

The treatment of atopic dermatitis with adjunctive high-dose intravenous immunoglobulin: a report of three patients and review of the literature

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Summary

There are few reports of the use of high-dose intravenous immunoglobulin (hdIVIg) in the treatment of atopic dermatitis (AD). We describe our experience using this therapy in three patients with severe AD, all of whom had steroid-related side-effects. These patients received either Alphaglobin® or Sandoglobulin® 2 g/kg monthly: all had improved skin scores, allowing reduction of their steroid dose. Total IgE fell in one of three patients. We discuss the side-effects of hdIVIg and their management, and detail the differences between the available immunoglobulin products available in the U.K. There are several proposed mechanisms of action of this therapy which may be operative, and those most important in AD are discussed. In view of the time and expense involved in the treatment of patients with hdIVIg, careful patient assessment is vital. We describe dose reduction strategies and methods for cost containment. In addition, one of the patients has embarked on IVIg home therapy training. This will be the first time this has been attempted for a dermatological indication. Training of this type may be available through an immunotherapy service such as exists for patients with primary immunodeficiencies.

Key words: atopic dermatitis, high-dose intravenous immunoglobulin

Atopic dermatitis (AD) has an overall prevalence of 2–3%,¹ and although most patients are satisfactorily managed with current, often steroid-based strategies, a small proportion has severe resistant disease. Significant morbidity may result with time off work or study, recurrent hospital admissions and disruption of personal and family life.^{2,3} Therapeutic advances are needed, especially for those resistant to standard second-line therapies or suffering from unacceptable drug-related side-effects.

There are several anecdotal reports of high-dose intravenous immunoglobulin (hdIVIg) therapy used in patients with AD. Four children (aged 2–6 years) were treated with hdIVIg 0.4 g/kg daily for 5 days as sole therapy for Kawasaki syndrome or idiopathic thrombocytopenic purpura, and all had a remission of their coexisting AD. Skin scores, itch and sleep improved and there was a decrease in IgE level, eosinophil

count and *in vitro* spontaneous IgE production. Sustained improvement was noted to last more than 6 months.⁴ In a further case report, an 8-month-old boy with thrombocytopenia and AD associated with Wiskott–Aldrich syndrome had no improvement in the skin after a single cycle of hdIVIg.⁵ Three adult patients with AD were treated for 6 months with IVIg 2 g/kg monthly in a small open study. All improved, although their response was short-lived. The most striking effect was a reduction in pruritus, but this was not associated with a fall in total IgE levels.⁶ No reduction in concurrent second-line treatments was described. We report our experience using hdIVIg as adjunctive therapy with prednisolone and hydroxychloroquine⁷ to treat three patients with resistant AD. Diagnosis of AD was made using the criteria described by Hanifin and Rajka.⁸ These patients had all had extensive out-patient and in-patient topical treatments, a full allergy assessment and a range of conventional second-line agents prior to consideration of hdIVIg.

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Patient 1

A 19-year-old man with resistant AD was referred to our unit. Potent topical steroids, systemic steroids, phototherapy including TL-01 ultraviolet (UV) B (37 treatments, cumulative dosage 27.6 J/cm²) and psoralen-UVA (30 treatments, cumulative dosage 60 J/cm²), azathioprine 2 mg/kg, hydroxychloroquine 400 mg daily for 9 months, dapsone 150 mg daily for 2 months, interferon (IFN)- γ 100 μ g daily for 7 months and cyclosporin 5 mg/kg had failed to control his disease. Azathioprine and cyclosporin were given for more than 4 months without effect. Quantitative measurement of erythema and surface damage (i.e. papulation, vesiculation, scaling, excoriation and lichenification) was made using a standard scoring system.⁹ Steroid-induced osteoporosis was established by bone densitometry. Recurrent staphylococcal infections resulted in numerous hospital admissions which disrupted his university studies. He had become socially isolated and clinically depressed. Laboratory results showed a total IgE of 32,000 kU/L and RAST tests (Pharmacia Cap system) were positive for house dust mite (grade 6), cat (grade 6) and pollen (grade 1).

Adjunctive hdIVIg treatment was commenced with his usual treatment of prednisolone 10 mg daily and hydroxychloroquine 200 mg daily. Sandoglobulin[®] (Novartis, Frimley, U.K.) was given using a 5-day protocol of 0.4 g/kg daily, and the rate gradually increased, allowing his monthly treatment to be completed in 2 days. After 10 treatments with hdIVIg, his skin score had declined from 180 to 30 (Fig. 1), with no significant change in total IgE. Apart from one severe episode of eczema herpeticum and staphylococcal infection, he had fewer episodes of skin infection, and reattended college. One year after this regimen was started, he developed a testicular teratoma which responded to chemotherapy. This was felt to be unrelated to the hdIVIg treatment. His AD remains in remission off immunoglobulin and his other treatments are being tapered gradually.

