

Intravenous immune globulin effects on serum-soluble CD5 levels in atopic dermatitis

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Summary

Background Intravenous immune globulin (IVIG) therapy has been tried in the treatment of atopic dermatitis. Recently, the presence of serum-soluble CD5 (ssCD5) in atopic dermatitis was reported.

Objective IVIG effects on ssCD5 levels in atopic dermatitis were examined and the correlation of ssCD5 level changes with clinical and laboratory parameters were investigated.

Methods IVIG therapy was tried on 40 atopic dermatitis and 17 recurrent spontaneous abortion patients. Five atopic dermatitis patients received normal saline as a placebo control group. The clinical and laboratory parameters were evaluated on day 0, 1, 7 and 21 after administering the IVIG therapy.

Results With IVIG therapy, in atopic dermatitis, the ssCD5 level was 5.5 ± 6.2 ng/mL before infusion (day 0), 15.2 ± 12.1 ng/mL on day 1, 13.8 ± 14.1 ng/mL on day 7, and 3.9 ± 4.1 ng/mL on day 21. The clinical severity score was 350.5 ± 120.3 on day 0, 420.4 ± 174.8 on day 1, 250.0 ± 121.2 on day 7, and 115.5 ± 53.9 on day 21. White blood cell (WBC) counts and serum IgE levels showed a gradual decrease with IVIG infusions. Blood eosinophil fractions were $5.3 \pm 2.8\%$ on day 0, $8.6 \pm 5.2\%$ on day 1, $7.3 \pm 3.7\%$ on day 7, and $6.8 \pm 4.0\%$ on day 21. Changes in the total eosinophil count were insignificantly parallel with those of blood eosinophil fractions.

Conclusion In atopic dermatitis, IVIG therapy increased the ssCD5 levels. Further studies concerning the exact role of ssCD5 are needed.

Keywords: atopic dermatitis, IVIG, soluble CD5, IgE, eosinophil

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Introduction

Until now, intravenous immune globulin (IVIG) therapy has been tried on atopic dermatitis (AD) with limited success. IVIG was first used in severe atopic dermatitis patients who were also suffering from Kawasaki disease or idiopathic thrombocytopenic purpura (ITP) [1]. IVIG therapy is effective in steroid-dependent AD expecting of steroid-sparing effects [2]. IVIG was beneficial in some cases of atopic dermatitis with some investigators [3]. In

our previous report [4], IVIG therapy was effective in a portion of steroid-resistant AD patients.

The mainstay of the immunopathogenesis of AD is known to be a Th1/Th2 imbalance [5] which leads to an increased interleukin (IL)-4 production and a decreased interferon (IFN)- γ production [6]. The ultimate pathologic condition is the elevation of IgE production from these immunological abnormalities [7]. Recently, heterogeneity in AD in clinical and laboratory aspects has been reported by many researchers [8,9] and numerous efforts have been made to locate the optimal candidate for each immunomodulatory drugs, including IVIG [4,10].

CD5/Leu-1 antigen is a 67 kDa glycoprotein which has

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been known to be present only on the cell surface of lymphocytes [11,12]. However, soluble CD5 was recently reported to be present in AD [13]. The significance of its presence, particularly the one concerning the immunological role in AD, is still unclear.

Although IVIG therapy is now widely used and is effective in many diseases [14,15], the exact action mechanisms of IVIG are still unclear. The purpose of this study was to clarify the effects of IVIG on serum-soluble CD5 (ssCD5) levels in AD. The correlation of changes in ssCD5 levels with the changes in clinical severity, serum IgE level and plasma cytokine level were also investigated.

