytosis, 1 a transient minor thrombocytopenia and 5 transient abnormalities in liver function tests. In the absence of defined protocols for the use of azathioprine in childhood AD, patients were treated for up to 2 years and then treatment was discontinued. These results appear to indicate that in children homozygous for the high-activity TPMT allele, azathioprine can be started at a dosage of 3 mg/kg/day. Blood cell counts should be performed at 3 and 12 weeks and at 3-monthly intervals thereafter.

Azathioprine could be used for short-term treatment in patients who are not eligible for, or are unresponsive to, ciclosporin.[16]

## 4. Interferon-γ

The rationale for the use of interferon (IFN)-γ in the therapy of AD is based on the evidence of reduced production of this glycoprotein *in vitro* by mononuclear cells of patients with AD, and on the fact that IFNγ causes an inhibition of IgE production mediated by IL-4.[38] This mechanism should be able to restore immune balance and lead to clinical improvement.[41]

The possible role of IFNγ ($1.5\times10^6$ IU/m$^2$ body surface area/day) in adulthood and childhood AD was investigated in two randomized controlled trials that showed superiority of IFNγ over placebo. Adverse events were not reported.[42,43] However, important quality criteria were not met in these trials, and therefore the role of IFNγ in AD systemic therapy is limited to those patients who are not eligible for, or are unresponsive to, ciclosporin.[16]

## 5. Intravenous Immunoglobulin

The role of intravenous immunoglobulin (IVIg) in the systemic therapy of recalcitrant AD has only been tested in small studies, but results did not indicate a good effectiveness and serious adverse events were highlighted (hypertension, transient serum creatinine increase and serum sickness-like reaction).[44-46]

## 6. Infliximab

Anti-tumour necrosis factor (TNF)-α drugs have been proposed for the treatment of severe, refractory AD. TNFα is a proinflammatory cytokine released by macrophages, monocytes, T cells, keratinocytes and dendrocytes. It promotes inflammation by inducing nuclear factor-κB, IL-1, IL-6 and IL-8, and upregulating the production of adhesion molecules, thus favouring extravasation and migration.[47]

Infliximab is a monoclonal antibody that binds and neutralizes TNFα, resulting in complement fixation and induction of antibody-mediated cytotoxicity against cells expressing the cytokine on their membrane.[47] The possible role of infliximab in allergic disorders is of increasing interest, mainly for severe, refractory asthma.[48,49] Few data are available for AD. A study conducted on nine patients with moderate to severe AD showed promising results.[50]

However, the possible adverse effects are noteworthy, including reactivation of latent tuberculosis and severe disseminated fungal or bacterial infections. Exacerbation or new onset of demyelinating disorders, and the development of autoimmunity and lymphoma are controversial but of concern.[47]

As far as present evidence shows, infliximab should be only considered in patients not

responding to ciclosporin, systemic corticosteroids, azathioprine or IFNγ.[16]

## 7. Antimicrobials

Because of both genetic and environmental factors, the skin of AD patients shows a striking susceptibility to overinfection by *Staphylococcus aureus*. In >90% of these patients, a massive skin colonization, with up to $10^7$ colony forming units/$cm^2$ of lesional skin, can be found, whereas only 5% of healthy individuals show skin colonization by the same pathogen.[51-53] In the case of widespread bacterial infection, treatment with first- or second-generation cephalosporins or semisynthetic penicillins for 7–10 days is usually effective; clindamycin or oral fusidic acid are possible alternatives in patients allergic to penicillin or cephalosporin. Recolonization after antibacterial therapy occurs rapidly, but maintenance antibacterial therapy should be avoided because meticillin-resistant organisms may develop.[15,18,54]

## 8. Antihistamines

The most common and least tolerated symptom of AD is itching, which is usually worse at night and frequently disrupts sleep. Patients with AD have a reduced threshold for pruritus and its control allows an important improvement in QOL for both patients and caregivers. Pathogenesis of pruritus in AD is complex and poorly understood. Allergen-induced release of histamine from skin mast cells is one of the implicated mechanisms even though it is not an exclusive cause; other substances are also responsible, such as cytokines, neuropeptides, proteases, eicosanoids and eosinophil-derived proteins.[18,55]

First-generation antihistamines may be helpful as a result of their sedative properties,[15,18] whereas second-generation antihistamines seem to have little or no value.[15,56] However, treatment with systemic or topical corticosteroids and calcineurin inhibitors, determining a decrease in the production of several proinflammatory cytokines, usually allows a rapid improvement of itching in AD patients.[15] Topical antihistamines should be avoided because of potential sensitization.[15]

## 9. Leukotriene Inhibitors

Cysteinyl leukotrienes are potent proinflammatory mediators and there is evidence of enhanced leukotriene production in AD pathogenesis.[57] By competitive binding to the cysteinyl leukotriene 1 receptor, leukotriene receptor antagonist drugs (montelukast, zafirlukast and pranlukast) block the effects of cysteinyl leukotrienes and alleviate the symptoms of chronic inflammatory diseases such as allergic asthma and rhinitis. A possible role of these drugs in AD has been suggested, but results are controversial.

