EDITORIAL

Time to Converge FDA Decisions and Evidence Syntheses for Long-Acting Muscarinic Antagonists and SMART in Guidelines for the Treatment of Asthma

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Asthma is a chronic pulmonary disorder characterized by variable levels of dyspnea, chest tightness, wheezing, and cough that can disrupt sleep, work, and school. Asthma is a major public health problem that affects 235 million people worldwide, including 25 million people in the United States alone. Uncontrolled asthma contributes to 10.5 million days of missed school, 14.2 million days of missed work, and more than 3600 premature deaths in the United States each year.[1,2]

Related articles pages 1473 and 1485

With support from the National Heart, Lung, and Blood Institute, the National Asthma Education and Prevention Program developed clinical guidelines for the diagnosis and management of asthma in 1991.[3] Almost 11 years have elapsed since the publication of the 2007 Expert Panel Report 3 (EPR-3) guidelines on asthma, which were the most recent update of the guidelines by National Asthma Education and Prevention Program.[4] Based on evidence from clinical trials and other types of studies, the EPR-3 includes recommendations for a stepped approach to asthma pharmacotherapy. After the use of as-needed short-acting β_2-agonists (SABAs; step 1) and the addition of a low dose of inhaled corticosteroids (step 2), steps 3 through 6 consist of increasing the dose of inhaled corticosteroids and the use of combination controllers (eg, addition of long-acting β_2-agonists [LABAs]). The EPR-3 guidelines also encourage clinicians to consider alternate diagnoses, inadequate medication adherence, appropriateness of inhaler technique, avoidance of environmental triggers, and evaluation and management of comorbid conditions when making decisions about asthma treatment intensification and de-escalation.

It is in this context that a pair of systematic reviews and meta-analyses by Sobieraj et al[5,6] in this issue of *JAMA* provide important information for the management of asthma. In the first report, Sobieraj et al[5] sought to address 3 questions about the efficacy of inhaled long-acting muscarinic antagonists (LAMAs) in adolescents and adults with uncontrolled asthma. Eight placebo-controlled clinical trials examined the clinical effects of adding LAMA or placebo in about 3700 participants with uncontrolled asthma despite low or medium dose of inhaled corticosteroids. Pooled data from these 8 trials indicate a significantly lower (absolute risk reduction of 2%) risk of asthma exacerbations requiring systemic corticosteroids and significantly better lung function in the LAMA plus inhaled corticosteroid groups compared with the placebo plus inhaled corticosteroid groups. However, no significant between-group differences were observed in rescue medication use or in scores on the questionnaires that assessed asthma control or asthma quality of life.

Another 8 randomized clinical trials compared the effects of adding inhaled LAMA or another controller (in most cases, LABA was the controller) in more than 4100 adults with uncontrolled asthma despite low or medium dose of inhaled corticosteroids. An additional 4 randomized clinical trials compared triple therapy of LAMA, inhaled corticosteroids, and LABA vs dual therapy with inhaled corticosteroids and LABA in nearly 1400 participants. The pooled analyses within each of these 2 groups of studies did not demonstrate a significant benefit on the risk of asthma exacerbations or other outcomes by adding a LAMA.

There were some limitations in the systematic reviews and meta-analyses of LAMAs for asthma. The clinical trials almost exclusively focused on tiotropium; therefore, the applicability to other LAMAs is less certain. The review also was limited to studies in patients aged 12 years or older. However, pooled data from 2 placebo-controlled clinical trials of tiotropium in 801 children aged 6 to 11 years with moderate or severe asthma demonstrated significant improvement in the peak forced expiratory volume in first second of expiration (primary end point) by 170 mL at 48 weeks.[7] On the basis of these additional studies in children aged 6 to 11 years and others included in the systematic review by Sobieraj et al,[5] in 2017 the US Food and Drug Administration (FDA) approved the use of inhaled tiotropium for long-term, once daily, maintenance treatment of asthma for patients aged 6 years or older.[7]

Another limitation of the report[5] is that the analyses focused on efficacy and did not examine the potential for harm or the relative costs of different regimens. Deaths were rare in the component trials and the meta-analyses were inadequately powered to assess this outcome. LAMAs have the potential to worsen narrow-angle glaucoma and urinary retention, especially in individuals who may be using other anticholinergic medications (or, in the case of urinary retention, individuals with prostatic hypertrophy or another anatomic predisposition to obstruction).

The second systematic review and meta-analysis in this issue of *JAMA* by Sobieraj et al[6] examined the relative efficacy of a single maintenance and reliever therapy (SMART) strategy containing inhaled formoterol and inhaled corticosteroids vs a single controller with inhaled corticosteroids or

dual therapy with inhaled corticosteroids and LABA used twice per day (scheduled inhaled corticosteroids and LABA dual therapy). Formoterol has a rapid onset of action similar to a SABA, but also offers the long-acting bronchodilator benefits of a LABA. Thus, a SMART strategy containing formoterol combined with inhaled corticosteroids in a single inhaler has the potential to provide quick symptom relief while also delivering inhaled corticosteroids that could reduce the subsequent risk of an exacerbation. In addition to being convenient for the patient, such a strategy could improve outcomes by titrating the dosage of inhaled corticosteroids to the frequency of the use of a rescue SABA and by eliminating the possibility that a patient would rely on frequent SABA use for symptom relief while not adhering to a separate regimen with an inhaled corticosteroid controller.