Materials and methods

Patients and IVIG therapy

Recalcitrant AD patients ($n = 45$) who visited the Atopic Dermatitis Clinic of Samsung Cheil Hospital, Korea participated in this study. They fulfilled the criteria of Hanifin and Rajka [16]. All patients had been suffering AD for over two years and they were patients who did not respond to any conventional therapy including antihistamine, systemic steroid, or local steroid ointment. Systemic steroid uses were completely stopped for at least 1 month before entering the study for all participants. However, topical steroid application of hydrocortisone 1% was allowed. The following tests were conducted on the white blood cell (WBC) counts, blood eosinophil fraction to WBC, total eosinophil counts, and serum IgE. Informed consent was obtained from all participating patients and this study was approved by the ethical committee of the Samsung Cheil Hospital.

A single-blinded placebo-controlled test was performed for this study. Patients were not aware of whether they had received an IVIG or a placebo for the test. Among the 45 AD patients, 40 had received an IVIG and 5 had received normal saline as a placebo. Recurrent spontaneous abortion patients ($n = 17$) who received an IVIG were enrolled as IVIG therapy controls. They had received an IVIG before pregnancy for a successful pregnancy and samples were collected before pregnancy. Thirty normal subjects who visited our hospital for regular health check-ups, had no family history nor past medical history associated with allergic diseases, and had no illness at the time of the test, were also enrolled as normal controls for the comparison of plasma cytokine levels. The presence of CD5 protein in IVIG solution (15 mg/mL) was tested.

Clinical severity and the extent of skin involvements were evaluated using the scoring system previously described [17]. Clinical status was evaluated with both objective and subjective criteria. Five parameters of skin involvements were as follows: (1) erythema, oedema; (2)

vesicle, pustules, crusts; (3) excoriation, cracking; (4) scaling, dryness; and (5) lichenification. These parameters were graded as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe). The extent of the dermatologic manifestations was evaluated in 20 topographic sites; scalp, ears, peribuccal region, periocular region, other parts of the face, neck, chest, abdomen, back, axillae, elbows (flexures), arms (forearms, hands), wrists (dorsal), palms (wrists), buttocks (groin), popliteal space, thighs, legs, arches, and soles. A score from a range of 0–3, depending on the percentage of skin surface affected, was assigned for each of these areas. Subjective criteria – pruritus and loss of sleep – were assessed on a scale of 0, 100, 200 and 300 and the score was added to the sum of points calculated for all sites involved as described above.

Patients who weighed less than 30 kg were administered with 500 mg/kg of IVIG (Green Cross, Seoul, Korea) and patients who weighed more than 30 kg were administered with 15 g of IVIG for 10 h. Clinical severity scoring and laboratory tests were conducted on the patients as well as the placebo-controlled subjects on days 0 (just before IVIG infusion), 1 (just after IVIG infusion), 3, 7 and 21 after an IVIG infusion. A detailed clinical examination, including a quantitative measurement of clinical severity, was undertaken by the same investigator.

Extraction of cellular proteins

Protein extracts were prepared from CRL-1929 (CD5⁺ B cell line) as a positive control and from CRL-9855 (28SC, human monocyte cell line) as a negative control. The cell lines were purchased from the American Type Culture Collection (Bethesda, MD, USA). A cell pellet of 5×10^8 cells was prepared. It was suspended and incubated for 5 min at 22 °C in 1 mL of 20 mM Tris-HCl, pH 7.5 2 mM MgCl₂ solution. Supernatant was removed and the cell pellet was suspended in 1 mL of the same solution containing 0.1% Triton X-100. After incubation for 5 min at 22 °C, the lysed cells were microcentrifuged. Aliquots of the supernatant were either immediately used for assay or were stored at –80 °C.

