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Editorial

Dupilumab Treatment for Asthma: On the Road to a New Horizon Beyond Ethnic Differences?

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▸ See the article "Effect of Dupilumab in Korean Patients With Uncontrolled Moderate-to-Severe Asthma: A LIBERTY ASTHMA QUEST Sub-analysis" in volume 14 on page 182.

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Asthma is a heterogeneous disease commonly classified into type 2 (T2)-high and T2-low asthma, according to the presence or absence of T2 inflammation in the airways. Interleukin (IL)-4, IL-5, and IL-13 are important cytokines that drive T2 inflammation. Recently introduced biologic therapies have provided hope for treating severe T2-high asthma that is not controlled by existing drugs such as inhaled corticosteroids plus second controllers and even oral corticosteroids (OCS). In Korea, 5 monoclonal antibodies have been approved for the treatment of severe allergic asthma (omalizumab), severe eosinophilic asthma (mepolizumab, reslizumab, and benralizumab), and severe asthma with the eosinophilic phenotype or OCS-dependent asthma (dupilumab).[1]

Dupilumab is a monoclonal antibody against the -IL-4 receptor α chain, and inhibits both IL-4 and IL-13 signaling pathways, exhibiting broad therapeutic effects on T2 inflammation including immunoglobulin E and eosinophilic inflammation. Several clinical trials have demonstrated the efficacy and safety of dupilumab in patients with uncontrolled severe asthma. In a phase 3 multicenter, randomized, double-blind, placebo-controlled study (LIBERTY ASTHMA QUEST; QUEST) of 1,902 patients with uncontrolled moderate-to-severe asthma, treatment with dupilumab resulted in significantly lower rates of severe asthma exacerbation, better lung function, and symptom control.[2] Similar beneficial effects of dupilumab were found in relatively large-scale phase 2a and phase 2b trials conducted before the QUEST study.[3,4] A phase 3 randomized control trial (RCT) conducted on 210 OCS-dependent severe asthmatic patients (the VENTURE study) revealed a reduction in OCS use without loss of asthma control, a reduction in asthma exacerbation rate, and improvement in lung function in patients treated with dupilumab.[5] The effects of dupilumab were also observed in real-world studies, such as a cohort of adult patients with severe asthma.[6,7] Dupilumab has also proven effective in controlling asthma comorbidities, such as chronic rhinosinusitis and atopic dermatitis.

Ethnic or racial differences are an important consideration in the treatment of asthma using biologics. Ethnic differences may be apparent when observing disease outcomes resulting from genetic, environmental, socioeconomic, and cultural factors. A recent pediatric population-based study suggested that eligibility for biologic therapies in asthmatics differed

across racial and ethnic populations, based on specific blood parameters, which also seem to be associated with asthma subtype and outcome.[8] A retrospective cross-sectional study of patients with rheumatologic diseases demonstrated a disparity in the uptake of biologic therapies among different ethnicities.[9] These pose the question of whether there may be ethnic differences in the efficacy of dupilumab in patients with uncontrolled moderate-to-severe asthma.

Although the QUEST trial revealed that dupilumab exerted significant positive effects on asthma management, only 4% (n = 74) of the patients studied (n = 1,902) were Koreans.[2] A *post hoc* analysis of the QUEST clinical trial found that the effects of dupilumab in Japanese asthmatic patients (n = 114) were comparable to those of the overall intention-to-treat population.[10] Since little is known regarding the effects of dupilumab in Korean patients with asthma, additional subgroup analyses are required. In this issue, Rhee *et al.*[11] reported the results of a subanalysis of the efficacy and safety of dupilumab in the Korean subjects of the QUEST study. They demonstrated decreased annual severe exacerbation rates, improved forced expiratory volume in 1 second (FEV1), and quality of life questionnaire scores compared to the control subjects. This implies that dupilumab did not have a negative impact on Korean patients with asthma.[11] In fact, the degree of reduction in severe exacerbation and improvement in FEV1 was much higher in Korean patients than in the original QUEST trial. A greater improvement in the incidence of severe exacerbation rates was noted in dupilumab-treated Korean patients than in Japanese patients (relative risk reduction of 87% *vs.* 62%).[10] Improvements in pre-bronchodilator FEV1 were observed with dupilumab treatment by the first assessment week (week 2), which were sustained throughout the 52-week treatment period. Additionally, the least-square mean difference in pre-bronchodilator FEV1 in week 12 was significantly greater in Korean patients than in the overall QUEST population.[2] These differences in dupilumab efficacy may have been due to the ethnic variations, drug responsiveness, and/or compliance of Korean patients. However, we do not have sufficient data to determine whether the effects of dupilumab in Korean patients are reproducible and whether the same results can be obtained from real-life studies as well as RCTs. If these better effects of dupilumab are repeatedly confirmed, the cutoff eosinophil count (≥ 50 cells/μL) or FeNO level (≥ 25 ppb), which is currently used to predict the efficacy of dupilumab, may need to be modified for Korean patients with asthma.

Since no direct comparative studies of biologics in asthma have been conducted, there is no evidence suggesting the superiority of one biologic over another. However, dupilumab has shown the highest numeric improvements in FEV1 compared to placebo, with consistent results across clinical trials.[1-4,12] This improvement in lung function is likely due to the mechanism of the drug, blocking both IL-4 and IL-13 signaling. IL-13 induces smooth muscle cell proliferation, goblet cell hyperplasia, collagen deposition, and transformation of fibroblasts into myofibroblasts. This may lead to airway remodeling and hyperresponsiveness. Therefore, inhibition of IL-13 by dupilumab is expected to positively affect tissue remodeling, for which there is no proven therapy. In the QUEST trial, an analysis of the post-bronchodilator FEV1 slope showed a loss of lung function of 40 mL per year with placebo and no loss with dupilumab, which also suggests the potential effect of dupilumab on airway remodeling.[2] If it affects the airway structure, dupilumab can also be used to treat patients with asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO). Although no specific data are supporting the use of dupilumab in treating ACO, there have been reports on the beneficial effects of biologics on ACO and COPD.[13,14]

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Therefore, based on the consistent results of several clinical studies, we have very high expectations for dupilumab in the treatment of severe asthma. However, the limited number of clinical studies in diverse patient groups and the post hoc nature of ethnic subgroup analysis with small sample sizes limit the discussion of the potential role of dupilumab in the treatment of asthma. These limitations can be overcome by nationwide multicenter co-working networks and cohort studies. Therefore, more extensive investigations, including RCTs and real-world studies, should be performed for dupilumab to reach a new therapeutic horizon for asthma. Until then, a precision medicine perspective is necessary for selecting appropriate biologics to treat different asthma phenotypes, after considering the appropriate use of asthma controllers and any accompanying diseases that may affect asthma.

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