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Triple Inhaler Therapy in Adolescents and Adults with Moderate and Severe Persistent Asthma

ABSTRACT

Expert guidelines, metanalysis, and multiple randomized controlled trials have demonstrated the effectiveness of long-acting inhaled antimuscarinic agents (LAMA) as an additive medication in poorly controlled moderate and severe persistent asthma. LAMAs play an essential role in blocking acetylcholine binding to muscarinic receptors and reducing bronchoconstriction and mucous production. By adding this medication to other combination inhalers - long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS), patients can utilize a triple inhaler to improve FEV₁ values and decrease exacerbations. Current treatment guidelines allow clinicians to develop more personalized treatment plans for their asthmatic patients.

Keywords: asthma, triple therapy, therapy, long-acting antimuscarinic agents (LAMA), phenotype, FeNO, long-term controllers

INTRODUCTION

According to national CDC statistics,¹ asthma in adolescents and adults continues to be a common disease with the highest prevalence rates in females, non-Hispanic black and American Indians / native Alaskans, and individuals 100% below the national poverty threshold. Data from 2019¹ estimates the frequency of emergency medical visits at 41.8%, and inpatient admissions at 4.1% in individuals seen with the diagnosis of asthma in the past twelve months. Moderate and severe persistent asthma accounts for 5-10% of the cases and attributes to more than 60% of the cost of healthcare.² Suruki and colleagues³ defined poorly controlled asthma as those requiring Steps 4 and 5 medication treatment, as well as frequent exacerbations, and high

asthma control test scores (ACT) or asthma control questionnaire (ACQ). The frequency of exacerbations doubles from patients on step 1 treatment as compared to step 5 treatment.³

Patients who have comorbidities are the ones who have a lower socioeconomic status.²

Eventually, patients have airway remodeling with features consistent with asthma and chronic obstructive lung disease (COPD) overlap syndrome.

Global initiative for asthma (GINA)⁴ has recommended the addition of LAMAs to be added to long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS) for steps 5 who have poorly controlled moderate and severe persistent asthma. LAMAs play an important role in blocking the binding of acetylcholine to muscarinic receptors, which are released during asthma exacerbations.^{5,6} Activation of these receptors leads to additional bronchoconstriction and mucus production. Many clinicians are familiar with the use of short-acting antimuscarinic agents during acute asthma exacerbation but may be unaware of LAMAs use in managing uncontrolled moderate and severe persistent asthma. This article aims to provide a clinical overview of asthma phenotypes with a focus on novel bronchodilator management strategies.

Significance to Primary Care

Asthma continues to be a very common diagnosis¹ that is managed in the outpatient setting, with frequent hospitalization for poorly controlled, and non-compliant patients.

According to Soriano et al,⁷ the overall prevalence of asthma has increased from 1990 to 2015 by 12.6%, and ranked 23rd for disease burden, which is measured by disability-adjusted life years (DALYs). Murrison and colleagues⁸ report multiple indoor and outdoor environmental pollutants increase the burden of allergies, which is a factor in these increasing prevalence rates of asthma. Another important issue with asthma is medication compliance, and the cost of

treatment. Finding an effective cost-effective therapy, which is user-friendly to utilize is of utmost importance. According to Jansen et al,⁹ medication adherence for asthma patients is as low as 22.2% in the United States. Adherence can be further broken down by poor understanding of inhaler frequency (once vs twice /day dosing), poor technique, and deliberate non-compliance. The healthcare costs of patients with asthma are 3.5 times greater than patients without asthma.⁹ The use of triple therapy (ICS/LABA/ LAMA) in moderate and severe poorly controlled therapy helps ease the complexity of the treatment plan by having just one inhaler and has demonstrated improved FEV₁ levels and decreased hospitalizations.^{10,11} Augusti et al¹² noted the cost of triple inhalers may be more expensive, but the benefit of reduced hospitalizations outweighs the cost to the healthcare system.