ELISA for serum-soluble CD5

Soluble CD5 were detected using the sandwich ELISA method using Cris 1 (IgG2a, anti-CD5 antibody) and biotin-labelled CD5-49 (IgG2a, anti-CD5 antibody) ascites monoclonal antibody. A 96-well flat bottom immunoplate (Costa Co., Cambridge, MA, USA) were coated with 100 µL of anti-CD5 mAb Cris-1 (5 µg/mL) in Tris buffered saline (TBS) (50 mM Tris-HCl pH 7.5, 150 mM NaCl) and were incubated overnight in a wet chamber at 4 °C. Wells were washed three times with TBS-Tween

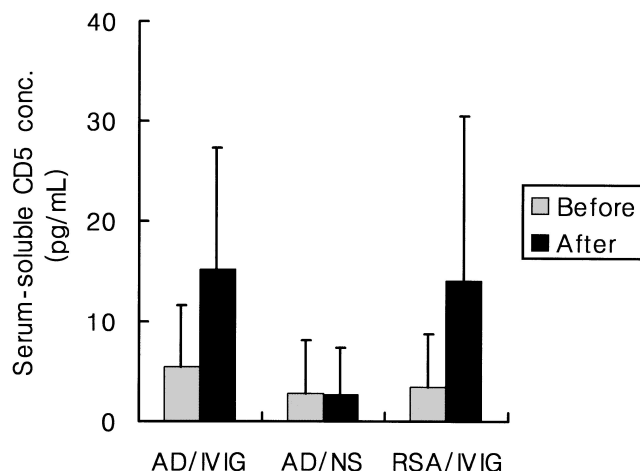


Fig. 1. Serum-soluble CD5 (ssCD5) level changes with IVIG therapy. IVIG therapy increases ssCD5 levels in atopic dermatitis (from 5.5 ± 6.2 ng/mL before treatment on day 0 to 15.2 ± 12.1 ng/mL on day 1) and in recurrent spontaneous abortion patients (from 5.7 ± 3.4 ng/mL before treatment on day 0 to 16.3 ± 5.3 ng/mL a day after IVIG infusion). Atopic dermatitis patients who received a normal saline as a placebo control showed no change in ssCD5 levels (from 2.8 ± 5.3 ng/mL on day 0 to 2.6 ± 4.8 ng/mL on day 1). IVIG preparation did not contain CD5 protein. AD/IVIG, atopic dermatitis patients with IVIG therapy; AD/NS, atopic dermatitis patients with normal saline as a control group; RSA/IVIG, recurrent spontaneous abortion patients with IVIG therapy; IVIG, intravenous immune globulin preparation.

0.05%. The wells were blocked by incubation with 200 μ L of TBS containing 5% non-fat milk for 30 min at 37 °C. Each well was incubated with 100 μ L of sera diluted at 1 : 4 ratio for 2 h at room temperature (24°C). For standard calibration, recombinant soluble CD5 was used in serial concentrations of 500 μ g/mL, 250 μ g/mL, 125 μ g/mL, 62.5 μ g/mL, 31.25 μ g/mL, 15.63 μ g/mL and 7.82 μ g/mL. Also, protein extracts from CRL-1929 (CD5⁺ B cell line) were used as positive and those from CRL-9855 (28SC, human monocyte cell line) as negative controls. IVIG solution (15 mg/mL) was tested for soluble CD5 and then the wells were washed three times with TBS-Tween 0.05%. The wells were then incubated with biotin-labelled CD5-49 monoclonal antibody in blocking solution for one hour at room temperature and then washed three times with TBS-Tween 0.05%. They were then incubated with 100 μ L of Streptavidin-HRP (Horse Radish Peroxidase) solution (Endogen, Woburn, MA, USA) and then diluted at 1 : 400 ratio for 30 min at room temperature before being washed a further three times with TBS-Tween 0.05%. TMB (3,3',5,5'-tetramethyl benzidine) substrate solution (Pierce, Rockford, IL, USA) was added to the wells for 15 min and 100 μ L of stopping solution was added. The plates were

inserted into an ELISA reader (Dynatech MR 600, Alexandria, VA, USA) and optical density (OD) values were measured at a wavelength of 450 nm.

