New Therapeutic Strategies for Asthma

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For more than 25 years, national and international guidelines have recommended standardized approaches to control the symptoms of asthma and reduce the risk of exacerbation using strategies that are relevant to the majority of patients with asthma.[1,2] As new evidence emerges from randomized clinical trials, clinicians must modify treatment strategies to be consistent with new evidence. In this issue of *JAMA*, 2 JAMA Insights articles[3,4] highlight new evidence that clinicians should consider when treating patients with asthma.

Related articles pages 561 and 563

In one article, Tripple and colleagues[3] review new strategies in chronic asthma management that differ from the 2007 National Institutes of Health (NIH) guidelines, the Expert Panel Report-3: Guidelines for the Diagnosis and Management of Asthma,[1] and are incorporated in the 2019 Global Initiative for Asthma Global Strategy for Asthma Management and Prevention.[2] The first of these new strategies involves treatment of adolescent and adult patients with mild and intermittent asthma with a daily inhaled corticosteroid (ICS). Previously, NIH guidelines stated that as-needed inhalation of short-acting β_2-agonists alone was sufficient treatment for these patients.[1] The rationale for the use of ICS in this setting is in part based on findings from a post hoc analysis of data from a large, multicenter clinical trial.[5] Results of the post hoc analysis showed that even patients with mild intermittent asthma were at risk of severe asthma-related adverse events (a composite outcome of hospitalization, emergency care, or death) and lung function impairment, and that the regular daily use of low-dose ICS reduced these adverse outcomes regardless of how infrequent asthma symptoms were reported to be at baseline.[5]

Two additional new strategies for adolescents and adults, symptom-driven ICS use and single maintenance and reliever therapy (SMART), allow a patient's symptoms to determine the dosage of ICS. These approaches link increased symptoms to a concomitant increase of underlying airway inflammation that can be countered by ICS. SMART involves the use of an inhaler that combines a long-acting β_2-agonist (LABA) with rapid onset of action (formoterol) with corticosteroid for both daily maintenance and additional as-needed use, whereas symptom-driven ICS use may be implemented with either an ICS inhaler or a combination ICS-LABA inhaler. Both of these strategies link the use of ICS, which improves asthma control and prevents exacerbations, to as-needed β_2-agonist treatment, which provides rapid symptom relief.

Tripple et al[3] discuss results of the SYGMA 1 and 2 trials,[6,7] which demonstrated that symptom-driven (ie, as-needed) combination budesonide-formoterol improved asthma control and reduced exacerbation risk in individuals with mild persistent asthma compared with symptom-driven short-acting β_2-agonists (SABAs) alone. Additionally, although regularly scheduled twice-daily low-dose budesonide provided better symptom control than symptom-driven use of the same medication, the approach of using combined budesonide-formoterol therapy as needed reduced exacerbation risk to a similar degree as twice-daily budesonide and was associated with lower total ICS exposure. Also, in a 2019 year-long, open-label trial of adults with intermittent or persistent mild asthma, severe exacerbations were reduced by as-needed budesonide-formoterol therapy compared with as-needed SABA alone and compared with twice-daily budesonide combined with symptom-driven SABA.[8] Furthermore, these trials demonstrated favorable safety profiles for low-dose ICS, and large-scale studies indicated that ICS with LABA therapy is associated with similar rates of serious asthma-related events and fewer exacerbations compared with daily ICS alone.[9]

Response to as-needed ICS or ICS-LABA is likely to vary by patient characteristics, such as adherence and the ability to perceive the worsening of asthma control. For example, improved outcomes with as-needed treatment might be expected among patients with poor adherence to daily ICS for mild asthma when symptoms are well controlled but with better adherence when symptomatic. In contrast, use of as-needed ICS or ICS-LABA may be severely delayed in patients with poor perception of bronchospasm. These individuals should be strongly encouraged to adhere to daily ICS regimens.[10]

For patients with persistent asthma severe enough to warrant daily ICS-LABA, the SMART approach is associated with improved outcomes. SMART replaces a SABA used for as-needed symptom relief with additional inhalations of ICS combined with rapid-onset LABA for symptoms, thereby intensifying anti-inflammatory treatment when asthma symptoms increase.[11] Multiple RCTs have shown that the SMART approach reduces asthma exacerbation risk.[11]

Benefits of long-acting muscarinic antagonists (LAMAs), such as tiotropium and umeclidinium, for asthma have been demonstrated by clinical trials that showed that adding inhaled LAMA to maintenance ICS reduced asthma exacerbation rates to a similar degree as add-on LABA in adults.[12] Thus, when patients report adverse effects attributable to LABA, it is reasonable to recommend ICS with a LAMA as an alternative to a LABA and expect similar risk reduction. Additional studies are needed to determine the magnitude of benefit when an inhaled LAMA is added to ICS-LABA treatment for asthma.

