

The Ideal Strategy of Asthma Treatment

¹Department of Allergy and Clinical Immunology, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Republic of Korea, ²Asthma and COPD center,
Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

You Sook Cho^{1,2}

Asthma is a heterogeneous disease characterized by chronic airway inflammation. Global Initiative for Asthma (GINA) and national guidelines recommend asthma management to achieve two ultimate goals as follows: 1) good control of symptoms; 2) minimizing future risk of exacerbations.¹ Asthma acute exacerbations are common events and it is believed that they are closely associated with poor asthma control. Indeed, asthma acute exacerbations is considered a serious medical condition with significant morbidity, risk of death and high treatment cost. Furthermore, recurrent asthma exacerbations lead to progressive airway remodeling and greater asthma severity.^{2,3} Therefore, it is critical to establish an appropriate asthma treatment strategy to achieve these pivotal goals in asthma management.

According to the global guidelines, treatment of asthma based on disease severity or level of control, typically initiates using inhaled corticosteroid (ICS).^{4,5} ICS have been the basis of asthma treatment for many years, with their effectiveness confirmed by large databases.⁶ Currently, ICS/long-acting β_2 -agonist (LABA) combination is maintenance therapy for patients with uncontrolled asthma on ICS alone.⁷ Recent study demonstrated that low dose ICS reduced the risk of severe asthma exacerbations, prevented decline in lung function, and improved day-to-day symptom control for the patients with mild, recently diagnosed asthma.⁸ In addition, it has been reported that ICS use can substantially reduce asthma exacerbations.^{9,10} Therefore, clinicians are advised not to completely withdraw ICS.¹ These results clearly show the importance of ICS in treatment of asthma.

In addition to these pharmacologic aspects, there are other issues to be considered in the management of asthma such as inhaler technique and adherence to achieve asthma treatment goals. One of the key components is a good collaboration between physicians and patients. Asthma medications are various, and moreover, these are being used in a variety of devices. Thus, it is pivotal to educate patients how to properly use these asthma medications. However, it appears that not all physicians are fully aware of the

importance of education. Some studies show that 32% of patients had never learned inhaler technique from their physicians.¹¹ As a result, more patients are considered uncontrolled asthmatics than they actually are, which lead to usage of high dose medications. Patient education should be done about proper device usage, appropriate dosing frequency, and self-management of exacerbation situations. Recently, international guidelines describe that when patients use ICS/LABA containing a quick onset LABA, the maintenance inhaler could also be used for occasional quick relief purposes. This strategy can be convenient and can reduce asthma exacerbations when compared with the use of ICS alone or low dose of ICS/LABA.¹²⁻¹⁵ However, some studies reported that this strategy produces poor day-to-day control of symptoms and increasing inflammation,¹² which could be results from lack of proper education by physicians and patients' misunderstanding about the strategy. In another study, initiating treatment with a once-daily combination provides better asthma control in real world practice.¹⁶

It is well known that asthma is a clinical syndrome that can't be explained by single disease mechanism and phenotype. Asthma is composed of various subtypes and each subgroup has different clinical manifestations and variety of pathophysiological mechanisms.¹⁷ This variety is affected by age, sex, race, and environmental factors, and each subtype has a different disease severity and prognosis.^{18,19} Thus, in order to achieve best management of asthma, it is undoubtedly important to define various subtypes of asthma and figure out predictable factors that influence the disease severity and treatment responses. Currently, direction of treatment is changing to the 'precision medicine' concept, and a variety of medications are developing. 'Precision medicine' is mainly targeting the endotype of each individual patient.²⁰ These days, about 10 years after the introduction of the first biologics, that is Omalizumab targeting for 'IgE mediated atopic' severe asthma, new biologics such as Mepolizumab and Reslizumab have been approved for 'eosinophilic' severe asthma in particular. We are also waiting for the other drugs (Benralizumab, Dupilumab, Tezepelumab) to be approved soon. We expect that better medications for each subtype of asthmatics can be available and achievement of ultimate goals in asthma management will be realized in the near future.

In conclusion, appropriate therapeutic strategies are definitely needed for proper management of asthma, because asthma is a complex and diverse disease syndrome. It is important to identify subtypes of the disease, and choose the right medications for each asthma patient. To achieve ideal therapeutic strategy for asthma, we should consider not only each medication's pharmacologic excellence but also non-pharmacologic aspects such as the best ways to improve patients' adherence to medications and understanding about the disease by continuous communication between patients and clinicians.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention: Global Initiative for

- Asthma; 2018 Available from: <http://www.ginasthma.org/>.
2. Jackson DJ, Bacharier LB, Mauger DT, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. *N Engl J Med.* 2018;378:891-901.
 3. Custovic A, Johnston SL, Pavord I, et al. EAACI position statement on asthma exacerbations and severe asthma. *Allergy.* 2013;68:1520-1531.
 4. Schmidt O, Petro W, Hoheisel G, Kannies F, Oepen P, Langer-Brauburger B. Real-life effectiveness of asthma treatment with a fixed-dose fluticasone/formoterol pressurised metered-dose inhaler - Results from a non-interventional study. *Respir Med.* 2017;131:166-174.
 5. James DR, Lyttle MD. British guideline on the management of asthma: SIGN Clinical Guideline 141, 2014. *Arch Dis Child Educ Pract Ed.* 2016;101:319-322.
 6. Adams N, Bestall J, Jones PW. Budesonide for chronic asthma in children and adults. *Cochrane Database Syst Rev.* 2001:Cd003274.
 7. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev.* 2010:Cd005533.
 8. Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *The Lancet.* 2017;389:157-166.
 9. Cho YS. Effective Strategies for Managing Asthma Exacerbations for Precision Medicine. *Allergy Asthma Immunol Res.* 2017;9:463-465.
 10. Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *Jama.* 2004;292:367-376.
 11. Chapman KR, Boulet LP, Rea RM, Franssen E. Suboptimal asthma control: prevalence, detection and consequences in general practice. *Eur Respir J.* 2008;31:320-325.
 12. Czarnecka K, Chapman KR. The clinical impact of single inhaler therapy in asthma. *Clin Exp Allergy.* 2012;42:1006-1013.
 13. Pilcher J, Patel M, Reddel HK, et al. Effect of smoking status on the efficacy of the SMART regimen in high risk asthma. *Respirology.* 2016;21:858-866.
 14. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin.* 2004;20:1403-1418.
 15. Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest.* 2006;129:246-256.
 16. Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. *The Lancet.* 2017;390:2247-2255.
 17. Kupczyk M, Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *J Intern Med.* 2012;272:121-132.
 18. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181:315-323.
 19. Dunn RM, Lehman E, Chinchilli VM, et al. Impact of Age and Sex on Response to Asthma Therapy. *Am J Respir Crit Care Med.* 2015;192:551-558.
 20. Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol.* 2011;127:355-360.