State of Practice:
Managing Uncontrolled Asthma: The Role of Long-Acting Muscarinic Antagonists (LAMA)

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CHEST Clinical Perspectives™

Symptoms Remain Uncontrolled in Many Patients With Asthma

In the United States, approximately 30%-50% of adult patients with asthma and who are receiving a medium- or high-dose inhaled corticosteroid (ICS)/long-acting β_2-agonists (LABA) are inadequately controlled despite being adherent to their controller medications.[1-4] Many of these symptomatic patients are at high risk of asthma exacerbations.[1,4] Uncontrolled asthma has been associated with worse health-related quality of life (HRQoL) and leads to disruptions at school and work and in social relationships and family life.[4,5]

Furthermore, individuals with uncontrolled asthma symptoms have increased health care use, such as unscheduled clinic visits, emergency department visits, and hospitalization, compared with those with well-controlled asthma.[6,7] Over a 20-year time span, the direct health care costs due to uncontrolled asthma are estimated to reach about $300 billion in the United States.[8] To reduce the disease burden of asthma and improve patient QoL, it is important for clinicians treating patients with asthma to be up-to-date on emerging therapies that help improve the management of uncontrolled disease.

CASE STUDY 1: Gary

Gary is a 37-year-old man with asthma and allergic rhinitis. His treatment includes high-dose inhaled corticosteroids and a long-acting beta-agonist in addition to a leukotriene receptor antagonist. Despite this therapy, he has experienced 3 exacerbations that required oral steroids in the past 6 months. His asthma control test score is 12, and FEV_1 is 72% predicted. His blood eosinophil count is 366 cells/µL and IgE is 360 IU/dL. Perennial allergy testing was positive for various grasses, trees, and weeds. He would like to know if there is any other treatment option to help control his asthma symptoms and reduce his exacerbations.

CASE STUDY 2: Martha

Martha is a 55-year-old woman with asthma, obesity, and diabetes. Her asthma symptoms are not controlled despite compliance with medium-dose inhaled corticosteroids and a long-acting beta-agonist. A trial of increasing inhaled corticosteroids to a high dose and a trial of adding a leukotriene receptor antagonist did not improve her symptoms. Spirometry showed FEV_1 of 68% predicted. Allergy testing was negative. She reports no exacerbations but has been using her albuterol every day and wakes up at night 1–2 times/week with wheezing and shortness of breath. She has an asthma control test score of 9. She would like to know how she can better control her symptoms and optimize her lung function.

Asthma Management Goals

The main goals for asthma management are to help patients better control their symptoms and to reduce the risk of exacerbations, medication side effects, and the development of fixed airflow limitation.[7] To achieve these goals, it is imperative that patients and their health care providers build a relationship based on open communication. Therefore, health care providers should work with their patients to address obstacles to treatment adherence and ensure that patients have a clear understanding of their disease and demonstrate proper inhaler technique.

Patients, together with their health care providers, should play an active role in determining a treatment plan that takes into consideration their individual comorbidities and risk factors, their access to medications, and their goals and preferences for their treatment.[7] Indeed, patients with asthma who engage in shared decision-making are more likely to adhere to recommended treatments. Shared decision-making has also been associated with improvements in patient satisfaction and QoL.[9,10]

