When single-inhaler triple therapy is a preferred option in asthma management?

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Abstract:
Asthma control is the main goal of management. Unfortunately, most asthma patients with moderate–severe asthma remain uncontrolled despite receiving standard treatment of inhaled corticosteroids (ICS) with long-acting β2 agonists (LABA). The addition of long-acting antimuscarinic agents (LAMA) has been shown to improve different aspects of asthma control, including symptoms, lung functions, and probably exacerbations. Such an option could be considered for low-T2 asthma phenotype. Umeclidinium and glycopyrronium bromide are other LAMA agents that have been recently made available in combination with ICS and LABA in single-inhaler triple therapy (SITT) devices. Here, we discuss the position of SITT as a new novel therapeutic option in asthma management and its clinical benefits, potential cost saving, and improved compliance.

Keywords:
Asthma, asthma control, asthma guidelines

Long-acting muscarinic antagonists (LAMA) are one of the major treatment options for chronic obstructive pulmonary disease (COPD). A decade ago, LAMA was approved for asthma management in the form of tiotropium bromide.[1‑4] As tiotropium was made available in a single inhaler, most asthma management guidelines recommend it as an alternative for long-acting β2 agonists (LABA) when combined with inhaled corticosteroids (ICS) for patients uncontrolled on low–medium-dose ICS. It was also recommended as an “add-on” therapy for patients uncontrolled on medium–high-dose ICS/LABA which was supported by evidence from randomized controlled studies.[5] Bateman et al. showed that tiotropium was more effective than placebo and as effective as LABA in maintaining improved lung function in patients with moderate persistent asthma.[2]
Peters et al. showed that when tiotropium was added to ICS, tiotropium improved symptoms and forced expiratory volume in 1 s (FEV1).[1] Moreover, Kerstjens et al.’s study revealed that tiotropium improved FEV1 in the same category of patients. The addition of tiotropium in this study increased the time to the first severe exacerbation, with an overall reduction of 21% in the risk of a severe exacerbation.[6] Based on that, most asthma guidelines in the past decade have included LAMA as an “add-on” therapy for moderate–severe asthma uncontrolled on moderate–severe-dose ICS/LABA combination.[7,8]

Single-Inhaler Triple Therapy for Asthma Management

Umeclidinium and glycopyrronium bromide are other LAMAs recently approved for asthma management. Like tiotropium bromide, they were initially approved for COPD management. They were made available as single-inhaler triple therapy, providing a convenient option for patients.

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available in fixed-dose combinations (FDCs) with ICS and LABA in single-inhaler triple therapy (SITT) devices.

Umeclidinium (62 μg) was combined with vilanterol (25 μg) and either fluticasone furoate 100 μg or 200 μg in Ellipta® device as SITT. Lee et al. in the CAPTAIN study concluded that in patients with uncontrolled moderate–severe asthma on ICS/LABA, adding umecclidinium improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations. SITT has also led to improvement in symptoms and asthma control in a dose-related manner. For such patients, SITT is an effective treatment option with a favorable risk–benefit profile. This study revealed significant improvement in FEV₁ from baseline for both doses of SITT compared to combination therapy of fluticasone furoate with vilanterol. Higher dose fluticasone furoate primarily reduced the rate of exacerbations, particularly in patients with raised T₃ inflammatory markers. Asthma phenotyping is traditionally practiced before biologics for severe asthma. However, to our knowledge, the CAPTAIN study is the first major study to investigate patients’ segregation based on phenotypes to select the type of inhalers for patients with uncontrolled moderate–severe asthma on medium–high-dose ICS/LABA. Data from this study suggest that patients with high blood eosinophils and/or FeNo will benefit from SITT with a higher dose of fluticasone furoate (200 μg), whereas those who are not will benefit more from SITT with medium-dose fluticasone furoate (100 μg).

