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Intravenous Immune Globulin (IVIG) Therapy in Steroid-Resistant Atopic Dermatitis

Many trials have been done on steroid-resistant atopic dermatitis. Recently, intravenous immune globulin (IVIG) was reported to be effective in the treatment of steroid-dependent atopic dermatitis. The aim of this study was to clarify whether IVIG therapy is effective in steroid-resistant atopic dermatitis. Forty-one steroid-resistant atopic dermatitis patients were tested in this study. Patients who weighed less than 30 kg were administered 500 mg/kg of IVIG. Patients who weighed 30 kg or more were administered 15 g of IVIG. Patient evaluations and laboratory tests with peripheral bloods such as eosinophil percentages and serum IgE levels were performed at days 0, 1, 7, and 21. In the present study, patients who responded to IVIG therapy were classified as Group A. Twelve patients who showed transient effects with lower clinical significance were classified as Group B (29.3%). Remaining 12 patients (29.3%) in Group C showed no improvement at all. Serum IgE levels and blood eosinophil percentages were markedly decreased in Group A. IVIG therapy may be recommended in the treatment of atopic dermatitis with extremely high serum IgE levels.

Key Words : *Eosinophils; IgE; Immunoglobulins, intravenous; Dermatitis, atopic; Drug resistance, steroid*

Geunwoong Noh, Ki Young Lee*

Department of Pediatrics, Sungkyunkwan University, College of Medicine, Samsung Cheil Hospital and Department of Pediatrics*, Yonsei University, College of Medicine, Seoul, Korea

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Address for correspondence
Dr. Geunwoong Noh
Department of Pediatrics, Sungkyunkwan University, College of Medicine, Samsung Cheil Hospital, 1-19, Mookjung-dong, Chung-gu, Seoul 100-380, Korea
Tel : +82.2-2262-7534, Fax : +82.2-2271-1734
E-mail : avdream@samsung.co.kr

INTRODUCTION

Atopic dermatitis is a chronically relapsing inflammatory skin disease, characterized by dysregulation of the immune system (1). The major immunologic abnormality is Th1/Th2 imbalance (2), which leads to increase of interleukin-4 production and decrease of interferon-γ production (3). This abnormality results in elevated IgE levels (4). Steroid therapy has been a one of treatment modalities for symptomatic relief of atopic dermatitis. Recalcitrant atopic dermatitis over a long period of time has been considered extremely troublesome. For recalcitrant atopic dermatitis, many trials have been performed. Recently, immunomodulatory therapies, including interferon-γ (5), interferon-α (6), thymopentin (7) and cyclosporin A (8), have been tried in steroid-resistant atopic dermatitis.

Intravenous immune globulin (IVIG) therapy has been widely used even though it is still unclear why IVIG is effective. IVIG therapy is effective for many diseases (9-11) including Kawasaki disease (12) and idiopathic thrombocytopenic purpura (ITP) (13). Since IVIG has been already tried in the treatment of allergy diseases in 1957 (14), many investigators have reported the use of IVIG in asthma treatment (15-18). IVIG was first used in the patients who had severe atopic dermatitis concomitantly with Kawasaki disease or ITP (19). Thereafter, IVIG has been used to treat Kawasaki disease and ITP, and atopic dermatitis improved simultaneously. In particular, IVIG was used in asthma in expectation of steroid-sparing effects (20). IVIG was reported to be effective in steroid-dependent atopic dermatitis (21). Then, the more difficult aspect in the treatment of atopic dermatitis is to control the recalcitrant atopic dermatitis resistant to such medical therapies as steroid and immunomodulatory drugs. Therefore, the purpose of this study was to clarify whether IVIG therapy is effective in steroid-resistant atopic dermatitis and to analyze the clinical characteristics of IVIG responses in this disease.