Plasma IFN- γ , IL-4, IL-5 and IL-10 assay

For cytokine assay, 2 mL of heparinized peripheral venous blood was drawn, and a sample was layered onto an aliquot (5 mL) of Ficoll-Paque (Pharmacia, Uppsala, Sweden) in a sterile conical tube (Falcon, Becton-Dickinson, Cowley, UK). After centrifugation at 1000 *g* for 20 min at 20 °C, plasma was collected for a cytokine analysis. The plasma samples were stored at -80 °C until they were used in plasma cytokine concentrations tests, which were measured using the highly sensitive IL-4 ELISA kit (sensitivity, 0.09 pg/mL; range, 0.25–16 pg/mL) (R & D, Minneapolis, MN, USA), IL-5 ELISA kit (sensitivity, 3 pg/mL; range, 7.8–500 pg/mL) (R & D), highly sensitive IL-10 ELISA kit (sensitivity, 0.5 pg/mL; range, 0.781–50 pg/mL) (R & D), and IFN- γ ELISA kit (sensitivity, 2 pg/mL; range, 9.4–600 pg/mL) (R & D). These procedures were carried out following the manufacturer's instructions. Cytokine concentrations were calculated using the calibration curve.

Statistical analysis

The data were shown as mean $\pm$ standard deviation and range. For an analysis of a significant difference among groups, statistical comparisons were made throughout this study using the Wilcoxon matched-paired signed-rank test and Mann-Whitney *U*-test. These statistical analysis were performed using SPSS. Differences associated with a probability of $P < 0.05$ were considered significant.

Results

Serum-soluble CD5 levels

IVIG therapy immediately increased mean ssCD5 levels from levels of 5.5 ± 6.2 ng/mL before treatment on day 0 to 15.2 ± 12.1 ng/mL levels on day 1 (Figs 1 and 2b). The levels gradually decreased to 13.8 ± 14.1 ng/mL on day 7, and to 3.9 ± 4.1 ng/mL on day 21 ($P < 0.05$ between day 0 and 1, $P > 0.05$ between day 0 and 21). In recurrent spontaneous abortion patients, ssCD5 levels were increased from 5.7 ± 3.4 ng/mL before treatment on day 0 to 16.3 ± 5.3 ng/mL, a day after an IVIG infusion ($P < 0.05$). In the placebo-controlled AD group, soluble CD5 levels did not change: from 2.8 ± 5.3 ng/mL on day 0 to 2.6 ± 4.8 ng/mL on day 1, 2.4 ± 4.4 ng/mL on day 7, and 2.1 ± 3.8 ng/mL on day 21 ($P > 0.05$). IVIG solution (15 mg/mL) was tested for the presence of CD5. However, CD5 was not detectable in IVIG.

