Adjuvant Low Dose Intravenous Immunoglobulin Treatment for Severe, Refractory Atopic Dermatitis – Pediatric Case Series

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ABSTRACT
Background: Background atopic dermatitis patients generally respond to conventional therapies. A small proportion of them have severe disease despite intensive treatment. Efficacy of intravenous immunoglobulin (IVIg) in severe, refractory atopic dermatitis has been reported.

Materials and methods: We present the cases of five children with severe atopic dermatitis. All patients were previously and/or currently treated with systemic steroids, phototherapy and a large selection of topical agents. Immunosuppressive therapy was refused by their legal representatives. Due to financial restraints, low dose IVIg was administered (approximately 0.3 g/kg/month for six months), while the corticosteroid dose was tapered. Disease outcome was measured using the eczema area and severity index (EASI) and the children’s dermatology life quality index (CDLQI).

Results: All five patients experienced clinical improvement with significantly reduced EASI and CDLQI scores. No adverse reactions were reported. During the six months follow-up period, no disease flare occurred in any of the patients.

Conclusions: Adjunctive IVIg is a useful therapeutic approach in selected patients with refractory atopic dermatitis. Even if most of the reported cases refer to high dose IVIg, low dose regimens are not to be discarded, since they can provide satisfactory results with reduced in-patient costs and high compliance.

Keywords: atopic dermatitis, intravenous immunoglobulin, immunomodulatory effects.

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**BACKGROUND**

Atopic dermatitis is a chronic, relapsing, inflammatory skin disease with a lifetime prevalence that exceeds 20% in many developed countries (1). It represents an important public health issue as it is the most common inflammatory skin disease in children worldwide, having a major psychologic and socioeconomic impact (2, 3). Topical treatment is the mainstay in mild cases, whereas widespread moderate or severe skin lesions usually require systemic therapy. Severe atopic dermatitis is managed using standard systemic therapy with H1 antihistamines and corticosteroids or other immunosuppressive agents (4). However, a small proportion of patients have treatment resistant disease with significant morbidity derived from specific symptoms and drug related adverse reactions, frequent hospital admissions for disease flares and disturbed quality of life. This is why, in selected cases, there is sometimes need for off label treatments.

Treatment with intravenous immunoglobulin (IV Ig) has been suggested to be beneficial to such patients, with better results in children than in adults (5, 6). IV Ig is an extremely complex therapeutic agent, acting via immunomodulatory and anti-inflammatory mechanisms and has an excellent safety profile, enabling the avoidance of the numerous side effects of steroids and immunosuppressive agents (7).

**MATERIALS AND METHODS**

We present the cases of five children with clinically severe, refractory forms of atopic dermatitis. The diagnosis of atopic dermatitis was made according to the UK Working Party’s Diagnostic Criteria (8). Table 1 summarizes the demographic characteristics and medical history of our patients. The clinical appearance of our patients is illustrated by Figure 1.

All five patients were previously treated with systemic steroids (initial prednisone dose of 0.5 mg/kg/day with gradual tapering over two weeks), oral H1 antihistamines, phototherapy – narrowband ultraviolet (UV) B 311 nm and a large selection of topical agents (dermatocorticoids, topical calcineurin inhibitors, antiseptics, antibiotics, emollients), presenting severe and early rebound after cessation of systemic corticotherapy. The patients presented progressive aggravation of the skin disease during the previous year, gradually more frequent and severe exacerbations, despite the above mentioned treatments. Second line therapy (cyclosporin, azathypoprine and other immunosuppressive drugs) was refused by their legal representatives.

We performed routine laboratory analyses in all patients at baseline. Serum IgA levels were found to be within normal limits. Screening for infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, as well as for the presence of rheumatoid factor and cryoglobulines was also performed before the initiation of IV Ig therapy. Results of relevant laboratory tests are listed in Table 2.

