

Patient Selection for Mepolizumab in Severe Asthma: Time for Reappraisal?



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Antibodies against the IL-5 pathway have been developed for the treatment of late-onset eosinophilic asthma having resistance to corticosteroids.¹ The prevalence of severe asthma has been estimated to be 5% to 10% of asthmatic patients.¹ In an adult-onset asthma population, 5.9% fulfilled the American Thoracic Society/European Respiratory Society criteria of severe asthma and 2% fulfilled the criteria for anti-IL-5 therapy based on trial inclusion eligibility.² In eosinophilic severe asthma, the anti-IL-5 therapies mepolizumab, benralizumab, and reslizumab have reduced exacerbations by approximately 55%, and in oral corticosteroid (OCS)-dependent patients, the median OCS dose by approximately 50%.¹ These therapies appear to have a good safety profile. Their use is limited by high cost of the drug and local payer eligibility criteria, and predictors of response need to be considered when choosing between available therapies.¹ Thus, the question remains: who should be treated with these expensive medications? A guideline-based approach begins with separation of difficult-to-treat asthma from severe asthma.^{1,3} Asthma may appear as difficult to treat because of modifiable factors such as poor adherence, incorrect inhaler technique, smoking, or comorbidities. Severe asthma remains uncontrolled despite adherence to optimal therapy and treatment of contributory factors or worsens when high-dose treatment is decreased.^{1,3} Anti-IL-5 therapy is recommended when severe asthma is

associated with eosinophilic inflammation: blood eosinophil count ≥ 300 cells/L and exacerbations in the last year.^{1,3}

In a single-center real-life registry study from Amsterdam University Medical Centres (UMC) reported in this issue of the journal, Richards et al⁴ evaluated the baseline characteristics, trial eligibility, and therapeutic response in patients receiving mepolizumab. They compared real-life patients with criteria and population characteristics of trials investigating mepolizumab in formal phase IIb/III trials. They evaluated whether the real-life patients would have fulfilled the inclusion and exclusion criteria of the trials. Of 119 patients receiving mepolizumab, a vast majority, 82%, did not meet the eligibility criteria and only 18% were eligible for these clinical trials. A similar finding was reported from Wessex Severe Asthma Cohort (WSAC).⁵ The most common reason for noneligibility was meeting at least 1 exclusion criterion (43%), most often due to the smoking history of ≥ 10 pack-years, concomitant bronchiectasis, or cardiovascular comorbidities. Almost 40% of patients did not meet the inclusion criteria, the most common reasons being good lung function (forced expiratory volume in 1 second [FEV₁] $\geq 80\%$ predicted), low blood eosinophil level (< 300 cells/ μ L), and low prescribed dose (< 880 μ g/day fluticasone or equivalent in adults) of inhaled corticosteroids (ICS). When compared with phase IIb/III trial populations, the UMC patients were older, more often males, and had better lung function and lower OCS dose. UMC noneligible patients⁴ (n = 98) were followed for 6 months, and of those patients having continuous OCS (n = 66), 42% halved their maintenance OCS dose, 50% reduced their maintenance OCS dose to a maximum of 5 mg/day, and 21% were able to stop maintenance OCS.⁴ The median maintenance OCS dose was halved from 10 to 5 mg.⁴ Unfortunately, data regarding exacerbations were not reported. In clinical trials with anti-IL-5 therapies, the median OCS dose was reduced by approximately 50% compared with placebo.¹

Real-life patients pose a challenge to the clinician with regard to treatment criteria. For example, smoking/significant smoking history and comorbidities are considered as factors contributing to symptoms, exacerbations, and poor quality of life¹ and are often considered as factors indicating “difficult-to-treat asthma” rather than true severe asthma.^{1,3} This is reasonable as, for example, smoking has been shown to increase negative asthma outcomes such as symptoms, comorbidities, and hospitalizations in a dose-dependent manner.⁶ Adult-onset asthma potentially predicts good response to anti-IL-5 biologicals,¹ and a large proportion of patients in formal phase IIb/III trials and in real-life cohorts have adult-onset asthma. However, patients with adult-onset asthma often have comorbidities and marked smoking history.² Thus, the clinician often faces an asthma patient with features of potentially treatable type 2 inflammation but also with features not favoring therapy with biologicals. In

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UMC⁴ and WSAC,⁵ a common reason for noneligibility for a clinical trial was the smoking history of ≥ 10 pack-years. In UMC, the second most common reason was bronchiectasis, a common comorbidity in severe asthma.³ Still, the benefit of mepolizumab with regard to OCS dose reduction was similar to that in the formal phase IIb/III trials.

The phase IIb/III trials required $FEV_1 < 80\%$ predicted,⁴ and reduced lung function is considered as one of the key features of severe asthma.³ A common reason not to fulfill inclusion criteria for trials in UMC⁴ and WSAC⁵ was lung function that was too good. Nonetheless, the OCS dose reduction in this cohort⁴ was similar to that in clinical trials. This suggests that we should not wait until lung function decreases before treating the patient with anti-IL-5 therapy.

