

VIEWPOINT

Paradigm Shift in Asthma Therapy for Adolescents Should It Apply to Younger Children as Well?

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Asthma is one of the most common chronic conditions of childhood and is associated with significant effect on quality of life. An ongoing controversy remains how to best treat asthma in children and adolescents. A provocative evolution in this controversy is the publication of new recommendations by the Global Initiative for Asthma (GINA), which present a significant change in asthma therapy.¹ Step 1 recommendations for mild asthma in adolescents 12 years and older and adults changed from as-needed short-acting β -agonist (SABA) to as-needed low-dose inhaled corticosteroid (ICS) formoterol (a long-acting β -agonist [LABA]). In children aged 6 to 11 years, GINA recommends that ICS therapy be used with SABA as needed or regular ICS with as-needed SABA as an alternative approach.

The GINA recommendations are based on increasing understanding that while overuse of SABA-only therapy is associated with risk of severe asthma exacerbations and death,² regular ICS use prevents exacerbations, reduces symptoms, and improves lung function in children.^{3,4} Moreover, there is evidence in adolescents that as-needed ICS-formoterol therapy has equivalent or superior outcomes to daily ICS therapy, as highlighted by 2 randomized clinical trials, the Symbicort Given as Needed in Mild Asthma (SYGMA1) and Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) studies.

The SYGMA1 trial randomized 3849 adolescents (12.5%) and adults to 1 of 3 treatment options over 52 weeks: twice-daily placebo and terbutaline as needed (terbutaline group), twice-daily placebo and budesonide-formoterol as needed (budesonide-formoterol group), or twice-daily inhaled budesonide and terbutaline as needed (budesonide maintenance group).⁵ Adherence was approximately 80% in each group. There was no difference between budesonide-formoterol and the budesonide maintenance group in annualized exacerbation rate, although the rate was low in both groups (annualized exacerbation rate 0.07 vs 0.20; rate ratio, 0.83; 95% CI, 0.59-1.16), and budesonide-formoterol was superior to terbutaline for asthma control (odds ratio, 1.14; 95% CI, 1.00-1.30). The median metered daily dose of ICS in the budesonide-formoterol group was 17% of that in the budesonide maintenance group.

Novel START, published after release of the GINA recommendations, randomized 668 adults with mild asthma to albuterol as needed (albuterol group), fixed-dose budesonide twice daily plus as-needed albuterol (budesonide maintenance), and budesonide-formoterol as needed (budesonide-formoterol group).⁶ The annualized rate of exacerbations was lowest in the as-needed budesonide-formoterol group (absolute rate, 0.175), did not differ significantly from the budesonide maintenance

group ($P = .65$), and was lower than the albuterol group ($P < .001$). The number of severe exacerbations was lowest in the as-needed budesonide-formoterol group, with a cumulative ICS dose that was 50% lower in the budesonide-formoterol group than the budesonide group. A limitation of this study was its enrollment of only adults, low frequency of exacerbations, and low mean adherence (56%).

It remains unknown whether combination therapy should be considered in children younger than 12 years. Thus far, the use of combination ICS plus LABA or ICS plus SABA as maintenance and reliever therapy has been evaluated in 2 randomized clinical pediatric trials.

The first was a post hoc evaluation⁷ of 341 children aged 4 to 11 years from a large clinical trial in which those with asthma uncontrolled receiving ICS therapy were randomized to budesonide-formoterol daily as maintenance and reliever therapy (ICS/formoterol single inhaler), budesonide daily as maintenance with terbutaline as needed (fixed-dose combination plus SABA), or a 4-fold dose of budesonide and terbutaline as needed (fixed-dose ICS plus SABA). There was increased time to exacerbation with the single inhaler ICS/LABA therapy compared with fixed-dose ICS plus SABA ($P = .02$) and fixed ICS/LABA combination plus SABA ($P < .001$). Exacerbations were significantly reduced in the single-inhaler group ($P < .001$), with approximately one-half dose extra per day of combined budesonide-formoterol, with no effect on linear growth.

In the Treating Children to Prevent Exacerbations of Asthma (TREXA) study, children aged 5 to 18 years with mild persistent asthma controlled receiving low-dose ICS were randomized to 1 of 4 treatment groups: twice-daily beclomethasone with beclomethasone/albuterol (SABA) as reliever (combined group), twice-daily beclomethasone with placebo/albuterol as reliever (daily beclomethasone group), twice-daily placebo with beclomethasone/albuterol as reliever (rescue beclomethasone group), or twice-daily placebo with placebo/albuterol as rescue (placebo group).⁸ Frequency of exacerbations was higher in the placebo group (23%) compared with the combined (5.6%), daily (2.8%), and rescue (8.5%) groups, in keeping with ICS/SABA being more effective as stepdown therapy than as-needed SABA alone. However, prebronchodilator percentage predicted FEV1 decreased in all treatment groups during the trial but was only significant in the placebo and rescue beclomethasone groups ($P = .001$ and $P = .02$, respectively). There were increases in fractional exhaled nitric oxide in the rescue beclomethasone and placebo groups compared with the combined and daily beclomethasone groups ($P < .001$).

There are no relevant studies in preschool children, an area where research is needed because airway remodeling begins in early childhood. When looking at predictors of response to ICS therapy in young children, the Individualized Therapy for Asthma in Toddlers (INFANT) trial randomized 300 children aged 12 to 59 months requiring daily asthma controller therapy to daily ICS, daily leukotriene receptor antagonist, or as-needed ICS with albuterol.⁹ The group that did best with daily ICS therapy had increased eosinophils and/or allergic sensitization. A small proportion of children did respond well to as-needed ICS/albuterol compared with daily ICS or daily leukotriene receptor antagonist. Moving forward, a better understanding of endotypic variation in asthma and response to various medications will be required.

The updated GINA recommendations represent a shift in management that is an exciting change to the asthma paradigm. It is a shift away from SABA use as needed and also a shift toward ICS/LABA or ICS/SABA use. However, questions remain. The GINA recommendations only apply thus far to ICS-formoterol and studies on other ICS/LABA or ICS/SABA combination inhalers are required. Cohesion in approach between international guidelines, such as the Expert Panel 3 guideline, is required. Finally, currently the use of ICS-formoterol is not approved for intermittent therapy by the US Food and Drug Administration.

Further research will be required to determine how these shifts will affect younger children, in whom a lack of trials to support any firm recommendations exists. Pediatric-focused research is critical if we are to offer patients the most effective approach to managing their asthma. The intermittent approach is particularly appealing for preschool children, where asthma worsenings are primarily driven by respiratory infections. In point of fact, given compliance data, many families already appear to have adopted this approach. For now, a substitute approach for as-needed ICS/LABA might be to use an ICS each time a SABA is administered for symptoms (off label), as demonstrated in the TREXA study, until a combination ICS/SABA product is available or perhaps as-needed ICS/LABA is approved in this age group.

There is a concerning potential that must be addressed that certain patients may be poor perceivers of a deterioration in lung function and thus might not react with appropriate therapy when required.¹⁰ The clinician must remember that frequent use of either SABA alone, as-needed ICS/SABA or ICS/LABA, or increased asthma exacerbations should prompt a step up in therapy to at least daily ICS therapy. Close monitoring of all patients with asthma, including clinical evaluation and pulmonary function testing, where possible, is required. Finally, prescribers should check both compliance and the coverage for their patients because this may vary in cost as well as coverage among various health care clinicians and across countries.

ARTICLE INFORMATION

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