MATERIALS AND METHODS

Forty-one atopic dermatitis patients who had characteristic clinical features of atopic dermatitis were included in this study. They had had severe atopic dermatitis for at least 4 years and had responded inadequately to systemic, oral and topical corticosteroid. They were resistant to or their condition was rather aggravated by steroid therapy. Diagnostic criteria for atopic dermatitis were those of Hanifin

and Rajka (22). The ratio of male to female was 19:22. Patients who weighed less than 30 kg were administered 500 mg/kg of IVIG and patients who weighed 30 kg or more were administered 15 g of IVIG for 10 hr (Green Cross, Seoul, Korea). All medications, including corticosteroid and systemic antihistamine, were withheld for at least 4 weeks before the treatment. During the study, local therapy with steroid-free hydrophilic or emolient ointment was allowed. The protocol of the study was approved by the ethical committee of Samsung Medical Center, Korea. All patients gave informed consent for all test procedures.

The clinical severity and extension of skin involvement were evaluated on days 0, 1, 7, and 21 by the scoring system described previously (23). Clinical status was evaluated in view of both objective and subjective criteria. Objectively, five parameters of skin manifestation including 1) erythema or edema, 2) vesicle, pustules or crusts, 3) excoriation or crackling, 4) scaling or dryness and 5) lichenification were graded as follows: 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The extent of the dermatologic manifestations was evaluated in 20 topographic sites: scalp, ears, peribuccal region, periocular region, face (other), neck, chest, abdomen, back, elbows (flexures), arms-forearms, axillae, hand-wrists (dorsal), palms-wrists, buttocks-groins, popliteal space, thighs, legs, arches and soles. A score of 0-3, depending on the percentage of skin surface affected, was assigned for each of these areas. Subjective criteria-pruritis and loss of sleep-were assessed on the scale 0, 100, 200, and 300, and the score was added to a sum of points calculated for all the sites involved as described above. Patients were evaluated before and at the end of the treatment with blood sampling. A detailed clinical examination was undertaken by the same investigator including a quantitative measurement of clinical severity. The following investigations were performed with clinical evaluations: blood eosinophil percentage and serum IgE which were measured by nephelometry. Statistical comparisons were made throughout this study using Wilcoxon matched-pair signed-rank test and Mann-Whitney U-test and the results were expressed as mean±SD.

RESULTS

IVIG was effective in treatment of steroid-resistant atopic dermatitis (Fig. 1). Clinical severity at day 0 was 543.8±101.2 (median 559). Mean clinical severity was increased at day 1 (577.0±95.2, median 602.0, $p<0.05$) and was markedly decreased at day 7 (487.6±123.3, median 506.0, $p<0.05$) and at day 21 (443.1±176.4, median 512.0, $p<0.05$) compared to it at day 0 (Fig. 1).

However, clinical responses were not similar in all patients. Patients showed one of three characteristic clinical responses (Fig. 2). Patients were classified by reduction of clinical severity at day 21 compared to day 0 and the time course of clinical responses. As a result, IVIG was effective for 17 patients (41.46%) who were classified as Group A. The severity score at day 0 (526.5±116.4, median 567.0) changed insignificantly at day 1 (561.8±104.3, median 599, $p>0.05$). The clinical severity scores at day 7 (409.2±102.5, median 401.5, $p<0.01$) and at day 21 (mean 293.8±116.5, median 296.5, $p<0.0001$) were significantly reduced.

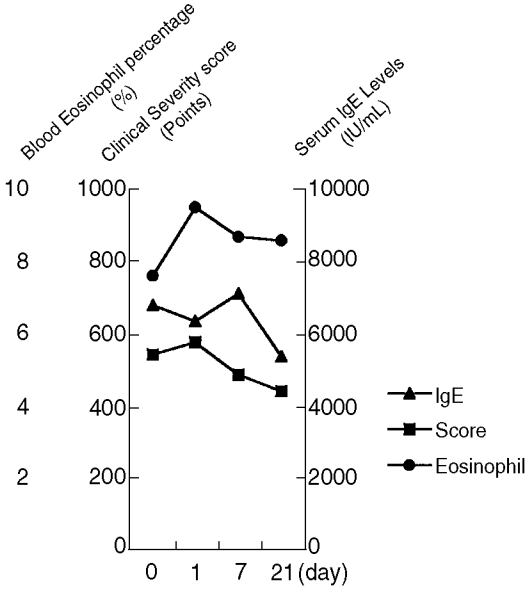

Fig. 1. IVIG effects on clinical severity, blood eosinophil percentage and serum IgE level in steroid-resistant atopic dermatitis. Data were shown by means plotted serially in the graph.

