EDITORIAL

How Should We Treat Patients with Mild Asthma?

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Asthma is one of the most common chronic respiratory diseases in the world. Despite advances in the understanding of the biologic characteristics of asthma and its treatment, many surveys continue to document suboptimal control in large proportions of patients around the world.[1,2] Both U.S. and international guidelines recommend the use of short-acting β_2-agonists (SABAs) as needed for the treatment of mild intermittent asthma.[3,4] When symptoms become persistent, the recommended treatment is an inhaled glucocorticoid taken on a regular basis, so-called maintenance therapy, which should lead to reduced use of a SABA. In reality, patients tend to rely on as-needed SABAs for symptom relief, whereas adherence to inhaled glucocorticoid maintenance therapy is rather poor. Recently, two trials — Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and SYGMA 2, the results of which were published in the *Journal* approximately 1 year ago — challenged the idea of inhaled glucocorticoid maintenance therapy for persistent asthma by showing that as-needed use of a budesonide–formoterol combination was as effective as budesonide maintenance therapy in the prevention of exacerbations, at a fraction of the overall exposure to inhaled glucocorticoids.[5,6] However, will this strategy be effective in patients with mild intermittent asthma? Patients with asthma who have eosinophilic airway inflammation may have a favorable response to inhaled glucocorticoid therapy. Will patients with asthma who do not have eosinophilic airway inflammation have a similar response to inhaled glucocorticoid therapy? Two trials, the results of which are now reported in the *Journal*, attempt to answer these important questions.

In the Steroids in Eosinophil Negative Asthma (SIENA) trial, a three-period, randomized, double-blind, placebo-controlled crossover trial conducted by Lazarus et al., patients who were at least 12 years of age and had mild, persistent asthma (i.e., met the guideline criteria of the National Asthma Education and Prevention Program for step 2 asthma treatment) were classified according to the sputum eosinophil level.[7] During the run-in period, patients had to provide two sputum samples that could be used for phenotyping of their airway inflammation. Patients were classified as having a high eosinophil level if eosinophils made up 2% or more of at least one of the sputum samples, and patients with two sputum samples that contained less than 2% eosinophils were classified as having a low eosinophil level. During each of the three 12-week periods after the run-in period, the patients received twice-daily mometasone (an inhaled glucocorticoid) at a dose of 220 μg, once-daily tiotropium (a long-acting muscarinic antagonist [LAMA]) at a dose of 5 μg, or twice-daily placebo. The percentage of patients in the enrolled population who had a low eosinophil level was higher than expected (76%), and the primary outcome was the response to mometasone as compared with placebo and to tiotropium as compared with placebo among patients with a low eosinophil level who had a prespecified differential response to a trial agent. The investigators used a hierarchical composite outcome that included treatment failure, asthma-control days, and forced expiratory volume in 1 second (FEV_1). Among the patients with a low eosinophil level who had a differential response, the percentage of patients who had a better response to mometasone (57%) than to placebo was not significantly different from the percentage who had a better response to tiotropium (60%)

than to placebo. It is not surprising that among the patients with a high eosinophil level who had a differential response, the response to mometasone was significantly better than the response to placebo (74% vs. 26%), whereas the responses to tiotropium and placebo were not significantly different. In exploratory analyses involving adults only, among those who were in the low-eosinophil stratum and who had a differential response, 62% had a better response to tiotropium, and 38% had a better response to placebo. In this relatively small trial with short trial periods, the difference in response between the two strata of patients was driven mostly by improvement in the FEV_1 rather than by other components of the composite outcome. The results showed that a high percentage of patients with persistent asthma had a low eosinophil level in the sputum and challenge the recommendation of the use of regular inhaled glucocorticoids in all patients with persistent asthma.

Among patients with persistent asthma, the SYGMA trials showed that budesonide–formoterol used on an as-needed basis was as effective as budesonide maintenance therapy in preventing asthma exacerbations but with a much lower exposure to inhaled glucocorticoids (17% of the exposure with budesonide maintenance therapy in SYGMA 1 and 25% of the exposure in SYGMA 2). However, control of asthma symptoms was still better among the patients who received budesonide maintenance therapy than among those who received as-needed budesonide–formoterol. It should be noted that adherence to treatment was 60 to 80% in the clinical trial settings of the SYGMA trials. In real-life settings, the adherence is likely to be much lower.

