

8. Treatment strategies and compliance for the adult patient with atopic eczema

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Adult atopic eczema is often chronic and with moderate to severe disease activity commonly complicated with *Staphylococcus aureus* infection. The ‘gold standard’ therapy is emollients in combination with topical steroids whose potency depends on the location of the eczema. A combination of a steroid and an antibiotic has shown its efficacy in infected eczema. If long-term control is needed the calcineurin inhibitors, pimecrolimus and tacrolimus, have shown their efficacy. Another option is the use of UV light, where narrowband UVB seems most beneficial. Only rarely is systemic immunosuppressive treatment necessary. It is important to discuss treatment strategies with the patients to secure long-term control of the eczema.

INTRODUCTION

Treatment options for adult atopic eczema are numerous and include self-applied topical therapies, UV light treatments, systemic antimicrobials and systemic immunosuppressive agents, Chinese ‘herbal remedies’, and general advice concerning allergen avoidance, dietary aspects and ‘behavioural strategies’.

The problem for the doctor is not so much a lack of effective treatments, but rather the interaction with patients who have a chronic condition, asking them how much effort they will put into its management. Do patients want to just live with atopic eczema or are they willing to invest a lot of effort and time to control it? The problem, put at its simplest, is to help the patients choose a treatment they are happy with. If you as a doctor do not take time for this discussion, then the patient will most likely continue to suffer from relapsing eczema. Again, it is important to emphasize the long-term perspective of any therapy. In the pocket of one of my patients I found six tubes of topical steroids (four antimicrobial steroid combinations and two tubes of topical antiseptics)! It is obvious that the most appropriate treatment for this patient was not established.

AVAILABLE TREATMENTS

Topical steroids

As can be seen from the results of a recently published study (Table I), topical steroids work (1). Maintenance treatment with emollient and intermittent fluticasone maintained absence of disease in 81% of patients over a

4-month period. The principle is the same as in asthma sufferers: *to prevent attacks by ‘prophylactic treatment’*. More emphasis should be placed on long-term treatment strategies to maintain patients’ disease-free status.

Infection by Staphylococcus aureus

S. aureus is found on the lesions of virtually all patients with atopic dermatitis (AD). Superantigens released by *S. aureus* can initiate and exacerbate inflammation in atopic skin. There are combined antimicrobial-corticosteroid topical therapies approved for use in patients with AD. Their use is supported by the invariable presence of *S. aureus* on eczematous skin, the lack of innate immunity to *S. aureus* and its toxins, and the documented effect of *S. aureus* superantigens on atopic skin eliciting or augmenting the inflammation.

There are few well-documented studies assessing the efficacy of combined antimicrobial-corticosteroid preparations. One of the few studies conducted assessed the comparative efficacy of 2 weeks’ therapy with combined fusidic acid/hydrocortisone cream with its individual components in AD. There was a statistically significant difference among the treatments, the greatest proportion of responders being with fusidic acid/hydrocortisone cream (Table II) (2).

The primary negative consideration as regards the use of combined antimicrobial-corticosteroids relates to the possible emergence of antimicrobial resistance in *S. aureus*. Evidence indicates that when used for short periods, corticosteroid combinations with fusidic acid do not result in resistance. In a small study of 24 patients, aged 9 months to 14 years, 22 of whom had *S. aureus* present (susceptible to fusidic acid in 21, resistant in 1), patients received a total of 2 months’ treatment,

Table I. *Efficacy of fluticasone in reducing risk of relapse in atopic dermatitis*

	Fluticasone propionate 0.05% twice weekly plus emollient	Placebo cream daily
Number of patients	70	84
Outcome after 16 weeks		
Relapse (%)	19	64
No relapse (%)	81	36

Taken from Berth-Jones et al. (1).