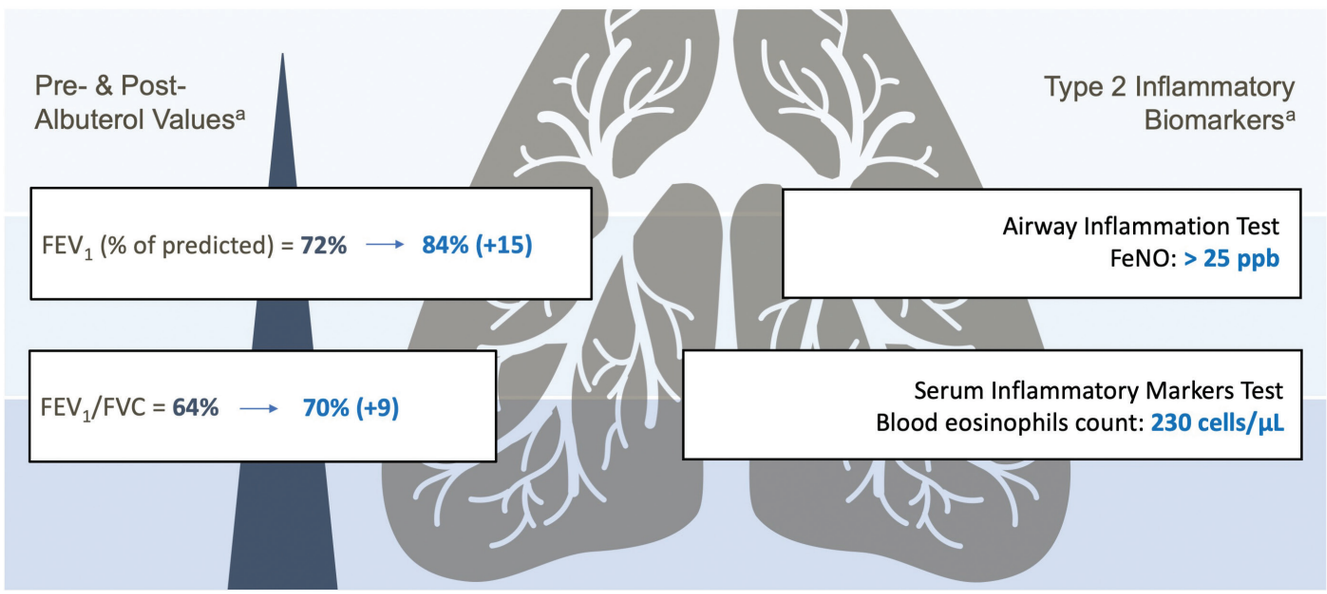
The case histories of Gary (Case Study 1) and Martha (Case Study 2) reflect uncontrolled asthma despite treatment with existing therapies. Such common management challenges are encountered on a daily basis by health care providers. What treatment options are available for them?

Assessing Asthma Control and Future Risk

To assess the effectiveness of therapy, it is important for clinicians to assess a patient's current symptoms and future risk for disease progression at regular intervals.[7] Asthma symptoms can vary greatly, and questionnaire-based assessments, such as the Asthma Control Test (ACT), may not fully capture symptom control or risk of future exacerbations and overall quality of life.[11]

Symptom-based assessments may result in asthma being under- or over-diagnosed and incorrectly treated.[12] Therefore, objective measures of lung function and biomarkers reflecting airway inflammation should also be used in addition to patient-reported outcomes.[13-15] An examination of variations in the forced expiratory volume in 1 second (FEV_1), as measured by spirometry, is an effective method to determine the level of airflow limitation at diagnosis or after exacerbations or to assess the patient's response to treatment.[7] With frequent evaluation of lung function, treatment can be stepped up or down in response to changes in airflow limitation.

Fractional exhaled nitric oxide (FeNO), blood/sputum eosinophil counts, and serum immunoglobulin-E (IgE) levels are biomarkers that reflect type 2 (T2) airway inflammation, which is found in approximately 50% of patients with asthma.[16] Elevated blood eosinophil count (>300 cells/μL) and FeNO levels (>25 ppb) have also been associated with increased risk of exacerbation.[17,18] Both of these measures can also help predict a patient's response to corticosteroids and certain biological therapies, such as monoclonal antibodies.



[a]Lung function test and lab values are for a hypothetical patient case.

FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ppb = parts per billion.

Q: How Would You Assess Lung Function and Biomarkers for this Patient Case Example?