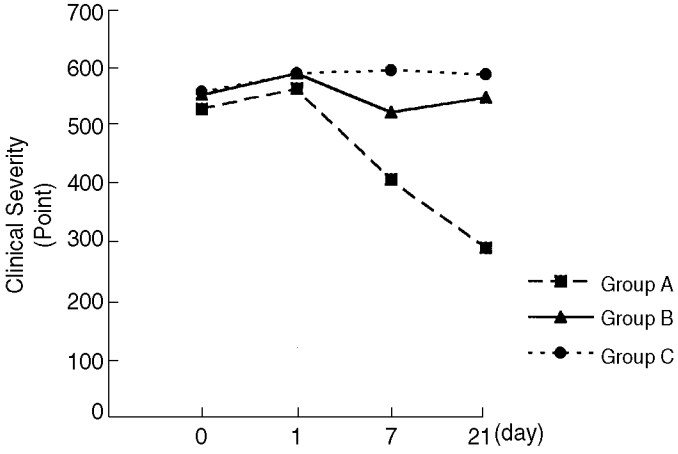

Fig. 2. Three typical courses of clinical responses to IVIG therapy in atopic dermatitis. Patients were classified into three groups according to the reduction of clinical severity at day 21. Data was shown by means plotted serially in the graph.

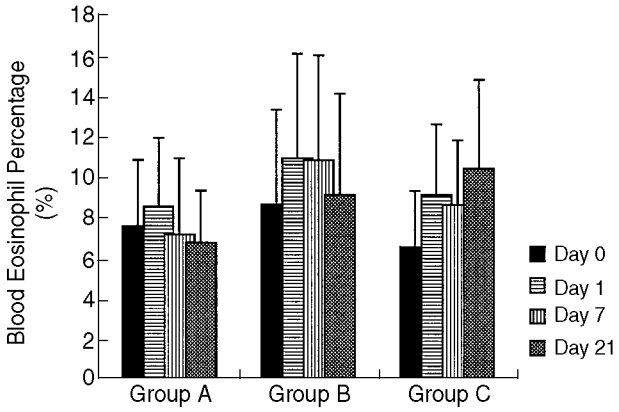

Fig. 3. Effects of IVIG on blood eosinophil percentage in three groups of steroid-resistant atopic dermatitis.

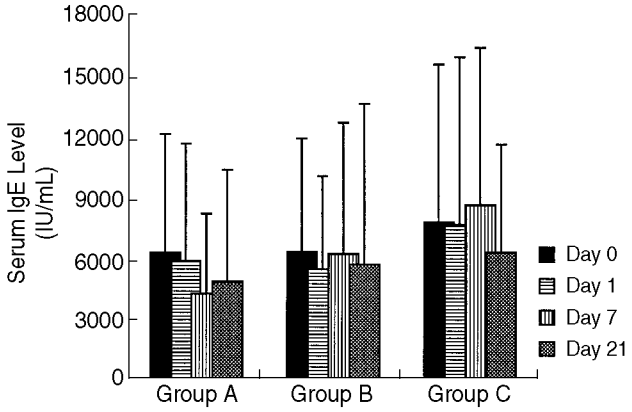

Fig. 4. Effects of IVIG of on serum IgE level in three groups of steroid-resistant atopic dermatitis.

