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As Needed Use of Inhaled Corticosteroids for Management of Mild Persistent Asthma in Children

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The National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3), *Guidelines for the Diagnosis and Management of Asthma*, provides recommendations for initial assessment of asthma severity based on both impairment and risk domains. Subsequently, the follow-up visits are designed to assess asthma control and to adjust the therapy to the lowest effective dose of inhaled corticosteroids (ICSs) or various combinations for optimal control. EPR3 recommends considering step down in therapy if patient is well controlled for 3 consecutive months, which may lead to discontinuation of daily medications for patients receiving low dose ICSs or other controller monotherapy. In addition, patients and parents have a tendency to stop the daily medications after having a period of controlled asthma. In these situations, the challenge is to find the best way to discontinue daily medications in patients with mild or intermittent asthma whose daily or weekly impairment is under good control but may still be at risk for asthma exacerbations. The question is, "May another regimen other than daily use of ICSs be used in these patients who become asymptomatic with appropriate treatment to decrease the risk of asthma exacerbation?"

In a recent publication, Martinez and colleagues reported a randomized, double-blind, placebo-controlled trial to assess effectiveness of ICSs when used as needed along with the patients' regular short-acting $\beta_2$agonists in children with well-controlled mild persistent asthma.[1] Children 6–18 years old with controlled asthma on low-dose ICSs were enrolled. Patients were excluded if they were admitted to the hospital for asthma exacerbation in the previous year, had an asthma exacerbation in the last 3 months or >2 in the previous year, had a baseline forced expiratory volume in 1 second of <60% predicted at the screening visit, or had a history of life-threatening asthma. Patients were enrolled in a 4-week run-in period, and those whose asthma remained controlled were randomly assigned to one of the 4 arms: beclomethasone (40 mcg/puff, one puff twice daily) with beclomethasone plus albuterol as rescue (combined group), beclomethasone twice daily with placebo plus albuterol as rescue (daily group), placebo twice daily with beclomethasone plus albuterol as rescue (rescue group), and placebo twice daily plus placebo and albuterol as rescue (placebo group). Two puffs from each rescue inhaler were used in an as-needed basis for relief of symptoms. Two hundred eighty-eight patients were randomized to one of the 4 treatment arms and followed for 44 weeks. The primary outcome was the time to first exacerbation defined as the requirement for oral prednisone, and the effect of each treatment group was compared to placebo. The result showed that the hazard ratio for asthma exacerbations was significantly lower only in the daily and combined group compared with placebo. About 50% of the patients in placebo group had asthma exacerbations, and the frequency of asthma exacerbation was lower in the daily group (28%, $P=0.03$), combined group (31%, $P=0.07$), and rescue group (35%, $P=0.07$) compared with the placebo group. In addition, 23% of the patients in the placebo group also experienced treatment failure, which was defined as use of a second burst of prednisone within any 6-month period. Frequency of treatment failure was significantly lower in all groups compared with placebo but not different from each other. From a practical point of view, patients in the placebo group represent those children with well-controlled mild asthma who discontinue their daily ICS on their own or per recommendation of a healthcare provider. Although this study was not powered to detect the differences between the treatment groups, the frequency of asthma exacerbation in the treatment groups was the same as has been reported for those on daily ICSs.[2,3] The authors concluded that use of rescue ICSs with albuterol may be considered in patients with well-controlled mild asthma as a step down when continuous ICSs are discontinued. Although the results suggested a decreased risk for a first exacerbation by more than a third when beclomethasone and albuterol were used as rescue medications, the effect was not significant compared with only albuterol as rescue medication. What is confirmed, once again, is that daily beclomethasone significantly reduced the risk for a first asthma exacerbation by half.