Patient 2

A 45-year-old man had a 30-year history of severe AD which had failed to respond to prolonged topical and oral steroid treatment, both as an in-patient and as an out-patient. He was commenced on cyclosporin 5 mg/kg with significant benefit, but he developed loin pain and eye complications and discontinued the drug after 2 months. A 6-month trial of 0.1% topical

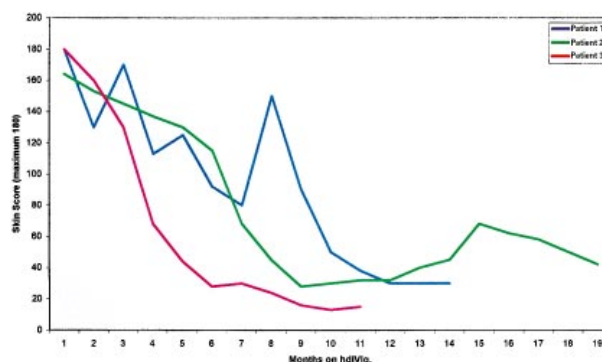


Figure 1. Eczema skin scores on monthly cycles of high-dose intravenous immunoglobulin (hdIVIg) at 2 g/kg for the three patients described. The maximum score possible is 180.

tacrolimus improved his condition, which relapsed when the treatment was withdrawn at the end of the trial. He had established osteoporosis measured at the spine and hip (2.91 and 3.37 SD below the normal, respectively) and was commenced on cyclical etidronate and calcium. Total IgE was 11,580 kU/L and RAST testing (Pharmacia Cap system) was positive for house dust mite (grade 6), grass pollen (grade 5) and mixed foods (eggs, fish, milk, wheat, peanuts and soya) (grade 4). He was given house dust mite avoidance advice, assessed by the dietician and excluded the excipient Sunset Yellow E110 contained in the calcium component of etidronate, as he noted worsening of his AD following this medication. He was started on Alphaglobin[®] (Grifols, Thetford, U.K.) IVIg at 2 g/kg monthly given over 3 days as an adjunctive treatment to prednisolone 35 mg daily. He experienced nausea and headache which settled over the subsequent two cycles of hdIVIg. His AD improved dramatically, allowing reduction of the prednisolone to 3 mg daily by the eighth cycle. His total IgE fell to 2450 kU/L. The duration between hdIVIg cycles has now been increased to 8 weeks.

Patient 3

A 30-year-old man who had had AD since 2 years of age presented with extensive low-grade disease involving 90% of his body surface area. This was unresponsive to azathioprine 2 mg/kg and cyclosporin 5 mg/kg, each given an adequate therapeutic trial over a period of months, and narrow-band UVB phototherapy (44 treatments, cumulative dose 35.4 J/cm²). Long-standing treatment with oral steroids resulted in osteoporosis at the hip and spine (1.55 and 2.02 SD below normal,

respectively). Results showed a total IgE of 12,570 kU/L and a house dust mite RAST (grade 6) (Pharmacia Cap system). He was commenced on Sandoglobulin® 2 g/kg monthly with hydroxychloroquine 200 mg daily and prednisolone 10 mg daily. The initial cycle of hdIVIg was given over 5 days at 0.4 g/kg daily without side-effects. The rate was increased to 1 g/kg daily and was well tolerated. His AD improved, allowing him to discontinue oral steroids and to increase the time between cycles to 8 weeks. He has been enrolled in the IVIg home therapy training programme run by the Department of Clinical Immunology. This will be the first time this has been attempted for a dermatological indication.

Discussion

IVIg is a blood product prepared from the pooled plasma of between 10,000 and 20,000 donors per batch by cold ethanol fractionation.¹⁰ Donors are carefully selected, and every donation is screened for hepatitis B virus surface antigen, antihepatitis C virus, antihuman immunodeficiency virus 1 and 2, syphilis serology and normal liver function. Each product also undergoes viral inactivation procedures in addition to the already high viral inactivation afforded by cold ethanol fractionation. These procedures vary from manufacturer to manufacturer, and include the use of trace pepsin, low pH, solvent/detergent and pasteurization. Most modern preparations now use either solvent/detergent or pasteurization.

