

What Is SMART for Some May Not Be Right for All



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Like most problems during adolescence, the treatment of chronic medical issues during this age is a challenging task. Despite the fact that adolescence is a time when individuals are learning to take responsibility for their own health as they forge into independence, it is well-documented that compliance with daily asthma maintenance medications drops significantly during adolescence for a number of reasons.¹ Concern about side effects, stigmatization among peers, decreased parental supervision, and increased risk-taking behaviors are a few reasons why adolescents may be less compliant with daily asthma medications. As such, there is a need to explore alternative options to maintain asthma control and prevent exacerbations among this group of patients more prone to noncompliance with daily medications.

The Symbicort Given as-needed in Mild Asthma (SYGMA 1 and SYGMA 2) trials,^{2,3} explore an attractive alternative treatment strategy for mild disease, which is gaining significant momentum in the asthma space. The use of a combination inhaled corticosteroid (ICS) and long-acting β -agonist as needed for mild asthma has been evaluated in several studies. SYGMA 1 demonstrated that among patients with mild asthma, the use of budesonide–formoterol as needed was equally effective as daily budesonide maintenance in preventing moderate to severe exacerbations with one-fifth the dose of inhaled corticosteroids, but this strategy was inferior to budesonide maintenance in meeting the primary end point of mean percent weeks of well-controlled asthma.² Similarly, SYGMA 2 demonstrated that in patients with mild asthma, the use of budesonide–formoterol as needed was noninferior to budesonide maintenance with respect to the rate of severe exacerbations but was inferior with respect to the control of asthma symptoms.³

The study by Reddel et al⁴ published in this month's issue of *JACI: IP* focuses on the specific subgroup of adolescents with mild asthma in these two trials. It provides a *post hoc* analysis of SYGMA 1 and SYGMA 2 trial data in the adolescent subgroup

aged 12 through 17 years. The effects of 3 treatment arms (placebo maintenance plus budesonide–formoterol rescue; budesonide maintenance plus terbutaline rescue; and placebo maintenance plus terbutaline rescue) on the annual severe exacerbation rate, time to first severe exacerbation, forced expiratory volume in 1 second (FEV₁) percent predicted, Asthma Control Questionnaire scores, adherence, daily ICS dose, and mean change in height from baseline were analyzed.

The findings of this *post hoc* analysis are largely consistent with those of the parent trials. Rates of severe exacerbation were similar between patients receiving placebo plus budesonide–formoterol rescue and budesonide maintenance plus terbutaline rescue. In addition, asthma control, as measured by Asthma Control Questionnaire, was improved from baseline in the 3 groups, but either the improvement was not significantly different between groups or the difference was not clinically important. There was a significantly different improvement in FEV₁ in favor of budesonide maintenance plus terbutaline rescue compared with placebo plus budesonide–formoterol rescue. In both studies, there was a significant difference in the daily dose of ICS in budesonide maintenance plus terbutaline rescue versus placebo maintenance plus budesonide–formoterol rescue. With respect to adverse effects, there was a significant difference in change of height between placebo maintenance plus budesonide–formoterol rescue and budesonide maintenance plus terbutaline rescue only among the younger subset (age ≥ 12 to < 14 years) in the pooled data for SYGMA 2, but not SYGMA 1.

This *post hoc* analysis shines a spotlight on a new treatment strategy that is now the preferred treatment for mild asthma according to Global Initiative for Asthma⁵ but has not been addressed by the 2020 Update to Asthma Management Guidelines by the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Group.⁶ Furthermore, a growing body of literature supports the use of Single Maintenance And Reliever Therapy (SMART) with budesonide–formoterol among asthmatic patients in need of daily therapy.⁷ Extending this strategy to mild asthmatics, the use of a combination ICS–long-acting β_2 -agonist (LABA) as needed in the treatment of mild asthma is truly an attractive option for those patients who are resistant to using a daily medication. The rate of exacerbation is similar to that achieved with daily ICS maintenance without the burden of daily medication and daily exposure to ICS. Pooled studies analyzed by Reddel et al⁴ provide data on a large number of subjects; the authors focus on an often unrecognized subgroup that deserves much more attention. If this strategy is adapted and incorporated into the way clinicians prescribe, it will contribute to a significant decrease in medication costs for the individual, because the use of daily ICS will be eliminated for a large number of asthmatic patients.⁸

The authors also report that the significant change in height between budesonide maintenance plus short-acting β_2 -agonist

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reliever versus placebo maintenance plus ICS-LABA reliever in the younger age group may warrant a shift in the treatment of mild asthma. However, this suggestion must be evaluated in the context of our knowledge regarding changes in growth velocity and attainment of adult height. The Childhood Asthma Management Program study⁹ is the largest and longest study that examined the use of ICS in children. It concluded that although the height deficit observed at 1 to 2 years after treatment initiation in children age 5 to 13 years persisted into adulthood, the adult height deficit was greater for participants who were younger at trial entry. This was due to findings that the deficit in growth velocity for the budesonide group (vs placebo) in the first 2 years of treatment was primarily in prepubertal children.¹⁰ Although the study by Reddel et al⁴ emphasizes height differences between budesonide maintenance and budesonide-formoterol as needed as the driving force to find alternatives to daily ICS use, the benefit was observed only in those age 12 or greater to less than age 14 years, and not older adolescents. The study does not follow these children to the point of their reaching adult height, so we do not know whether the height deficit persists. In addition, the pubertal status of those in the study is not determined, and this may be a more accurate way of determining whether the risks of daily use are outweighed by the benefit.

Because the results of Reddel et al⁴ do not demonstrate superiority of as-needed ICS-LABA compared with ICS maintenance therapy for patients with mild asthmatics in terms of FEV₁, exacerbation rates, and symptom control, we must be careful in globally abandoning daily ICS therapy for these adolescents. The most practical benefit of daily ICS use, which is more apparent in the parent trials, is the higher rate of symptom control. In the study by Reddel et al, this may be reflected by the significantly greater improvement in FEV₁. Adolescents, especially those with asthma, must remain physically active for a multitude of reasons. If poor asthma control prevents them from doing so, this can lead to weight gain, which in turn will contribute to even poorer asthma control.¹¹ The 1-year follow-up of this study does not provide an adequate scope for understanding the long-term growth consequences or exacerbations and asthma control. Furthermore, asthma is a heterogeneous disease, and as allergists we are in tune with the significant role of atopy in modifying asthma phenotypes. All adolescent patients with mild asthma should not be treated homogeneously with this approach; a more multifaceted approach to management is

required. Analyzing the data with respect to atopic status may uncover differences in outcomes.

The privilege of being a clinician is that we provide patients with a personalized approach to managing asthma. Our goal of optimizing asthma control, and minimizing their risk for exacerbations and any side effects, requires the use of our clinical skills and also the art of medicine. Optimization requires a nuanced and personalized approach to each patient, and even more so for adolescents. Further studies that promote a change in standard asthma management should address the heterogeneity of asthma and consider compliance, pubertal status, atopy, and asthma control, among other factors. By considering the lack of uniformity, especially in adolescent asthmatic patients, we can optimize control of their asthma.

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