

5. New therapeutic targets in atopic eczema

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The rationale for new targets in atopic eczema depends upon the results of basic research. For example, assessment of data from gene research may indicate a new therapeutic target. Similarly, key results from new clinical trials in other atopic diseases including asthma can also be helpful in the search for new treatment strategies.

NEW APPROACHES TO OLD TARGETS

One of the recent developments is to treat the disease very early in its development, exactly as is being done in asthma. The aim is to evaluate whether it is possible to modify the disease with long-term management. Can flare-ups be prevented? Is it possible to prevent the 'atopic march'? The typical progress of a patient with atopic dermatitis (AD) was documented by Kissling & Wuthrich (1). They documented the development of eczema in 106 patients from the infantile phase, through childhood and adolescence into adulthood. The majority of patients experienced recurrent cycles of flare-ups, each of which was controlled by steroids. This recurrent cycle of events is distressing to parents who are also concerned about the 'atopic march' (2). Atopic eczema is in most cases the first manifestation of atopic disposition; eczema in childhood, compounded by food allergy, leading to asthma and long-term rhinitis.

The general approach to treating AD is to treat relapses/flare-ups and when controlled to withdraw active treatment and use emollients (until the next flare-up). A recent trial has investigated whether continued application of a steroid can prevent or delay the cycle of relapses and treatment. Berth-Jones et al. (3) conducted a randomized vehicle (emollient) controlled trial in patients aged 12–65 with moderate to severe disease, to determine whether fluticasone propionate (at two strengths of 0.05% and 0.005%) can prevent relapses. There was a 1-month stabilization phase, followed by maintenance treatment of both 'healed' skin and new areas. The primary end point of the study was the time to relapse. A significant ($p < 0.001$) prolongation of remission with application of fluticasone propionate 0.05% was seen. Significant benefit was also seen with fluticasone propionate 0.005%, but the benefit and statistical significance was reduced ($p = 0.01$).

NEW THERAPEUTIC STRATEGIES AND TARGETS

Strategies to affect T cells are shown in Table I. Alefacept binds to CD2 and FcγRII, a dual mechanism of pathogenic T-cell inhibition leading to apoptosis of T cells. Alefacept has been investigated in psoriasis and will no doubt be tested in AD in the future. Alternative concepts involve binding to CD2 and intracellular binding (4).

Blocking of T-cell activation is best exemplified by the calcineurin inhibitors tacrolimus and pimecrolimus. Several studies have been conducted with these topical immunomodulators, which have shown good efficacy in randomized double-blind studies (5, 6). Tacrolimus (0.03% and 0.1%) showed dose-related superiority over vehicle during a 12-week study in moderate to severe disease (5). Pimecrolimus cream (1%) similarly was more effective than vehicle during a 6-week study in around 400 children and adolescents with mild to moderate disease (6). An interesting aspect with these compounds is that lesions on the face tend to respond better than those on the rest of the body. As with the study by Berth-Jones et al. (3) with fluticasone propionate, prevention of relapse has been investigated with calcineurin inhibitors. Three controlled studies are under way with pimecrolimus in infants aged 3–24 months, in children aged 2–17 years, both with mild/moderate disease, and in adults with severe disease. A long-term disease-modification study is also under way with pimecrolimus in approximately 1100 infants, who

Table I. Strategies to deplete T cells/T-cell subsets

Agent	Route of administration	Design	Mechanism
Alefacept (Amevive)	IV IM	Ig/receptor Fusion protein	Binds CD2 and FcγRII Apoptosis
MEDI-507 (Siplizumab)	IV SC	Humanized monoclonal antibody	Binds CD2 – ADCC
IL-2 DAB (Ontak)	IV	Cytokine/toxin Fusion protein	DT introduced into T cells
Anti-CD3a (Visilizumab)	IV	Humanized monoclonal antibody	Binds activated T cells – apoptosis

DT, diphtheria toxin; IM, intramuscular administration; IV, intravenous administration; SC, subcutaneous administration.

are enrolled within 3 months of initial diagnosis. There is a 3-year double-blind treatment period followed by an open label extension for up to 6 years. The treatment regimen is flexible according to the severity of the disease. Dose finding studies with systemic pimecrolimus have been conducted in psoriasis and in AD. A clear dose response effect was seen. Unlike cyclosporine there is no effect on renal function (assessed by serum creatinine) and blood pressure. Although there was an increase in infections in the pimecrolimus group, these were not serious. Oral pimecrolimus 30 mg daily has the potential to become a key systemic therapy for inflammatory skin diseases. It is effective in controlling signs and symptoms of atopic eczema and psoriasis.