Glycopyrronium (150 μg) with indacaterol (150 μg) and either medium-dose (80 μg) or high-dose mometasone (160 μg) were made available together in Breezhaler® device as SITT. Kerstjens et al. in an IRIDIUM study concluded that once-daily SITT with either medium-dose or high-dose mometasone improved lung function versus the combination of mometasone with indacaterol or fluticasone propionate with salmeterol in patients with inadequately controlled asthma. Both doses of SITT showed similarly large improvements in asthma control from baseline, with no significant difference when compared with the combination of ICS/LABA. The annualized rate of exacerbations was numerically lower with SITT versus the ICS/LABA comparators. The safety profile was similar across treatment groups. Therefore, they further concluded that SITT of mometasone with indacaterol and glycopyrronium constitutes a good treatment option in these patients.

Glycopyrronium (100 μg) was also combined as SITT with formoterol fumarate (6 μg) and either medium-dose budesonide (100 μg) or high-dose budesonide (200 μg) in Respimat® devise. In the TRIMARAN and TRIGGER study, Virchow et al. compared this SITT with the combination of formoterol fumarate and budesonide with and without tiotropium bromide in the Respimat® device. They concluded that, in uncontrolled asthma, the addition of a LAMA to ICS and LABA improves lung function and reduces exacerbations and time to the first exacerbation.

A recent meta analysis concluded that “FDCs of ICS/LABA/LAMA are effective and safe in uncontrolled asthma and that the dose of ICS in the combination represents the discriminating factor to treat patients with a history of moderate or severe exacerbation”.

### Compliance and Cost Saving with Single-Inhaler Triple Therapy

Patients receiving multiple inhalers tend to have more errors in their techniques. One study showed that of 208 adult asthma patients with only one inhaler, 71% made no inhalation errors versus 61% of 113 patients with two or more different inhalers. There is an observed low adherence and substantial rates of step down/discontinuation among patients initiating multiple inhalers as one study from Spain showed that only 16% of patients were considered adherent. A meta-analysis of a total of 114 articles revealed that simplifying inhaler regimens by applying the same type of inhaler over time minimizes device misuse and led to improved clinical outcomes and reduced health-care use in patients with asthma or COPD. A randomized, open-label, single-visit, crossover study compared SITT with dual inhaler combinations in asthma patients revealed that patients who used single inhaler had less critical errors compared to dual inhalers. Based on these studies, it is preferable to have asthma inhalers given as a combination of ICS/LABA or SITT of ICS/LABA/LAMA.

Retrospective and prospective studies showed that single-inhaler use was associated with decreased health-care resource utilization and improved cost-effectiveness compared with multiple inhalers. For patients with asthma who require inhaled triple therapy, SITT has cost saving when compared to ICS-LABA plus tiotropium in separate inhalers. Based on the Saudi Food and Drug Authority drug list, the cost of multiple inhalers triple therapy is at least 50% more than SITT.

### Guidelines Recommendation for Use of Single-Inhaler Triple Therapy in Asthma Management

Global Initiative for Asthma (GINA) strategies adopted a five-step model for asthma management. The latest update in 2021 recommends choosing one of two tracks...
for asthma management. In step 4, Track 1 recommends a maintenance and reliever approach (MART) by giving medium-dose ICS and formoterol as maintenance and reliever, a track with the preferred combination reliever. While patients on Track 2 are recommended to have nonformoterol LABA added to medium-dose ICS with a short-acting bronchodilator (SABA) as a reliever. GINA recommends LAMA either as a single inhaler added to ICS/LABA or as part of SITT. If a LAMA in a single-inhaler device is added to a combination of ICS with formoterol, the ICS/formoterol combination could be continued as a maintenance and reliever. However, if a LAMA is combined with ICS and any LABA (including formoterol) in a SITT, GINA recommends SABA as a reliever meaning shifting patient from Track 1 to Track 2. Currently, there is a lack of evidence to support the use of formoterol containing SITT as MART.

