PERSONAL REVIEW

Recent developments in the treatment of adult atopic dermatitis

Vernon SC Pua and Ross StC Barnetson

Department of Dermatology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

SUMMARY

Atopic dermatitis is a common inflammatory skin condition with increasing incidence in recent decades. The mainstay of treatment has been the combination of emollients and topical corticosteroids, with the addition of systemic therapies in severe cases. New drugs such as the topical calcineurin inhibitors have shown promise in treating mild-to-severe atopic dermatitis. Other novel therapies that have been reported in the literature include leukotriene antagonists, monoclonal antibodies such as infliximab, lefunomide, recombinant interferon gamma and intravenous immunoglobulin. This review will focus on the treatment of adult atopic dermatitis.

Key words: basimixilab, eczema, infliximab, intravenous immunoglobulin, lefunomide, montelukast, pimecrolimus, recombinant interferon-γ, tacrolimus, zafirlukast.

INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin disease with complex aetiology. The interactions between the environment, genes, defects in skin barrier function, systemic and local immunological responses play a role in the manifestation of AD. Although most AD patients have high IgE concentrations, there is no objective diagnostic test. The diagnosis is predominantly clinical and includes features such as pruritus, chronic or chronically relapsing course, typical morphology, typical distribution of lesions for age and a personal or family history of asthma and allergic rhinitis.

The relapsing and remitting course of AD can place an enormous psychological, social and financial burden on patients and their families. The prevalence of AD in Europe is estimated to range between 5% and 20%. In Australia, the age- and sex-adjusted point prevalence of AD in children aged 5 years and younger is 50.8% (95% CI 28–35.5%). The overall prevalence of AD in school children aged 4–18 years is 16.5% (95% CI 14.1–18.5%) based on clinical examination and 10.8% (95% CI 9.5–12.3%) based on the UK Working Party Diagnostic Criteria. Epidemiological studies show increasing incidence over the past three to four decades and higher prevalence in wealthier classes and in more developed regions. The phenomenon in which children with AD proceed to develop asthma and allergic rhinitis as the symptoms of AD recede is known as the ‘atopic march’. There is speculation that aggressive treatment of AD in children may halt the atopic march thus aborting the progression to respiratory diseases.

The principles in treating AD are reducing symptoms, preventing exacerbations and minimizing side-effects from medications. This incorporates the use of emollients, wet dressings, topical corticosteroids, antibiotics for infections, antihistamines, stress management, counselling and avoidance of allergens or triggers.

In severe or difficult-to-control AD, systemic therapies are used. Systemic corticosteroids usually achieve control of severe exacerbations; however, there are important side-effects (Table 1). Other problems include tachyphylaxis and the risk of rebound and disease instability upon withdrawal of systemic corticosteroids. Oral cyclosporin, azathioprine and mycophenolate mofetil can be effective for severe AD, but the side-effects of these

Abbreviations:

AD: atopic dermatitis
CI: confidence interval
EASI: Eczema Area and Severity Index
IFN: interferon
IL: interleukin
IVIg: intravenous immunoglobulin
LTA: leukotriene antagonist
M/S: moderate-to-severe
RCT: randomized controlled trial
SCORAD: scoring atopic dermatitis
TCI: topical calcineurin inhibitor
TNF: tumour necrosis factor
VAS: visual analogue scale

Correspondence: Professor Ross StC Barnetson, Department of Dermatology, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. Email: ross.barnetson@email.cs.nsw.gov.au

Vernon SC Pua, MB BS(Hons), Ross StC Barnetson, MD.

Submitted 5 April 2005; accepted 15 September 2005.

