



Dilemma of Asthma Treatment in Mild Patients

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Inhaled corticosteroids (ICSs) have been widely used as a key medication for asthma control. However, ICSs have been known to cause respiratory infections, such as pneumonia and pulmonary tuberculosis. Consequently, a dilemma exists regarding recommendation of persistent lifetime use of ICSs to mild asthma patients. Short-acting β -agonists (SABAs) have also been widely used for symptom relief. However, SABAs have been reported to increase the risk of asthma-related death, though incidences have been very rare. Consequently, a dilemma exists regarding recommendation of a SABA alone without an ICS or a controller to asthma patients even with very mild disease. In the real world, asthma patients tend to intermittently use ICS and more likely to be dependent on SABA since many patients want immediate relief of their symptoms. Consequently, a dilemma exists regarding the underuse of ICSs but the overuse of SABAs. One strategy for solving the presented dilemma would be identification of patients with asthma who require persistent use of asthma controllers. Such patients, who may be referred to as “persistent controller users,” should continuously receive ICSs, even under controlled states of asthma. Another strategy would be a patient-adjusted, symptom-driven, intermittent-to-regular treatment combining low-dose ICS/rapid-onset long-acting β -agonists instead of using a SABA alone or with low-dose ICS for the asthma patients with mild disease. Both of these two strategies could avoid the risky treatment of a SABA alone without an ICS and could reduce the dose of ICS with the maintenance of asthma control.

Keywords: Asthma; Therapeutics

Introduction

Asthma is a major disease with a high prevalence rate for all ages and a high mortality rate for the elderly^{1,2}. Fortunately, the asthma medications have been developed over the last few

decades and have imposed dramatic success on the history of modern medicines³.

Inhaled corticosteroids (ICSs), as an asthma controller, and short-acting β -agonists (SABAs), as a symptom reliever, are widely used for asthma management. However, these two inhaler medications have adverse effects which we should pay attention to.

In the real world, asthma patients tend to intermittently use ICS and more likely to be dependent on SABA since many patients want to immediate relief of their symptoms. Consequently, a dilemma exists regarding the underuse of ICSs but the overuse of SABAs has been observed.

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Success and Dilemma of ICSs

1. Effect of ICSs on reduction of asthma exacerbation

The development of asthma controller medications (e.g., ICSs) is one of the most successful stories in modern medicine. Modern medicine has contributed widely in the man-

agement of asthma, one of the leading respiratory diseases. Even in the early 1990s, patients with asthma exacerbations were more frequent in the emergency room. Some of them had to undergo airway intubation and mechanical ventilation. However, as the use of asthma controller medications in the early 2000s began to increase, the number of asthmatic patients who visited the emergency room decreased sharply, and the number of hospitalized asthmatic patients decreased even more, making it difficult to see asthmatic patients in the hospital wards.

2. Efficacy of ICSs and recommendations by the guidelines for asthma management

Asthma controller medications have proven to be efficacious in many aspects through large-scale observational studies and randomized clinical trials. ICSs, for example, have been shown to reduce asthma mortality, reduce asthma exacerbations, and improve asthma symptoms and lung function⁴.

Due to the proven strong efficacy, ICSs are recommended as the most important asthma controller medications in both international and domestic asthma guidelines^{5,6}.

3. Adverse effects of ICSs

ICSs have been reported to have few adverse effects, unlike oral or injectable corticosteroids, but to increase the risk of adverse effects when used in high doses. For example, the risk for respiratory tract infections such as pneumonia, pulmonary tuberculosis, and non-tuberculous mycobacterial infections has been reported to increase⁷⁻⁹. It has also been reported that the risk of cataract increases and bone density slightly decreases¹⁰⁻¹².

4. ICSs dilemma at the step 1 of mild asthma management

Because the ICSs have adverse effects, it is recommended in the guidelines that if asthma is controlled, the treatment level should be lowered to reduce the dose of ICSs and to use the minimum maintenance dose. Furthermore, the guidelines state that asthma controller medications may not be used for the patient at the step 1 of mild asthma management. This strategy is advantageous in reducing the adverse effects of ICSs, but it also has the disadvantage in that the deterioration of asthma may not be prevented.

In particular, given the insufficient use of asthma controller medications, which is true in current practices, the recommendation of only SABAs without ICSs may not be appropriate.

Success and Dilemma of SABAs

1. Rapid symptom improvement by SABAs

SABAs (e.g., salbutamol in metered dose inhaler [MDI]) are not asthma controllers, but they have a rapid symptom-relieving effect and so have widely been used by asthma patients. For example, the salbutamol MDI, which is widely used in Korea, starts the action of bronchodilator is about 4 minutes, and reaches the peak at about 80 minutes¹³.

Due to the rapid action of SABAs, it is advisable to use them when needed.

However, because SABAs do not have any anti-inflammatory effect but only have bronchodilation, they cannot prevent the asthma worsening and should be used as a temporary symptom reliever. Therefore, the asthma guidelines recommend that SABAs be used temporarily only when the asthma symptoms are worse⁵.

Although a SABA has the effect of promptly improving symptoms, it might cause asthma death, a rare but serious adverse effect. The adverse effect of asthma death problems was raised from the 1980s when the use of SABAs increased, and it has been repeatedly observed through large-scale observational studies^{14,15}.

2. Dilemma of SABAs at the step 1 of the asthma management guidelines

At the step 1 of the asthma management guidelines, asthma patients with intermittent symptom may be treated only with a SABA⁵. However, the SABAs should not be encouraged to use only because the SABAs have no anti-inflammatory effect but have a rare but cardiac death¹⁶. Moreover, even mild asthma may change to moderate or severe during the disease course. Asthma is well known to be characterized by the variation of symptoms and also disease course. So the dilemma of SABAs at the step 1 of the asthma management should be solved.