In a clinical double-blind study of patients aged 6–16 years with moderate to severe AD, administration of montelukast 5 mg/day for 4 weeks resulted in significant decrease in AD severity. However, in another study in patients with severe AD that used different dosages (5, 10 and 20 mg/day), there was a partial improvement in only a few patients.

At present, no actual benefit of these drugs in AD has been shown.[58]

## 10. Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive agent derived from mycophenolic acid, which has immunomodulatory effects that are due to inhibition of inosine monophosphate dehydrogenase. It regulates the *de novo* purine biosynthesis, and particularly of the type II isoform that is expressed in activated B and T cells. This inhibits the proliferation of these cells, which need purine *de novo* production; unwanted effects on other cell types are minimized.[59]

The first reports of successful use of MMF in ten adults with severe recalcitrant AD were published in 1999 and 2001.[60,61] Neuber et al.,[62] and Benez and Fierlbeck[63] reported similar results in adult populations, whereas Hansen and colleagues[64] described failure of treatment with MMF in five adults with refractory AD.

In 2007, Heller et al.[65] reported results on the use of MMF in 14 children affected by severe refractory AD. Most patients successfully responded to the treatment and no severe adverse effects, such as infectious complications, myelodepression or elevated liver enzymes, developed. The most common adverse effects, occurring in 10–30% of patients, were nausea, vomiting, diarrhoea and abdominal discomfort.

Oral MMF at dosages of 30–50 mg/kg/day or 1200 mg/m$^2$/day seem to be a safely used, well tolerated and effective treatment for severe AD of childhood.

## 11. Efalizumab and Omalizumab

The use of monoclonal antibodies in AD systemic therapy is still in a clinical trial phase.

Efalizumab is an inhibitor of T-cell activation and migration that acts by binding to CD11a, which is a subunit of a T-cell surface molecule with important roles in cell activation, migration to skin and cytotoxic function. The binding of efalizumab to CD11a prevents migration of T cells from blood vessels to the skin.[66] Efalizumab is approved for the treatment of psoriasis and has been tested, on an off-label basis, in a pilot study of ten adults affected by severe AD.[67] This study showed significant clinical improvements in six of ten subjects. A previous report indicated a gradual clinical improvement in a child and an adult with severe AD who were treated for 3–6 months.[68] However, further studies are needed to establish the effective role of this drug in AD therapy.

Omalizumab is a humanized monoclonal anti-IgE antibody that binds to the IgE molecule at the high-affinity receptor binding site, significantly reducing the amount of free IgE circulating in serum. It has to be administered subcutaneously according to the patient's weight and baseline IgE titres (0.016 mg/kg/IU). Its efficacy in asthma, allergic rhinitis, food allergy and latex allergy has been demonstrated for patients aged ≥12 years, but its role in AD has not yet been established.[69] A few years ago, omalizumab was tested on three adults with severe AD and baseline serum IgE levels of 5440–24 400 IU/mL, but results were not positive.[70] In 2006, three case reports of children aged 10–13 years with refractory AD and total serum IgE levels of 1990–6120 IU/mL describing successful treatment with omalizumab were published.[71] Vigo et al.[72] published preliminary data of a trial of omalizumab for allergic asthma involving seven patients aged 7–58 years who were affected by concomitant moderate to severe AD refractory to conventional treatments and with total serum IgE levels of 226–2020 IU/mL. They showed an evident decrease in AD severity after 7 months of therapy in the absence of severe adverse effects. The reasons for the discrepancy of the previous results could be referred to the very high levels of IgE titres in the study by Krathen and Hsu,[70] so that the dosage of omalizumab was much lower (0.002–0.00005 mg/kg/IU) than the recommended dosage. However, omalizumab might be an interesting and useful tool to establish the role of IgE in AD.[69] It has also been suggested that it might have a role in patients with AD and concomitant food allergy.[15]

## 12. Conclusions

At present, the only drug showing convincing evidence for its use in the systemic treatment of severe, recalcitrant AD is ciclosporin.[15,16] However, because of its possible important adverse effects, its dose should always be adapted to the individual patient in order to reach the lowest possible dose. Systemic corticosteroids are frequently used for short-term therapy of severe AD, but their use is not evidence based and patients often have severe symptom flares when the drugs are tapered or discontinued.[3,14] Alternative drugs, such as azathioprine, IFNγ, IVIg and infliximab should only be considered when ciclosporin is not suitable or does not produce a suitable response. At present, MMF, efalizumab and omalizumab are possible future treatments, but further studies are needed.

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