Table II. Efficacy of fusidic acid/hydrocortisone cream in atopic dermatitis

	Fusidic acid/ hydrocortisone	Hydrocortisone	Fusidic acid
Number of patients	124	83	32
Responders (%)	63.7	50.6	34.4
Non-responders (%)	36.3	49.4	65.6

$p=0.007$, χ^2 test and Cochran-Mantel-Haentzel.
Taken from Ramsay et al. (2).

comprising two weekly rotations of fusidic acid/hydrocortisone and hydrocortisone alone. At the end of treatment, the eczema was controlled satisfactorily in 22 (91.7%) subjects. *S. aureus* could be isolated from the lesions of 17 patients and all bacteria were susceptible to fusidic acid (*, 3). In a review of results from eight studies involving short-term topical fusidic acid/beta-methasone therapy of over 1000 patients with eczema, there was little selection pressure for the development of resistance to fusidic acid in *S. aureus* (4). Examples of the clinical efficacy of fusidic acid/hydrocortisone can be seen in Fig. 1.

An interesting animal 'eczema model' is the NC/Nga mouse, which develops an atopic eczema-like condition if left in a normal environment. However, if kept in sterile conditions it does not develop eczema. The development of eczema is due to an interaction between the environment and the immune system of the mouse. The effect of clarithromycin, cefaclor and dexamethasone in preventing the appearance of eczema at 5, 6 and 9 weeks compared with an untreated group was investigated. At all assessments, clarithromycin prevented the appearance of eczema, and both antibiotics reduced the number of *S. aureus* on the skin. Dexamethasone only

affected the presence of eczema at 5 weeks, but not at 6 and 9 weeks (5). This again indicates the importance of *S. aureus* as a significant environmental factor in atopic eczema.

Topical immunomodulators (TIMs)

Pimecrolimus 1% is of value in mild to moderate AD and tacrolimus 0.03% is useful in mild (low concentration), moderate and severe (both at 0.1% concentration) disease, both as second-line treatment. These drugs are very useful for long-term control. Their drawbacks are expense, a burning sensation after application in a significant proportion of patients, particularly with tacrolimus, and a slight increased risk for outbreaks of herpes labialis.

Ultraviolet therapy

The benefits of UV therapy for the patients are the ease of use and the low cost, although the cost for health care providers is high. The negative aspects are that it is time-consuming, has moderate efficacy and involves a risk of skin cancer. Up to 40% of patients receiving UV therapy do not follow the treatment schedule and additional therapy is usually required, at least in the early stages – for example topical steroids – as otherwise the UV will exacerbate the condition.

Fig. 2 shows the comparative efficacy of narrowband UVB, UVA and visible light. The study involved 73 patients receiving twice-weekly treatment for a total of 12 weeks (maximum number of exposures 24) and allowed concomitant emollients and topical steroids. A total of 47 patients completed the treatment schedule. Although initially effective, relapse is seen within 3 months of completing UVA therapy, whereas with narrowband UVB there is no relapse (6), and the response is superior. Therefore, make sure that the

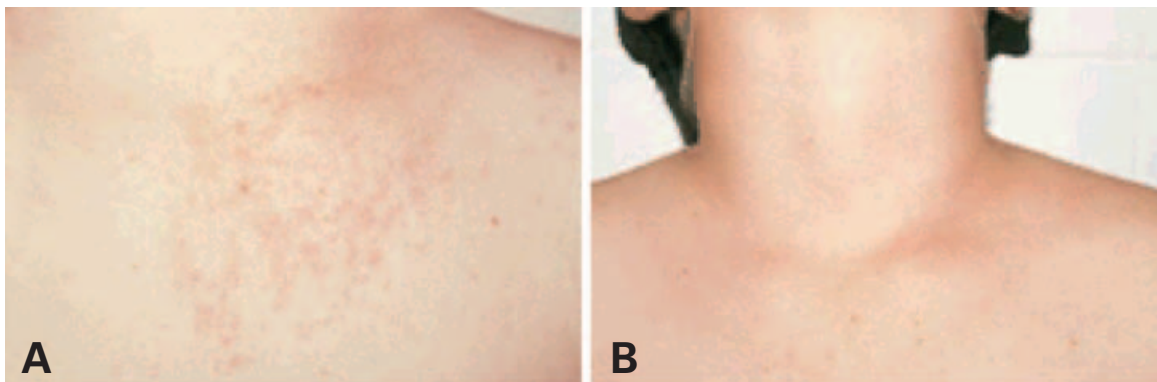


Fig. 1. Atopic eczema before (A) and after (B) treatment with Fucicort® twice daily.

