Editorial
Allergy Asthma Immunol Res. 2018 March;10(2):95-96.
https://doi.org/10.4168/aair.2018.10.2.95
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Is Omalizumab a Problem-Solving Remedy in Severe Asthma?

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Severe asthma has been a serious health burden worldwide, although its pathophysiology has been explored during several decades. In most of the asthmatic patients, inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs) ameliorate clinical symptoms, enhance pulmonary function, and reduce the frequency of acute exacerbation. However, severe uncontrolled asthma still remains problematic in clinical practice. Even though the prevalence of severe asthma is low (3%-10% of all asthmatics),[1,2] the socioeconomic burden of severe asthma is very huge and the overall cost for severe asthmatic patients is assumed to be more than 60% of the whole cost associated with all asthmatic patients.[3] Therefore, the development of appropriate therapeutic strategies to manage patients with severe uncontrolled asthma is becoming more important and urgent.

Many clinical trials have recently been performed on severe asthmatic patients to evaluate the effectiveness of add-on therapies, such as long-acting muscarinic antagonist (LAMA), including tiotropium bromide, and bronchial thermoplasty, molecular-targeted agents, such as anti-immunoglobulin E (anti-IgE, omalizumab) and anti-interleukin-5 (mepolizumab and reslizumab).[4] Nevertheless, effectiveness of these approaches has not yet been fully validated and clinical responses are variable among patients. Thus, tailored management based on individual phenotypic or endotypic characteristics of asthma should be considered especially in severe asthmatic patients who are refractory to standard treatment. Among novel targeted agents, omalizumab is the first anti-IgE monoclonal antibody approved as a phenotype-guided add-on therapy in severe asthmatic patients. The current 2017 GINA guidelines recommend the use of omalizumab for patients aged ≥6 years with moderate to severe allergic asthma which is uncontrolled on step 4 treatment with evidence A.[5]

In this issue of the *AAIR* journal, Lee *et al.*[6] have confirmed the real-world effectiveness of omalizumab in Korean patients with severe asthma for the first time. In contrast to previous real-world studies, their outcomes were compared between patients treated with omalizumab for 6 months (OT group) and control patients treated with standard treatment alone who were defined by propensity score matching, and changes in outcomes were also compared between the baseline and outcome periods within and between groups. Although 6 months of treatment might be not long enough to fully evaluate omalizumab effects, the mean reduction rate of 46% exacerbation and the responder proportion of 68%, which were similar to those of previous real-world studies,[7,8] were observed in the OT group.[6] Omalizumab effectively reduced the number of asthma exacerbations, hospitalization, hospitalized days, the mean daily requirement of systemic corticosteroid (SCS) per person, and sputum eosinophil without obvious adverse events in Korean patients. The results of real-world study are useful in that patients with severe asthma often have multiple comorbidities and different socioeconomic statuses which can affect outcomes of omalizumab treatment. The real-world effectiveness would differ from those of prospective randomized controlled clinical trials. Thus, the results presented in the work of Lee *et al.*[6] provide us practically valuable information on omalizumab treatment in Korean patients with severe asthma regardless of baseline clinical and socioeconomic characteristics.

Basically, omalizumab has been recommended for allergic asthma and most commonly used for patients showing increased serum IgE level or at least 1 positive aeroallergen on skin prick test or an elevated serum specific IgE level to common aeroallergens.[9] However, reports supporting the extended role of omalizumab in nonatopic asthmatic patients have been increasing. A Spanish multicenter registry study demonstrated that significant improvement in the clinical status of nonatopic asthmatics as measured by global evaluation of treatment effectiveness (GETE) and by the asthma control test.[10] Another report showed a significant reduction in FcεRI expression on

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Received: December 18, 2017; Accepted: December 19, 2017
• There are no financial or other issues that might lead to conflict of interest.

basophils and dendritic cells, an overall increase in FEV1 with statistical significance, and a trend toward improvement in GETE and asthma exacerbation rate in nonatopic asthmatic patients treated with omalizumab.[11] In the work of Lee *et al.*,[6] the rate of exacerbation, hospitalization, hospitalized days, and mean daily requirement of SCS were not significantly different between atopic and non-atopic patients in the OT group. However, the fact that a significant proportion of patients (30% of the OT group) showed no benefits from omalizumab treatment also emphasizes the need for more clarified and detailed criteria for selecting candidates for omalizumab treatment. Total IgE level has been suggested as a predictor of responder in a randomized controlled study, but pooled analysis showed treatment benefits irrespective of IgE levels.[13] Recently, fractional exhaled nitric oxide , blood eosinophil, and serum periostin have been suggested as biomarkers for predicting omalizumab responders.[8] However, no definite predictors for favorable responses were identified in the work of Lee *et al.*[6] More studies are needed to support extended use of omalizumab in nonatopic asthmatic patients. Further development of biomarkers and characterization of phenotypes that can predict responsiveness of omalizumab are mandatory.

Allergic reactions and viral respiratory infections are 2 most common causes of asthma exacerbation, and their interactions and IgE-mediated inflammation in viral infections have long been implicated. The potential role of short-term omalizumab treatment in preventing asthma exacerbation was investigated in children with persistent allergic asthma in fall season, and a low exacerbation rate and a decreased risk of rhinovirus infections were observed in children.[12,13] In the work of Lee *et al.*,[6] omalizumab reduced the frequency of exacerbation in adult patients, especially during winter season. They suggested the beneficial effect of omalizumab on respiratory virus infection in adult asthmatic patients during winter, because it is the most common cause of seasonal exacerbation in adult asthmatics. This finding raises the question whether the effect of omalizumab in nonatopic asthma might be the result of its effect on viral infection during winter season, although evidence is not sufficient.

Current GINA guidelines recommend long-acting muscarinic antagonists as another choice of add-on therapy for step 5 treatment,[5] and it has been known that these antagonists improve lung function and delay time to first exacerbation.[14] Because of its economical advantage, LAMA is frequently used as first add-on treatment than omalizumab in real-world practice. Therefore, more important questions arise whether: (1) the effectiveness of omalizumab is superior to triple inhaler combination therapy with LABA/LAMA/ICS in atopic or nonatopic asthmatic patients, (2) the effectiveness of triple inhaler treatment is enhanced by omalizumab, (3) it is necessary to establish a new criteria for the use of omalizumab in Korean patients to achieve more clinical benefits, and (4) omalizumab use in severe asthmatic patients in Korea is costly effective in reducing health care burden. We are looking forward to further knowledge that enable us to better treat severe asthmatic patients in near future.

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