© 2006 The Australasian College of Dermatologists
TOPICAL CALCINEURIN INHIBITORS

Topical calcineurin inhibitors are probably the most important therapeutic advance in the treatment of AD in five decades as they are the first real alternative to topical corticosteroids. The mode of action of TCI is more targeted than corticosteroids. They block T-cell activation via binding to cytoplasmic immunophilin FKBP12, forming a complex that inhibits the activity of the enzyme calcineurin. The inhibition of calcineurin prevents the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T-cells, which regulates mRNA transcription of some inflammatory cytokines such as IL-2 and IFN-γ (T helper 1 cell pathway) and IL-4 and IL-10 (T helper 2 cell pathway). In addition, TCI also inhibit production of histamine, eicosanoids and proinflammatory cytokines by basophils and mast cells.

In short term (5 months), vehicle-controlled studies of M/S AD adults (n = 562), tacrolimus 0.1% ointment and tacrolimus 0.05% ointment were significantly more effective than vehicle. For example, the rate ratios for tacrolimus 0.1% versus vehicle at 12 weeks of two RCT were 4.51 (95% CI 2.20–9.23%) and 7 (95% CI 5.10–15.79%), respectively. Tacrolimus 0.1% ointment was more effective than tacrolimus 0.05% ointment and this was statistically significant (P = 0.041). In a longer-term (12 months) open-label, non-comparative study of adults with M/S AD, treatment with tacrolimus 0.1% ointment showed improvement by the first week of treatment based on EASI, patient/carer assessment of pruritus and percentage of affected body surface area. This was subsequently maintained for the duration of the trial. In another study, tacrolimus 0.1% ointment and hydrocortisone butyrate 0.1% ointment were equally efficacious but more effective than tacrolimus 0.05% ointment (both P < 0.05) in adults with severe AD at 5 weeks. A large RCT of M/S AD adults (n = 968) compared tacrolimus 0.1% ointment with a combined treatment of hydrocortisone butyrate 0.1% ointment (trunk and extremities) plus hydrocortisone acetate 1% ointment (head and neck). Tacrolimus was significantly more effective at 12 weeks with a rate ratio of 1.67 (95% CI 1.41–1.98%). A small RCT (n = 50) comparing 0.1% tacrolimus ointment with oral cyclosporin 5 mg/kg concluded that there was statistically significant improvement early on (day 0–42) in the tacrolimus group. However, after day 42, overall SCORAD index, itching, erythema and number of nights without interference of sleep between the two groups were equivalent.

Pimecrolimus 1% cream significantly reduced the incidence of flares compared with vehicle (P < 0.001) in M/S AD patients (n = 192) in a 6-month trial: 44.8% of the treated group versus 18.8% of the vehicle group did not require corticosteroids. When this RCT was further analysed based on the subgroup with moderate AD only, 59.7% of the pimecrolimus group had no flares compared with 22.1% in the control group (P < 0.001) indicating that pimecrolimus is more effective than vehicle alone in controlling moderate AD than M/S AD. A 5-week study (n = 260) concluded that betamethasone-17-valerate 0.1% cream was superior to pimecrolimus 1% cream.

The TCI are well-tolerated with the most common adverse events being skin burning and pruritus at application sites. Skin burning and pruritus usually resolve with improvement of AD as percutaneous penetration is greatest at inflamed skin sites and minimal at normal skin. Several studies also demonstrate low or negligible systemic absorption following topical application. However, there is a theoretical risk of photocarcinogenicity and patients must be advised to use sunscreens and to practise other sun protection measures. This is especially important in Australia.

Tacrolimus 0.1% ointment is as effective as potent topical corticosteroids and more effective than mild topical corticosteroids, therefore it can be useful for resistant AD in the head and neck region where potent topical corticosteroid use leads to thinning of the skin and telangiectasia. Based on current evidence, the European Working Group on AD has the following recommendations: tacrolimus can be prescribed for patients of all ages with mild-to-severe AD. It should be prescribed as a second-line treatment when topical corticosteroids do not provide disease control or in corticosteroid-phobic patients. Pimecrolimus can be prescribed for mild-to-moderate AD, but it is not as effective in severe AD. Initially, the TCI should be commenced as a twice-daily application for a period of 1–5 weeks to assess therapeutic response and they can be used as monotherapy in combination with emollients. Although they are used for maintenance and prophylactic treatment, optimum duration, dose and frequency are not known and therapy is tailored on an individual basis. The TCI are expensive: in