*Chu AC: Incidence of resistance to fusidic acid in atopic eczema patients treated with topical fusidic acid, with or without topical steroid. Poster at the American Academy of Dermatology, 2001.

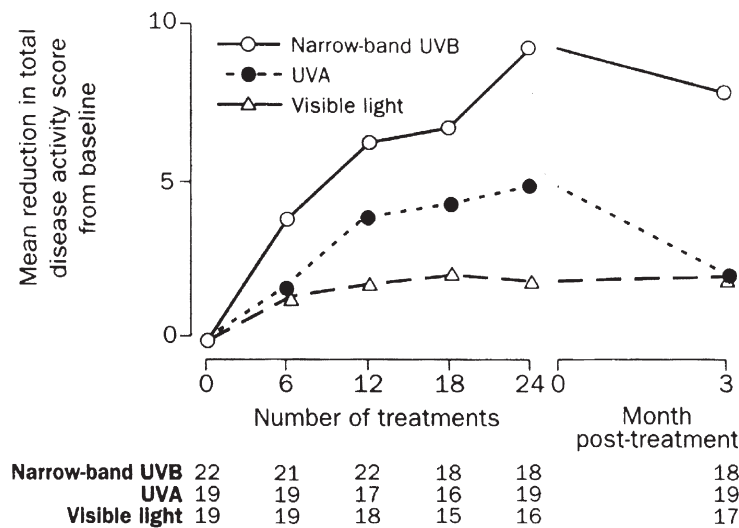


Fig. 2. Therapy with narrowband UVB, UVA and visible light. Reprinted with permission from Elsevier (The Lancet 2001; 357: 2012–2016).

patient has sufficient time to go through a UV therapy schedule and always combine with topical steroids plus emollients.

Systemic antibiotics

Systemic antibiotics are used frequently and there is no doubt that patients like them. However, evidence-based support for their efficacy is lacking (7) – it seems to be necessary to attack the *S. aureus* on the skin surface itself.

Systemic immunosuppression

- i) **Prednisone:** There are no valid studies on the use of prednisone, given either as short-term or long-term treatment. Prednisone at a low dose of 5–10 mg daily for up to 6 months is useful in small children whose parents are not able to cope with the rigours of topical therapy. They can be used in a similar way in adults, if compliance with topical therapy is poor. It also appears that whilst there may be a short-term growth-suppressive effect of whole body steroid therapy, there is a ‘catch up’ growth period when the eczema clears and the steroid treatment is stopped. Some of the modern steroids which are inactivated when passing through the liver may prove valuable. Similarly, we have occasionally found long-acting systemic steroids useful in adults given as one monthly injection. However, calcium and vitamin D supplementation should be given.
- ii) **Cyclosporin:** Efficacy ranges from being effective to very effective. The starting dose is 5 mg/kg daily in divided doses tapering down to 2–3 mg/kg daily. It may have to be given for 6 months to 2 years. The efficacy of cyclosporin is shown in

Table III, which also shows the limitations of therapy, namely that relapse is common afterwards. Cyclosporin is an expensive treatment for the patient. Pimecrolimus – systemically - may be the ‘new’ systemic treatment.

