Review Article

MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Review of Recent Asthma Treatment Guideline Updates

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Abstract

Asthma affects an estimated 262 million people globally and caused 455,000 deaths in 2019 alone. There have been significant changes to asthma treatment guidelines in response to new clinical trial data in recent years. The Global Initiative for Asthma (GINA) Science Committee conducts an asthma-related scientific literature review biannually to evaluate published research on asthma management and prevention and was most recently updated in 2023. The Expert Panel Report 3 (EPR-3) published an update to their guideline in 2020. This review highlights important changes in asthma treatment recommendations, primarily focused on rescue inhaler use and maintenance and reliever therapy (MART).

Asthma is a respiratory disease characterized by chronic airway inflammation, which may present as wheezing, shortness of breath, chest tightness, and/or cough due to airflow limitations. The most common clinical phenotypes of asthma include allergic, non-allergic, adult-onset, asthma with persistent airflow limitation, and asthma with obesity.[1]

Asthma treatment is centered on rescue and maintenance inhaler therapies. Rescue inhaler therapy is used as needed (PRN) to address acute symptoms, and maintenance inhaler therapy is used on a scheduled basis to prevent symptoms. Asthma treatments can be escalated and deescalated to meet a patient's treatment needs. There are two primary asthma treatment guidelines: the Expert Panel Report 3 (EPR-3) and the Global Initiative for Asthma (GINA) Report.

The National Heart, Lung, and Blood Institute (NHLBI) created the National Asthma Education and Prevention Program (NAEPP) in 1989 with the goal of enhancing the quality of life for patients with asthma and reducing asthma-related morbidity and mortality.[2] This organization puts forth the Expert Panel Report, first published in 1991, to address the diagnosis and management of asthma. Subsequent reports include the EPR-2 published in1997 and EPR-3 published in 2007, with notable updates added in 2020.

In 1993, the NHLBI, in collaboration with the World Health Organization (WHO), also established the Global Initiative for Asthma (GINA), which aims to broaden asthma awareness as well as improve prevention and management. With updates made on an annual basis, supported by twice-yearly comprehensive literature review, the GINA report serves as a useful resource to guide clinical practice. The GINA report holds a strong level of validity with over 70 publications, from clinical trials to systematic reviews, all meticulously analyzed for clinical applicability by at least two committee members.

Recent Asthma Guideline Changes

Rescue Inhaler Use

Previous iterations of the GINA Report endorsed the utilization of PRN SABA frequency as the cornerstone of assessment, separating based on whether the patient required the SABA reliever < 2 days per week or ≥ 2 days per week to manage symptoms. Patients requiring their reliever inhaler two or more days per week would ultimately require either an increased dose or the addition of controller therapy. The largest change in recent guidelines is the recommendation to avoid using short-acting bronchodilators without concurrent ICS use. Historically, SABA alone has served as a go-to reliever therapy. Rescue inhaler treatment options now include PRN ICS-formoterol, ICS-SABA, or SABA alone. The use of SABA alone for rescue therapy is now recommended only when the patient is on an ICS inhaler for maintenance.

Starting in 2019, the GINA Report no longer recommends SABA-only treatment, as evidence has shown increased incidence of asthma-related death and requirement of urgent intervention. Three main theories persist related to the desensitization of beta-2-adrenergic receptors (β_2AR):

phosphorylation of internalized receptors, adenylate cyclase uncoupling from the receptors, and internalization of uncoupled receptors.[3] These adverse effects are amplified when patients are not on an ICS.

The GINA members sought funding for randomized controlled trials to investigate the use of ICS-formoterol as a potentially safer but effective alternative to SABA. Formoterol was chosen as it has the fastest onset of action of all long-acting beta agonists (LABA). This funding led to the completion of the Symbicort Given as Needed in Mild Asthma (SYGMA) trials, which evaluated the safety and efficacy of ICS-formoterol in patients whose asthma was poorly controlled on PRN SABA (subgroup 1) or controlled on ICS or leukotriene receptor antagonists (subgroup 2). The SYGMA studies utilized a double-blind, randomized parallel-group study design, in which 6,735 patients were randomly assigned to either PRN ICS-formoterol, low-dose ICS plus PRN SABA, or PRN SABA monotherapy. The PRN ICS-formoterol treatment was non-inferior to low-dose ICS plus PRN SABA for reducing the rate of severe exacerbations while being exposed to less ICS. ICS-formoterol PRN was inferior to low-dose ICS plus PRN SABA for controlling asthma symptoms, but ICS-formoterol PRN was superior to PRN SABA for controlling asthma symptoms and reducing rate of severe exacerbations.[4]

