

PHARMACOLOGICAL TREATMENT OF ATOPIC DERMATITIS

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ABSTRACT

Pharmacological treatment is required for almost all cases of atopic dermatitis. All require topical treatment and a sedating antihistamine, while the minority will, in addition, need a more aggressive form of systemic therapy. These modalities are discussed and motivated, with some suggestions on their use.

INTRODUCTION

Patients suffering from atopic dermatitis (AD) invariably require some form of pharmacological intervention. As one can never rely on the drugs alone to control the dermatitis, they should be used in addition to the conservative and non-pharmacological measures mentioned elsewhere. Treatment always takes on the form of topical medication, but more severe cases may also require systemic treatment.

TOPICAL MEDICATION USED FOR AD

TOPICAL CORTICOSTEROIDS (TCS)

TCS are, after several decades of use, still the mainstay of treatment for AD and are still the most useful, effective and affordable group of products for this indication¹. They affect their anti-inflammatory-, immunosuppressive-, antiproliferative- and vasoconstrictive effects through a variety of mechanisms. It would be unthinkable to try and manage AD without constant access to these valuable drugs. If TCS is used correctly, the side-effect profile is excellent, with the so-called "steroid phobia" being largely unfounded.

The available TCS are not all the same. Knowledge about the strength of individual molecules and the role that the vehicle in which the drug is presented plays in its effect is essential. This enhances the efficacy and limits the unwanted side-effects.

When deciding on a specific product to be used from the bewildering array of products available, the following factors have to be taken into consideration every time:

- Nature of the skin lesions (acute, sub-acute or chronic dermatitis);
- Extent of involvement;

- Skin areas affected (face versus skin folds versus limbs versus trunk);
- Age and size of the patient;
- Potency of the molecule;
- Vehicle (formulation) of the product;
- Quantity to dispense;
- Price.

TCS are available in several different strength classes (three to seven, depending on one's taste for detail); three classes usually suffice for practical purposes: Potent, medium potency and weak. Side-effects are loosely linked to the potency profile of each molecule, but this has changed over the years with some of the newer drugs having less severe side-effects than one would expect from their potency². Within a particular potency group, there is no evidence that one molecule is superior to another.

Examples in the potent group include clobetasol, betamethasone, diflucortolone and fluocinolone. In the medium potency group, we find mometasone furoate, methylprednisolone aceponate, fluticasone propionate, beclomethasone dipropionate, clobetasone butyrate and hydrocortisone 17-butyrate. The weak group consists mostly of the 1% hydrocortisone preparations.

More potent preparations are recommended for thick (more chronic) dermatitis lesions and thick skin areas (limbs, trunk, scalp). The weak potency group should be used on thin skin areas (face, genitals) and skin folds.

The effects and absorption of TCS are also dependent on the state of the skin where applied. It is more effective and more readily absorbed in inflamed areas, skin folds, occluded areas (especially the diaper area) and thin skin areas. In young children, the area treated may be proportionally large

with a bigger chance for systemic absorption of the drugs. "Wet wrap" therapy greatly enhances systemic absorption.

Broadly speaking, TCS are available as fatty ointments, ointments, lipocreams, creams, gels, water-based lotions and alcohol-based lotions. For a specific molecule, ointments are the most potent and penetrate the deepest, with the highest potential for atrophy, while lotions are the weakest and penetrate the least. Creams and gels fall in between. We recommend ointments for thick, dry lesions and for thick skin areas, creams for sub-acute, thinner lesions on thin skin areas and lotions for scalp (alcohol-based) and wet lesions (water-based).

TCS are often compounded into a variety of cream bases, mostly for financial reasons, in order to "stretch" the medication. The efficacy and side-effects of the drugs are not significantly affected by this. The TCS should not be mixed into aqueous cream, as the steroids are not stable in this base for prolonged periods. Cetomacrogol is the preferred base for the dilution of TCS.

TCS may be used in pregnancy and lactation. The weak or moderately potent products are preferred, as a significant association with fetal growth retardation has been found with the use of potent TCS³. TCS should not be applied on the nipples during lactation.

When calculating the quantity to be prescribed, the fingertip unit (FTU) is useful. The adult index finger, from distal crease to the tip equals 0.5 g. This aids monitoring compliance and use. A useful guideline for the amount to be prescribed is shown in Table I.

The potential side-effects of TCS are numerous, with steroid acne, peri-oral rosacea, skin infections, skin atrophy and systemic absorption the most important. Details can be found elsewhere⁶.

