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Management of Severe Atopic Dermatitis

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The lack of knowledge concerning the pathophysiology of atopic dermatitis (AD) explains the absence of any specific treatment specially in severe atopic dermatitis. New treatments were recently suggested for the management of the disease. They all act on some component of the immune mechanisms which provoke the eczematous reactions. Among recent treatments proposed, I will discuss the use of cyclosporin A, puva therapy, thymopoietin and thymostimulin, antifungal therapy, alpha and gamma interferon, and treatment with interleukin 2.
Key words: atopic dermatitis; cyclosporin A; photochemotherapy; Thymic hormone; gamma interferon; alpha interferon; interleukin 2.

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CYCLOSPORIN A

Cyclosporin A reduces the number of CD4 cells in the dermis and the secretion of interleukins by these cells. It has also been shown recently that it inhibits the function of Langerhans cells in vitro (1). This effect is dose-dependent.

Van Joost was the first to treat female patients suffering from severe AD, with 5 mg/kg/day of Cyclosporin for one month (2). The treatment yielded a profound clinical improvement, but the lesions reappeared on discontinuing the treatment. Other authors, such as Kamp and Cooper, have treated small numbers of patients suffering from severe dermatitis, with the same results. Harper obtained four good results in 6 patients, including one in whom a remission was observed after tapering the doses very gradually over a 4-month period (3).

At our Department, we have now treated 6 patients with severe AD, using doses of 4 or 5 mg per kg daily. An 11-year-old girl remains in remission after reducing the treatment very gradually over 6 months, with a follow-up of 2 years, but a 17-year-old youth had only a moderate improvement with relapse during treatment. The third case showed good improvement but relapse after cessation of treatment. In 3 other patients, we obtained good results, but without sufficient follow-up. Immunohistologic studies in lesional skin showed a decrease in CD3, CD4, HLADR and CD25 during treatment. For the moment, the decrease in these antigens during treatment has already been shown by Wahlgren and collaborators, in a series of 10 subjects, with good effect especially on pruritus (4).

Munro et al. reported the treatment of 14 adult patients, with 5 mg/kg/day for 7–16 weeks (5). All showed a marked clinical improvement, but 2 relapsed despite ongoing treatment; the other relapsed after stopping CsA. Serum IgE and prick test results were not modified by CsA. Immediate and late phase cutaneous reactions to intradermal house dust mite antigen were significantly increased during treatment (but a delayed response, present at 24 and 48 h was unaffected). Thus cyclosporin A has a powerful therapeutic effect in AD but does not reduce allergic responses to inhalent antigens.

Although the action of oral cyclosporin at moderate doses was constant and rapid in all these trials, the risk of serious side effects and the reappearance of progressive disease after stopping the treatment limits the indications for this drug in AD and encourages trials with local applications of cyclosporin (6).

PHOTOCHEMOTHERAPY

Photochemotherapy has been used in severe recalcitrant AD. Falk evaluated 106 patients who were given either ultraviolet B or a mixture of A and B (7). The percentage of remission was better with UVA and B combined (94%) than with UVB alone (84%). Neither treatment produced long-term responses. Similar results were obtained in a group of 30 patients studied by Jekler & Larko in a paired comparison study with a combination of UVA and B on one side of the body and UVB on the other side during an 8-week period (8).

Atherton et al. treated 15 patients with severe AD, using PUVA therapy at the dose of one joule per square centimetre and 0.6 mg/kg of psoralen, two or three times a week (9). Almost complete clearance was achieved in 14 of the patients within 10–25 weeks. Long-term remission was obtained in 9 of the patients. Of the 7 children with complete data, 6 had a growth retardation below the third percentile prior to treatment. During and after PUVA, all 6 achieved a rate of growth between the fiftieth and ninety-seventh percentile.

In a recent paper, Jekler et al. reported that the erythemally effective dose received during a course of phototherapy for AD (normally one course per year) is about 10,000 joules per m^2 and is considerably less than the median dose of 40,000 J/m^2 required to clear psoriasis by phototherapy (10).

Thymic hormone: TP5 and TP1

Thymic hormone extract has also been used in the treatment of AD. The aim is to repair the deficit in cellular immunity found in these patients. *Hanifin* reported a trial involving 100 patients who received injections of 50 mg of thymopoietin (TP5) or placebo, three times a week. Patients responded to treatment at the sixth week, but the improvement was only moderate, with relapse after the seventh week of treatment. In a similar study, Harper et al. used thymostimulin (TP1) in a double-blind controlled study of 29 adults with severe AD (11). He used twice weekly injections of 1.5 mg/kg for 10 weeks. A 20% reduction in clinical severity was observed, compared with placebo-treated patients, but the T8 lymphopenia, high IgE levels and blood eosinophilia were unaffected.