Sixteen clinical trials examined the efficacy of a formoterol-based SMART strategy (15 of 16 using combined formoterol and budesonide via a dry-powder inhaler) in about 23 000 children, adolescents, and adults. Across treatment approaches and ages, SMART significantly reduced the risk of asthma exacerbations compared with a combination of same-dose inhaled corticosteroids and LABA as scheduled therapy or compared with inhaled corticosteroids alone at the same or a higher dose. In the small subset of children aged 4 to 11 years (about 1% of 23 000 participants), SMART also significantly reduced the risk of asthma exacerbations compared with a combination of the same dose of inhaled corticosteroids and LABA as scheduled therapy or with a higher dose of inhaled corticosteroids alone.

Given the relatively few children aged 4 to 11 years included in this study, there is less confidence regarding the benefits of SMART in this population than among adolescents and adults. Also, the studies included in the review of SMART nearly exclusively used the combination of formoterol and budesonide delivered as a dry-powder inhaler. However, the combination of formoterol and budesonide is delivered only via a metered-dose inhaler in the United States[8]; therefore, the applicability to a US population of SMART studies based on the use of a dry-powder inhaler is less clear.

Another important limitation was that the review focused on efficacy of SMART and did not assess the potential for harms. The FDA-approved prescribing information for the combination of formoterol and budesonide via a metered-dose inhaler indicates the potential for several adverse effects, including nasopharyngitis, oral candidiasis, and (among children) a reduction in growth velocity.[8] Deaths were rare in the trials that examined SMART, and these studies were inadequately powered to assess this outcome. However, the results from 4 FDA-mandated postmarketing randomized clinical trials in about 41 000 children, adolescents, and adults did not identify an increased risk of serious asthma-related events, including deaths, when LABAs were taken with inhaled corticosteroids as scheduled therapy compared with the same dose of inhaled corticosteroids alone.[9] These findings, taken together with the efficacy of SMART in reducing the risk of asthma exacerbation, are reassuring.

How do these studies affect the treatment of asthma? Updates to EPR-3 are planned[3] and the results of the meta-analyses of inhaled tiotropium by Sobieraj et al[5] suggest that LAMA should be offered as a treatment option in steps 3 through 6 in the updated guidelines. Such changes to the EPR-3 guidelines would help to harmonize the approval by the FDA for inhaled tiotropium and the clinical guidelines in the United States. For patients and clinicians, the results from these meta-analyses[5,6] suggest that dual therapy with scheduled doses of inhaled corticosteroids and LABA or inhaled corticosteroids and LAMA should help reduce the risk of future asthma exacerbations in patients with inadequate asthma control while using inhaled corticosteroids alone. There is no clear difference between these 2 options based on inhaled corticosteroids for dual therapy in reducing the risk of asthma exacerbations, suggesting that patients and clinicians be given flexibility in selecting either option based on the potential for adverse events specific to LABA or LAMA, relative costs, and preference for inhaler device.

More challenging are the next steps given the evidence about SMART presented in the second meta-analysis by Sobieraj et al.[6] Although the EPR-3 guidelines should also be updated to reflect the evidence supporting the use of SMART, the dry-powder inhaler device for combination formoterol and budesonide is not currently approved by the FDA.[8] It is possible that SMART was more effective than scheduled doses of inhaled corticosteroids and LABA because of a faster onset of action from formoterol; however, the beneficial effects could also be specific to the inhaler device. Dry-powder and metered-dose inhaler devices require different techniques that could contribute to different types of errors in inhaler use, differences in drug deposition in the airways, and different clinical outcomes. Thus, the efficacy and safety of medications using one type of inhaler device should not be presumed to be equally efficacious using another device. Studies assessing the efficacy of SMART using combination formoterol and budesonide via a metered-dose inhaler are needed.

It is time to connect the efforts of the FDA, the evidence presented by Sobieraj et al,[5,6] and support from the National Asthma Education and Prevention Program to update the 2007 EPR-3 guidelines on asthma. However, updating the guidelines alone is insufficient to improve public health. Therefore, partnerships among the National Asthma Education and Prevention Program and government agencies, payers, health systems, patients, clinicians, professional societies, researchers, and other asthma stakeholders are recommended to accelerate the implementation of updated guidelines into clinical practice.[10]

ARTICLE INFORMATION

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Published Online: March 19, 2018. doi:10.1001/jama.2018.2029

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Krishnan reported receiving compensation from Sanofi for participating on an independent data monitoring committee. Dr Au reported receiving compensation from Novartis for participating on a data monitoring committee and serving as a consultant to Gilead Sciences.

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