TCS should be used for all symptomatic AD lesions. Available evidence suggests that once-daily use is as effective as twice-daily use.

No definite guidelines are available regarding maintenance treatment with TCS for AD. Long term, daily use will obviously increase the risk for side-effects, like skin atrophy and adrenal axis suppression (children, large skin areas). Regimens of intermittent treatment have become popular. One option is treating patients on week days only, skipping weekends, while another recommends treating on weekends only, skipping week days. Both options have been shown to be effective⁷. Combining TCS with topical calcineurin inhibitors (TCI), as maintenance, with TCS used only for flares of the dermatitis, further confuses the issue.

The ideal approach is to use TCS for active dermatitis until clearance has been achieved, TCI used to maintain the remission in symptoms, with TCS reintroduced for flares. The high cost of TCI, though, makes one of the intermittent TCS regimens attractive as maintenance option. Cases have to be individualised, with surface area and skin areas affected, stability or instability of the dermatitis, age of the patient and financial factors taken into account.

TOPICAL CALCINEURIN INHIBITORS (TCI)

TCI have been proven as effective, reliable and safe treatment for AD. The main advantage of TCI over TCS is

Table I. Calculating the required quantity of topical steroids*

Anatomical area	Adults		Children < 6 years	
	# of FTU to cover	Amount for once daily use (g)	#FTU to cover	Amount for once daily use (g)
Face and neck	2.5	1.5	1.5	0.75
Anterior trunk	7	3.5	2.5	1.5
Posterior trunk	7	3.5	3.5	2
Arm	3	1.5	1.5	0.75
Hand, both sides	1	0.5	0.5	0.25
Leg	6	3	2.5	1.5
Foot	2	1	1	0.5

*Simplified from ^{4, 5}

the absence of side-effects, like skin atrophy and adrenal axis suppression. They do not act as rapidly and are not as potent as some of the TCS, but are the products of choice for sensitive skin areas (face, skin folds, and diaper area). They are thus potentially safer for long term use than TCS.

Two preparations are available in South Africa: Pimecrolimus and tacrolimus. Tacrolimus is more potent in action^{8,9} and registered for use for moderate to severe AD, while pimecrolimus is registered for moderate AD. Both have similar side-effect profiles, usually limited to transient stinging on application, with a theoretical risk of increased cutaneous infections with prolonged use. The "Black Box" warning in the package insert refers to the potential development of cutaneous lymphoma after long term use. This fear has been proven to be largely unfounded¹⁰.

In South Africa, tacrolimus is registered for use in children from the age of two years (0.03% strength) and in adults and adolescents from the age of 16 years (both 0.03% and 0.1% strengths). Treatment is initiated with the weaker strength twice daily until cleared. This can be changed to the 0.1% preparation if needed and, if after three weeks no response is seen, alternative treatment should be used.^{11,12,13} Response can usually be expected within 48 hours.

Both TCI's can be used for prevention of flares of AD, shown in several studies^{14,15} and proactive treatment with tacrolimus two or three times weekly, as maintenance can significantly prevent flares in paediatric and adult patients^{14,15}.

TCI can thus be used for active dermatitis of the face and skin folds with good effect, and be used as maintenance treatment in patients in remission with mild symptoms, together with emollients (see earlier), reserving TCS for flairs of dermatitis. Maintenance can be structured as for TCS.

Systemic absorption of both products has been reported as negligible in several studies^{16,17}, except in patients suffering from the very rare Netherton's syndrome.

SYSTEMIC MEDICATION FOR AD

Systemic treatment is reserved for AD that, despite implementing all the conservative measures and using appropriate topical treatment correctly, continues to be active, symptomatic, with severe impact on the quality of life of the patient. The topical management has to continue, regardless of the systemic method used.

ANTIHISTAMINES

Sedating antihistamines have excellent antipruritic effects and are indispensable in AD management. Hydroxyzine is the gold standard for all age groups. Chlorpheniramine and promethazine can also be used. These drugs should be used at bedtime to avoid sedation during the day.

Non-sedating antihistamines uniformly show disappointing efficacy in AD treatment.