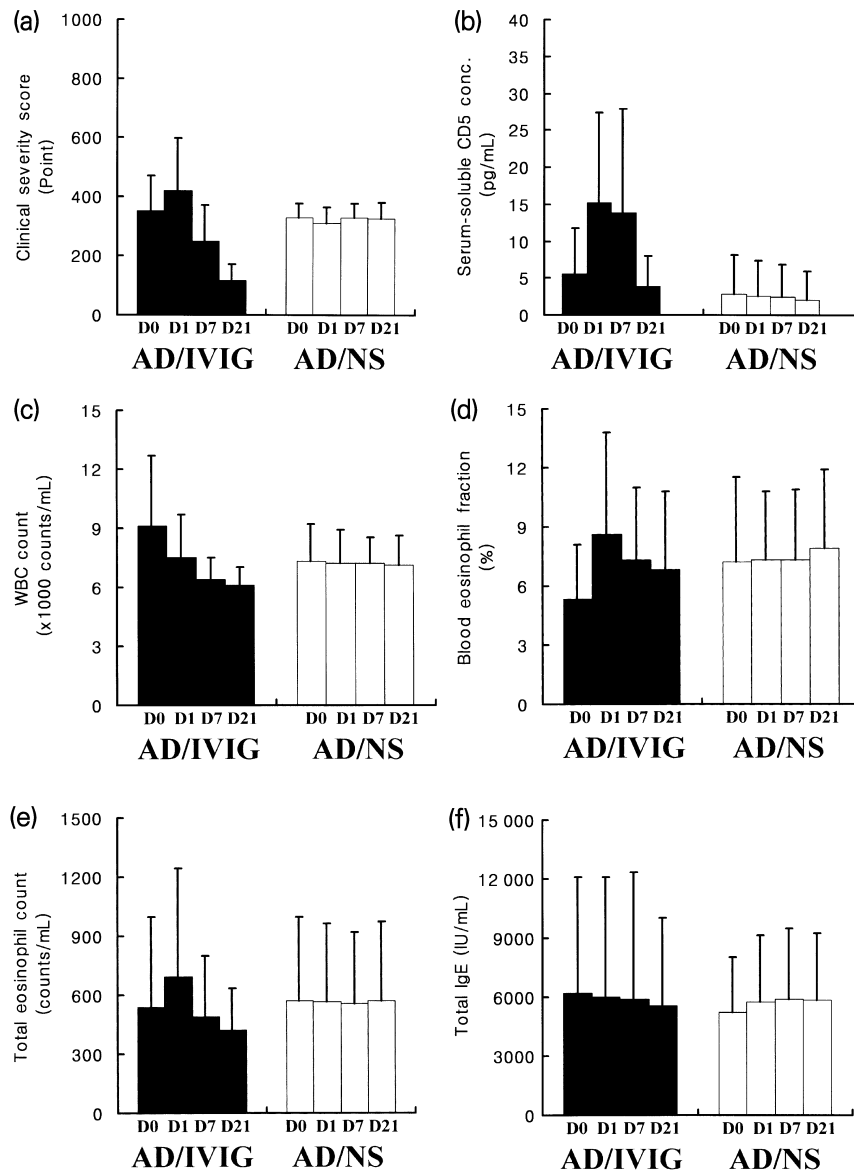


Fig. 2. Clinical and laboratory changes in IVIG therapy in atopic dermatitis. (a) Clinical severity scores, (b) serum-soluble CD5 levels, (c) WBC counts (d), blood eosinophil fraction, (e) total eosinophil counts, and (f) total IgE. AD/IVIG, atopic dermatitis patients under IVIG therapy; AD/NS, atopic dermatitis patients with normal saline as a control group.

Clinical and laboratory effects of IVIG in atopic dermatitis

With IVIG therapy, the clinical severity scores increased only on day 1 (from 350.5 ± 120.3 on day 0 to 420.4 ± 174.8) after an IVIG infusion. The scores showed a gradual decrease to 250 ± 121.2 on day 7 and 115.5 ± 53.9 on day 21 (Fig. 2a) ($P < 0.05$ between day 0 and 1, 1 and 7, 7 and 21, and 1 and 21). In the placebo-controlled group which received a normal saline as a placebo, clinical severity scores were transient and showed a slight decrease from 328.0 ± 50.0 (day 0) to

311.0 ± 52.9 (day 1) and returned to 330.0 ± 47.3 on day 7 and 325.0 ± 54.6 on day 21 ($P < 0.05$ between day 0 and 1, $P > 0.05$ between 0 and 21).

WBC counts gradually decreased after an IVIG infusion – from $9.1 \pm 3.6 \times 1000/\text{mL}$ on day 0 to $7.5 \pm 2.2 \times 1000/\text{mL}$ on day 1, $6.4 \pm 1.1 \times 1000/\text{mL}$ on day 7, and $6.1 \pm 0.9 \times 1000/\text{mL}$ on day 21 ($P < 0.05$ between day 0 and 21, Fig. 2c). In the placebo-controlled group, WBC counts did not change – from $7.3 \pm 1.9 \times 1000/\text{mL}$ on day 0 to $7.2 \pm 1.7 \times 1000/\text{mL}$ on day 1, $7.2 \pm 1.3 \times 1000/\text{mL}$ on day 7, and $7.1 \pm 1.5 \times 1000/\text{mL}$ on day 21 ($P > 0.05$).

