

High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome

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Background: High dose intravenous immunoglobulin (IVIG) has immunoregulatory and anti-inflammatory properties that might benefit illnesses with exaggerated IgE responses including atopic dermatitis and hyper-IgE immunodeficiency syndrome.

Objective: To determine if high-dose IVIG would be of benefit to patients with severe atopic dermatitis and/or hyper-IgE syndrome using serial clinical, pulmonary, and laboratory studies for evaluation.

Methods: This was an open label study in which we gave patients with hyper-IgE syndrome ($n = 1$) or severe atopic dermatitis ($n = 9$) IVIG as a 10% solution (Venoglobulin I-Alpha Therapeutic Corporation, Los Angeles, CA) at a dose of 2 g/kg every 30 days for seven infusions.

Results: Therapy was completed in nine of the ten patients. Skin disease improved slightly in six patients, remained unchanged in two patients, and worsened slightly in one patient. The average daily prednisone dosage was 6.8 mg/day prior to treatment and 5.1 mg/day during IVIG therapy ($P = .1250$). The three patients with abnormal pulmonary function showed very mild improvement of pulmonary function during treatment, but returned to baseline during follow-up. Flow cytometric studies showed no consistent pattern of change. IgA and IgM levels were unchanged. The mean serum IgE levels went from 3221 ± 2454 IU/mL (SD) before IVIG to 2944 ± 2491 IU/mL ($P = .4609$) during IVIG and then to 2321 ± 2229 IU/mL ($P = .1484$) during the 6-month follow-up period. In vitro IgE production of peripheral blood mononuclear cells (PBMC) following IL-4 and anti-CD40 stimulation before IVIG was 6.6 ± 3.1 ng/mL (SD) and 4.3 ± 3.1 ng/mL ($P = .1641$) after six IVIG treatments. There were no significant trends in lymphocyte proliferative responses to PHA (phytohemagglutinin), Candida, tetanus, and anti-CD3 monoclonal antibody. Radioallergosorbent (RAST) testing showed no clear changes from positivity to negativity.

Conclusion: We conclude that IVIG was of no clear clinical benefit in these nine patients and did not significantly decrease IgE levels, IgE synthesis, or other measures of immunologic function.

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INTRODUCTION

Intravenous immunoglobulin has been used successfully for the past 15 years in the management of primary and secondary antibody deficiencies.¹⁻³ Dur-

ing this period the value of high-dose IVIG (2 g/kg) in the treatment of several autoimmune and inflammatory diseases has been proven (ie, immune thrombocytopenic purpura, Kawasaki disease) or proposed (ie, lupus erythematosus, rheumatoid arthritis).¹⁻⁸

The mechanisms of action of IVIG in autoimmune and systemic inflammatory diseases may include inhibition of antibody synthesis or function, modulation of cytokine synthesis or action, inhibition of immune activation, decrease of immune complexes, inhibi-

tion of Fc-mediated, antibody-dependent cellular cytotoxicity (ADCC), and interference with complement-induced cell damage.^{1,3,5,9-12}

Since inflammatory changes are an important component of the pathology of several diseases such as asthma, atopic dermatitis, and hyper-IgE syndrome, high-dose IVIG (2 g/kg) might be of benefit in these disorders. Mazer and Gelfand⁷ treated eight patients with severe steroid-dependent asthma with high dose (2 g/kg) intravenous immunoglobulin and found a 3-fold decrease in both maintenance steroids and additional doses of oral corticosteroids needed. They also noted a significant reduction in serum IgE [from 324 ± 100 IU/mL (SD) before treatment to 133 ± 57 IU/mL after treatment] and a significant decrease in cutaneous IgE-mediated reactivity to antigens.⁷ Kimata¹³ also observed that eczema of patients treated with IVIG for immune thrombocytopenic purpura (ITP) and Kawasaki disease improved, along with a decrease in serum IgE levels, blood eosinophil count, and in vitro spontaneous IgE production.