Treatment of fungal skin infection in AD

The hypersensitivity to pityrosporon in AD, well known since the works of Rokugo, Svejgaard, Young (12) encouraged Svejgaard and collaborators to treat adolescents and adults with AD localized primarily on the face, neck and shoulders, with 200 mg/day of Ketoconazole (12). They observed an improvement in the pruritus within 3 days and in the skin lesions within 2 weeks. This therapeutic trial is interesting with regard to the pathophysiology of AD, but one has to consider that it was an open study involving a small number of patients and therefore requires confirmation by a controlled trial.

Recombinant gamma interferon

Gamma Interferon can inhibit IgE synthesis induced by interleukin 4 in vitro and in vivo in rodents, and in vitro in humans. Furthermore, it has been reported that the capacity of human and mouse T-cell clones to induce IgE synthesis is directly correlated with the amount of secreted IL4 to interferon. Moreover, patients with AD have been reported to have an impaired capacity to produce IFN-γ in response to a number of stimuli. Boguniewicz and colleagues stated the effect of recombinant gamma Interferon treatment in 22 patients with chronic severe AD (13). In part I of their study, 14 patients were treated with daily subcutaneous injections at three successive dose levels (0.01 mg/m^2, 0.05 mg/m^2) and 0.1 mg/m^2 for 5 days with a 2-day interval between each dose level; In part II of the study, 8 patients received 0.05 mg/m^2 daily for 6 weeks. 9 patients received maintenance therapy three times a week for up to 14 months. Total clinical severity score showed improvement at each dose level, but worsening 3 days after discontinuing treatment. The improvement was sustained in the maintenance therapy group. Transient headaches, myalgia, fever, or nausea occur with dosage exceeding 0.05 mg/m^2. Spontaneous *de novo* IgE synthesis by peripheral blood mononuclear cells was inhibited in 10 patients given 0.01 mg/m^2 and in 9 at 0.1 mg/m^2. Serum IgE levels did not decline at any of the three dose levels. Perhaps at this dosage, gamma IFN cannot inhibit IgE production by circulating B cells, but does induce other immunomodulatory effects, including the increased expression of Fc-γ receptors and increased superoxide production by circulating monocytes.

In a recent issue of *The Lancet*, Reinhold et al. reported the effect of treatment with recombinant interferon-γ (14). The 3 adult patients had unremitting severe AD with high serum IgE concentrations. Subcutaneous injections of 100 mg interferon were given on 5 days of the first week of treatment, followed by three injections per week for a further 3 weeks. After 2 weeks of therapy the inflammatory skin process had improved and after 4 weeks the eczema had nearly disappeared. Serum IgE levels gradually decreased during therapy and spontaneous IgE production in vitro was reduced.

Treatment with interferon alpha

Souillet et al. reported that interferon inhibited IgE synthesis in a patient with hyper-IgE syndrome (15). Serum IgE levels fell and the patient's eczema improved after 4 weeks of treatment with 3 miion U of IFN-α twice a week.

Rona MacKie reported in *The Lancet* the treatment of 2 patients suffering from severe AD with α-interferon (16). These 2 patients obtained no benefit from 12–14 week courses of IFN-α at 3 million units thrice weekly.

Treatment with complexes of allergen and specific antibodies

A successful treatment of AD with complexes of allergen and specific antibodies to *Dermatophagoides pteronyssinus* was recently published by J. M. Saint Remy and collaborators. This work is detailed in another paper in this journal.

Treatment with interkeukin 2

Recently, Kue-Hsiung-Hsieh and collaborators published in the *Journal of Clinical Immunology* a therapeutic trial of interleukin 2 in 6 children aged from 2 to 11 years, suffering from severe AD (17). Human recombinant interleukin 2 was injected via intravenous infusion. The initial dose was 20,000 U/kg/ every 8 h. It was later adjusted according to tolerance. The lichenification and the pruritus improved 5 days after commencing the treatment. However, the dermatitis flared up in all cases 2–6 weeks after discontinuing IL2. There were no consistent changes in CD3, CD8 cells, CD4/CD8 ratio, serum IgE, in vitro IgE production, serum IL-2, or mitogen response. Immunohistological studies on the skin showed a decreased number of CD4 cells and an increased number of CD25 cells after IL2 therapy. As the therapeutic effect was transient and the IL2 therapy was rather toxic (chills, malaise, hepatomegaly, bodyweight gain, edema, pleural effusion), the potential harm of IL2 should be seriously considered in a non-fatal disease such as atopic eczema. The action of IL2 is unknown and the clinical efficacy of IL2 has no relationship with IgE production.

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