- iii) **Azathioprine:** There are few data on the efficacy of azathioprine. Optimal use is when combined with systemic steroids, where it has a ‘steroid-sparing effect’. It should only be used for very severe cases, and the dosage should be increased up to 3–4 mg/kg daily whilst watching for signs of toxicity. It may take 6 months before any effect is observed. Monitoring of leucocytes and platelets is important to observe any bone marrow suppression.
- iv) **High dose immunoglobulin (Ig):** It is not effective and not worth the cost.
- v) **Behavioural intervention:** This affects the patient’s attitude to the disease and its management. It is time-consuming and whilst beneficial

Table III. Efficacy of cyclosporin in atopic dermatitis

	Mean sleep score		Mean itch score	
	Placebo/ cyclosporin	Cyclosporin/ placebo	Placebo/ cyclosporin	Cyclosporin/ placebo
Baseline	47.6	44.7	56.6	51.1
8 weeks	43.3	13.2	53.0	23.4
16 weeks	13.8	41.3	9.9	50.9
Cyclosporin		13.5		16.6
Placebo		41.9		51.2
Difference	-28.4 (-41.9; -14.8)		-34.6 (-46.0; -23.2)	
p value	<0.001		<0.001	

Taken from Sowden et al. (7).

in increasing patient acceptance of the condition, it does not influence the disease status per se.

- vi) Chinese herbal medicines: There is evidence of clinical efficacy, but it is not standardized. It tastes awful, is expensive, and liver toxicity has been observed.

CONCLUSION

There are effective treatments available for AD which should be selected in considering disease severity. Systemic immunomodulators and UV therapy may be appropriate in the severe disease stage. Steroids/antibiotics can be used for up to 2 weeks at flare-ups, in order to eradicate *S. aureus*. Topical steroids and topical immunomodulators can be used to further control the disease once *S. aureus* has been eradicated. Emollients alone are suitable when the condition is under control.

Fig. 3 shows when the topical treatments could be used in relation to the stage and/or severity of the disease.

DISCUSSION

Thestrup-Pedersen; I would like to know from the group how common you believe urticaria is in atopic dermatitis and thus the need for the use of antihistamines.

Taieb; It is food allergy driven, particularly in children. The incidence in one study was around 30% and could be halved by using antihistamines.

Diepgen; We found no effect of antihistamine on the itching part of the SCORAD. However, antihistamines appear to have a steroid-sparing effect.

Thestrup-Pedersen; Cetirizine is a useful non-sedating antihistamine as it seems to carry anti-inflammatory capacities – especially on the eosinophils.

Diepgen; The sedating antihistamines may be preferable in some instances.

Agner; Is there any evidence of immunosuppression with long-term use of topical immunomodulators?

Thestrup-Pedersen; No, there is not a strong immunosuppressive effect in the skin – neither of topical steroids – nor of the new calcineurin inhibitors, although this issue is heavily discussed.

Langley; Studies of up to 3 years have not shown any immunosuppressive effect, nor has there been any apparent increase in cancer incidence.

Agner; I am a little concerned about long-term use, especially with regard to infections.

Andersen; I do not use topical immunomodulators in combination. What advice is there on use in the summer, should patients avoid exposure to sunlight and are there any data on the incidence of skin cancer?

Taieb; At the European Task Force on Atopic Dermatitis Meeting in Barcelona (EADV 2003) some *in vitro* data suggested that tacrolimus has photoprotective effects.

Diepgen; Tacrolimus has been combined with UV therapy in vitiligo.