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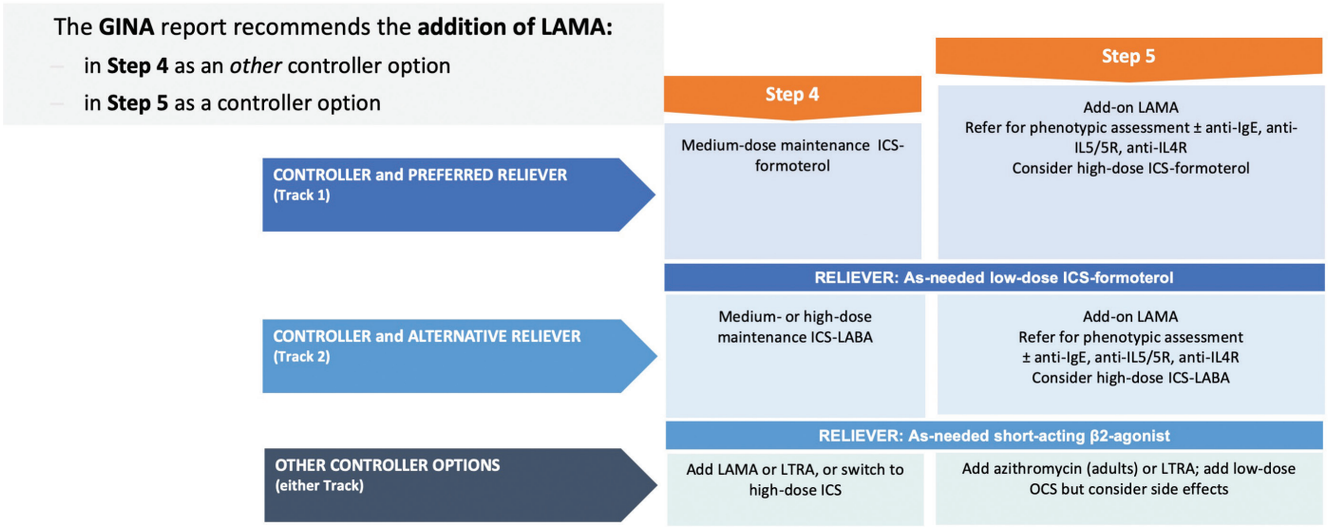
Current Landscape of Asthma Therapy

Several US Food and Drug Administration (FDA)-approved medications are available for asthma treatment, including short- and long-acting β_2-agonists (SABA and LABA), muscarinic antagonists, inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRA), and monoclonal antibodies (ie, biologics).[7] The Global Initiative for Asthma (GINA) strategy document no longer recommends the use of SABA alone as first-line reliever therapy. Instead, GINA recommends that all adults and adolescents with a confirmed diagnosis of asthma use ICS-containing controller medications regardless of disease severity and symptom frequency. In patients with symptoms less than twice a month and a history of good medication adherence, low-dose ICS whenever SABA is taken may be considered as a controller option. For those with mild asthma who have symptoms less than twice a month, low-dose ICS/LABA (eg, formoterol) is recommended on an as-needed basis.

As disease severity worsens, the recommended treatment is stepped up to a daily ICS/LABA combination, with progressively higher dosing at each step.[7] Individuals with persistently uncontrolled asthma despite adherence to low- or medium-dose ICS/LABA therapy may benefit from the addition of a long-acting muscarinic antagonist (LAMA) (Figure 1). Other add-on options include an LTRA although this is considered a less efficacious option. For individuals who continue to be not well-controlled despite good adherence with medium- or high-dose ICS/LABA treatment, GINA recommends increasing the ICS/LABA dose for a trial basis and considering add-on therapy with LAMA and/or biologic therapies.

Figure 1: GINA Recommends the Addition of LAMA Therapy as an Option for Patients With Uncontrolled Asthma