Strategies of Solutions for Asthma Treatment Dilemmas

1. Strategy of solution for the ICSs dilemma

A solution strategy for the ICSs dilemma may be suggested with defining asthma patients who need a controller persistently. ICSs are a mainstay medication for asthma control but have some adverse effects as mentioned in this article. Considering the balance between the necessity and adverse effects of ICSs, persistent use of low dose ICS should be suggested the asthma patients who need a controller persistently. We may name the patient, a 'persistent controller user'. For the

persistent controller user, a controller(s) should be used for a lifetime, because the necessity of controller (e.g., ICS) outweighs the adverse effects

Then, who are the persistent controller users? They may be the two groups of asthma patients (Table 1 and strategy 1 of Table 2). One is the group of patients at risk for exacerbation

Table 1. Suggested definition of persistent controller users

Asthma patients requiring a controller medication(s) persistently even under controlled
Asthma patients with a high risk of exacerbation even under controlled
Low FEV ₁ , especially if < 60% predicted
Allergen exposure if sensitized; confirmed food allergy
Sputum or blood eosinophilia; elevated FeNO in adults with allergic asthma
Uncontrolled comorbidities like obesity or rhinosinusitis
Pregnancy
Ever intubated or in intensive care unit for asthma
≥1 severe exacerbation in last 12 months
Asthma patients who have failed the trial of a controller discontinuation

Adopted and modified from the GINA documents 2017, with permission from the GINA Committee⁹.

FEV₁: forced expiratory volume in 1 second.

and the other is the group of patients who have failed the trial of a controller discontinuation.

Conversely, if an asthma patient is not the “persistent controller user,” he or she will be able to try to discontinue the asthma controller. Even when discontinued, the asthma controller (e.g., a ICS) should be restarted whenever the asthma state is uncontrolled.

2. Strategy of solution for the SABAs dilemma

The SABAs dilemma may be solved by using a combined inhalation of ICS and rapid onset long acting β-agonist (LABA) (strategy 2 of Table 2). Asthma is a disease with its variation of course, good and bad, so it sometimes is necessary to use bronchodilator immediately when symptoms develop. However, as described above, the single use of β agonist cannot be expected to have an anti-inflammatory effect, so there is a risk of asthma exacerbation and rarely asthma death. Therefore, O’Byrne et al.¹⁷ recently proposed to use a combined inhalation of ICS and rapid onset LABA (e.g., formoterol) at the earlier steps of asthma treatment. Formoterol is an example of the rapid onset LABA, which is known to start its effect at 5 minutes and peak at about 2 hours due to its short onset time¹³.

The main advantage of the combined ICS and rapid onset LABA together is that it can prevent the risk of asthma death albeit rare. In addition, we can use the combination of ICS and rapid onset LABA in a single device with convenience compared to using the two inhalers separately. So from the step 1

Table 2. Step-wise asthma treatment comparing a current guideline to strategies for solutions of asthma treatment dilemma

Step	Current guideline*		Strategy 1		Strategy 2	
	Preferred controller	Reliever	Preferred controller	Reliever	Preferred controller	Reliever
Step 1	None	SABA as needed	Low-dose ICS [†]	SABA as needed	Patient-adjusted, symptom-driven, intermittent-to-regular treatment with low-dose ICSs/rapid-onset LABAs [‡]	
Step 2	Low-dose ICSs					
Step 3	Low-dose ICSs/LABAs					
Step 4	Medium/high ICS/LABA	SABA as needed or low-dose ICSs/rapid-onset LABAs [§]		Same as the current guideline (see the column of Current guideline)		
Step 5	Refer to add-on treatment					

*Adopted and modified from the Korean Asthma Guideline 2014, according to the Creative Commons license Korean Academy of Tuberculosis and Respiratory Diseases⁶. [†]For persistent controller users. [‡]The strategy might be applied from the step 1 to some cases of the step 2 in the Asthma Guideline. [§]Formoterol is an example.

ICS: inhaled corticosteroids; SABA: short-acting β2 agonist; LABA: long acting β2 agonist.

to some cases of the step 2, patients may by themselves adjust the use of low dose ICS/rapid onset LABA from intermittent to regular. This patient-adjusted symptom-driven intermittent to regular treatment with low dose ICS/rapid onset LABA would be one strategy of solution to solve the dilemma¹⁸.

Conclusion

ICSs and SABAs, which are key medications for asthma treatment, are widely used as an asthma controller and a symptom reliever, respectively. Because of adverse effects, there is a dilemma that is difficult to recommend for a persistent lifetime use of ICS for mild asthma patients. In this article, we suggested that the ICSs dilemma should be solved by defining a 'persistent controller user' who should use the ICS persistently and that the SABAs dilemma might be solved by using patient-adjusted symptom-driven intermittent to regular treatment with low dose ICS/rapid onset LABA to mild asthma patients at the step 1 and some patients of the step 2.

Both of these two strategies could avoid the risky treatment of a SABA alone without an ICS and could reduce the dose of ICS with the maintenance of asthma control.

Authors' Contributions

Conceptualization: Cho YS, Oh YM. Article searching and curation: Oh YM. Review of the articles: Cho YS, Oh YM. Writing - original draft preparation: Oh YM. Writing - review and editing: Cho YS, Oh YM. Approval of final manuscript: Cho YS, Oh YM.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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