The Saudi Initiative for Asthma (SINA) guidelines released its fifth update in January 2021 and adopted a 5-step model for asthma management. It recommends a combination of medium-dose ICS with LABA at step 4 without suggesting any preference. If the patient does not achieve control, based on medication availability at that time, SINA recommends once a day combination of fluticasone furoate (100 μg), umeclidinium (62.5 μg), and vilanterol (25 μg).[9] Stepping up to SITT with a higher dose of fluticasone furoate (200 μg) primarily reduces the rate of exacerbations, particularly in patients with raised T2 inflammatory markers. Adding tiotropium in HandiHaler® device to the combination of medium-dose ICS and LABA is another option that is limited by using multiple inhalers and some extra cost on the patients’ side. Other SITT devices and tiotropium in Respimat® were not available in Saudi Arabia at the time of publishing the guidelines.

Spanish guidelines update was published in 2022 and adopted a six-step model.[22] It positioned LAMA as an add-on therapy for a patient uncontrolled on medium-dose ICS with LABA at step 4. It was also considered as an add-on therapy for step 5. Based on approved LAMAs by the European Medicines Agency, their guidelines have recommended to add either tiotropium in a single device or glycopyrronium in a SITT device. Both Canadian guidelines (2021) and Japanese guidelines (2020) recommend tiotropium as the only LAMA for add-on for patients uncontrolled on medium-dose ICS and LABA.[23,24] Other LAMAs were not included in these guidelines.

### Reliever Therapy for Patients Require Single-Inhaler Triple Therapy

GINA strategies have two tracks stratified based on the choice of the inhaler. Track 1 recommends low-dose ICS formoterol as the option with a preferred reliever. For patients uncontrolled on low-dose ICS or low-dose ICS with LABA, GINA recommends ICS with formoterol as MART. At Track 2, SABA is the alternative reliever for patients at steps 2–5 for patients who cannot follow Track 1, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy. For patients uncontrolled on medium-dose ICS and any LABA, SITT is one of the recommended options for a step up. For this category of patients, the use of ICS with formoterol as MART is not supported by any currently available evidence. Hence, they must be shifted to Track 2 and use SABA as a reliever.

The argument behind the preference of Track 1 is related to the use of ICS with formoterol as MART which reduces the risk of severe exacerbations compared to using as-needed SABA with similar symptom control. However, a recent study showed that severe asthma exacerbation was significantly lower by 26% for patients on as-needed FDC of SABA with ICS compared to as-needed SABA alone for patients with uncontrolled moderate–severe asthma who were receiving a wide range of ICSs maintenance therapies.[23] Another study showed that reliever-triggered ICS among adults with moderate-to-severe asthma led to a lower rate of severe asthma exacerbations when compared to as-needed SABA.[23] The recommendation of as-needed SABA with ICS as FDC or separately is not yet reflected in guidelines recommendation for the management of moderate–severe asthma. This approach has also cost-saving benefits.

### Conclusion

LAMA use as an add-on to medium-dose ICS/LABA is a common practice and approved by most asthma guidelines for the past decade. Tiotropium is the first LAMA introduced for asthma management that significantly improved lung function in uncontrolled cases and modestly reduced asthma attacks. However, LAMA adoption in practice is hindered due to a lower rate of adherence related to using multiple inhalers each with a different technique, unavailability of Respimat® devices in some countries, and extra cost on the patients’ side. With the availability of evidence related to SITT, it is expected to have its position in the management of uncontrolled asthma on moderate–high-dose ICS with LABA. SITT with medium-dose ICS could be recommended for patients with low-T2 inflammatory markers and no prior exacerbations as it will allow them some improvement in FEV1, and symptoms. The SITT with high-dose ICS could be recommended for patients with high-T2 inflammatory markers with prior exacerbations. Therefore, SITT is expected to have its position in the management of uncontrolled asthma on
moderate-dose ICS with LABA. Patients prescribed SITT would be placed on GINA Track 2 regardless of their prior track with SABA as their reliever inhaler. Patients on Track 2 may be denied the benefits of as-needed ICS with formoterol. However, recent evidence suggests that this benefit could be extended by prescribing as-needed SABA with ICS as FDC or separately, a recommendation that is not yet reflected in asthma guidelines recommendation for patient’s moderate–severe asthma.

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Conflicts of interest
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