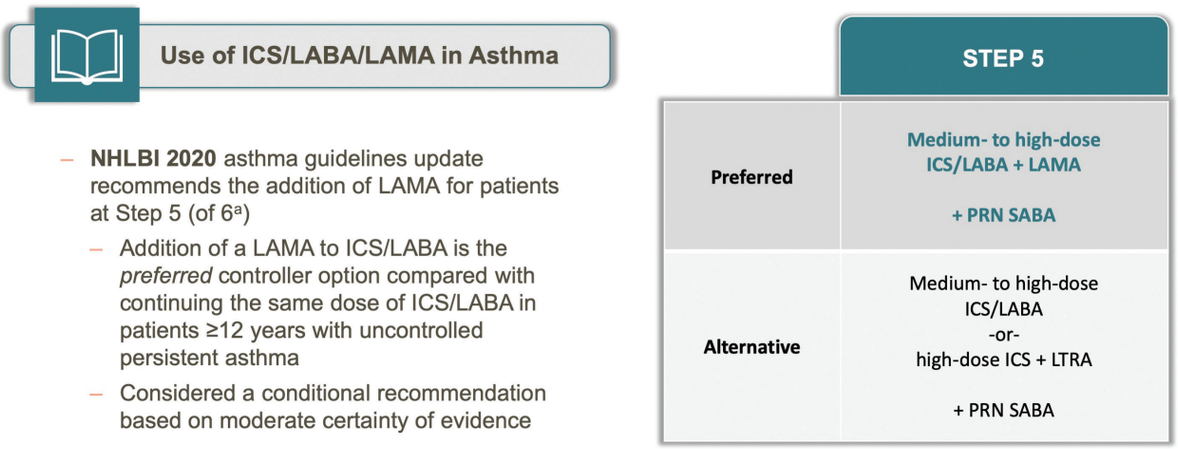


GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; IL = interleukin; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. www.ginasthma.org.

The National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel Working Group recommends starting patients with intermittent asthma symptoms on as-needed SABA-only treatment.[19] At the next step, a low-dose ICS may be used with SABA therapy to control symptoms. The NAEPCC prefers ICS/LABA compared with ICS/LAMA in patients with uncontrolled asthma despite low-dose ICS with SABA, and as disease severity worsens, patients may be stepped up to a low-dose or medium-dose ICS/formoterol combination for maintenance and reliever therapy. For patients with uncontrolled asthma despite treatment with a medium-dose ICS/LABA combination, add-on LAMA therapy is recommended (Figure 2). In the most severe cases of uncontrolled asthma, NAEPCC recommends escalating to a high-dose ICS/LABA with oral systemic corticosteroids, and SABA therapy as-needed. Biologics may also be considered as add-on therapy for more severe patients in Steps 5 and 6 of the stepwise approach.

Figure 2: NHLBI 2020 Update – Recommendations for Use of LAMA in Patients Uncontrolled on an ICS/LABA



[a]Data on the use of LAMA therapy in individuals with severe persistent asthma (ie, Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

AHRQ = Agency for Healthcare Research and Quality; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist, NHLBI = National Heart, Lung, and Blood Institute, National Institutes of Health; PRN = as-needed; SABA = short-acting β_2-agonist.

Cloutier MM, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217-1270.

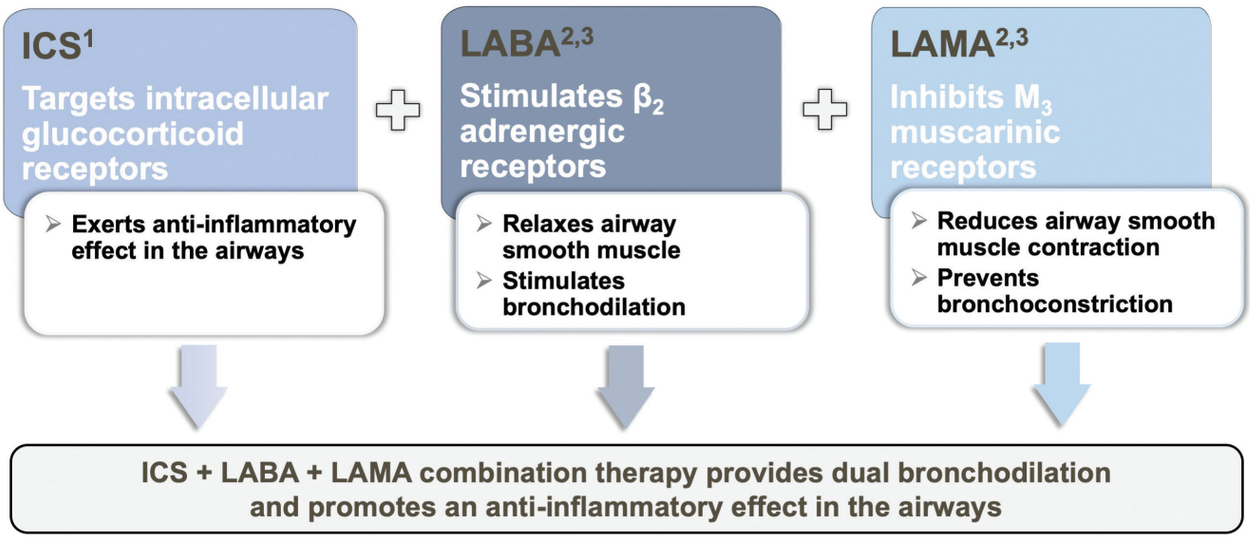
The presence of T2 airway inflammation may necessitate the need for more treatment options in patients with uncontrolled asthma despite high-dose ICS/LABA therapy.[7] T2 airway inflammation is driven by allergic and non-allergic mechanisms through inflammatory cells and cytokines, including interleukin-4 (IL-4), IL-5, and IL-13, and IgE.[16,17,20] These inflammatory cytokines and IgE are currently being targeted by novel therapeutic agents.

