

# Single Inhaler as Maintenance and Reliever Therapy (SMART) in Childhood Asthma in 2021: The Paradigm Shift in the Inhaled Corticosteroids Reliever Therapy Era



Youn Ho Shin, MD, PhD<sup>a</sup>, Seung Won Lee, MD, PhD<sup>b</sup>, and Dong Keon Yon, MD<sup>c</sup> Seoul, Republic of Korea

Asthma is the most common noncommunicable and chronic respiratory disease in children and adolescents, affecting over 339 million people worldwide.<sup>1,2</sup> Since the introduction of inhaled corticosteroid (ICS) treatment for asthma in the 1970s, ICS treatment has provided an effective option for maintenance therapy in asthma.<sup>3</sup> However, in the past several years, we observed one of the greatest paradigm shifts, in which ICS was used not only for maintenance but also for symptom relief in the management of asthma among adults and adolescents. This paradigm shift in the treatment for adults and adolescents with asthma is changing from a fixed combination of ICS/formoterol (a long-acting  $\beta_2$ -agonists [LABA] with rapid onset action) as a daily controller with as-needed short-acting  $\beta_2$ -agonists (SABA) for symptom relief to the combination of ICS/formoterol as single inhaler maintenance and reliever therapy (SMART).<sup>3</sup> Yet, uncertainties regarding the management of children with asthma still remain.

The concept of the SMART regimen was first proposed at the International Pediatrics Respiratory and Allergy Congress in 2001 in an attempt to address the concern that previous studies in pediatric populations found no benefits from a fixed-ICS/LABA combination regimen with regard to asthma exacerbations.<sup>4</sup> In an effort to provide alternative treatment options for subjects with asthma, O'Byrne et al<sup>5</sup> reported novel results for both the children and adult protocols in a 1-year double-blind, randomized, parallel-group study in 2760 patients aged 4 to 80 years with asthma uncontrolled on ICS, stating that the SMART regimen yielded favorable outcomes when compared with other fixed regimens. After this study, Bisgaard et al<sup>6</sup> investigated a separate pediatric protocol within the main study<sup>5</sup> and determined the clinical

effectiveness of budesonide/formoterol as the SMART regimen in 388 children with asthma uncontrolled on ICS (age range, 4-11 years). The SMART regimen significantly (1) prolonged the time to first exacerbation compared with both fixed-dose regimens; (2) decreased the risk of exacerbations requiring medical intervention when compared with both fixed-dose regimens; (3) significantly reduced the rate of exacerbations requiring medical intervention by 70% to 79% compared with both fixed-dose regimens; (4) reduced the risk of having a mild exacerbation compared with both fixed-dose regimens; (5) improved morning and evening peak flow measurements compared with fixed-dose budesonide; (6) reduced nighttime awakenings compared with both fixed-dose regimens; (7) was associated with an increased annual growth rate compared with fixed budesonide; and (8) decreased the mean number of as-needed inhalations in children compared with both fixed-dose regimens. All of these findings also inferred that the SMART regimen may be cost-effective.

Nonetheless, no studies in the literature have determined whether the SMART regimen is the preferred treatment option with regard to both effectiveness and cost. This matter is particularly of importance in low- and middle-income countries, in that asthma places a substantial economic strain on health systems across the globe.<sup>7</sup> Addressing this question, Rodríguez-Martínez et al<sup>8</sup> in this issue of the *Journal of Allergy and Clinical Immunology: In Practice* reported the cost-effectiveness of budesonide/formoterol for SMART compared with fixed-budesonide/formoterol plus as-needed albuterol reliever for pediatric asthma in the previous randomized control trial.<sup>6</sup> The authors used a Markov simulation model with a cycle length of 1 week, a time horizon of 12 months, and 3 labeled states (no symptom, sub-optimal control but no exacerbation, and asthma exacerbation) assumed by the Colombia Healthcare System. The base-case incremental cost-utility analysis showed that, compared with the fixed-dose combination therapy, budesonide/formoterol as the SMART regimen reduced the total medication costs (US\$1826.6 [SMART] vs US\$3523.2 [fixed-dose combination] average cost per patient), increased the number of quality-adjusted life-years (QALYs) (0.8537 [SMART] vs 0.8391 [fixed-dose combination] QALYs on average per patient), and increased economic benefit in terms of cost/effectiveness (2139.6 [SMART] vs 4198.6 [fixed-dose combination] on average per patient). This study shows that the SMART regimen is more cost-effective than fixed-dose combination therapy in Colombia, which is a middle-income country.