Long-term controllers of asthma are broken down into three categories; Inhaled Corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting antimuscarinic agents (LAMA). The major role of these medications is to reduce airway inflammation, and recent literature supports the usefulness of measuring fractionated exhaled nitric oxide (FeNO) levels to be a predictor of airway inflammation and responsiveness to the effects of these medications.¹³ FeNO levels are increased in type 2 inflammation which occurs by activating cytokines, and excessive production of FeNO from epithelium cells.¹⁴ FeNO Levels > >50 ppb in adults are considered high, and 25 to 50 ppb are considered intermediate.¹³ Monitoring FeNO is an important measurement in patients, to evaluate change in inflammation. Currently, there are several handheld devices on the market that can be utilized to measure this inflammatory marker.

CLINICAL PRESENTATION

Clinical signs and symptoms of asthma include shortness of breath, cough, and wheezing. Symptoms may be triggered by exercise or exposure to allergens, and the cough is often worse at night or early morning. Once a clinician suspects asthma, pulmonary function tests (PFT) are generally performed to help confirm the diagnosis. PFTs can demonstrate an obstructive pattern - decreased FEV₁, and FEV₁/FVC ratio < 0.7-.85 % of predicted value, and an improvement with post-bronchodilator therapy or improvement at 4 weeks of anti-inflammatory treatment of an FEV₁ by 12% of predicted value and 200ml.⁴

ONGOING CLINICAL ASSESSMENT

Once a diagnosis of asthma is established, patients should be reassessed utilizing a combination of both subjective and objective measures. The asthma control test (ACT) and asthma control questionnaire (ACQ) are useful validated measures of subjective asthma symptoms and control. Home peak flow trends and in-office comparisons can also be used as objective measures. PFTs should also be performed on at least a yearly basis to evaluate for improvement and to confirm if non-reversible disease has occurred. For patients with poorly controlled moderate and persistent asthma, additional testing is warranted and helps distinguish specific phenotypes which guide further treatments. Levels of FeNO, serum IgE, sputum, and blood eosinophil can be used to demonstrate increased type 2 inflammation within the airways.¹⁵ Allergy testing with RAST or skin prick testing can further identify specific allergens which may include food, animal, dust, pollen, and insect allergies. The results of this additional testing will designate patients into specific phenotypes (Figure 1) and help customize appropriate treatment.

Figure 1

Phenotype	Biomarker	Treatment Options
Allergic asthma	Elevated IgE	Anti-IgE (omalizumab)
Eosinophilic asthma	Elevated eosinophils (blood \geq 300 u/L, sputum \geq 3%)	Anti-IL-5 treatment (mepolizumab, reslizumab, benralizumab) Anti-IL-4 and IL-3 (dupilumab)
Non-eosinophil asthma	Absence of increased eosinophils, and normal IgE levels	Long-acting bronchodilators (LAMA/LABA/ICS)

Elevated FeNO levels demonstrates ongoing airway inflammation and signifies the need for additional anti-inflammatory medications and referral to an asthma specialist. Elevation in IgE is categorized as allergic asthma, and signifies the need for further allergy testing. Elevation in eosinophils in the sputum or blood is categorized as eosinophil asthma, and lack of eosinophils with normal IgE as non-eosinophilic asthma.

ASTHMA TREATMENT

Asthma treatment has changed significantly over the past 5 years, with more customized management based on ongoing inflammation, poor control, phenotyping, and advances in therapy. GINA often releases new recommendations yearly and has updated its stepped

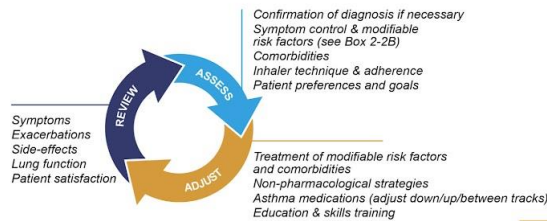
treatment approach in 2022 (Box 3-5a).¹⁶

Box 3-5A. Personalized management for adults and adolescents to control symptoms and minimize future risk