In view of these encouraging results, we undertook a study of high-dose IVIG in patients with severe atopic dermatitis and/or hyper-IgE syndrome using serial clinical, pulmonary, and laboratory studies as criteria for evaluation. Our results provide insufficient evidence of therapeutic benefit.

SUBJECTS

The atopic dermatitis ($n = 9$) and hyper-IgE ($n = 1$) patients ranged in age from 7 to 64 years of age. The IgE levels ranged from 176 IU to 8390 IU/mL. The subject and/or parent or legal guardian agreed to and signed an informed consent for participation in the clinical trial under guidelines ap-

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Entry criteria for patients with atopic dermatitis included all of the following:

- (1) chronic or relapsing dermatitis with short remissions
- (2) involvement of skin areas >40 cm²
- (3) severe pruritis with disturbed sleep and/or excoriations
- (4) failure of 6 months or more of standard intensive therapy (eg, hydration therapy, lubricants, topical steroids, and antibiotics).

Entry criteria for patients with the hyper-IgE syndrome included all of the following:

- (1) recurrent staphylococcal abscesses of the skin, lungs, and joints
- (2) coarse facial features
- (3) serum IgE greater than 1000 IU/mL.

MATERIALS AND METHODS

Venoglobulin-I (10%) used in this trial was provided by Alpha Therapeutic Corporation (Los Angeles, CA) and is derived from units of human plasma that have been tested and found negative for hepatitis B surface antigen and antibody to human immunodeficiency virus and hepatitis C virus using FDA approved assays.

All patients received infusions in the UCLA clinical research center at UCLA. They were infused with 2 g/kg body weight of Venoglobulin-I (10%) once a month for seven infusions. If an adverse reaction occurred, the rate was reduced or the infusion was interrupted until the symptoms subsided. The infusion was then restarted at a tolerable rate. One patient (a 47-year-old white man with severe atopic dermatitis) developed a reaction that will be discussed later and withdrew after the first infusion.

Prednisone doses were obtained by review of weekly diaries. The severity of the eczema was determined by a skin score on physical examination based on an ordinal scale ranging from 0 to 5:

0 = no dermatitis

1 = mildly dry skin, minimal erythema, no sites of inflammation/excoriation, with minimal erythema

2 = small patches of eczema usually on flexor/extensor areas; skin is globally dry

3 = moderate eczema with active inflammation/excoriation that involves larger areas of skin beyond the flexor/extensor surfaces

4 = large patches of inflamed skin involving all limbs; all areas had significant excoriation/lichenification and possible secondary infection

5 = Global eczema with inflamed skin involving all limbs and trunk, obvious secondary skin infection and large patches of excoriation/lichenification.

Laboratory studies performed on enrollment and at intervals throughout the study included complete blood count (CBC), blood chemistry tests, hepatitis testing, and IgG, IgA, and IgM levels. These were performed at the UCLA Clinical Laboratories. IgE levels were performed at Mayo Laboratories by nephelometry.

Radioallergosorbent studies were performed at three different laboratories (Damon Labs, Clinical Labs, and Physician's Clinical Labs) throughout the study and expressed as degrees of reactivity. Results were placed into 5 classes of reactivity. A significant reduction necessitated a decrease of 2 or more classes of reactivity.

Two color flow cytometry on peripheral blood mononuclear cells (PBMC) was performed on a FACScan® and analyzed by Lysis II software using standard methods. We measured the number and percentage of natural killer cells (CD56), monocytes (CD14), B cells (CD20), total T cells (CD3), CD4 T cells, and CD8 T cells. These cells were further assessed for their expression of CD23, the low affinity IgE receptor. Ten microliters of the appropriate antibody [CD23-phycoerythrin (PE) and fluorescein-isothiocyanate (FITC)-labeled CD4, CD8, CD14, CD20, or CD56] was added to each tube. CD23 PE and monoclonal antibody tagged to FITC were added to the cells for 30 minutes in the dark at 4 °C

and then washed twice. Cells were fixed with 2% paraformaldehyde and kept in the dark until analyzed.