Consequently, all patients in Group A showed an improvement in the clinical severity score of more than 20% at day 21 compared to day 0. The mean age of Group A was 13.4 ±9.5 years (male 9, female 8). By IVIG therapy, 12 patients (29.27%) showed improved scores of 20% or less at day 21 compared to day 0, they were included in Group B. Clinical severity at day 0 was 550.5±50.1 (median 553.0) and increased significantly at day 1 (mean 587.4± 51.8, median 585.0, $p<0.05$). Clinical severities at day 7 (mean 521.9±53, median 509.0, $p>0.05$) and at day 21 (mean 547.9±52.9, median 544.5, $p>0.05$) changed insignificantly compared to day 0. The mean age of Group B was 11.2±8.7 years (male 5, female 7). Patients in Group B showed improvement of clinical severity scores by at day 21 and IVIG was clinically ineffective in Group B. The remaining 12 patients (29.27%) were included in Group C and they showed no improvement at all through the whole test period. The mean age of Group C was 14.3±9.3 years (male 5, female 7). The clinical severity score at day 0 was 556.2±102.5 (median 608.5). The scores changed insignificantly at day 1 (mean 587.5±88.2, median 628.0, $p>0.05$), at day 7 (mean 593.2±85.9, median 640.0, $p>0.05$) and at day 21 (mean 587.1±88.2, median 619.5, $p>0.05$).

Blood eosinophil percentage (BEP) was increased by use of IVIG therapy in atopic dermatitis. BEP at day 0 was 7.6 ±3.7% (median 6.7%). BEP significantly increased at day 1 (9.5±4.1%, median 8.1%, $p<0.0001$). Thereafter, BEP at day 7 (8.7±4.2%, median 8.5%, $p<0.05$) insignificantly decreased and returned to initial level at day 21 (8.6± 4.1%, median 8.2, $p>0.05$) (Fig. 3). BEP at day 0 was 7.6 ±3.3% (median 6.3%) in Group A and was significantly increased at day 1 (8.6±3.4%, median 7.5%, $p<0.05$). BEP at day 7 (7.2±3.8%, median 6.4%, $p>0.05$) and at day 21 (6.8±2.6, median 6.6, $p>0.05$) in Group A was decreased gradually to BEP of day 0. In Group B, BEP at day 0 was 8.7±4.7% (median 8.1%) and also increased significantly at day 1 (11.0±5.2%, median 12.2%, $p<0.001$). Thereafter, BEP was decreased at day 7 (10.9±5.2%, median 13.0%, $p<0.05$) and at day 21 (9.2±5.0, median 9.6, $p>0.05$) in Group B. BEP at day 21 decreased to that of day 0. In Group C, BEP at day 0 was 6.6±2.6% (median 6.4%). BEP in Group C was significantly higher at day 1 (9.2±3.5%, median 7.9%, $p<0.01$), at day 7 (8.7± 3.2%, median 8.5%, $p<0.0001$) and at day 21 (10.5±4.4, median 9.7, $p<0.001$) than it at day 0.

IVIG infusion decreased serum IgE levels immediately from 6792.2±6352.5 IU/mL at day 0 (median 5264 IU/mL) to 6348.5±6400.5 IU/mL at day 1 (median 4500 IU/mL, $p<0.05$). Serum IgE level was 7124.7±8338.3 IU/mL (median 4845.0 IU/mL, $p>0.05$) at day 7 and consequently was decreased significantly to 5391.3±5604.1 IU/mL (median 3216.0 IU/mL, $p<0.05$) at day 21. In Group A, serum IgE level at day 0 was 6327.1±5913.7 IU/mL (median 4534.0 IU/mL) and continuously decreased significantly at day 1 (mean 5918.4±5864.2 IU/mL, median 4349.5 IU/mL, $p<0.005$), at day 7 (mean 4300.1 ±3994.5 IU/mL, median 3299.5 IU/mL, $p<0.005$), and at day 21 (mean 4899.7±5575 IU/mL, median 2981.0 IU/mL, $p<0.01$). In Group B, serum IgE level at day 0 was 6387.8±5663.5 (median 5203.0). Serum IgE level at day 1 (mean 5498.0±4670.5 IU/mL, median 4837.5 IU/mL, $p<0.05$) showed a significant transient reduction. Serum IgE level at day 7 (mean 6269.2±6569.6 IU/mL, median 5403 IU/mL, $p>0.05$) and at day 21 (mean 5749.0± 8023.2 IU/mL, median 5014 IU/mL, $p<0.005$) was not different from that at day 0. In Group C, serum IgE level at day 0 was 7855.2±7877.5 (median 5574.0). Serum IgE level at day 1 (mean 7750.7±8683.0 IU/mL, median 4473 IU/mL, $p>0.05$) showed an insignificant decrease. Serum IgE level at day 7 (mean 8736.2±7852.4 IU/mL, median 7767.0 IU/mL, $p>0.05$) showed an insignificant change while serum IgE level at day 21 (mean 7352.0±7401.5 IU/mL, median 5346.5 IU/mL, $p<0.05$) significantly was