SYSTEMIC CORTICOSTEROIDS (SCS)

SCS are not recommended for routine use for AD, because of the chronic, long term nature of the disease and the propensity for tachyphylaxis that is so common in AD. AD responds dramatically well initially when SCS are administered, but the effect tends to wear off with repeated use, necessitating increase in dosage and frequency of administration, often resulting in severe side-effects. Long term use should therefore be avoided¹⁸. The habit of giving regular intramuscular injections of long-acting SCS should specifically be strongly discouraged, because patients become dependent on these and often seek this treatment from multiple practitioners as "an easy way out". Alternative systemic medications as discussed below are not as rapidly effective as SCS, but much more acceptable for long term use.

CICLOSPORIN (CS)

This systemic calcineurin inhibitor is an excellent treatment option for AD in adults and children^{19,20,21,22}. It is highly effective and safe, as long as appropriate monitoring is in place. It is faster acting than MTX and has fewer side-effects, but the high cost is often prohibitive.

Serious adverse effects are rare, with relatively frequent, minor reversible alterations in renal function reported.^{19,20} Contra-indications to the use of ciclosporin include renal- or liver function impairment, immunodeficiency, malignancies, previous PUVA therapy (controversial) and hypertension.

The drug is a potent immunosuppressant and tuberculosis has to be excluded beforehand. Renal functions and blood pressure have to be checked and regularly tested during treatment. Ideally, trough blood levels of the drug should be tested at follow-up visits and dosage adjusted accordingly, until a steady state is achieved. Increase in skin cancers in older individuals, hypertrichosis and gingival hyperplasia are other side-effects.

Ketoconazole, itraconazole, erythromycin, clarithromycin and certain non-steroidal anti-inflammatory drugs²³ will increase blood levels of ciclosporin and may induce toxicity.

Patients are started at a dosage of about 2,5 to 5 mg/kg/day in divided doses and one can expect response within two or three weeks. Treatment continues until complete clearance has been achieved and is then stopped, to be recommenced if needed. Relapses frequently occur, but sustained improvement is often seen, provided the skin barrier has been stabilised and maintained. Long term maintenance is not recommended at this stage, as the chances for renal toxicity increase with long term use.

METHOTREXATE (MTX)

MTX is an effective, safe and inexpensive systemic treatment for severe AD resistant to topical medications^{24,25}. The regimen recommended is similar to that used for psoriasis. Dosages range from 5-25 mg per week, administered as a single once-weekly dose. Treatment should commence at the higher end of dosages, and continue for at least 8 weeks, to achieve maximum effect before dosage is adjusted up or down, depending on response. Once complete control has been achieved, the dosage can be slowly reduced over a two-monthly period, to end up at the minimum dosage required for each individual case.

Nausea is a common side-effect. Myelosuppression, interstitial pneumonitis and liver cirrhosis (after long term use) are the more feared potential side-effects. Contraception is essential in females. Tuberculosis should be excluded before treatment starts and bone marrow-, liver- and renal functions should be checked. Significant alcohol use is a relative contraindication to the use of MTX. Liver enzymes and serum albumin, together with full blood count, should be monitored at 1 week, 4 weeks and 12 weeks of treatment, and then three-monthly, as long as treatment is needed. Liver biopsy is still recommended after the patient had used a total of 2,5 g, which is seldom necessary in patients with AD. Full guidelines on the monitor of methotrexate treatment can be found elsewhere.²⁶

AZATHIOPRINE

Azathioprine provides a less expensive alternative to ciclosporin, or for patients with severe AD that failed to respond to ciclosporin or MTX.^{27,28}

Side-effects include myelosuppression, hepatotoxicity, lymphomas²⁹ and immunosuppression. Dosages range from 1-3 mg/kg/day. Ideally, thiopurinemethyltransferase (TPMT) levels of the patient should be determined before

a starting dose is calculated³⁰. Treatment can continue for up to two years and, as with ciclosporin, prolonged improvement may continue if conservative treatment of the dermatitis is sustained.

MYCOPHENOLATE MOFETIL (MMF)

MMF, most often used for prevention of graft rejection, is effective in treating severe refractory AD in adults and children^{31,32} with similar efficacy to azathioprine³³ and ciclosporin³⁴, with long term success.

The standard dosage in adults is 1 g orally twice daily, on an empty stomach. It is available as a 250 mg capsule. Blood counts have to be checked regularly to exclude neutropenia.

ANTIBIOTICS

Infected dermatitis should be treated with penicillinase-resistant penicillins, cephalosporins or clindamycin^{35,36}. Long term systemic antibiotics are contraindicated. Intranasal mupirocin combined with sodium hypochlorite (bleach) baths showed promise in a recent RCT in children³⁷. Oral antibiotics have no benefit on AD when used for skin that is not clinically infected.