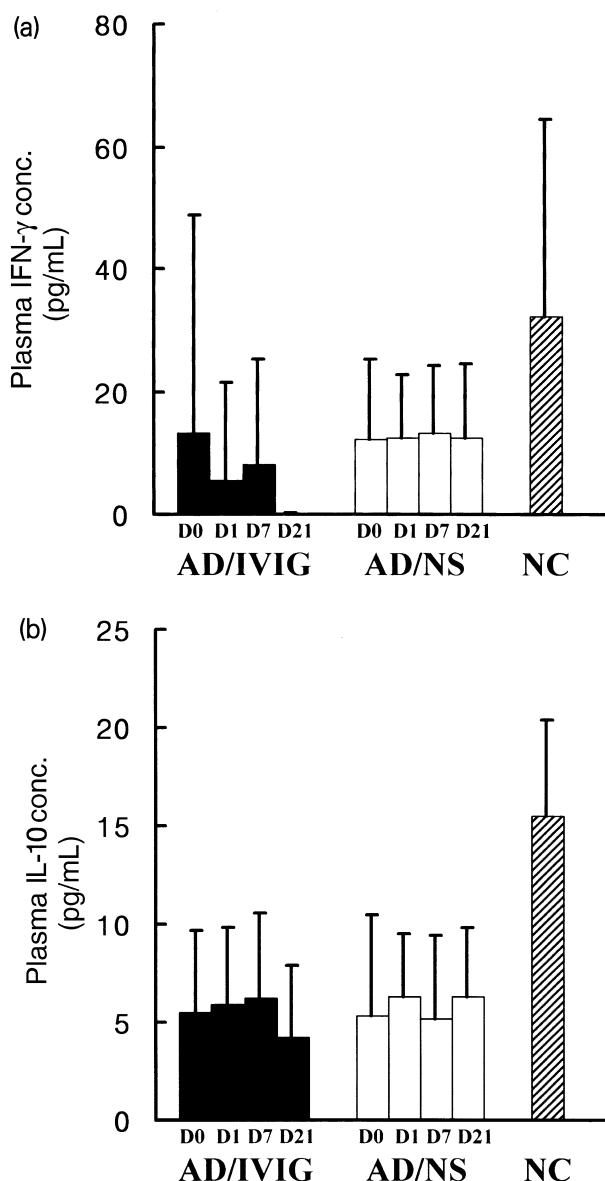


Fig. 3. Plasma IFN- γ and IL-10 concentration changes with IVIG therapy. (a) IFN- γ , (b) IL-10. D0, just before treatment; D1, a day after treatment; D7, 7 days after treatment; D21, 21 days after treatment, AD/IVIG, atopic dermatitis patients with IVIG therapy; AD/NS, atopic dermatitis patients with normal saline as a control group; NC, normal control group.

Blood eosinophil fractions (BEF) immediately increased from $5.3 \pm 2.8\%$ on day 0 to $8.6 \pm 5.2\%$ on day 1, but decreased to $7.3 \pm 3.7\%$ on day 7 and to $6.8 \pm 4.0\%$ on day 21 ($P < 0.05$ between day 0 and 1, $P > 0.05$ between day 0 and 21, Fig. 2d). In the placebo-controlled group, mean BEFs did not change – from $7.2 \pm 3.4\%$ on day 0 to $7.3 \pm 3.5\%$ on day 1, $7.3 \pm 3.6\%$ on day 7, and $7.9 \pm 4.0\%$ on day 21 ($P > 0.05$). In IVIG therapy, the changes