Patients were advised to use moderate potency dermatocorticoids on active lesions and antiseptic compresses on exudative ones. Use of bland emollients was encouraged. We recommended continuation of oral non-sedating H1 antihistamines. Due to the severity of the atopic dermatitis flare, oral corticotherapy was restarted (initial prednisone dose of 0.5 mg/kg/day,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>17</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Family history of allergic disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Allergic personal medical history</td>
<td>Yes (asthma, rhinoconjunctivitis, recurrent lip angioedema)</td>
<td>Yes (rhinitis)</td>
<td>Yes (asthma)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Non-allergic personal medical history</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (hemorrhagic acute gastritis)</td>
<td>No</td>
</tr>
<tr>
<td>Age of atopic dermatitis onset</td>
<td>10 years</td>
<td>7 years</td>
<td>6 months</td>
<td>4 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

**TABLE 1.** Demographic characteristics and medical history of our patients
IVIg treatment was concomitantly initiated and was administered in a low dose regimen (approximately 0.3g/kg monthly for six months) due to financial restraints. Patients received premedication with H1 antihistamines. In order to avoid infusion related side effects, the infusion rate was initially very slow and increased after 30 minutes. Vital signs were monitored throughout the administration of IVIg and patients were asked to report any new signs and symptoms.

Disease outcome was evaluated both clinically and paraclinically. The eczema area and severity index (EASI) and the children’s dermatology life quality index (CDLQI) were measured at each of the six treatment visits and two follow-up visits (three months and six months respectively after the last IVIg infusion).

EASI (0-72) is the sum of the eczema severity score assessed for each of the four regions of the body multiplied by the area score (0.1 for the head and neck, 0.3 for the trunk, 0.2 for the upper limbs and 0.4 for the lower limbs). The severity score is the sum of the intensity scores [none (0), mild (1), moderate (2) and severe (3)] for four signs: erythema, induration, excoriation, and lichenification.

CDLQI is a 10 items questionnaire for patients aged 4–16 that evaluates the impact of a certain skin disease in the preceding week on six areas of daily activities, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. Each question is answered on a 4-point scale scored from 0 to 3 and the sum of the 10 answers gives a minimum score of 0 and a maximum score of 30.

We also monitored the changes in eosinophil count and total serum IgE levels.

### TABLE 2. Results of relevant laboratory tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophil count (N≤700/mm³)</td>
<td>836/mm³</td>
<td>1210/mm³</td>
<td>770/mm³</td>
<td>380/mm³</td>
<td>120/mm³</td>
</tr>
<tr>
<td>Total serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE level</td>
<td>1215 UI/ml</td>
<td>1871 UI/ml</td>
<td>53.7 UI/ml</td>
<td>326 UI/ml</td>
<td>60 UI/ml</td>
</tr>
<tr>
<td>Specific IgE levels (N≤0.35 IU/ml)</td>
<td>6.80 (cat dander)</td>
<td>12.30 (ambrosia elatior)</td>
<td>8.80 (der.p)</td>
<td>2.36 (der.f)</td>
<td>0.00</td>
</tr>
<tr>
<td>Total serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

### FIGURE 1. Clinical appearance of our patients

Patient 4 also needed systemic antibiotic treatment.

FIGURE 1. Clinical appearance of our patients
RESULTS

We observed progressive improvement of the skin lesions in all patients, reflected by a statistically significant decrease in mean EASI score (p=0.0001) and CDLQI (p<0.001) (Figure 2), with no exacerbation upon cessation of systemic corticotherapy. Disease control was maintained with topical treatment and oral H1 antihistamines. None of the patients needed another course of systemic corticotherapy during IVIg treatment. After the fourth IVIg administration, complete remission of skin lesions was achieved in Patient 1. Furthermore, the six months follow-up showed no disease flare (no systemic corticosteroid treatment needed) in all five patients.

The changes in total serum IgE level, as well as the eosinophil count did not consistently correlate with clinical improvement (Figure 3).

No adverse events were observed.

DISCUSSION

IVIg is successfully used as an off label treatment in a constantly growing number of immune and inflammatory diseases (6, 9, 10). The doses used in such disorders are much higher than those recommended for antibody replacement in immune deficiency syndromes, i.e., 2 g/kg/month administered either as 1 g/kg/day for two days or 0.4 g/kg/day for five days.

The immunomodulatory effects exerted by IVIg are responsible for its promising results in immune mediated diseases. These effects are complex and incompletely understood and are mediated by the variable (Fab) and constant (Fc) immunoglobulin regions, as well as by the complement binding to the Fc fragment and by a series of immunomodulatory substances other than antibodies present in IVIg products (cytokines, cytokine receptors, soluble class II major histocompatibility complex molecules (MHC), soluble CD4, etc). Interestingly, a certain mechanism seems to predominate in each disorder, depending on its pathogenesis (11,12).