Thus far, five monoclonal antibodies have been approved for use by the FDA in patients with severe asthma who continue to have symptoms and exacerbations despite medium- to high-dose ICS/LABA treatment.[21] In addition to reducing the cellular processes of key inflammatory mediators, these biologic therapies have been shown to improve lung function and QoL, reduce exacerbations, and can potentially lead to reductions in ICS and OCS dosing.

Role of LAMA in Asthma Management

Recently, several studies reported the benefit of adding a LAMA to ICS/LABA therapy.[22-26] Together, the three drugs work via different mechanisms of action to reduce airway inflammation and stimulate bronchodilation.[27-29] (Figure 3)

Figure 3: Rationale for Use of ICS/LABA Plus LAMA in Asthma



ICS = inhaled corticosteroid; LABA = long-acting beta^2-agonist; LAMA = long-acting muscarinic antagonist.

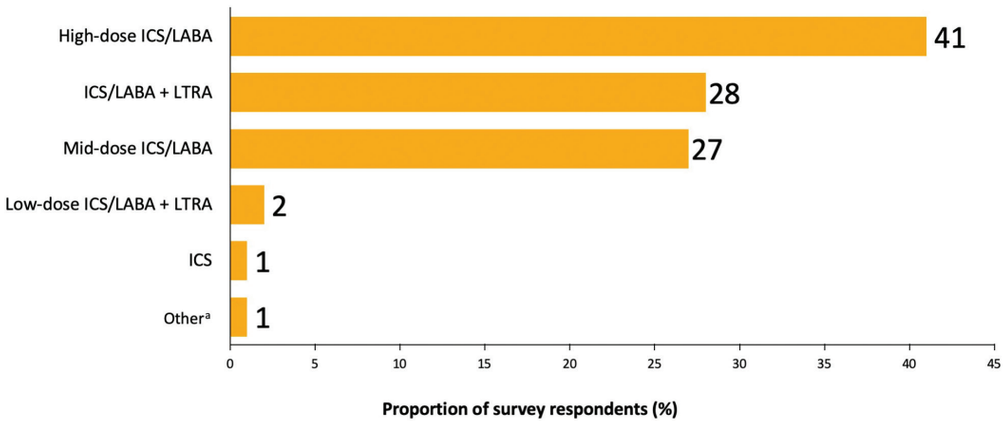
1. Johnson M. *Proc Am Thorac Soc.* 2005;2(4):320-5. 2. Cazzola M, et al. *Pulm Pharmacol Ther.* 2010 August;23(4):257-67. 3. Jones R, et al. *Prim Care Respir J.* 2011 March;20(1):33-45.

The 2021 GINA strategy recommends the addition of LAMA to medium- or high-dose ICS/LABA treatment when asthma is not well-controlled.[7] Similarly, the NAEPPCC recommends adding LAMA (eg, tiotropium) to medium-dose ICS/LABA treatment.[19] The addition of tiotropium to ICS/LABA therapy helps control asthma symptoms and reduces exacerbations requiring the need for oral steroids in individuals with severe asthma.[22] Furthermore, several clinical trials have shown that this benefit is independent of the presence of T2 airway inflammation.[23] New single-inhaler triple therapy options combine an ICS, a LABA, and a LAMA, offering added convenience for treating uncontrolled asthma.[24-26] Twice-daily and once-daily triple therapy options have been shown to improve lung function while reducing moderate to severe exacerbation rates.[24,25]