ANTI-FUNGALS

Malassezia spp sensitisation plays an important role in AD in adults with head and neck dermatitis³⁸. IgE-mediated reactions to the fungus can be demonstrated in such patients. Systemic itraconazole³⁹ and ketoconazole⁴⁰ have shown significant benefit in such patients.

OTHER SYSTEMIC TREATMENT MODALITIES

Intravenous immunoglobulins (IVIg) may have a beneficial effect in the treatment of AD⁴¹, with a better response in children⁴² than adults. However, double-blind placebo-controlled clinical trials did not confirm this^{43,44}.

Interferon-gamma may be a useful modality for severe AD in children and adults, who have a history of recurrent viral skin infections⁴⁵.

None of the **biological drugs** have been convincingly shown to be effective in AD.

CONFLICT OF INTEREST:

The author was involved in the compilation of a publication on the guidelines for the management of atopic dermatitis, the costs of which was carried jointly by Astellas (SA) and Galderma SA.

REFERENCES

1. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology. *J Am Acad Dermatol* 2004;50:391-404.
2. Korting HC, Kerscher MJ, Schafer-Korting M. Topical glucocorticoids with improved benefit/risk ratio: do they exist? *J Am Acad Dermatol* 1992;27:87-92.

3. Chi CC, Kirtchig G, Gabbud JP, et al. Evidence-based (S3) guideline on topical corticosteroids in pregnancy. *Br J Dermatol* 2011;Jul 5. Doi:10.1111/j1365-2133.2011.10513.x.[Epub ahead of print]
4. Long CC, Finlay AY. The fingertip unit – a new practical measure. *Clin Exp Dermatol* 1991;16:444-7.
5. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *Br J Dermatol* 1998;138:293-6.
6. Gabbedy R, Kuhn B. *Comprehensive Dermatological Drug Therapy*. Third Edition 2013. Saunders. (Elsevier). 496-9.
7. Peserico A, Stadler G, Sebastian M, Suarez Fernandez R, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol* 2008;158:801-7.
8. Abramovits W, Fleischer AB Jr, Jaracz E, et al. Adult patients with moderate atopic dermatitis: tacrolimus ointment versus pimecrolimus cream. *J Drugs Dermatol* 2008;7(12):1153-8.
9. Kirsner RS, Heffernan MP, Antaya R. Safety and efficacy of tacrolimus ointment versus pimecrolimus cream in the treatment of patients with atopic dermatitis previously treated with corticosteroids. *Acta DermatoVenereol* 2010;90(1):58-64.
10. Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. *Br J Dermatol* 2011;165(3):465-73.
11. Kalavala M, Dohil MA. Calcineurin inhibitors in pediatric atopic dermatitis: A review of current evidence. *Am J Clin Dermatol* 2011;12(1):15-24.
12. Yang LP, Curran MP. Spotlight on topical pimecrolimus in pediatric atopic dermatitis. *Am J Clin Dermatol* 2010;11(4):295-8.
13. Chen SL, Yan J, Wang FX. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: A meta-analysis of randomized clinical trials. *J Dermatol Treat* 2010;21(3):144-56.
14. Thaci D, Chambers C, Sidhu M, et al. Twice weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: clinical efficacy and economic impact over 12 months. *J Eur Acad Dermatol Venereol* 2010;24(9):1040-6.
15. Paller AS, Eichenfeld LF, Kirsner RS, et al. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics* 2008;122(6):e1210-8.
16. Krueger GG, Eichenfeld L, Goodman JJ, et al. Pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adult and pediatric patients with moderate to severe atopic dermatitis. *J Drugs Dermatol* 2007;6(2):185-93.
17. Eichenfeld LF, Ho V, Matsunaga J, et al. Blood concentrations, tolerability and efficacy of pimecrolimus cream 1% in Japanese infants and children with atopic dermatitis. *J Dermatol* 2007;34(4):231-6.
18. Raimer SS. Managing pediatric atopic dermatitis. *Clin Pediatr* 2000;39:1-14.
19. Sowden JM, Berth-Jones J, Ross JS, et al. A multicentre, double blind, placebo controlled crossover study to assess the efficacy and safety of cyclosporin in adult patients with severe refractory atopic dermatitis. *Lancet* 1991;338:137-40.