decreased.

DISCUSSION

IVIG may be recommended as an alternative therapy in steroid-dependent atopic dermatitis for steroid-sparing effects (20, 21). In addition to steroid overuse, steroid-resistance is a particularly serious problem in atopic dermatitis. For recalcitrant atopic dermatitis, including steroid-resistant atopic dermatitis, many clinical trials such as cytokines or immunosuppressive drugs have been performed with limited success (5-8). This study suggests IVIG as a possible immunomodulatory drug for steroid-resistant atopic dermatitis. It is well known that IVIG is a safe drug with few side-effects (24) and complications compared to any other immunomodulatory or immunosuppressive drug. There have been only two reports concerning IVIG therapy in atopic dermatitis. IVIG was first used in atopic dermatitis patients with Kawasaki disease or idiopathic thromobocytopenic purpura (19). Then IVIG was cautiously tried on three atopic dermatitis patients and was reported to be effective in steroid-dependent atopic dermatitis (21). In this study, IVIG was used in 41 steroid-resistant patients and the patients did not respond in a same pattern of clinical responses. Heterogeneity of atopic dermatitis has been suggested in various aspects by some investigators (25, 26). If atopic dermatitis is regarded as a disease with identical pathogenesis in all patients, clinical responses to a certain drug should be similar. However, for example, steroid-responsiveness can be variable as shown by steroid-dependent and steroid-resistant atopic dermatitis. Our study showed similar results that clinical responses to IVIG therapy were not homogeneous in all steroid-resistant atopic dermatitis patients. Clinically, IVIG was effective only in Group A, but not in Group B and C (Fig. 3). These results may be supportive evidences for the heterogeneity of atopic dermatitis. Further investigation on predictors for responses of IVIG therapy in atopic dermatitis may be needed.

Elevation of IgE has been regarded as a major problem in atopic dermatitis (4). Serum IgE was reported to be dramatically reduced at days 4, 7, and 14, and near normal 6 months after IVIG therapy in a previous report (17). In another report, serum IgE levels were unchanged following the six months of IVIG therapy (19). In this study, the changes of serum IgE were examined at day 1 immediately after IVIG infusion. Serum IgE level was decreased at day 1 after IVIG therapy. Serum IgE levels in Group A and C were decreased significantly at day 21, while the serum IgE level in Group B was insignificantly decreased. Serum IgE levels decreased at day 21 by IVIG therapy as previously described (17). Only in Group A, serum IgE was continuously and effectively decreased. It is certain that IVIG had immediate and long-term effects of lowering serum IgE levels (19, 21). In other report (21), the reduction of serum IgE levels by IVIG therapy in atopic dermatitis was not marked. In our study, atopic dermatitis patients showed different clinical reponses and laboratory findings.