Atopic dermatitis represents an important dermatological indication for IVIg treatment. Significant and sustained clinical improvement has been reported in children with refractory atopic dermatitis treated with high dose IVIg as monotherapy (13, 14). On the other hand, the published case reports show that adult atopic dermatitis patients benefit from the association of IVIg with corticosteroids or other immunosuppressants, but not from IVIg monotherapy (7, 15-17). In addition, a limited number of studies show efficacy of low dose IVIg in atopic dermatitis (18).

The benefits of IVIg in atopic dermatitis can be explained by a series of mechanisms of action.

Several studies showed that IVIg treatment leads to a decrease in serum IgE levels (14, 17). This effect is most probably due to the action of anti-idiotypic antibodies found in IVIg products. Such antibodies bind to IgE, clearing them from the circulation. They could also bind to the Fc receptor on B cells and thus prevent B cell activation and IgE production (19).

IVIg also influences T cell function, presumably by interference with antigen presentation through the soluble MHC II and CD4 molecules that it contains (19). IVIg treatment induces a decrease in interleukin (IL) 4 and IL2 production (20, 21) that contributes to the amelioration of the disease.
Moreover, as these two cytokines are known to alter glucocorticoid receptor binding affinity (22), an indirect effect of their decreased production is the improved sensitivity to corticosteroids observed in patients receiving IVIg (23).

The low amounts of anti-idiotypic antibodies and soluble immunomodulatory molecules in IVIg preparations explain the need for high doses of IVIg in immune disorders (19).

Most surely, multiple other mechanisms are also involved in IVIg action in atopic dermatitis. Among them, interference with staphylococcal superantigens, perturbed recirculation of skin homing T cells, changes in the costimulatory molecules (CD28 and CD40) and chemokines levels ought to be considered (7).

All our five cases of refractory childhood atopic dermatitis achieved significant clinical amelioration, reflected by progressive decrease in EASI/CDLQI following low dose IVIg treatment. The most impressive and quick response was observed in Patient 1, characterized by high pretreatment total serum IgE levels and eosinophil count. It can be speculated that patients with exaggerated IgE responses are more likely to respond to such immunomodulatory treatments.

IVIg side effects are usually mild and self-limiting, often infusion-related, like flushing, myalgia, arthralgia, headache, low-grade fever, etc. Premedication with hydrocortisone and/or oral H1 antihistamines and setting a slow infusion rate can prevent the appearance of such adverse effects. If, however, they occur, slowing or stopping the infusion is usually enough to control them (24, 25). High dose IVIg treatment can rarely induce serious side effects like hypotension, cytopenia, serum sickness, disseminated intravascular coagulation, aseptic meningitis, alopecia, acute renal failure, thrombotic events, Stevens–Johnson syndrome, hemolysis, seizure, syncope, acute respiratory distress, pulmonary edema/embolism, acute bronchospasm (6). An IgA-depleted preparation of IVIg should be used in IgA-deficient patients as they possess anti-IgA antibodies and are prone to anaphylaxis.

CONCLUSIONS

Adjuvant treatment with IVIg represents an efficient therapeutic option for patients with severe, refractory atopic dermatitis. Unfortunately, at the moment, evidence to support this observation comes from only a few limited, uncontrolled studies that lack a strict methodology.

The mechanism of action of IVIg in atopic dermatitis is still unclear, but it may involve inhibition of T cell and B cell function, and implicitly the reduction of T helper 2 cytokines and IgE synthesis. Additionally, IVIg potentiate the effect of corticosteroids by increasing their affinity for the glucocorticoid receptor.

Due to its high financial costs, association of IVIg to classic treatment regimens is reserved for severe, unresponsive cases or for patients who do not tolerate conventional medication. Nevertheless, the cost-benefit ratio of IVIg therapy is superior to that of conventional immunosuppressive treatments.

Moreover, low dose IVIg adjuvant treatment in atopic dermatitis should not be discarded, as it can bring significant benefit. Further large, controlled studies are needed.

Based on our experience, we encourage the use of IVIg in both children and adults with resistant atopic dermatitis. It is well tolerated, especially when administered in a low dose regimen. Adverse events are scarce, generally mild and self-limited, therefore the fear of secondary effects should not deter doctors or patients from using IVIg in appropriate clinical situations.

Conflicts of interest: none declared.

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