concerning total eosinophil counts were insignificantly parallel to those of BEFs from $535.5 \pm 461.9/\text{mL}$ on day 0 to $692.7 \pm 550.9/\text{mL}$ on day 1, $487.1 \pm 311.5/\text{mL}$ on day 7, and $418.7 \pm 212.8/\text{mL}$ on day 21 ($P < 0.05$ between day 1 and 21, Fig. 2e). The placebo-controlled group did not show any remarkable change in the study – from $571.9 \pm 425.3/\text{mL}$ on day 0 to $567.4 \pm 396.5/\text{mL}$ on day 1, $558.5 \pm 359.8/\text{mL}$ on day 7, and $571.2 \pm 402.0/\text{mL}$ on day 21 ($P > 0.05$).

Serum IgE levels changed from 6209.6 ± 5892.2 IU/mL on day 0 to 5991.7 ± 6095.7 IU/mL on day 1, 5885.1 ± 6441.4 IU/mL on day 7, and 5562.2 ± 4443.3 IU/mL on day 21 ($P < 0.05$ between day 0 and 21, Fig. 2f). In the placebo-controlled group, serum IgE levels did not show change – from 5245.2 ± 2792.6 IU/mL on day 0 to 5755.4 ± 3372.0 IU/mL on day 1, 5913.8 ± 3579.2 IU/mL on day 7, and 5857.2 ± 3385.0 IU/mL on day 21 ($P > 0.05$).

Plasma IFN- γ , IL-4, IL-5 and IL-10 level changes with IVIG therapy in atopic dermatitis

Plasma IFN- γ levels gradually decreased with IVIG therapy – from 13.2 ± 35.6 pg/mL on day 0 to 5.3 ± 16.0 pg/mL on day 1, 8.1 ± 17.3 pg/mL on day 7, and undetectable (0.1 ± 0.1 pg/mL) on day 21 ($P < 0.05$ between day 0 and 21, Fig. 3a). In the control group, those levels did not change – from 12.2 ± 13.2 pg/mL on day 0 to 12.5 ± 10.1 pg/mL on day 1, 13.1 ± 11.2 pg/mL on day 7, and 12.3 ± 12.2 pg/mL on day 21. The IFN- γ level in the normal control group was 32.3 ± 32.2 pg/mL, higher than the initial levels with the IVIG-treated group and the control group ($P < 0.05$).

IL-4 levels changed insignificantly with IVIG therapy – from 2.17 ± 1.5 pg/mL on day 0 to 2.2 ± 1.7 pg/mL on day 1, 1.0 ± 2.5 pg/mL on day 7, and 2.0 ± 1.1 pg/mL on day 21 ($P > 0.05$). In the control group, those levels also showed an insignificant change – from 1.0 ± 2.1 pg/mL on day 0 to 2.1 ± 0.0 pg/mL on day 1, 2.1 ± 1.1 pg/mL on day 7, and 1.7 ± 1.8 pg/mL on day 21 ($P > 0.05$). IL-4 was not detectable in normal control subjects. IL-5 was not detectable in any sample.

IL-10 levels increased insignificantly with IVIG therapy in AD – 5.5 ± 4.2 pg/mL on day 0 to 5.9 ± 3.9 pg/mL on day 1, 6.2 ± 4.4 pg/mL on day 7, and decreased to 4.2 ± 3.7 pg/mL on day 21 ($P > 0.05$, Fig. 3b). IL-10 levels in control groups did not change – 5.3 ± 5.2 pg/mL on day 0 to 6.3 ± 3.2 pg/mL on day 1, 5.2 ± 4.2 pg/mL on day 7, and 6.3 ± 3.5 pg/mL on day 21 ($P > 0.05$). IL-10 level in the normal control group was 15.5 ± 4.9 pg/mL and that was higher than the initial levels shown with the IVIG-treated group or with the control group.