Although not a focus of the updates published in this issue of *JAMA*, recombinant humanized monoclonal antibodies directed against IgE, interleukin 5, the interleukin-5 receptor, or the interleukin 4/interleukin 13 receptor (ie, biologic agents) are new treatments that are substantially altering treatment approaches for some severe forms of asthma.[13] While primary care clinicians may not routinely prescribe these expensive injections, they should recognize potential indications for their use, such as the need for long-term maintenance oral corticosteroid treatment or frequent exacerbations requiring short-term oral corticosteroid treatment despite ICS-LABA therapy in patients with asthma with atopy, eosinophilia, or both. These patients may benefit from referral to an asthma specialist to select the biologic agent most likely to be beneficial.

An effective alternative to systemic corticosteroids for managing asthma exacerbations is desirable. As reviewed in the JAMA Insights article by Zaidan and colleagues,[4] an unblinded, randomized trial (N = 1922) indicated that adolescents and adults with asthma randomized to follow a self-management plan that included temporarily quadrupling ICS dose during periods of worsening asthma symptoms had fewer severe asthma exacerbations compared with individuals randomized to follow a self-management plan that included inhaled bronchodilator administration alone during such periods.[14] However, a double-blind randomized trial of children with asthma showed no effect of quintupling the ICS dose during periods of worsening asthma symptoms on the rate of severe exacerbations requiring systemic corticosteroid treatment or on the frequency of rescue albuterol needed to relieve symptoms during such periods.[15] Further research is needed to identify the specific circumstances during which increasing ICS dosage prevents progression to severe asthma exacerbations.

Another treatment approach reviewed by Zaidan et al[4] is long-term azithromycin for patients with asthma that remains poorly controlled despite ICS treatment. The largest trial (N = 420) of this treatment showed a significant and substantial reduction in asthma exacerbations in the group assigned to 500 mg of azithromycin 3 times weekly compared with placebo (1.07 per patient-year [95% CI, 0.85-1.29] vs 1.86 per patient-year [95% CI, 1.54-2.18]; P <.001).[16] A smaller trial (N = 109) revealed that chronic azithromycin did not reduce severe asthma exacerbations overall, although reduced exacerbations occurred among patients with blood eosinophil count less than 200/μL in a prespecified subgroup analysis.[17] The mechanism by which long-term macrolide therapy may improve asthma control is uncertain, but may involve its antimicrobial action in some patients[18] and anti-inflammatory activity in others. Additional research is needed.

The expert panel that is currently developing updated NIH asthma management guidelines (Expert Panel Report-4), which will be released later this year, has complex issues to address as it considers these new treatment approaches (a draft report was available for public comment through January 17, 2020). The evidence that ICS treatment is warranted for mild intermittent asthma is largely derived from a post hoc analysis of clinical trial data.[5] As-needed ICS treatment and SMART using ICS-LABA, as well as quadrupling the ICS dose when asthma symptoms increase, involve dosing patterns and use of these medications that are currently off-label in the United States. These novel approaches require that prescribers, pharmacies, and payers adopt patterns of dispensing ICS and ICS-LABA inhalers that differ from than the traditional 1 inhaler per month. The efficacy of long-term azithromycin therapy to reduce asthma exacerbation frequency must be balanced against the risk of side effects and potential promotion of resistance in microbial pathogens. Choosing the clinical threshold for prescribing an injectable biologic agent must balance the benefit of reduced asthma morbidity with cost, inconvenience, and adverse effects. As additional evidence from clinical trials becomes available, the roles of these new treatments in asthma management will continue to evolve.

ARTICLE INFORMATION

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