Langley; The reason for the concern is that there are data on tacrolimus from animal studies and this is included on the product literature. A pimecrolimus study did not produce the same results, so there is

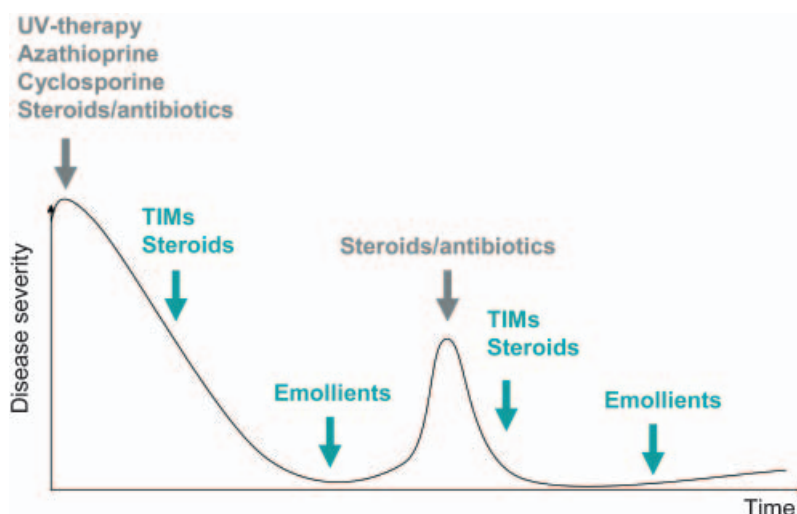


Fig. 3. The figure summarizes various treatment options for adults with atopic dermatitis – from the very severe group of patients to patients with more controllable disease. As atopic eczema in adults is often a chronic disease lasting from months to years, it may be of value to change the treatment options over time. TIMs, topical immunomodulators.

some confusion here. However, there has been no evidence of increased cancer in patients. The risk is probably simply theoretical. We should all be aware of phototherapy and sunlight damage regardless of TIM therapy.

Thestrup-Pedersen; There could be a risk in patients who have already got skin damage from excessive sunlight exposure.

Taieb; How long should azathioprine be given for? Could the new immunomodulators be used as replacement for cyclosporine?

Thestrup-Pedersen; Long-term treatment shows a reduced amount of medication over time. You need to use full dosage for some months until the inflammation is under control, then you can reduce usage.

McFadden; That is not unique to TIMs, the same applies with other topical therapies.

Langley; We need long-term controlled studies to see if these agents are disease modifying or not. We then have the study design problems and the placebo/control group problem.

McFadden; The problem with the theoretical cancer risk is that it will be years before we get the full data and you only need to get a scare story in the press. When tacrolimus is prescribed, are patients informed of the cancer risk?

Thestrup-Pedersen; Yes, and they also find the information on the internet.

Agner; What about use of these agents in children?

Thestrup-Pedersen; It does appear that if you give them early, they may ameliorate the disease. If you could prevent the IgE phenomenon by using TIMs early, this would be very useful. Maybe stopping the inflammation early might prevent food allergies. This is a nice thought. Early use of antimicrobials like fusidic acid may be similarly advantageous.

REFERENCES

- Berth-Jones J, Damstra RJ, Golsch S, Livden JK, van Hooiteghem O, Allegra F, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double-blind parallel group study. *BMJ* 2003; 326: 1367–1370.
- Ramsay CA, Savoie JM, Gilbert M, Gidon M, Kidson P. The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. *J Eur Acad Dermatol Venereol* 1996; 7(Suppl 1), S15–S22.
- Sowden JM, Berth-Jones J, Ross JS, Motley RJ, Marks R, Finlay AY, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991; 338: 137–140.
- Menday AP, Noble WC. Topical betamethasone/fusidic acid in eczema: efficacy against and emergence of resistance in *Staphylococcus aureus*. *J Dermatol Treat* 2000; 11: 143–149.
- Hashimoto Y, Kaneda Y, Takahashi N, Akashi S, Arai I, Nakaike S. Clarithromycin inhibits the development of dermatitis in NC/Nga mice. *Chemotherapy* 2003; 49: 222–228.
- Reynolds N, Franklin V, Gray J, Diffey B, Farr P. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001; 357: 2012–2016.
- Ewing CI, Ashcroft C, Gibbs AC, Jones GA, Connor PJ, David TJ. Flucloxacillin in the treatment of atopic dermatitis. *Br J Dermatol* 1988; 38: 1022–1029.