In a recent study, the combination of ICS/LAMA/LABA demonstrated improvement in lung function over ICS/LABA treatment in patients with uncontrolled asthma.[24] Numerical trends favored of triple therapy for exacerbation reduction, but results were not statistically significant; however, this study was unique in that it also evaluated outcomes (eg, exacerbations) related to T2 inflammatory markers. Specifically, when the ICS dose in either the ICS/LABA or the triple therapy combination was increased, there was a dose-response improvement in FEV_1 and a reduction in exacerbation rates in patients with elevated baseline blood eosinophil and FeNO levels. Importantly, the addition of a LAMA to ICS/LABA showed benefit in FEV_1 irrespective of T2 inflammatory marker levels (ie, T2-low and T2-high).

A recent survey polled 100 US pulmonologists on their perceptions surrounding the utility of LAMA for the treatment of uncontrolled asthma.[30] (Figure 4) Half of the surveyed pulmonologists reported that, in their experience, over 20% of patients taking ICS/LABA had uncontrolled asthma. For symptomatic patients on a medium-dose ICS/LABA regimen, the pulmonologists were more likely to escalate the ICS dose of the current regimen, and approximately 20% reported that they would add an LTRA at this stage, and 17% would add a LAMA.

Figure 4: Survey of US Pulmonologists - Perceptions on Use of LAMA in Uncontrolled Asthma



[a] Patients with air trapping on pulmonary function test.

Figure 4. Treatment characteristics of the most appropriate patient for addition of a LAMA (n=100). 41% of Asthma Pulse Survey respondents considered patients that are symptomatic despite high-dose ICS/LABA as the most appropriate for the addition of a LAMA, with 27% indicating patients who are symptomatic despite mid-dose ICS/LABA, and 28% indicating patients who are symptomatic despite ICS/LABA + LTRA, as the most appropriate for addition of a LAMA, respectively.

Ramesh N, et al. *Chest*. 2020;158(4):A1699-A1700.

Importantly, the largest portion (41%) of surveyed pulmonologists thought LAMA was most appropriate when patients remained symptomatic with high-dose ICS/LABA treatment.[30] The second most frequent add-on for treating patients who were symptomatic with high-dose ICS/LABA treatment was an LTRA. Approximately 31% of the respondents reported that they would add an LTRA at this stage, and only 16% of survey respondents would turn to biologic therapy.

The addition of a LAMA and/or a biologic for uncontrolled asthma in individuals taking high-dose ICS/LABA is in keeping with the current GINA recommendations.[7] However, recent clinical trials have demonstrated that there is an overarching benefit of ICS/LABA/LAMA triple therapy and that the benefit of a LAMA add-on to ICS/LABA therapy is independent of the presence of the T2 airway inflammation phenotype.[23-26] Therefore, earlier LAMA use may be warranted because of its benefits in reducing exacerbations and improving lung function.

Summary

Uncontrolled asthma continues to be a challenge for patients, caregivers, and health care providers.[5-8] Our improved understanding of the heterogeneity of asthma and its clinical presentation has allowed for the introduction of new therapies, such as add-on LAMA or in combination as “triple therapy”, that aim to improve current symptoms and reduce future exacerbations.[7,22-26]

Based on their case histories, Gary and Martha have an option to treating their uncontrolled asthma with existing therapy. Despite their different asthma phenotypes—Gary has T2-high asthma and Martha has T2-low asthma—adding a LAMA in combination with their standard ICS/LABA therapy could improve lung function and reduce exacerbations for both. This change could help improve their QoL. Gary should also be evaluated for add-on biologic therapy based on the presence of T2-high inflammation and his exacerbation history.

The NAEPPCC guidelines recommend adding a LAMA to medium-dose ICS/LABA therapy and GINA recommends a LAMA add-on to medium- or high-dose ICS/LABA treatment when asthma remains uncontrolled.[7,19] Adding a LAMA to an ICS/LABA combination improves lung function and reduces the time to exacerbations that require systemic corticosteroids in patients with uncontrolled asthma—and the benefits are independent of the T2 inflammatory endotypes.[23-26]

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