Is "Yellow Zone" Management Effective in Reducing Asthma Flares in Children?

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. N Engl J Med 2018;378:891-901.

BACKGROUND

Asthma flares are a common and potentially life-threatening complication of asthma. Current guidelines include the option (Class B evidence) of "yellow zone" management to increase the dose of inhaled corticosteroids (ICSs).[1,2] This was developed from early observational studies indicating that this may reduce the risk of flares.[3-5] However, randomized controlled trials and a systematic review found that this strategy was not effective.[6-8] The reviewed study aimed to evaluate the efficacy and safety of increasing the ICS dose as a "yellow zone" management strategy in children.

METHODS

This was a randomized, double-blind parallel group trial conducted in the United States. Five- to 11-year-old children with physician-diagnosed mild-to-moderate asthma and at least 1 asthma exacerbation in the last year were enrolled between July 2014 and March 2016.

Per protocol, while in the "green zone" (well-controlled asthma), all 254 patients used low-dose fluticasone. This inhaler was stopped during any "yellow zone" blinded treatment, and during this period subjects were randomly assigned to either low-dose (44 μg per inhalation) or high-dose (220 μg per inhalation) fluticasone at 2 inhalations twice daily for 7 days. Any of the following qualified as a "yellow zone" episode: 2 doses of albuterol in 6 hours, 3 doses of albuterol in 24 hours, or nighttime symptoms treated with albuterol. The 52-week trial included a 4-week run-in period to establish at least 75% compliance with "green zone" therapy and a 48-week period where patients would use "yellow zone" plan as needed.

RESULTS

The study enrolled 444 children in total. One hundred ninety were excluded during the run-in period (43% because of nonadherence; for other exclusion reasons, please see full article). This resulted in randomization of 254 children. Of the 127 in the low-dose group, 98 completed the study and of the 127 in the high-dose group, 94 completed the study; reasons for noncompletion of the study were mostly treatment failure, lost to follow-up, or no longer participating. Both groups had a comparable rate of "yellow zone" episodes, with 2.01 episodes per year in the high-dose group and 1.96 episodes per year in the low-dose group ($P = .90$).

Primary outcome

The primary outcome measure was the rate of severe asthma exacerbations treated with systemic glucocorticoids during the treatment phase. The low-dose group had 0.37 asthma exacerbations per year (95% CI, 0.25-0.55), and the high-dose group had 0.48 per year (95% CI, 0.33-0.70). This is a relative risk (RR) of 1.3 (95% CI, 0.8-2.1; $P = .30$), indicating no statistically significant difference between the 2 groups.

Secondary outcomes

Secondary outcome measures were the time to first asthma exacerbation, treatment failure (for definition, please see full article), area under the curve for symptom scores and albuterol use, emergency department (ED) or urgent care visits for asthma, total steroid exposure, and linear growth. The number of ED or urgent care visits did not differ between the 2 groups (RR, 1.3; 95% CI, 0.8-2.4; $P = .30$). There was also no difference in total steroid exposure, as the relative difference between the 2 groups was 1.16 g (95% CI, 1.10-1.22) per year of equivalent hydrocortisone exposure. During "yellow zone" episodes, there was no difference in symptom scores ($P = .30$) or albuterol inhaler use ($P = .30$).

Adverse effects

The growth rate among the high-dose group (5.43 cm/y) was 0.23 cm/y less than the growth rate among the low-dose group (5.65 cm/y; 95% CI, −0.47 to 0.01; $P = .06$). When stratifying growth rate by age group, there was a statistically significant

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difference in the 5- to 7-year-old subgroup (difference of −0.12; 95% CI, −0.22 to −0.02; $P = .02$).

CRITICAL APPRAISAL

By adding to a previous body of literature,[6-8] this article may increase confidence against the approach of increasing the dose of ICS for the treatment of a pending asthma flare. Indeed, this strategy did not decrease the number of exacerbations per year, number of ED or urgent care visits, time to first exacerbation, rate of treatment failure, symptom scores, or albuterol use. These outcomes were appropriate for evaluation because they are clinically relevant and contribute to the cost and complications associated with asthma exacerbations. It is unclear why the authors used quintupling of ICS dose as opposed to the more common practice of quadrupling. However, this nuance is irrelevant because even the higher dose increase did not show efficacy.

The observation of decreased growth rate was statistically significant only within the subgroup of 5- to 7-year-old children. This overall difference of 0.23 cm/y may seem minimal, but these children also had, on average, 2 "yellow zone" episodes per year. The authors raise a valid concern that if glucocorticoids were the cause, then more frequent use of this strategy could lead to a greater difference.

Notably, the conclusions of this study may not be applicable beyond the sample population of 5- to 11-year-old children with only mild-to-moderate asthma. There may also be selection and attrition bias. This study had a higher than expected dropout rate (25%, compared with the anticipated 15%). Although an intention-to-treat analysis was done, one should be aware that this study may have selected for more adherent patients, especially given the 4-week run-in period. Also, subjects were seen for 8 visits over 52 weeks, which is more frequent than clinically relevant, and also likely contributed to adherence. This high adherence rate is evidenced by the asthma exacerbation rates being lower than the anticipated 0.9 events per year.

This discrepancy between observational studies supporting "yellow zone" management and subsequent randomized trials may be because previous studies lacked control groups. Because not all "yellow zone" episodes progress to severe exacerbations, there may be a risk of bias in interpreting the results. Indeed, in this study, 81% did not progress to requiring systemic steroids; this is significantly higher than a previous study whose rate was 30%.[9]

RECOMMENDATION

For children aged 5 to 11 years with mild-moderate asthma, this study suggests that increasing the ICS dose is not an effective strategy to decrease asthma exacerbations, systemic glucocorticoids, use of albuterol inhaler, or asthma symptoms. In addition, there was a trend toward decreased growth rates in patients who quintupled glucocorticoids for "yellow zone" treatment compared with those who maintained a stable ICS dose.

REFERENCES

1. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma summary report 2007. J Allergy Clin Immunol 2007;120:S94eS138 (Ia).
2. Dinakar C, Oppenheimer J, Portnoy J, Bacharier LB, Li J, Kercsmar CM, et al. Management of acute loss of asthma control in the yellow zone: a practice parameter. Ann Allergy Asthma Immunol 2014;113:143-59.
3. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Arch Dis Child 1990;65:407-10.
4. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. Arch Dis Child 1993;68:85-7.
5. Volovitz B, Nussinovitch M, Finkelstein Y, Harel L, Varsano I. Effectiveness of inhaled corticosteroids in controlling acute asthma exacerbations in children at home. Clin Pediatr (Phila) 2001;40:79-86.
6. Kew KM, Quinn M, Quon BS, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database Syst Rev 2016;6:CD007524.
7. Oborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med 2009;180:598-602.
8. Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet 2004;363:271-5.
9. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011;365:1990-2001.