In vitro IgE production by unstimulated, IL-4, anti-CD40, and IL-4 plus anti-CD40 stimulated PBMC was measured as reported previously.¹⁴ Cells were cultured for 14 days.

Mitogen and antigen stimulations were performed in standard fashion using 1×10^5 PBMC in 10% human AB serum. Stimuli were PHA (1 µg/mL), OKT3 (1 µg/mL), Candida (50 and 10 µg/mL), and tetanus (2.5, and 1.25 µg/mL). Phytohemagglutinin and OKT3 incubation was three days and Candida and tetanus was five days. After a 6-hour pulse with tritiated thymidine, cells were harvested and counted in a scintillation counter. Results are expressed as the stimulation index (mean cpm in the presence of antigen divided by the mean cpm in culture medium alone).

Statistical Analysis

For analyses, IgE levels, IgE production, prednisone dose, and skin scores were collapsed into mean values before, during, and after treatment. Due to the small sample size and non-normality of the data, each variable was analyzed using the Wilcoxon signed rank test to detect change in the variables of interest between successive intervals.^{15,16} IgE levels of one patient (#126) were excluded because laboratory errors were suspected. The enrollment IgE value of one patient (#127) was omitted because of suspected lab entry error. Standard deviation is used throughout the text of this paper. Standard error of the mean bars are shown in Figures 2 and 4.

RESULTS

Most of the atopic dermatitis patients and the hyper-IgE patient tolerated the IVIG infusions well. The most common complaints, as in other studies^{1,17,18,19} were headache, myalgia, and fatigue.

One patient (#121) with atopic dermatitis developed hypertension during his first infusion. This lasted 1 week. He also developed mild desquamation

of the hands that lasted for 3 months. There was 3+ hematuria that lasted approximately 3 months and a transient increase in serum creatinine (from 1.4 mg/dL to 1.7 mg/dL then back to 1.5 mg/dL) and blood urea nitrogen (from 15 mg/dL to 22 mg/dL). A serum sickness-like reaction was diagnosed and he was withdrawn from the study.

Skin scores improved slightly in six patients (#122, #123, #124, #125, #126, #130), were unchanged in two (#128, #129), and worsened slightly in one (#127). These results, however, were confounded by many factors.

The five patients (#124, #125, #126, #127, #129) receiving systemic prednisone at the onset of the study had a mean initial prednisone dose of 6.8 mg/day and 5.1 mg/day during IVIG therapy ($P = .1250$). Prednisone dose decreased in four patients (#124, #125, #126, #129) during IVIG therapy, but increased posttreatment in two of these four (#125, #129); steroid dosage increased in one (#127) patient during treatment. Prednisone was started in

one patient (#128) during treatment with IVIG.

The forced expired volume at one second (FEV_1) and/or forced expiratory flow (FEF_{25-75}) of three patients were less than 85% predicted at the onset of the study. Patient #123 had hyper-IgE syndrome with severe asthma and chronic lung disease. Patient #125 had atopic dermatitis and a history of wheezing. Patient #124 had atopic dermatitis but no history of prior lung disease. All three showed mild improvement of pulmonary function during treatment, but their pulmonary function returned to baseline after IVIG treatment (Fig 1).

The IgE levels pre, during, and following-IVIG treatment in seven patients are shown in Figure 2. The serum IgE level went from 3221 ± 2454 IU/mL prior to treatment to 2944 ± 2491 IU/mL ($P = .4609$) during IVIG, and to 2321 ± 2229 IU/mL ($P = .1484$) during the followup period. Seven of eight patients (#122, #123, #124, #125, #127, #128, #130) showed decreases in IgE during the treatment

period; the largest decrease (patient #123) was from 6878 to 2317 IU/mL. Five patients (#122, #123, #124, #125, #130) exhibited improvement in skin scores (Fig 3), and two (#124, #125) had a decrease in prednisone dosage during IVIG.

