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Editorial

Alternative Immunomodulatory and Disease-Modifying Treatment for Atopic Dermatitis: Autologous Total Immunoglobulin G

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▸ See the article "Efficacy, Safety, and Immunomodulatory Effect of the Intramuscular Administration of Autologous Total Immunoglobulin g for Atopic Dermatitis: a Randomized Clinical Trial" in volume 12 on page 949.

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Atopic dermatitis (AD) is a chronic relapsing eczematous cutaneous disease whose incidence is rapidly increasing worldwide.[1] In the recent few decades, tremendous advances in cutaneous immunology have detailed documentation on the pathophysiology of AD. Understanding of immune cell functions and interactions of cytokines with AD have helped discover various therapeutic target molecules. Especially, dupilumab, which binds to interleukin (IL)-4 receptors and interferes with Th2-immune responses, has shown their efficacy and lower rate of adverse events in clinical trials as well as real clinical settings.[2,3] Nevertheless, AD treatment has not been completely successful. There are some patients who do not respond well to dupilumab; especially in Korea, even though the cost for biologics is very high, very few patients can be covered by an insurance because strict conditions have to be fulfilled. In addition, it has not yet been determined whether the efficacy of dupilumab continues even after cessation of injection. In this circumstance, the most frequently asked question from patients benefit from dupilumab therapy is whether they should receive dupilumab injections for a lifetime. Therefore, many studies are being conducted to find out the alternative treatment modalities which can assist in traditional treatments or biologics.

In the current issue of the *Allergy, Asthma & Immunology Research*, Nahm *et al.*[4] assessed the efficacy, safety and immunomodulatory effects of intramuscular autologous immunoglobulin G injection (AIGT) for AD. Before this research, the authors consistently reported the efficacy of AIGT in AD for years. In 2015, the authors first demonstrated the efficacy of AIGT, which was a pilot study of 17 adult patients with severe AD.[5] In that study, AIGT given twice a week for 4 weeks significantly decreased clinical severity and serum immunoglobulin (Ig) E concentration in all 17 patients. In addition, clinical and laboratory improvements by AIGT lasted for 8 weeks even after its cessation. After publication of that pilot study, the authors proceeded to a 2-year long-term follow-up of 3 severe AD patients with the same protocol for AIGT,[6] which showed the possible residual effect of AIGT for about 1 year. For the immunologic mechanisms of AIGT, the authors attempted to define immunomodulatory effects of AIGT using objective measurements of serum Ig levels, including IgE, IgG, and IgG4 and serum cytokine levels, including IL-10, IL-4, IL-12, and interferon (IFN)-γ.[7] In that study, a decrease in IgE and an increase in IgG and IgG4 (especially for *Dermatophagoides farinae*) were noted. Also, the authors

inferred that the main immunomodulatory effect of AIGT might be achieved through regulatory T-cell response which was suggested by the increased levels of IL-10 and IFN-γ. However, those studies were neither randomized nor double-blinded, and the number of subjects was too small to confirm sure the efficacy and safety of AIGT.

Based on those studies, Nahm *et al.*[4] conducted the randomized, double-blind, well-fashioned clinical trials with AIGT. After 7 weeks of overall 8 injections of autologous IgG, a significant improvement in clinical severity (*e.g.* EASI and SCORAD) was noted. Also, the study showed that there might be a residual effect of AIGT. The study was conducted using a single center-based protocol. Thus, large-scale, multi-center, randomized, clinical trials would be needed to confirm the exact efficacy and safety, including the residual effects of AIGT for AD. Also, comparisons between autologous IgG and commercially available IgG could be one needed to explore whether the clinical efficacy proposed by the authors is attributed to the 'autologous' nature of AIGT.

The authors showed that intramuscular AIGT might exert their efficacy via modulation of regulatory T-cell functions, which was inferred from increased IL-10 and IFN-γ-producing T cells in AD patients.[4] However, detailed mechanisms how the IgG provokes regulatory T-cell responses are still unclear. In a study, the authors suggested that the idiotype network theory might be one of the underlying mechanisms of AIGT. The idiotype network theory proposes idiotype-anti-idioytpe immune responses, which not only induce immune tolerance in humans, but also actively suppress pathological immune responses.[8,9] Although this theory might be one of the explanations of the mechanism of action of AIGT, there still remains a big gap between AIGT and regulatory T-cell responses. For example, IgG is known to interact with various immune cells via cellular Fcγ-receptors (FcγR). In humans, there are 3 kinds of activating FcγR (Ia, IIa and IIIa) and 1 inhibitory FcγR (IIb). According to previous studies on autoimmune disease, IFN-γ or tumor necrosis factor-α can alter the expression ratio of activating to inhibitory FcγR, so that the thresholds for provoking immune responses can be modulated in immune cells.[10] Therefore, it is conceivable that the interaction between IgG and FcγR on immune cells can be another plausible explanation. In this way, there are many theories to explain the efficacy of AIGT in AD patients.

In conclusion, effective biologics are currently used even in real-world settings, although clinical efficacy is still insufficient to satisfy all AD patients with various immunologic, clinical phenotypes.[11] Also, moderate to severe AD patients might suffer from the high cost of these new targeted antibodies, which is being a constant stumbling block to AD patients who are willing to, even ought to benefit from emerging advancement in understanding the pathophysiology of AD.[12] In this circumstance, long-term effects of AIGT which are shown by Nahm *et al.*[4] might lead to the cost-effective, safe alternative treatment modality in AD, or even the mainstay of AD treatment. Thus, these AD-modifying treatment strategies for AD could be widely used, evidence-based treatment modalities if its underlying immunologic mechanisms is clearly elucidated with further studies.

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