20. Van Joost TH, Heule F, Korstanje M, et al. Cyclosporin in atopic dermatitis: a multicentre placebo controlled study. *Br J Dermatol* 1994;130:634-40.
21. Berth-Jones J, Finlay AY, Zaki I, et al. Cyclosporin in severe childhood atopic dermatitis: a multicentre study. *J Am Acad Dermatol* 1996;34:1016-21.
22. Haw S, Shin MK, Haw CR. The efficacy and safety of long-term oral cyclosporine treatment for patients with atopic dermatitis. *Ann Dermatol* 2010;22(1):9-15.
23. Gabbedy R, Kuhn B. *Comprehensive Dermatological Drug Therapy*. Third Edition 2013. Saunders. (Elsevier). 205-6.
24. Zoller L, Ramon M, Bergman R. Low Dose Methotrexate Therapy is Effective in Late-Onset Atopic Dermatitis and Idiopathic Eczema. *Israel Med Assoc J* 2008;10:413-4.
25. Lyakhovitsky A, Barzilai A, Heyman R, Baum S, Amichai B, Solomon M, Shapiro D, Trau H. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol* 2010;24:43-9.
26. Roenigk HH, Auerbach R, Maibach HI, et al. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1998;38:478-85.
27. Lear JT, English JSC. Severe and chronic allergic contact dermatitis responding to azathioprine therapy. *J Dermatol Treat* 1996;7:109-10.
28. Akhavan A, Rudikoff D. Atopic Dermatitis: systemic immunosuppressive therapy. *Semin Cutan Med Surg* 2008;27:151-5.
29. Parakkal D, Sifuentes H, Semer R, Ehrenpreis ED. Hepatosplenic T-cell lymphoma in patients receiving TNF-alpha inhibitor therapy: expanding the groups at risk. *Eur J Gastroenterol Hepatol* 2011;23:1150-6.
30. Ricci G, Dondi A, Patrizi A, Masi M. Systemic Therapy of Atopic Dermatitis in Children. *Drugs* 2009;69(3):297-306.
31. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007;157:127-32.
32. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007;32:23-7.
33. Waxweiler WT, Agans R, Morrell DS. Systemic Treatment of Pediatric Atopic Dermatitis with Azathioprine and Mycophenolate Mofetil. *Pediatric Dermatology* 2011;28(6):689-94.
34. Haecck IM, Knol MJ, Ten Berge O, Van Velsen SGA, De Bruin-Weller, Buijnzeel-Koomen CAFM. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: A randomized controlled trial. *J Am Acad Dermatol* 2011;64(6):1074-84.
35. Abeck D, Mempel M. Staphylococcus aureus colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol* 1998(139) Suppl. 53:13-6.
36. Niebuhr M, Mai U, Kapp A, Werfel T. Antibiotic treatment of cutaneous infections with Staphylococcus aureus in patients with atopic dermatitis: current antimicrobial resistances and susceptibilities. *Exp Dermatol* 2008;17:953-7.
37. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema. *Cochrane Database Syst Rev*. 2008; CD003871.
38. Schmid-Grendelmeier P, Scheynius A, Cramer R. The role of sensitization to Malassezia sympodialis in atopic eczema. *Chem Immunol Allergy* 2006;91:98-109.
39. Svejgaard E, Larsen PO, Deleuran M, Ternowitz T, Roed-Petersen J, Nilsson J. Treatment of head and neck dermatitis comparing itraconazole 200 mg and 400 mg daily for 1 week with placebo. *J Eur Acad Dermatol Venereol* 2004;18:445-9.
40. Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo K. Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. *Allergy* 2001;56:512-7.
41. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002;27:3-7.
42. Jee SJ, Kim JH, Baek HS, et al. Long-term efficacy of intravenous immunoglobulin therapy for moderate to severe childhood atopic dermatitis. *Allergy Asthma Immunol Res* 2011;3:89-95.
43. Paul C, Lahfa M, Bachelez H, et al. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002;147:518-22.
44. Bermanian MH, Movahedi M, Farhoudi A, et al. High doses intravenous immunoglobulin versus oral cyclosporine in the treatment of severe atopic dermatitis. *Iran J Allergy Asthma Immunol* 2005;4:139-43.
45. Frisch S, Siegfried EC. The clinical spectrum and therapeutic challenge of eczema herpeticum. *Pediatr Dermatol* 2011;28:46-52.