In vitro IgE production by 1×10^5 IL-4 and anti-CD40 stimulated PBMCs went from a mean of 6.6 ± 3.1 ng/mL before IVIG to 4.3 ± 3.1 ng/mL after IVIG ($P = .1641$). In vitro IgE production decreased in five patients (#122, #123, #126, #128, #129), increased in three patients (#125, #127, #130), and remained unchanged in one patient (#124). Two patients (#122, #123) who had decreases in IgE levels following IVIG also had decreases in in vitro IgE production and both showed improvement in skin scores. One patient (#128) had both a decrease in serum IgE and IgE production, but skin scores remained the same.

Flow cytometric studies showed no consistent pattern of change in T cells (CD3, CD4, CD8), B cells (CD20), monocytes (CD14), or NK cells

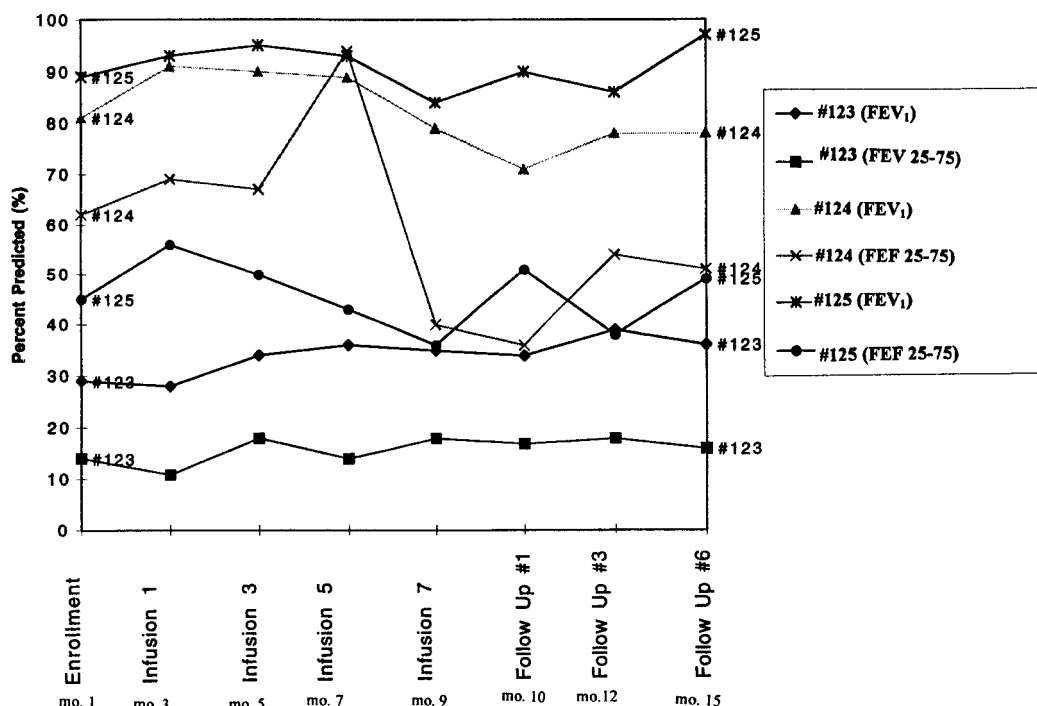


Figure 1. Pulmonary function tests of the three patients who began the study with abnormal results. There seemed to be a very slight improvement in FEV_1 and FEF_{25-75} during IVIG treatment which did not seem sustained during the followup period.