IVIG was effective in lowering blood IgE levels in hyperimmunoglobulin E syndrome (HIES). Serum IgE level was dramatically reduced in 4 weeks (27). The reduction of serum IgE levels in Group A was similar to the effects of IVIG in HIES. Atopic dermatitis patients of Group A and HIES patients in the previous report (27) share several similar characteristics. First of all, HIES has clinical characteristics of atopic dermatitis. In the case of atopic dermatitis of Group A in this study and HIES studied in the previous report (27), steroid therapy was unhelpful and patients had extremely high IgE levels. So, there might be a possibility that atopic dermatitis patients of Group A would had characteristics of HIES. Therefore, the possibility of sharing any pathogenesis or mechanisms by IVIG-responsive atopic dermatitis (Group A) and HIES needs further investigated.

In other reports, IVIG was administered at a dose of 2 g/kg/month (19) and at a dose of 400 mg/kg for five consecutive days from day 1 of treatment (21) in atopic dermatitis. In this study, low-dose IVIG therapy was tried at a single dose of 500 mg/kg or less on the first day of a 3-week observation period. The differences in effects of IVIG on clinical responses, serum IgE levels and blood eosinophil percentages from the results of other investigators can be explained that they may vary depending on a dose and a method of IVIG administration.

IVIG infusion immediately increased BEP at day 1 (Fig. 4). In Group A, BEPs at days 7 and 21 were decreased insignificantly and were restored to BEP at day 0 statistically. In Group B, BEP was reduced only at day 21. BEP at day 21 was not returned to BEP at day 0 in Group C. In this study, the clinical responses may be closely related with BEP. Eosinophilia is known to be related with clinical severity (28). Initial aggravation immediately following IVIG infusion seemed to be related with the rapid increase of BEP, and the clinical course seemed to be dependent on the changes of BEP. Eosinophil counts were dramatically decreased in atopic dermatitis by IVIG therapy in the previous report (19). In other report, the effects of IVIG on quantitative changes of blood eosinophil in atopic dermatitis were not described (21). In this study, BEP was notably increased by IVIG therapy initially in atopic dermatitis.

Atopic dermatitis is an inflammatory disease caused by a disorder of allergic mechanisms. Although the behavior of IVIG is poorly understood, IVIG exhibits anti-inflammatory activity (29). Pooled IgG may mediate immunomodulation through direct effects on cytokine production (30) and on T-cell proliferation (31). Anti-inflammatory effects of IVIG may play a role in clinical improvement of atopic der-

matitis by IVIG therapy. Interestingly, interferon (IFN)-γ production was also down-regulated by IVIG (31). Defect of IFN-γ production is known to be an important defect in the pathogenesis of atopic dermatitis (3). Therefore, IVIG effects on IFN-γ production may not be appropriate in the treatment of atopic dermatitis. There is a possibility that an immediate aggravation episode after IVIG infusion results from IVIG effects on IFN-γ production. Whether IVIG down-regulates IFN-γ production, and whether it plays a different role in atopic dermatitis should be investigated further.

IVIG has anti-allergic actions in several ways. In particular, IVIG may modulate IgE-mediated responses. IVIG may inhibit the differentiation of B cells to antibody-secreting cells (32). Moreover, in vitro synthesis of human IgE was reported to be suppressed by human IgG (33). Allergen-specific IgG present in IVIG may neutralize the allergen, preventing (blocking) their interactions with cell-bound IgE (21). IVIG may also down-regulate allergen-specific IgE production through anti-idiotype antibodies, which have been shown to be present in IVIG (34). These anti-allergic actions may also explain IVIG effects in atopic dermatitis.

Conclusively, IVIG therapy was effective in steroid-resistant atopic dermatitis. Atopic dermatitis patients showed three typical clinical responses. IVIG decreased serum IgE levels and increased blood eosinophil percentages immediately. The IVIG action lowering serum IgE levels was significant in atopic dermatitis. Clinical responses may depend on the changes of blood eosinophil percentages. Due to the effects of lowering serum IgE levels and elevating blood eosinophil percentage, IVIG therapy may be recommended for atopic dermatitis patients with extremely high serum IgE levels, but it may not be appropriate for patients with high blood eosinophil percentages. The precise action mechanism of IVIG and the practical indication for IVIG therapy in atopic dermatitis needs further investigation.

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