Surprisingly, a low eosinophil number in peripheral blood (< 300 cells/ μ L) at baseline was found quite often (41%) as well as low prescribed dose (< 880 μ g/day fluticasone or equivalent in adults) of ICS (31%).⁴ One problem is that OCS use reduces blood eosinophils to normal or low levels, even though eosinophilic inflammation may still be present in the lungs and high eosinophil numbers may have been found in the past. Thus, the blood eosinophil count at baseline may not reflect the disease phenotype. Severe asthma is often considered steroid-resistant, and one may question whether higher ICS dose had improved the situation. However, given that the dose response of ICS is flat, it is unlikely that a higher prescribed ICS dose would have been beneficial. This is supported by a recent finding that good long-term adherence to ICS was not associated with less symptoms or fewer OCS courses in adult-onset asthma.⁷

Real-life studies on the effectiveness of mepolizumab originating from severe asthma registries are now published.⁸⁻¹⁰ In most of these, the inclusion criteria resemble those of the formal phase IIb/III mepolizumab trials but without strict exclusion criteria.^{4,8-10} Despite also including populations with significant smoking histories and greater comorbidity profiles, the efficacy of mepolizumab was confirmed.⁸⁻¹⁰

Several questions remain unanswered. First, the well-described benefit of anti-IL-5 compounds is the reduction of exacerbations.^{1,3} The efficacy of mepolizumab on exacerbations in trial noneligible patients should be confirmed, either in a formal placebo-controlled trial or in real-life registries. Secondly, a larger number of patients should be evaluated so as to determine whether the effect of mepolizumab on exacerbations or OCS use is similar in different subgroups (eg, those with or without smoking history > 10 pack-years or with $FEV_1 < \text{or} > 80\%$ predicted). Thirdly, the current study⁴ did not address 2 important aspects, namely age and obesity. The efficacy and safety of biologicals in older severe asthmatics remain less studied. Obesity is a significant factor in severe asthma, and patients

eligible for anti-IL-5 therapy may be leaner than those having other types of severe asthma.² However, there is no evidence to guide us when we face an obese patient with eosinophilic severe asthma. Results from an Australian real-life cohort suggest that obesity may impair the efficacy of mepolizumab.¹⁰

In summary, Richards et al⁴ suggest that, in real life, a number of patients possibly benefitting from mepolizumab therapy do not fulfill the inclusion and exclusion criteria of formal phase IIb/III mepolizumab trials, due to smoking history, concomitant lung disease (bronchiectasis), or comorbidities (cardiovascular); or due to not having high enough ICS dose or eosinophil count; or due to having lung function that is too good. The current results by no means guarantee that patients with severe asthma who lack eligibility criteria for phase IIb/III trials will benefit from anti-IL-5 therapy. However, these results suggest that patients outside the current criteria may well benefit from anti-IL-5 therapies and that, for example, patients with asthma with longer smoking histories or comorbidities should not be categorically left without treatment. It will be of utmost importance that the findings of the current study will be confirmed in larger trials and/or real-life registries.

REFERENCES

1. Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients. Diagnosis and management. A GINA pocket guide for health professionals, V2.0. April 2019. Available from: www.ginasthma.org. Accessed September 4, 2019.
2. Ilmarinen P, Tuomisto LE, Niemelä O, Kankaanranta H. Prevalence of patients eligible for anti-IL-5 treatment in a cohort of adult-onset asthma. *J Allergy Clin Immunol Pract* 2019;7:165-74.
3. Porsbjerg C, Ulrik C, Skjold T, Backer V, Laerum B, Lehman S, et al. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. *Eur Clin Respir J* 2018;5:1440868.
4. Richards LB, van Bragt JJMH, Aarab R, Longo C, Neerinx AH, Sont JK, et al. Treatment eligibility of real-life mepolizumab-treated severe asthma patients. *J Allergy Clin Immunol Pract* 2020;8:2999-3008.
5. Brown T, Jones T, Gove K, Barber C, Elliott S, Chauhan A, Howarth P, on behalf of the Wessex Severe Asthma Cohort (WSAC) team. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. *Eur Respir J* 2018;52:1801444.
6. Tommola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Niemelä O, Nieminen P, et al. Disease burden and multimorbidity in adult-onset asthma increase dose dependently with smoked pack-years. *Eur Respir J* 2019;54:1801580.
7. Vähätalo I, Ilmarinen P, Tuomisto LE, Tommola M, Niemelä E, et al. 12-year adherence to inhaled corticosteroids in adult-onset asthma. *ERJ Open Res* 2020; 6:00324-2019.
8. Schleif F, Graff S, Nekoe H, Moermans C, Henket M, Sanchez C, et al. Real-world experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy* 2020;50:687-95.
9. Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Roxas C, et al. Real-world effectiveness and the characteristics of a 'super-responder' to mepolizumab in severe eosinophilic asthma. *Chest* 2020;158:491-500.
10. Harvey ES, Langton D, Katelaris C, Stevens S, Farah CS, Gillman A, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. *Eur Respir J* 2020;55:1902420.