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Potential side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>Cushingoid features, cataracts, decreased immunity, mood changes, hyperglycaemia, osteopenia, osteoporosis, hypertension, myopathy</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Nephrotoxicity, tremor, hypertension, increased risk of cutaneous malignancies and lymphoma</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Myelosuppression, gastrointestinal disturbances, hepatotoxicity, increased susceptibility to infections, possible development of cutaneous malignancies</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Nausea, vomiting, leukopenia, profound immunosuppression</td>
</tr>
</tbody>
</table>

© 2006 The Australasian College of Dermatologists
Australia, pimecrolimus 1% cream 30 g is approximately AUD$70.95. Tacrolimus is currently not available commercially.

LEUKOTRIENE ANTAGONISTS
Leukotrienes are metabolites of the arachidonic acid pathway and are important proinflammatory mediators in atopic diseases. They induce bronchoconstriction, mucous hypersecretion and increase airway vascular permeability. Leukotriene antagonists are used in the treatment of asthma especially in children. Although the role of leukotrienes in AD is not well-understood, there are a few reports regarding the success of LTA in treating AD.

Oral zafirlukast 20 mg twice daily and oral montelukast sodium 10 mg daily were shown to be useful in achieving resolution or control of AD.\textsuperscript{34–36} A small (\(n = 6\)) open-label pilot study of oral zileuton 600 mg q.i.d. (6 weeks) in moderate AD adults showed improvement in objective skin scores.\textsuperscript{37} A double-blinded RCT (\(n = 20\)) of severe AD adults showed that there was a 20% reduction in SCORAD index, which was statistically significant in the oral montelukast 10 mg daily group compared with the placebo group.\textsuperscript{38} Another RCT (\(n = 32\)) of adult patients with M/S AD concluded that oral montelukast 10 mg/day was as effective as combination therapy (oral cetirizine and clarithromycin, topical corticosteroids and hydrating preparations) based on similar improvements on SCORAD and laboratory measurements.\textsuperscript{39} A small (\(n = 8\)) RCT of mild-to-moderate AD adult patients demonstrated modest but significant alleviation of AD when oral montelukast 10 mg/day was used as an adjunct over a 4-week period.\textsuperscript{40}

Overall, LTA are well-tolerated. The most common adverse effects of zafirlukast and other LTA are headaches, pharyngitis and transient raised alanine aminotransferase.\textsuperscript{54} However, they have been associated with precipitating Churg–Strauss syndrome. The LTA could be a useful adjunct in the treatment of AD patients with asthma, but larger RCT are needed to evaluate this.

MONOCLONAL ANTIBODIES
Monoclonal antibodies are a rapidly growing treatment modality showing promise in controlling diseases such as psoriasis, rheumatoid arthritis and Crohn’s disease.

The chimeric monoclonal antibody infliximab binds to TNF-\(\alpha\) and inhibits the migration of leukocytes and the release of TNF-\(\alpha\) proinflammatory cytokines. Studies have shown that patients with AD have elevated serum and tissue concentrations of TNF-\(\alpha\).\textsuperscript{41,42}

A recent open, prospective, pilot study of intravenous infliximab (5 mg/kg) was conducted in nine patients with M/S AD resistant to conventional therapy.\textsuperscript{43} Improvement in EASI (mean EASI decreased from 22.5 to 10.6 by week 2, \(P = 0.05\)) and pruritus severity assessment were achieved early on. However, efficacy was not sustained. Only two patients qualified for and completed the ‘treatment’ phase that is additional infusions of infliximab until week 46. Patients with a reduction of EASI of at least 50% qualified for ‘retreatment’ phase. Interestingly, both those patients who achieved excellent response up to week 46 with infliximab had severe AD. Non-responders may have developed anti-TNF-\(\alpha\) antibodies. Paradoxically, there have also been reports of AD-like eruptions precipitated by infliximab,\textsuperscript{44,45} possibly due to downregulation of T helper 1 cytokines, resulting in manifestation of T helper 2 disease.