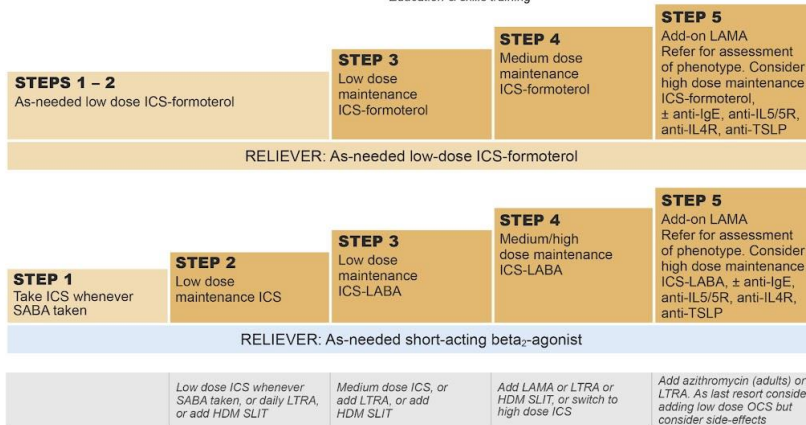


**Adults & adolescents
12+ years**

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and PREFERRED RELIEVER (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever



See GINA severe asthma guide

For steps 1 and 2 treatment in the mild intermittent asthma classification, the use of an ICS/LABA in the form of ICS-formoterol is indicated.^{4,16} The addition of a LAMA to all patients in step 5 and as an alternative treatment in step 4 is in alignment with severe persistent and moderate persistent asthma respectively. The use of these triple inhalers (ICS/LABA/LAMA) has simplified inhaler administration with this use of one controller inhaler. In addition, more customized treatment plans for moderate and severe asthma are based on phenotyping.¹⁶

DISCUSSION

Early use of medications that reduce that reduces inflammation is essential to the control of asthma. A randomized controlled study by O’Byrne and colleagues¹⁷ demonstrated the benefit of improved symptom control and reduction in exacerbation which lead to the changes in the GINA step 1 guideline.⁴ Additionally, recognizing the signs and symptoms of poorly

controlled asthma warrants additional measures to look for airway inflammation as measured by elevated FeNO levels, in addition to phenotyping to further customize therapy.^{13,18}

The addition of LAMAs to uncontrolled moderate and severe persistent asthma had been proven to significantly reduce exacerbations and improve FEV₁ values over time with their use.^{10,12,19} Kim and associates¹⁹ reported a reduction of severe asthma exacerbations from 27.4% with ICS/LAMA to 22.7% with ICS/LABA/LAMA use, and an improvement of FEV₁ from 37% to 47% of patients using ICS/LABA vs ICS/LABA/LAMA respectively. Triple inhalers (ICS/LABA/LAMA) allow patients to have the benefit of all three controller medications in one and have the benefit of better compliance.^{19,20} Singh et al²¹ noted that patients with more reversible disease in the TRIMARAN and TRIGGER double-blinded randomized control study, had better efficacy with triple inhaler use, than those on ICS/LABA.

As reported by Kim et al¹⁹ self-reporting tests such as ACT and ACG showed an improvement in the patient's asthma symptoms with the addition of the triple inhaler, but didn't show a significant improvement in quality of life measures. There were no significant differences in mortality with the addition of LAMA with these triple inhalers. The most commonly reported side effects were dry mouth and dysphonia.

Conclusion

Asthma care continues to have new advances, with the focus being on more individualized treatments. Preventing airway inflammation is of utmost importance, and newer treatment modalities aim to do this. GINA has recommended the addition of LAMAs to poorly controlled moderate and persistent asthma. The use of a triple inhaler enhances compliance and has been shown to cause improvement in symptoms, improved FEV₁, and reduction in asthma

exacerbations with minimal side effects. Additional concerns about cost need to be addressed since some insurances are still not including triple inhalers on their formulary.

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Key Points

Addition of LAMA in a triple inhaler should be considered in poorly controlled moderate and severe persistent asthma

FeNO testing will determine the effectiveness of anti-inflammatory medications

LAMA use could improve symptoms, improve FEV₁, and reduce exacerbations of asthma