Selection of an appropriate asthma treatment regimen is highly dependent on the severity of a patient's asthma symptoms, and adherence to medications. For patients with infrequent exacerbations who are adherent to their inhaler regimens, maintenance use of an ICS-containing inhaler along with rescue use of a SABA may continue to be most appropriate, as previously utilized in practice. However, it should be noted that the overuse of rescue SABA inhalers presents some risk, especially when patients are not adherent to their maintenance ICS therapy. The use of PRN ICS-formoterol or ICS taken every time a SABA is taken provides both adequate asthma symptom control and reduces the risk of severe asthma exacerbations while avoiding the need for urgent intervention and asthma-related death associated with PRN SABA monotherapy.[5]

Maintenance and Reliever Therapy

Additionally, the GINA Report recently introduced the idea of using the same ICS-formoterol inhaler as both the maintenance and reliever therapy (MART). Utilization of MART has been noted to reduce the time to first asthma exacerbation when compared to ICS-LABA maintenance plus SABA reliever. In a systematic review and meta-analysis conducted with 5 RCTs (n = 4863), researchers assessed patients with ill-controlled asthma status between two comparators: MART vs. same step maintenance with ICS-LABA plus SABA. Patients undergoing MART therapy showed a prolonged time to first severe exacerbation and a 30% reduced risk for severe exacerbations HR 0.70 (95% CI, 0.58-0.85). Within this same group, the MART regimen offered a 40% severe exacerbation reduction RR 0.60 (95% CI, 0.48-0.74) when compared to same step maintenance with ICS-LABA plus SABA.[6] Additionally, consolidation to MART therapy can improve adherence-related concerns as it eliminates the previous requirement of a separate reliever inhaler.

The addition of a single maintenance and reliever therapy such as ICS-formoterol to replace a SABA such as albuterol reduces the risk for severe asthma exacerbations with an overall lower ICS exposure.[7] While the safety and efficacy of budesonide-formoterol and beclomethasone-formoterol have been established, further research is needed on other combinations.

An important consideration related to execution of these recommendations is patient cost and insurance coverage. Updates in prescription insurance formularies and coverage algorithms are needed to match current guidelines and literature recommendations. While many current insurance plans cover only a 30-day supply of ICS-formoterol inhalers, PRN use in replacement of a SABA may result in the need for more frequent refills. The cost of SABA inhalers is often more affordable than ICS-containing inhalers. Educating patients on the financial implications of a treatment change is important. For example, explaining that the ICS-formoterol combination inhaler has a longer duration of action and could result in a less frequent need and net use of rescue inhalations could be persuasive for a patient to be agreeable to a switch. The extra investment in dual therapy for specific patients may be offset by savings from the reduction in emergency room visits and additional exacerbation treatment costs. Proper education, effective communication, and shared decision-making to create individualized plans will result in increased patient adherence, satisfaction, and improved health outcomes.

GINA (2023 Update)

In previous years, the GINA Report has detailed a two-track treatment system that provided guidance on treatment decisions. Track 1 involves using PRN low dose ICS-formoterol as rescue therapy. This treatment is referred to as anti-inflammatory reliever (AIR) and is useful in symptom relief and reduction of inflammation. This regimen gives rise to improvement in lung function, reduction of exacerbation risk and promotion of proper adherence. Track 2 offers the option of a low-dose ICS taken whenever a PRN SABA is used or using PRN SABA alone for rescue therapy as long as the patient is on an ICS-containing maintenance inhaler. In both tracks escalation and supplementation with a controller is warranted on various levels relative to the frequency of symptom presentation. The recommendation to include PRN low-dose ICS-formoterol as part of Step 1 is due to the potential for patients with even intermittent asthma symptoms to experience severe exacerbations.