Basiliximab is a chimeric monoclonal antibody that binds to IL-2 receptor and inhibits IL-2-mediated T-cell proliferation. A patient with severe AD on oral cyclosporin who was treated with basiliximab 20 mg i.v. twice daily for 4 days had a reduction in SCORAD from 68.6 to 37.1 by day 4, with further decrease to 14.25 by day 14. Benefits were maintained for another 2 weeks before AD relapsed.\textsuperscript{46}

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, rapidly reduces IgE and expression of high-affinity IgE receptors and has been effective in reducing asthma exacerbations and allergic rhinitis.\textsuperscript{47–51} To date there are no reports of its use in the treatment of AD. Total IgE levels in AD may be too high to be neutralized.

Side-effects of infliximab include infection especially reactivation of tuberculosis, infusion reactions, pancytopenia and systemic lupus erythematosus-related autoantibodies and clinical features. The role of monoclonal antibodies in treating AD is still experimental and further trials are needed. Future studies on AD using infliximab should consider the addition of an immunosuppressive agent as the concurrent use of methotrexate with infliximab in rheumatoid arthritis has been shown to prevent the development of antichimeric antibodies.\textsuperscript{52}

LEFLUNOMIDE
Leflunomide is a pyrimidine \(de\) \(nuovo\) synthesis-inhibiting immunosuppressant, which exhibits a long \textit{in vivo} half-life (15 days) of its metabolite that inhibits T-cell proliferation. It is an established treatment for rheumatoid arthritis.

Two patients with severe AD recalcitrant to different systemic therapies achieved stable remission with oral leflunomide.\textsuperscript{53} The loading dose was 100 mg daily for 5 days, followed by maintenance dose of 20 mg daily. Within 4 weeks, the first patient had a reduction of EASI from 40 to 4.8 and VAS from 10 to 5. Leflunomide was then reduced to 10 mg daily and subsequently, 10 mg every other day. By week 72, this patient had an EASI of 4.2 and VAS of 2. Leflunomide was discontinued at week 72 and 6 months later, AD was still in remission. The second patient achieved partial remission with EASI reduction from 43 to 11.7 and VAS from 8 to 5 after 4 weeks. Remission was maintained from week 7 to 21 until an episode of relapse, which was treated with oral prednisolone (tapering dose) and tacrolimus ointment. Once disease was stable, leflunomide was reduced to 10 mg. This was changed to 10 mg and 20 mg on alternate days at week 69 due to increase in EASI to 14.7 and VAS to 3. Stable partial remission was achieved and maintained until the end of the study in week 81 (EASI 8.4 and VAS 2).

The major side-effect of leflunomide is raised liver function enzymes, which occurs in approximately 5% of
patients taking this drug. Leflunomide may join the ranks of other systemic immunosuppressive agents such as cyclosporin as an effective second-line agent in severe AD although larger studies are required to confirm this.

RECOMBINANT INTERFERON-γ

One of the immunological abnormalities of AD is the deregulation of IFN-γ secretion, which inhibits IgE synthesis and T helper 2 cell function. The reduced production of IFN-γ with concurrent upregulation of IL-4 and IL-5 could be critical in the pathogenesis of AD.

A pilot study of recombinant IFN-γ showed significant reduction in total clinical severity \((P < 0.04)\) in 22 patients with severe AD over a 6-week period when treated daily, although IgE levels were unchanged. A double-blind RCT \((n = 51)\) of high-dose \((1.5 \times 10^8 \text{ IU/m}^2)\) and low-dose \((0.5 \times 10^8 \text{ IU/m}^2)\) recombinant IFN-γ subcutaneously three times per week for 12 weeks versus placebo-control in adults with severe AD showed statistically significant reduction in clinical severity of AD determined by physicians' estimates and patients' global estimates in the recombinant IFN-γ groups. Response to treatment was more rapid in the higher-dose group, which achieved statistically significant improvement \((P < 0.05)\) in total clinical severity by week 4 and maintained this until the end of the study. The lower-dose group achieved statistically significant improvement by week 8. Similar success was reported in other open-label studies.