Previously, Volovitz and colleagues evaluated a different approach to manage asthma exacerbation in their practice.[4] They reported their outcomes after implementing a new protocol for control of asthma exacerbation in a real-life setting of their outpatient pediatric asthma clinic. Children on ICSs for at least 1 year were included in the program and were instructed to start the rescue protocol with inhaled budesonide at the first sign of an asthma exacerbation starting with 200–400 mcg budesonide 4 times daily in combination with albuterol and decreasing the dose in 4–8 days regardless of their daily asthma medication. Children were advised to stop their daily budesonide and follow only

the rescue protocol on an as-needed basis if they became symptom free for 6–8 weeks and remained asymptomatic for an additional 3 weeks off their daily medication. Patients were followed every 2 to 3 months as they were enrolled in the program for assessment of their asthma control. The median follow-up time was 1 year (range 3 months to 5 years). Data analysis included 150 children who were followed regularly and were compliant with the program. At the beginning of the program, the median age of the children was 6 years (range 1–16 years). Three treatment groups were identified at the end of follow-up: management of exacerbations per rescue protocol as needed, daily use of budesonide and then only management of exacerbations per rescue protocol as needed, and continuous daily use of budesonide. The outcomes were compared with asthma status of all the patients in the 3 months preceding enrollment. During the entire follow-up, 7% of children used oral corticosteroids and none were hospitalized compared with 67% and 33% of the patients, respectively, in the 3-month period before enrollment. Although the rate of exacerbation included all 3 treatment groups in the clinic and it cannot be applied to only those with well-controlled asthma, 75% of the cohort were only on an as-needed rescue protocol at the time of the analysis. The authors concluded that managing asthma exacerbations with a high dose of budesonide followed by a rapid reduction over 4–8 days results in a decreased rate of hospitalization and oral corticosteroid use. Further, they reported that the rate of asthma exacerbations was significantly lower (3.8 versus 5.5 per year) when daily budesonide group was compared with treatment only during exacerbations. Needless to say, this publication was not a controlled trial but just a report of outcomes after implementing an as-needed rescue protocol for management of asthma exacerbations. This report has many limitations, but it is one of the only reports in a cohort of pediatric population of whom 75% had controlled asthma and exacerbations were managed on an as-needed basis with ICSs.

Many studies have investigated the use of ICSs for management of asthma exacerbations while patients are still on daily medications. These studies have been inconclusive as they have been small trials and different doses, duration of regimen, and route of administration have been used. Although some of these trials have reported a decrease in the severity of exacerbations, they have not been able to show any change in the use of oral corticosteroids or hospitalizations.[5–11] The focus of this review is mainly a step-down approach when patients with mild asthma have been well controlled.

In a similar study in adults, patients with well-controlled mild persistent asthma were randomly assigned to one of the 4 arms: placebo twice daily with beclomethasone 250 mcg/puff and albuterol 100 mcg/puff in a single inhaler as rescue (rescue group), placebo twice daily with albuterol as rescue (placebo group), beclomethasone 250 mcg/puff and albuterol 100 mcg/puff in a single inhaler twice daily with albuterol as rescue (combination daily group), and beclomethasone 250 mcg/puff twice daily plus albuterol as rescue (daily group).[12] At the end of the 6-month trial, about 20% of the patients on albuterol and placebo group had at least one exacerbation. The percentage of patients with at least one asthma exacerbation was significantly lower in the daily group and daily combination group compared with the placebo group. In addition, the morning peak expiratory flow was also significantly higher in the daily group and rescue group compared with the placebo group.

Use of the combination of ICSs and albuterol as needed seems attractive, as it may address 2 issues in pediatric patients with mild asthma: improving compliance and decreasing side effects with lower doses of ICS. Education remains as important to manage daily asthma and asthma exacerbation episodes regardless of alternative approaches. Martinez and colleagues reported that children in the combination or daily medication groups grew significantly less than the placebo group by 1.1 cm, whereas the patients in the rescue group grew only a nonsignificant 0.3 cm less than the placebo group. The decrease would be expected with the dose of beclomethasone used in the study. It is important that the safety result of this and other trials should be reviewed cautiously with special attention to the ICS dose and delivery systems used as other low-dose ICSs have not shown a significant growth effect in children.[13] Long-term follow-up trials of 100 mcg/day fluticasone dry powder inhaler (DPI) and mometasone DPI in prepubertal children did not show any significant reduction in growth compared with placebo.[14–16]

In conclusion, the evidence clearly supports that the ICSs are the preferred long-term controller medications for all levels of persistent asthma due to their consistent efficacy.[17] As emerging evidence for the rescue approach in patients who are well controlled is compelling, current data provide the opportunity for future trials to investigate better step-down strategies with different ICSs and delivery devices for the management of asthma. These current data cannot be extrapolated to management of mild persistent asthma in those who have not used daily ICSs previously.

Disclosure Statement

No conflicting financial interests exist.

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