The GINA update, following the Track 1 treatment algorithm, recommends that for patients utilizing PRN ICS-formoterol greater than 2 days per week, this inhaler is inherently serving as controller therapy; therefore, escalation is not warranted. When compared to increased use of PRN SABA, the ICS-formoterol reliever allows for maintained relief with lower risk for severe exacerbation of symptoms. For this reason, the arbitrary 2 days/week and < 2 days per week frequency categorization has been forgone, and recommendations support the assessment of average frequency of PRN ICS-formoterol usage over a four-week period. Beyond this assessment, clinicians should determine whether the patient has any other risk factors for poor asthma outcomes (i.e., exposure to tobacco, FEV1 <60%, obesity, major psychological problems, socioeconomic problems, sputum eosinophilia, or ≥ 1 sever exacerbation in

last year).

Difficult-to-treat or severe asthma describes a category of asthma defined as uncontrolled despite proper use of medium- to high-dose ICS-LABA. Roughly 3-10% of all asthma patients fall into the category of severe asthma and its diagnosis is often preceded by several comorbidities. Patients with severe or difficult-to-treat asthma carry a large burden from their disease as it impedes their daily life in several ways, including but not limited to the following: physical activities, mental capacity, emotional endurance, social life, and economic status. The GINA Report breaks down the treatment of severe/difficult-to-treat asthma in a 10-step algorithm. Generally, this algorithm prioritizes accurate diagnosis, non-pharmacologic/inhaler technique therapies, directing therapy towards patient specific symptoms, and use of biologic therapy as last line (discontinuing if no response after 4 months). Specific therapy changes would include attempting to change controller inhaler to ICS-formoterol whenever available.[8]

The 2020 update strongly discourages long-acting muscarinic antagonist (LAMA) or LABA monotherapy. A JAMA randomized controlled trial, Salmeterol or Corticosteroids (SOCS), conducted in 2001 examined the effectiveness of salmeterol (LABA) as replacement therapy for patients maintained on low-dose triamcinolone (ICS) monotherapy. A total of 164 patients were randomly assigned to receive either LABA, continue ICS therapy or placebo medication. Changes in peak expiratory flow (PEF), forced expiratory volume (FEV1), self-reports, reliever usage, asthma exacerbations, and markers of airway inflammation were compared between the three comparators. Results showed that patients receiving LABA as monotherapy experienced more treatment failures (24% vs 6%; P = 0.004), and asthma exacerbations (20% vs 7%; P= 0.04) when compared to the ICS treatment group. The SOCS trial concluded that a switch from ICS to LABA monotherapy poses the threat of clinically significant loss of asthma control.[9]

Biologic Add-On Therapy

In patients with severe asthma, evidence has showcased the potential of biologics as add-on therapy. This therapy is appropriate for patients with allergic (elevated IgE), eosinophilic (elevated blood eosinophils), or severe asthma. The GINA Report recommends biologic add-on therapy, which includes anti-immunoglobulin (omalizumab), anti-interleukin-5-5R (mepolizumab, reslizumab or benralizumab), anti-interleukin-4R (dupilumab), and anti-thymic stromal lymphopoietin (tezepelumab) agents, for patients with severe, uncontrolled asthma on maximal inhaled therapy.