We have also worked with a cyclosporine analogue ISA 247 (0.75 and 0.25 mg/kg twice daily) in psoriasis. Reduction in the PASI was seen and the results compare favourably with cyclosporine itself. Preliminary data indicate a less nephrotoxic effect than cyclosporine and ISA 247 compound will be studied in AD.

Immune deviation of T cells, shifting the Th1 and Th2 balance, is exemplified by interferon-gamma. The rationale for its use is that AD is a prototypical Th2 disease and interferon-gamma inhibits the Th2 response. The postulated benefit of recombinant interferon-gamma would be decreased IgE levels, decreased IL-4 levels, decrease in other Th2 responses, leading to restoration of the immune balance and clinical improvement. A double-blind study was done some years ago by Hanifin et al. (7). Some benefit was seen in some parameters – erythema, oedema/induration, pruritus, excoriations, dryness and lichenification and overall clinical benefit. However, there was no reduction in serum IgE levels as expected from the rationale. Little recent work has been done with interferon-gamma.

Another molecule that theoretically is interesting in trying to cause a cytokine shift is M50367 (8). *In vitro* studies showed that it increases the Th1/Th2 ratio.

An alternative way of looking at anticytokine effects is to consider blocking IL-12 to shut down the Th1 response. Kauffman et al. (9) have looked at a human monoclonal antibody to IL-12 in moderate to severe psoriasis. A reduction in PASI of 75% at 8 weeks was seen following single doses, which were well tolerated. There were reductions in CD16 and 56 counts (NK cells) and interferon-gamma levels in lesions were significantly reduced within 2 weeks. Other studies are currently under way.

Mepolizumab, an anti-human IL-5 monoclonal antibody, is an example of the strategy to bind inflammatory cytokines or immunoglobulins. The rationale is that IL-5 is the major haematopoietin responsible for growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab blocks binding of human IL-5 to its receptor on the eosinophil cell surface and demonstrates consistent and significant lowering of

eosinophils in volunteer studies and in patients across various diseases.

Similarly, omalizumab is a humanized monoclonal antibody against IgE, which prevents IgE from attaching to mast cells and other effector cells.

Genome-based therapy is an emerging platform. Antisense drugs could be an interesting area for future exploration.

CONCLUSION

There is still the opportunity for control of AD to be achieved with older targets and treatments. Enhanced knowledge of the pathophysiology of AD is providing new therapeutic targets and preliminary results are promising.

Patients want a simple, effective and safe treatment and this is the primary goal.

DISCUSSION

Thestrup-Pedersen; Oral pimecrolimus took around 4–5 weeks before there was any apparent benefit, is this correct?

Langley; These were severe cases, but benefit was seen from early in treatment at the higher dose. The patients were adults who show a somewhat slower response than children.

Diepgen; On what basis were the doses of ISA 247 selected?

Langley; By extrapolation from the cyclosporine dosages. ISA 47 is a potent molecule.

Leung; Did you see any systemic immunosuppression?

Langley; This was a short-term 12-week study, but nothing was seen. Long-term data are pivotal of course.

Hamberg; How long is it before you see an effect?

Langley; The onset is pretty quick: within 4–6 weeks. In general these types of drugs can be classified as quick onset, e.g. ISA 247, pimecrolimus and cyclosporine, but when withdrawn relapse is apparent. The Alefacept type takes 12–16 weeks to produce a response, but there is a long period before relapse.

There are many new biotech companies emerging and many have drug patents against specific immunological targets in AD and psoriasis. Whether such specific targets will be beneficial clinically remains to be seen. The drugs which we know are effective and have a more broad spectrum of activity.

Bieber; Will we have enough patients for all these studies? All the study designs will have exactly the same inclusion and exclusion criteria!

Taieb; It is just the same in rheumatoid arthritis and it may be a technique to block the clinical trial procedure and by that possible competitors.

Leung; Interferon-gamma is very expensive and there are few companies making any now. The only patients who respond are those who get suppressed eosinophil counts. We still use it in people who fail other treatments. Interferon-alpha will also work.

Thestrup-Pedersen; We treated 12 adult atopic eczema patients with interferon-alpha and couldn't see any improvement clinically or on the total IgE level.

Taieb; We have two patients also on interferon-gamma for Job-Buckley syndrome, and it works.

Leung; If we had to design the studies again we would select a dose that suppresses the eosinophils. The subcutaneous dose we gave probably did not get therapeutic concentrations in the skin.

Leung; Studies to date show that mepolizumab doesn't work well in asthma.

Taieb; We participated in an AD study in adults with mepolizumab but details on outcome are not available yet.

Taieb; The anti-IgE approach is interesting, but the data are only in asthma. The problem is that existing drugs cannot block very high levels of IgE.

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