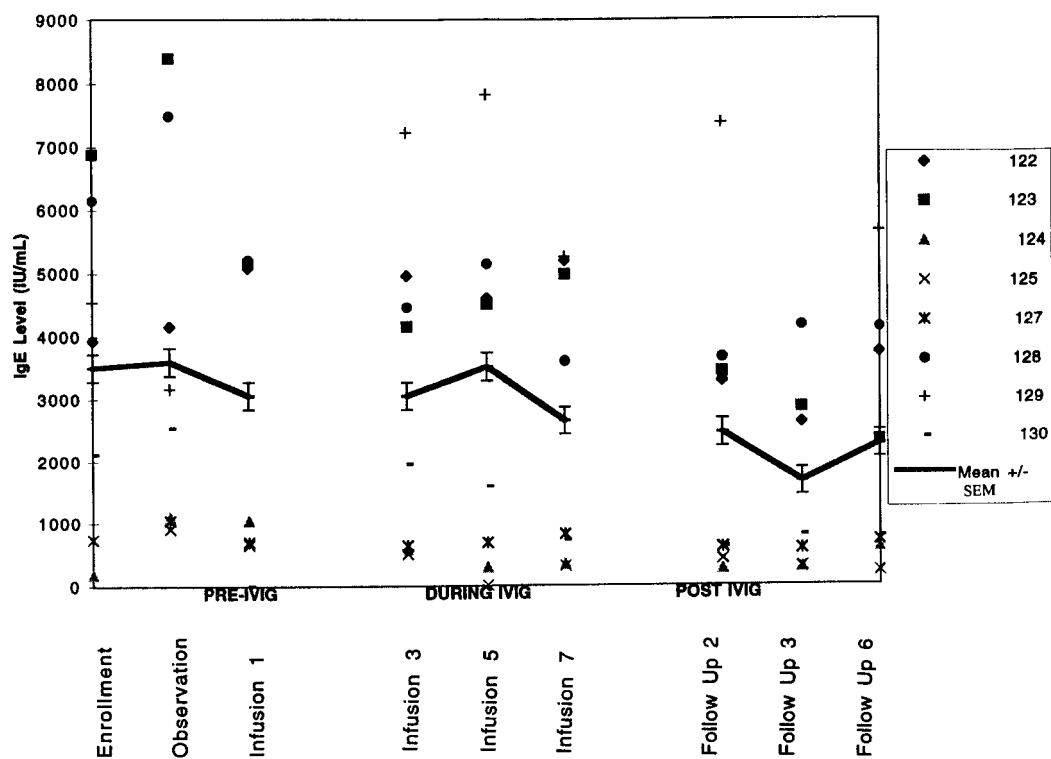


Figure 2. Mean IgE levels of the group as a whole. No significant decreases in IgE levels are noted when pretreatment levels are compared to during and post-treatment IgE levels.

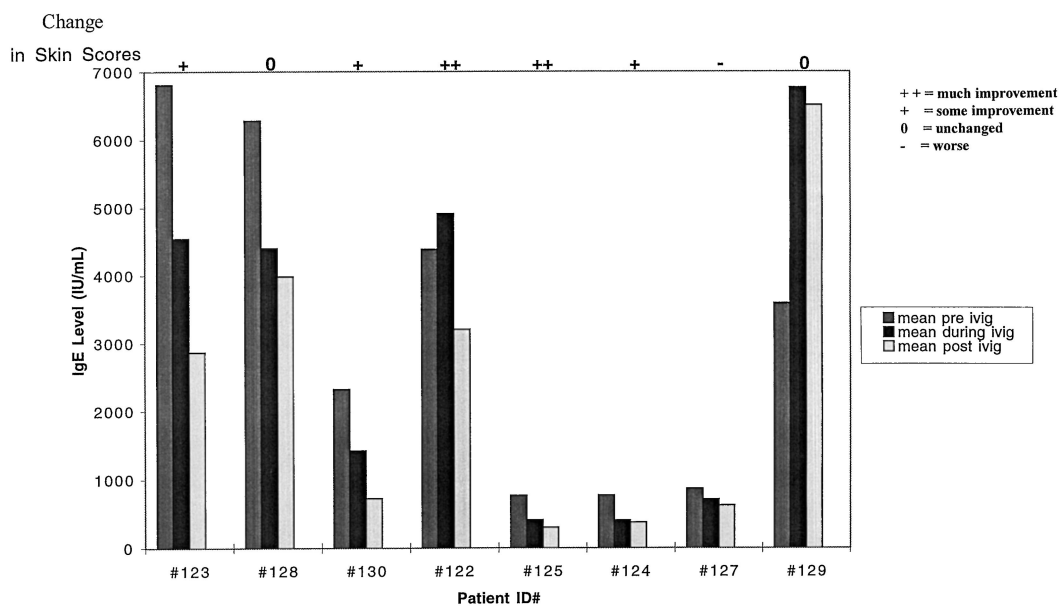


Figure 3. Change in skin scores (+, ++, 0, -) are noted at the top of the diagram for each patient listed on the x axis below. Bar graphs show the pre, during, and post-treatment mean IgE levels for each patient.