Twenty-four patients who successfully completed an initial double-blind study were treated with daily subcutaneous injections of 50 \(\mu\text{g/m}^2\) recombinant IFN-γ for 1–2 years. Patients maintained significant improvement in erythema, oedema, pruritus, excoriations, dryness and lichenification. Another 15 patients treated with subcutaneous 50 \(\mu\text{g/m}^2\) recombinant IFN-γ daily or every other day for 22 months also had statistically significant improvement \((P < 0.001)\) in mean total body surface area of involvement and total clinical severity.

The longer studies indicate that recombinant IFN-γ is safe and well-tolerated with the most common reported side-effect being 'flu-like symptoms. These were effectively prevented by pretreatment with paracetamol and by dosing at bedtime. Patients with the lowest serum IgE levels and blood eosinophil percentage at baseline seem to benefit the most from recombinant IFN-γ. Although recombinant IFN-γ is expensive and requires daily subcutaneous administration, it appears to be a safe alternative for adult patients with severe AD who have failed other forms of treatment.

INTRANEOUS IMMUNOGLOBULIN

Intravenous immunoglobulin displays various immunomodulatory and anti-inflammatory properties. It has been used in autoimmune blistering disorders such as bullous pemphigoid, pemphigus vulgaris, mucous membrane pemphigoid and linear IgA disease. Its mechanism of action is not completely understood but is thought to be mediated via the Fc portion of IgG or the antigen binding sites, the variable regions of the antibody molecule F(ab′)₂ or by substances other than antibody in the IVIg preparations.

There are a few reports that IVIg is efficacious in the treatment of AD; however, large RCT are lacking. In the studies that showed improvement with IVIg, high doses \((\text{approximately } 2 \text{ g/kg body weight})\) were used in several cycles and an additional agent such as prednisolone was used. A small \((n = 9)\) RCT of one dose of IVIg \((2 \text{ g/kg body weight})\) for severe AD evaluated by SCORAD did not show any clinically significant change at day 50.

Side-effects of IVIg are generally mild. They occur 50–60 min after the onset of the infusion and include flushing, myalgia, headache, fever, chills, nausea or vomiting, chest tightness, low backache and wheezing. Aseptic meningitis can occur up to 11 days later. Although there is potential for IVIg as a third-line agent in treating severe AD, large RCT are required to determine this. Other considerations when using IVIg include its high cost and the potential for transmission of infectious diseases as it is prepared from the pooled plasma of between 10 000 and 20 000 donors.

CONCLUSION

There is no single treatment to date that has proven to be the magic bullet in treating AD. Topical corticosteroids are still the mainstay of treatment in AD, but their utility is limited by the side-effects from long-term use. While novel treatments are being developed and trialled, the corticosteroid-sparing agents tacrolimus and pimecrolimus have emerged as the most promising alternatives to topical corticosteroids. Tacrolimus 0.1% ointment can control severe AD, as is effective as potent corticosteroids and can be used on the face or neck region without causing telangiectasia or thinning of the skin. Other treatments such as ILTα, recombinant IFN-γ and IVIg warrant larger RCT. More studies on the monoclonal antibodies and leflunomide are also needed. As AD is a chronic illness, future studies should address efficacy of treatments, optimum dose and duration of treatment over a long trial period. Long-term safety data and studies comparing the different treatments would be beneficial. Further advances into the understanding of the key immune pathways that lead to different phenotypes of AD will likely yield better treatments in the future.

REFERENCES


© 2006 The Australasian College of Dermatologists