The most recent biologic, tezepelumab, was approved in 2021. Tezepelumab may be suitable for patients experiencing severe exacerbations whose lab work does not reflect elevations in IgE or eosinophils. Notoriety for this biologic option came from a randomized controlled trial published in *New England Journal of Medicine (NEJM)*. The primary endpoint assessed the rate of asthma exacerbations between patients receiving subcutaneous tezepelumab and placebo drug every four weeks over a one-year treatment period. Tezepelumab was stratified into three dose categories: 70 mg as low-dose, 210mg as medium-dose, and 280mg as high-dose. The annualized asthma exacerbation rates within the treatment group were 0.27, 0.20, and 0.23, with respect to the dose categories. This same outcome when measured in the placebo group yielded a rate of 0.72 exacerbation events per patient-year. This translates to a 72%, 71%, and 66% lower rate of exacerbation vs the placebo group ($P < 0.001$).[10] The phase III continuation of this trial narrowed its focus onto the 210 mg tezepulumab dose against placebo administered every 4 weeks for another one-year treatment period. A total of 1,061 participants were randomly assigned to either comparator. Within the tezepulumab group the rate of exacerbation was determined to be 0.93 (95% CI, 0.80 to 1.07), and in the placebo group it was 2.10 (95% CI, 1.84-2.39), RR, 0.44 (95% CI, 0.37 to 0.53; $P < 0.001$).[11] While there are no definitive criteria to assess a good response to medication, biologic therapy aims to reduce frequency of asthma exacerbations and decrease need for systemic corticosteroids. Biologic therapy can take several months to start adding benefit.

Expert Panel Report – 3

The EPR-3 Guideline was updated in 2020. One notable difference between this guideline and the GINA Report is that it allows PRN SABA monotherapy to be used for patients with intermittent asthma (i.e., when the amount of SABA the patient will need is presumed to be very minimal). Otherwise, the stepwise therapy is very similar to the GINA report with options for a variety of different rescue therapies.

When comparing the harms and benefits of ICS + placebo against ICS-LAMA, a series of five randomized controlled trials (RCTs) (n = 3,036) were reviewed. The ICS-LAMA comparator yielded a smaller rate of exacerbation, 4.2 percent lower than the control group. The results did not conclude a significant improvement in asthma control. However, in the Blacks and Exacerbations on LABA vs. Tiotropium (BELT) study, it was determined that there was a 2.6-fold higher rate of asthma-related hospitalizations in the group treated with ICS-LAMA when compared to the ICS-LABA group. Given that this study only assessed the comparators within a sample of Black participants, the Expert Panel (EP) could not generalize these conclusions to other populations.[12] Additionally, outcomes from two RCTs (n = 1,982) indicated no differences in asthma-control when comparing patients treated with LAMA vs. LABA.[13-15]

The studies included regarding LAMA utilization focus primarily on efficacy, broader conclusions regarding clinical applications and implications cannot be drawn from this data alone. It is understood that the addition of a LAMA may have potential to improve asthma-control, but minimal impact on asthma exacerbations.

The 2020 EPR-3 update altered its previous recommendations for step 3 (with similar conditional recommendations for step 4) treatment in their algorithm for the management of moderate persistent asthma in patients ≥ 12 years of age. This recommendation has changed to highlight the superiority of ICS-formoterol used as both daily controller and reliever therapies. Previous recommendations illustrated ICS use as daily controller with SABA PRN for symptom exacerbations; however, research has continued to illustrate the importance of utilizing these to medication classes in tandem.

Future Direction

In January of 2023 the FDA approved the first and only as-needed ICS-SABA rescue inhaler for individuals older than 18. This is the first medication containing an ICS that has been FDA approved as reliever treatment rather than controller. Approval was made after results of the MANDALA study, conducted in 2021, which is a multinational, phase 3, double-blind, randomized controlled trial that compared the safety and efficacy of albuterol-budesonide (Airsupra™) PRN in patients with moderate-to-severe asthma compared to albuterol alone in 3,132 patients. Patients were stratified into three groups: high-dose combination receiving 2 actuations of 90 µg albuterol and 80 µg budesonide per dose, low-dose combination receiving 2 actuations of 90 µg albuterol and 40 µg budesonide per dose, and the albuterol-alone group receiving 2 actuations of 90 µg albuterol per dose. The risk of severe asthma exacerbation was significantly lower in the high dose combination group compared to ICS alone (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P=0.001). Adverse events amongst the three groups were comparable and not statistically significant. Research on the safety and efficacy of PRN ICS-SABA in children needs to be further evaluated. While the MANDALA study did include a population of 37 children in the treatment and evaluation phase, no children received high-dose ICS-SABA.[16] A larger population will also be needed for potential approval in this population. Further research is needed to compare superiority between PRN ICS-formoterol and ICS-SABA in regard to safety and efficacy.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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