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Editorial

Does Monthly Dupilumab Therapy Maintain its Clinical Efficacy in Moderate-to-Severe Atopic Dermatitis?

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▸ See the article "Real Clinical Practice Data of Monthly Dupilumab Therapy in Adult Patients With Moderate-to-Severe Atopic Dermatitis: Clinical Efficacy and Predictive Markers for a Favorable Clinical Response" in volume 13 on page 733.

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Atopic dermatitis (AD) is a recurrent, chronic eczematous skin condition with a rapidly rising global frequency.[1] Massive advances in cutaneous immunology have provided thorough documentation on the pathophysiology of AD in the last few decades. These innovations revealed a large number of candidate therapeutic targets, and it is now beginning to bear fruit with the advent of various biologics and small molecules. In particular, dupilumab, a fully humanized anti-IL4Rα monoclonal antibody, has demonstrated to have remarkable efficacy and relative safety in the aspects of adverse events in both clinical trials and real-world settings.[2-9] Nonetheless, the cost of dupilumab is quite exorbitant, particularly in Korea, and only a small percentage of patients can be covered by the national health insurance program due to stringent requirements. In spite of the situations where dupilumab can be used, it is often the case that the use of dupilumab is given up for economic reasons. Also, adverse events, including dupilumab-induced facial erythema[10] and dupilumab-induced ocular surface diseases,[11] occasionally limit the consistent injection of dupilumab. Even if the efficacy is good and well tolerated, there may be cases where it is required to increase the interval of dupilumab injections.

In the current issue of the *Allergy, Asthma & Immunology Research*, Lee *et al.*[12] assessed the efficacy of dupilumab and predictive biomarkers for favorable responses. In total, 57 moderate-to-severe AD adult patients who received dupilumab every 4 weeks for 16 weeks were analyzed. In this article, the Eczema Area and Severity Index (EASI) at baseline was compared with that at week 16. Also, the proportion of patients with a 50% or 75% decrease in EASI at week 16 was evaluated (EASI-50 or EASI-75). They showed that monthly dupilumab therapy significantly decreased EASI (27.8 ± 11.1 at baseline vs 8.7 ± 7.8 at week 16; $P < 0.001$); EASI-50, EASI-75, and EASI-90 responses at week 16 were observed in 48 (84.2%), 27 (47.4%), and 9 (15.8%) patients, respectively. Considering the efficacy results from 2 phase III clinical trials (SOLO 1 and SOLO 2) whose EASI-50, EASI-75, and EASI-90 responses at week 16 were 69%, 51%, and 36%, respectively, for SOLO 1[13] as well as 65%, 44%, and 30% for SOLO 2,[13] it seems that the efficacy of the monthly dupilumab use could be comparable to that of the 2-week interval use. However, these results may have been attributed to a relatively small number of subjects and its study design of retrospective analysis, so these data should be interpreted with caution.

Recently, as new therapeutics which reflect the pathophysiology of AD have emerged, much research focuses on changes in histological and/or serological biomarkers that occur along with clinical improvement when biologics and/or small molecules are used. In particular, a considerable number of studies on dupilumab biomarkers were published in 2020. Katoh *et al.*[14] suggested the thymus and activation-regulated chemokine (TARC) and immunoglobulin E (IgE) as serum biomarkers based on the clinical response with Japanese subgroup phase III clinical trial data. Also, Kato *et al.*[15] analyzed 54 Japanese adult AD patients and reported that higher serum lactate dehydrogenase (LDH) levels might be associated with poor response to dupilumab. Ariëns *et al.*[16] analyzed 35 adults AD patients from BioDay registry, and demonstrated that TARC, pulmonary and activation-regulated chemokine (PARC), Periostin, and interleukin (IL)-22 showed a tendency to decrease upon dupilumab treatment. In addition to simply analyzing a single serological marker, most recent studies have attempted to combine previously suggested serum biomarkers in order to predict the clinical response to dupilumab. Bakker *et al.*[17] analyzed 25 adults with moderate-to-severe AD. They combined TARC, soluble IL-2 receptor, and IL-22 to provide predictive-EASI (p-EASI) which predicts the real EASI. This model demonstrated that the p-EASI corresponds well with disease severity in AD patients, especially before and after 8–16 weeks of dupilumab treatment. Most recent reports conducting mathematical model-based meta-analyses of dupilumab clinical trials showed that the baseline level of IL-13 can be used to stratify dupilumab responders.[18] In this article, they also identified candidate biomarkers to predict the response to dupilumab. When the criterion for good or bad responses is set at EASI-75, lower baseline blood eosinophil count and baseline LDH level were significantly associated with better response to dupilumab.[12] Although many studies, including this article, have intended to define biomarkers to predict dupilumab response or follow up clinical improvement after dupilumab treatment, most of them contains a relatively low number of subjects. Also, the retrospective nature of the above studies limits further generalized interpretation in real clinical settings.

In the era of new pathophysiology-based therapeutics in AD, understanding of AD is becoming better and facing the unprecedented phase. Since the appearance of dupilumab, other biologics including tralokinumab and lebrikizumab as well as small molecules such as Janus Kinase (JAK) inhibitors (baricitinib, *etc.*), are emerging in real clinical practice. However, it is time to start to fully understand and to re-define the vague concept of AD. In the article by Lee *et al.*,[12] even if there are still some limitations, continuous accumulation of studies reflecting the actual clinical environment would be able to extend the use of biologics such as dupilumab, and also could help us select a proper interval based on the severity of AD and control side effects of biologics. Eventually, a new protocol for using biologics including dupilumab, will be established, so that biologics and small molecules can replace conventional immunosuppressants.

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