

cal advice for what seem to be innocuous symptoms. Both the USPSTF¹⁰ and GOLD³ recommend that persons who have a history of exposure to risk factors for COPD such as cigarette smoke and have symptoms such as dyspnea, chronic cough, or sputum production should be evaluated for COPD. Once these patients are identified, is it worth treating patients with mild or moderate disease (GOLD stage 1 or 2) with the aim of slowing the decline in lung function and reducing the frequency of exacerbations? These were secondary end points in the trial conducted by Zhou et al., and the data are probably not strong enough for clear recommendations to be made at this stage. Furthermore, the rate of COPD exacerbations requiring hospitalization in this trial was not significantly lower in the tiotropium group than in the placebo group. The rate of adherence to the trial regimen was more than 90%; outside the context of a clinical trial, patients with mild symptoms may not be as adherent to medication regimens, because their symptoms are not as bothersome.

With the development of new drugs, would treatment with another drug in the class of long-acting muscarinic antagonists (LAMAs) or long-acting beta-agonists (LABAs) or a combination of LAMAs and LABAs help to improve lung function, slow the decline in lung function, improve quality of life, and decrease the incidence of exacerbations among patients with early COPD? Early intervention and treatment for patients with diabetes mellitus and hypertension certainly lead to better outcomes. Is such an early treatment strategy possible and effective for patients with mild COPD? Further studies of the newer drugs and longer-term studies are needed to improve available treatments for millions of patients with

early-stage COPD worldwide. For now, the evidence supports the judicious use of treatment in patients with symptomatic early-stage COPD or in those who are recovering from an exacerbation.

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From the Departments of Medicine and Therapeutics (F.W.S.K.) and Pediatrics (G.W.K.W.), Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, China.

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Moving Upstream — Anti-TSLP in Persistent Uncontrolled Asthma

Elisabeth H. Bel, M.D., Ph.D.

At least 15% of patients with asthma have a poor response to standard therapy with inhaled glucocorticoids and long-acting bronchodilators.¹ Even after nonadherence to treatment and inadequate inhalation technique are addressed, a

substantial percentage of patients continue to have frequent exacerbations and hospitalizations.² Over the past three decades, research has led to an improved understanding of the complex biologic mechanisms of airway inflammation. This,

in turn, has led to the development of several monoclonal antibody–based, targeted add-on treatments for asthma that are approved by the Food and Drug Administration or are in phase 3 of development. These include monoclonal antibodies against IgE (omalizumab), interleukin-13 (tralokinumab), interleukin-5 (mepolizumab and reslizumab), and the alpha subunits of the interleukin-4 and interleukin-5 receptors (dupilumab and benralizumab).³ Although these therapies are very effective in subgroups of patients, they are not a panacea for uncontrolled asthma, probably because these biologics are directed against targets downstream in the inflammatory cascade.

In this issue of the *Journal*, Corren and colleagues⁴ report on the results of a phase 2, dose-ranging, proof-of-concept study of tezepelumab, a humanized monoclonal antibody that blocks the action of thymic stromal lymphopoietin (TSLP), a cytokine whose effects on lymphocyte maturation through activation of antigen-presenting cells are probably upstream of the agents mentioned previously. In this randomized, double-blind, placebo-controlled trial, the effects of three doses of tezepelumab on asthma exacerbations were compared with placebo in adults with moderate-to-severe poorly controlled asthma despite the combined use of long-acting bronchodilators and medium-to-high doses of inhaled glucocorticoids. The primary end point was met for all three doses of tezepelumab (low, medium, and high), with reductions relative to placebo in annualized exacerbation rates of 61%, 71%, and 66%, respectively. In addition, levels of biologic markers that are thought to reflect the inflammation of asthma also decreased, as noted below. This study has several important implications for our understanding of the pathobiologic basis of asthma and for the management of persistent uncontrolled asthma.

Tezepelumab is the first biologic that has a substantial positive effect on two important markers of the inflammation of asthma — namely, blood eosinophil counts and the fraction of exhaled nitric oxide (FENO). Other biologics tested to date in patients with asthma show differential effects on these inflammatory markers. For example, anti–interleukin-5 treatment reduces blood eosinophil counts but does not influence FENO levels, which suggests that a main glucocorticoid-sensitive pathway remains activat-

ed in patients receiving this treatment.⁵ On the other hand, biologics that block interleukin-4 or interleukin-13 signaling reduce FENO levels but do not affect the number of circulating eosinophils,⁶ again leaving a key driver of inflammation untouched. The observation that tezepelumab reduces the level of both inflammatory markers shows that it hits a more upstream target and that it blocks at least two relevant inflammatory pathways in asthma. This is likely to be clinically relevant, since simultaneously increased FENO levels and blood eosinophil counts are related to increased morbidity due to asthma.⁷

On the basis of this broad upstream blocking effect, it is not surprising that tezepelumab, unlike other biologics, is equally effective in reducing asthma exacerbations in patients with different asthma phenotypes: eosinophilic (allergic and nonallergic) asthma and noneosinophilic asthma. The question then arises why all exacerbations are not prevented by tezepelumab. What could be responsible for the remainder of the exacerbations? One possible explanation is that asthma exacerbations induced by invading pathogens (bacteria, viruses, or fungi) that cause neutrophil recruitment and activation and the formation of neutrophil extracellular traps⁸ are not prevented by tezepelumab. In these situations, other therapies, such as macrolides (although not approved for this indication), might be more appropriate.⁹

Targeting upstream cytokines may have downsides as well. Although the safety profile of tezepelumab in the study by Corren et al. is reassuring, the number of people at risk was small and the treatment period was only 1 year. Thus, there is reason to be concerned about infections as a risk of inhibiting the action of TSLP; a role for this cytokine in host defense against infection has been suggested in atopic dermatitis, a related chronic inflammatory disorder.¹⁰ Impaired host defense could also possibly explain the three serious drug-related adverse events that were reported by Corren et al.: pneumonia and stroke in the same patient and the Guillain-Barré syndrome in another patient. Confirming the safety of tezepelumab should therefore be a priority in future trials.

In conclusion, tezepelumab appears to be the broadest and most promising biologic for the treatment of persistent uncontrolled asthma to date. It reduces the asthma exacerbation rate by

more than half and improves lung function irrespective of asthma phenotype. Future studies should confirm the efficacy and safety of this upstream biologic, and researchers should move forward in the field and elucidate the mechanisms of asthma exacerbations that are not inhibited by targeted biologics such as tezepelumab.

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From the Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam.

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