Discussion

Serum-soluble CD5 (ssCD5) concentration was measured

for the first time in this study. IVIG infusions increased the ssCD5 levels in atopic dermatitis. The IVIG preparations itself did not contain CD5 protein. Not only was ssCD5 detected in recurrent spontaneous abortion group, but the group also showed an increase in ssCD5 levels with IVIG infusion. From these results, it can be said that the presence of ssCD5 was not a unique marker of allergic diseases including AD and that IVIG increased ssCD5 levels *in vivo*.

Anti-CD5 antibody was present in normal human IVIG preparation for therapeutic use [18]. Anti-CD5 in IVIG can neutralize the soluble CD5 in patients' serum or stimulate cells by binding to CD5 on cell surface. Results in this study showed an abrupt increase in ssCD5 levels with an IVIG infusion in AD. The stimulation of CD5-positive cells was more possible rather than the neutralization of soluble CD5 by anti-CD5 antibody in IVIG preparation.

IL-4 inhibits the CD5 protein expression on activated B cells by either reducing the amount of CD5 mRNA transcription or by increasing the degradation of CD5 mRNA [19]. CD5 expression or production is affected by factors such as IL-4 which is a key cytokine in the immunopathobiology of allergic diseases. IL-4 was reported to be decreased with an IVIG therapy [20]. However, plasma IL-4 did not change in IVIG therapy despite the increase of ssCD5 in this study.

Interestingly, these clinical aggravations and the changes in BEF were parallel to the changes of ssCD5 levels. It is a well known fact that eosinophilia shows a correlation with the clinical severity of AD [21]. In this study, the change of total eosinophil counts was not always parallel to the changes of blood eosinophil counts since the total eosinophil counts depended on the WBC counts. In the previous report [10], the BEF was suggested as a prognostic factor. However, it is not clear which has more clinical significance – the BEF or the total eosinophil counts. The significance of both the total eosinophil counts and BEF needs to be clarified.

IVIG exhibits anti-inflammatory activity [22] though its behaviour is poorly understood. Anti-inflammatory effects of IVIG may play a role in clinical improvements of AD. IVIG was also beneficial in steroid-resistant [4] and steroid-dependent [2] AD. In this study, IVIG gradually decreased WBC counts and plasma IFN- γ levels. IFN- γ and WBC count indirectly reflect inflammation and the decreases in plasma IFN- γ levels and WBC count suggested a firm evidence of anti-inflammatory actions of IVIG in this study. However, a decrease in plasma IFN- γ level was not consistent with the classical pathogenesis of AD. Accordingly, it was discovered in this study that a decrease in IFN- γ as a pro-inflammatory cytokine improved the allergic inflammation of skin lesions and led to clinical improvements.

IVIG effects on IFN- γ production are still controversial. IFN- γ production was reported to be down-regulated [23], or not changed [20,24], or rather induced [25] with IVIG. In views of Th1/Th2 balance in AD, the decrease of plasma IFN- γ by IVIG in this study suggest the controversial aspects. Classically, IFN- γ production is decreased in AD which enhance IgE synthesis [7]. However, IFN- γ also play a role as a pro-inflammatory cytokines in skin lesions of AD [26]. Therefore, IFN- γ has chimerical aspects of action mechanisms in allergic inflammations. In this study, IVIG effects on IFN- γ levels act as the anti-inflammatory effects in AD and these actions improved the clinical conditions of patients.

IL-10 was reported as a major cytokine in the sites of chronic atopic eczematous lesions [27]. In a previous report [10], plasma IL-10 levels of AD were lower than those of normal subjects. IVIG therapy decreases IL-10 levels in Kawasaki disease [28]. In this study, IL-10 levels did not show any significant increase with IVIG therapy in AD.

It can be concluded that the IVIG therapy immediately increased the ssCD5 levels in atopic dermatitis. Further studies for determining the exact roles of ssCD5 in the immunopathogenesis of atopic dermatitis may be needed.

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