To better reflect real-world clinical practice, Beasley et al.[8] conducted an open-label trial — the Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) trial — that involved patients with mild intermittent asthma as well as patients with mild persistent asthma (i.e., patients met the guideline criteria of the National Asthma Education and Prevention Program for step 1 or step 2 asthma treatment). In the 52-week multicenter study, adults were randomly assigned to one of three treatments: albuterol as needed for relief of asthma symptoms; budesonide, 200 μg twice daily, as maintenance therapy plus as-needed albuterol; or budesonide–formoterol as needed for relief of symptoms. The primary outcome was the annualized rate of asthma exacerbations. The secondary outcome measures included the score on the Asthma Control Questionnaire–5 (ACQ-5, which assesses asthma symptoms during the previous week, with higher scores indicating greater impairment), the on-treatment FEV_1, the fraction of exhaled nitric oxide (Feno), and the number of severe exacerbations (with a severe exacerbation defined as worsening asthma leading to the prescription of systemic glucocorticoid treatment for at least 3 days or hospitalization or an emergency department visit leading to systemic glucocorticoid treatment). The overall exacerbation rate per patient per year among patients who received as-needed budesonide–formoterol (0.195) was significantly lower than that among patients who received as-needed albuterol (0.400) and did not differ significantly from the rate among patients who received maintenance budesonide (0.175). Maintenance treatment with budesonide was superior to budesonide–formoterol used as needed for control of asthma symptoms, as reflected by a lower score on the ACQ-5 among patients who received maintenance budesonide, a finding that was similar to those in the SYGMA trials. Furthermore, the median Feno value was lower among both patients who received maintenance budesonide and patients who received as-needed budesonide–formoterol than among those who received as-needed albuterol, which showed the long-term antiinflammatory effect of budesonide maintenance therapy and as-needed budesonide–formoterol. The results of this trial, together with the findings of the SYGMA trials, provide convincing evidence that budesonide–formoterol used as needed is an acceptable alternative to maintenance budesonide maintenance therapy for patients with mild asthma.

Both the SIENA trial and the Novel START trial showed that patients with mild asthma whose only asthma treatment was a SABA as needed for relief of asthma symptoms were at considerable risk for exacerbations. Replacement of as-needed SABA treatment with as-needed budesonide–formoterol or inhaled glucocorticoid maintenance therapy could reduce such risk by approximately 50%. When considering maintenance therapy for persistent asthma, one must be aware that not all types of airway inflammation respond equally well to inhaled glucocorticoid therapy. The SIENA trial clearly showed that a large group of patients with persistent asthma might not have eosino-

philic airway inflammation, and thus, inhaled glucocorticoid therapy would not be the best treatment for them. To facilitate a personalized approach in the treatment of severe asthma, the use of biomarkers, such as blood eosinophil level, is crucial in determining which patients may have a favorable response to treatment with an anti–interleukin-5 monoclonal antibody.[9] Such an approach of biomarker-guided treatment is likely to be important in the management of milder forms of asthma. Given all these results, we should carefully review the current guideline recommendations for treating mild asthma. Evidence is building to question the role of as-needed SABAs as the step 1 treatment for mild intermittent asthma. Furthermore, larger trials with adequate power to detect all important asthma outcomes are needed to evaluate whether LAMAs would be an effective alternative for the treatment of persistent asthma in patients who do not have eosinophilic airway inflammation.

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1. Nathan RA, Thompson PJ, Price D, et al. Taking aim at asthma around the world: global results of the Asthma Insight and Management survey in the Asia-Pacific region, Latin America, Europe, Canada, and the United States. J Allergy Clin Immunol Pract 2015;3(5):734.e5-742.e5.

2. Rabe KF, Adachi M, Lai CK, et al. Worldwide severity and control of asthma in children and adults: the global Asthma Insights and Reality surveys. J Allergy Clin Immunol 2004;114:40-7.

3. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007 (http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf).

4. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018 (https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf).

5. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.

6. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.

7. Lazarus SC, Krishnan JA, King TS, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med. DOI: 10.1056/NEJMoa1814917.

8. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide–formoterol as needed for mild asthma. N Engl J Med. DOI: 10.1056/NEJMoa1901963.

9. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973-84.

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