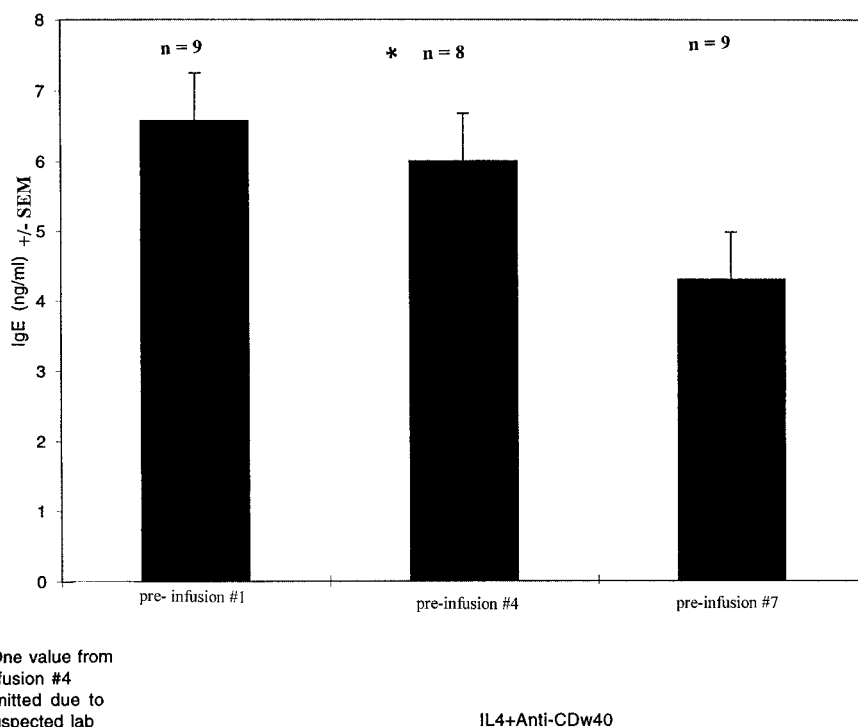


Figure 4. In vitro IgE production by IL-4 and anti-cdw40 stimulated PBMC's shows no significant decrease after 6 infusions of IVIG.

(CD56). CD23 is the low affinity IgE receptor, so it was of special interest to determine if any alteration occurred in this receptor as a result of therapy. CD23⁺ expression varied from 63% to 85% of B cells pretreatment to 52% to 95% of B cells post-treatment in eight of nine patients. In patient #125, 27% and 32% of B cells were CD23⁺ pretreatment and post-treatment, respectively.

There was essentially no expression of CD23 detectable on T cells or natural killer cells. Monocyte CD23 expression was highly variable and no pattern was seen with treatment.

T cell proliferative responses to PHA, Candida, tetanus, and anti-CD3 showed no trends. Some fluctuations of proliferative responses occurred during IVIG therapy, but no consistent pattern was discerned. All nine patients had normal proliferative response to PHA (with a stimulation index (SI) of 14.5 to 1588) and to anti-CD4 (with a SI of 50 to 1574).

Five patients (#123, #126, #127, #128, #130) showed a decreased PHA response while on IVIG and three (#124, #129, #130) showed a decreased response to anti-CD4.

Radioallergosorbent testing was done in all patients with two to four antigens selected by history. A total of 28 tests were performed on the 9 patients. Prior to treatment, 24 of 28 were positive. No significant change occurred during or after treatment.