Clinical guidelines regarding asthma management are in place, including the Global Initiative for Asthma (GINA) Guidelines and the National Asthma Education and Prevention Program

<sup>a</sup>Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea

<sup>b</sup>Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea

<sup>c</sup>Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF2019R1G1A109977913).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 6, 2021; accepted for publication July 8, 2021.

Corresponding author: Dong Keon Yon, MD, Department of Pediatrics, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: [yonkkang@gmail.com](mailto:yonkkang@gmail.com).

J Allergy Clin Immunol Pract 2021;9:3819-20.

2213-2198

© 2021 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2021.07.009>

(NAEPP) Guidelines.<sup>9</sup> Although the 2 guidelines are comparable for most issues, the approach for administering the ICS/LABA combination for children aged 4 to 11 years with asthma uncontrolled on ICS varies such that the GINA guideline recommends 3 preferred treatment options (low-dose ICS/LABA, medium-dose ICS as a daily controller with as-needed SABA for symptom relief, or the SMART regimen) and the NAEPP guideline suggests the combination of ICS/formoterol for SMART as the preferred treatment option.<sup>9</sup> This difference may be ascribed to the disparate guideline designs (ie, GINA is designed to improve asthma awareness and NAEPP is based on a systematic review of previous studies, which evaluated the evidence), differences in risk/benefit assessment in asthma management, and lack of high-quality studies unlike the evidence in adults and adolescents.<sup>3</sup>

Despite these discrepancies, it is worth considering unifying the approach between the GINA and NAEPP guidelines and international integrative management for pediatric asthma. To achieve tailored asthma management in children, we need more sophisticated trials using ICS-SABA and several ICS-LABA devices; more data regarding the pharmacokinetics, pharmacodynamics, and adverse effects of LABA; and approval for the intermittent use of ICS/formoterol treatment by the US Food and Drug Administration.<sup>10</sup>

As we enter the ICS (anti-inflammatory) reliever therapy era, the SMART regimen should be used for the consistent management of asthma across all age groups, including children, which may lead to an improvement in medication adherence and tailored management for asthma. Despite the fact that pediatric asthma is underdiagnosed and undertreated due to uncertainties in management, the SMART regimen will contribute to

internationally consistent benefits regarding the care and outcomes of children with asthma.

## REFERENCES

1. Wright RJ. Influences of climate change on childhood asthma and allergy risk. *Lancet Child Adolesc Health* 2020;4:859-60.
2. Ha J, Lee SW, Yon DK. Ten-year trends and prevalence of asthma, allergic rhinitis, and atopic dermatitis among the Korean population, 2008-2017. *Clin Exp Pediatr* 2020;63:278-83.
3. Abrams EM, Shaker M, Greenhawt M, Fernandes RM, Sinha I. Treatment of mild-to-moderate asthma in childhood and adolescence in 2021. *Lancet Respir Med* 2021;9:443-5.
4. Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003;124:70-4.
5. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
6. Bisgaard H, Le Roux P, Bj  rmer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
7. Mathioudakis AG, Custovic A, Deschildre A, Ducharme FM, Kalayci O, Murray C, et al. Research priorities in pediatric asthma: results of a global survey of multiple stakeholder groups by the Pediatric Asthma in Real Life (PeARL) think tank. *J Allergy Clin Immunol Pract* 2020;8:1953-1960.e9.
8. Rodr  guez-Mart  nez CE, Sossa-Brice  o MP, Nino G. Budesonide/formoterol as maintenance and reliever therapy compared to fixed-budesonide/formoterol plus albuterol reliever for pediatric asthma: a cost-utility analysis in Colombia. *J Allergy Clin Immunol Pract* 2021;9:3816-8.
9. Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, 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;146:1217-70.
10. Abrams EM, Becker AB, Szeffler SJ. Paradigm shift in asthma therapy for adolescents: should it apply to younger children as well? *JAMA Pediatr* 2020; 174:227-8.