Side-effects of IVIg are generally mild and self-limiting, often occurring 30–60 min after the onset of the infusion. These include flushing, myalgia, headache, fever, chills, low backache, nausea or vomiting, chest tightness, wheezing, changes in blood pressure and tachycardia. Aseptic meningitis may occur up to 11 days after the infusion.¹¹ These reactions are thought to be due to aggregated immunoglobulin, antibody–antigen complex formation with subsequent complement activation, or stabilizing carbohydrates used during manufacture. Adverse effects can be minimized by following the guidelines in the physicians' checklist,¹² but are generally easily managed by slowing or stopping the infusion, or by prior administration of hydrocortisone and/or antihistamine.¹³

Very rare episodes of anaphylaxis have occurred, particularly in those IgA-deficient patients with anti-IgA antibodies. IgA deficiency occurs in approximately 1 in 700 of the population, and should be screened for

prior to hdIVIg; if present, anti-IgA antibodies should be excluded, but even if detected, it is possible to use an IgA-depleted preparation of IVIg.^{13,14} Gammagard® (Hyland Immuno, Newbury, U.K.) has the lowest IgA content; however, it may be possible to use other products such as Octagam® (Octapharma, Solihull, U.K.) and Alphaglobin®, where the anti-IgA titre is also very low.

The immunomodulatory mechanisms of IVIg are mediated via the Fc portion of IgG (which interacts with Fc receptors and complement) or the antigen-binding site and the variable regions of the antibody molecule F(ab')₂. There are six main non-exclusive mechanisms which have been proposed:¹⁵ (i) functional blockade of Fc receptors on splenic macrophages; (ii) inhibition of complement-mediated damage; (iii) modulation of the production of cytokines and cytokine antagonists; (iv) neutralization of circulating autoantibodies by anti-idiotypic antibodies in IVIg; (v) neutralization of pathogens involved in the aetiology of the autoimmune disease; and (vi) blockade of Fas receptors by anti-Fas antibodies present in IVIg.¹⁶ Other immunologically active substances present in IVIg, e.g. class II human leucocyte-associated antigens, soluble CD4 and IFN- γ have also been suggested to play a part.¹⁷

In the setting of AD, one possible mechanism is the modulation of cytokines and cytokine antagonists, diverting a Th2 [interleukin (IL)-4 and IL-5] mediated disease¹⁸ towards a Th1 cytokine profile. We were able to demonstrate a reduction in intracellular IL-4 following hdIVIg in patient 1.¹⁹ Adding to the complexity is that in early disease a Th2 profile predominates, but later, in chronic AD Th1 cytokines play a greater part.²⁰ Other mechanisms which should be considered are interference with staphylococcal superantigens, alteration in the recirculation of skin-homing T cells, changes in the costimulatory molecules (CD28 and CD40) required for activation and proliferation, and alterations in chemokines such as eotaxin.

Prices vary between products, but will also depend on local contracts with individual companies for each hospital. At an average cost of £15/g, a 70-kg man receiving hdIVIg would have a drug bill of £25,200/year, before any in-patient costs are added. Patients with resistant AD who are being considered for a therapeutic trial of hdIVIg need careful selection and warrant a formal allergy assessment. There is strong indirect evidence that hdIVIg should be used as an adjunctive therapy in the treatment of dermatological disease. When all reports of hdIVIg for dermatological

indications are analysed, the success of monotherapy and adjunctive therapy is approximately 40% and 80%, respectively, in spite of a probable reporting bias for successful outcomes.¹²

Drug costs may be reduced by closely monitoring disease indices and making adjustments in dose only when remission has been achieved. The first step at this stage is gradually to reduce the second-line therapies such as steroids while maintaining the hdIVIg. If this is successful, it is often easiest to increase the interval between doses from 4 to 5 weeks, then 6 weeks, addressing the question of duration of immunomodulation rather than dose required to immunomodulate. This means fewer hospital visits for the patient, and information may be gleaned about the possible recurrence of symptoms just before the next infusion. Dose reduction may be possible where a lowering in steroid dose has led to weight loss and therefore the overall dose of IVIg required. In-patient costs may be reduced by using day-case facilities and by making use of an existing IVIg home therapy training programme in the hospital, as is the case for primary antibody deficiencies. Both these options have proved attractive to patients, especially to young adults with chronic disease.

A double-blind placebo-controlled trial of hdIVIg in AD is required to decide if this form of treatment has a place in the management of the subset of patients with severe, therapy-resistant disease.

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