DISCUSSION

This study was done to determine if the immunoregulatory and anti-inflammatory properties of high-dose IVIG would benefit patients with severe atopic dermatitis and/or hyper-IgE syndrome as indicated by improvement of skin lesions, decrease in steroid medication, improvement of PFTs, or normalization of immunologic abnormalities (ie, decrease in IgE levels and IgE production).

Although changes of skin scores, steroid dose, and PFTs showed trends towards improvement, they did not reach statistical significance. Laboratory studies such as IgE serum levels and IgE production showed downward but insignificant trends.

Our results differ from those of Mazer and Gelfand⁷ in that we did not note a significant decrease in oral prednisone dosage. There was slight improvement in pulmonary function in three patients but not to the extent that Mazer and Gelfand reported. They studied severe asthmatic subjects and only one of our patients was a known severe asthmatic. Our RAST testing results are much less impressive than the changes in cutaneous IgE-mediated reactivity to antigen that they reported. It is possible that IVIG affects skin test reactivity to allergen without decreasing IgE antibody levels. We, as Kimata,¹³ noticed a trend towards a decrease in serum IgE levels and in vitro IgE production, but our findings were not significant. Unlike his patients, our patients had no remarkable and/or sustained clinical improvement.

These results suggest no dramatic clinical or laboratory improvement with the use of IVIG in the treatment in this group of patients. If used for the exceptional refractory patient, an improvement in pulmonary function or a significant decrease in IgE might be an indication of improvement justifying a longer course of treatment.

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REFERENCES

1. Stiehm ER. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. *Pediatr Infect Dis J* 1997;16:696-707.
2. Ballou M. Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. *J Allergy Clin Immunol* 1997; 100:151-7.
3. Gordon DS. Intravenous immunoglobulin therapy. New directions and unanswered questions. *Am J Med* 1987;83: 52-6.

4. Bussel JB, Kimberly RP, Inman RD, et al. Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. *Blood* 1983;62:480–6.
5. Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med* 1992;326:107–16.
6. Fehr J, Hofmann V, Kappeler. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med* 1982;306:1254–8.
7. Mazer B, Gelfand E. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87:976–83.
8. Mobini N, Sarela A, Ahmed AR. Intravenous immunoglobulins in the therapy of autoimmune and systemic inflammatory disorders. *Ann Allergy Asthma Immunol* 1995;74:119–28.
9. Basta M, Langlois PF, Marques M, et al. High-dose intravenous immunoglobulin modifies complement-mediated in vivo clearance. *Blood* 1989;74:326–33.
10. Frank MM, Basta M, Fries LF. The effects of intravenous immune globulin on complement-dependent immune damage of cells and tissues. *Clin Immunol Immunopathol* 1992;62:S82–86.
11. Rossi F, Kazatchkine MD. Anti-idiotypes against autoantibodies in pooled human polyspecific Ig. *J Immunol* 1989;143:4104–9.
12. Shimozato T, Iwata M, Kawada H, Tamura N. Human immunoglobulin preparation for intravenous use induces elevation of cellular cyclic adenosine 3'5-monophosphate levels, resulting in suppression of tumor necrosis factor alpha and interleukin-1 production. *Immunology* 1991;72:497–501.
13. Kimata H. High dose gamma globulin treatment for atopic dermatitis. *Arch Dis Child* 1994;70:335–6.
14. Zhang KE, Clark EA, Saxon A. CD40 stimulation provides an interferon- γ dependent IgE specific differentiation signal directly for human blood and tonsil B cells. *J Immunol* 1991;146:1836–42.
15. Armitage P, Berry G. Statistical methods in medical research. Oxford, London: Blackwell Scientific Publications, 1971, 1987:408–20.
16. Degroot M. Probability and statistics. Reading, MA: Addison Wesley, 1989.
17. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Clin Exp Immunol* 1994;97(Suppl 1):79–83.
18. Ruggeri M, Castaman G, De Nardi G, Rodeghiero F. Acute renal failure after high-dose intravenous immune globulin in a patient with idiopathic thrombocytopenic purpura. *Haematologica* 1993;78:338–9.
19. Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. *Haematologica* 1993;78(Suppl 2):35–40.

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