

Temporary Increased Dose of Inhaled Corticosteroids in Yellow Zone, Does It Work?

Hengameh Raissy, PharmD¹ and Kathryn Blake, PharmD²

There are limited data as how to manage the “yellow zone” in children with asthma. Although increasing the dose of inhaled corticosteroids (ICSs) has been practiced by some providers, the efficacy and safety of this strategy remain unclear. This review presents the existing data for use of adjustable dose of ICSs for prevention of asthma exacerbation in children in yellow zone. The current evidence does not support increasing the dose at early signs of loss of asthma control to prevent asthma exacerbation in children. Well-designed clinical trials are needed to identify potential benefits of this strategy.

Keywords: pediatric asthma, yellow zone, inhaled corticosteroid

IT IS WELL UNDERSTOOD that asthma self-management education is a necessary component to manage asthma symptoms and potentially prevent exacerbations.¹ A written asthma action plan has been recommended by the National Asthma Education and Prevention Program’s Expert Panel Report 3 (EPR3), Guidelines for the Diagnosis and Management of Asthma to instruct the patient on how to recognize the asthma worsening symptoms, and what actions to be taken in a stepwise approach.¹ As the EPR3 recommends to increase the use and frequency of short-acting β_2 agonists (SABAs) as specified in the action plan, the Global Initiative for Asthma guideline recommends to at least doubling the dose of inhaled corticosteroids (ICSs) being used as a controlled medication² in addition to use of an SABA. Whether temporarily temporally increasing the dose of ICSs during the yellow-zone episode would decrease the risk of an exacerbation remains a controversial topic.

Randomized clinical trials do not support doubling the dose of ICSs to prevent severe asthma exacerbations (exacerbations requiring systemic corticosteroids).^{1,3,4} Interpretation of clinical trials when higher doses of ICSs were administered during yellow-zone episodes reports conflicting results, and most of them lack safety reports of the proposed strategies.^{1,5}

A Cochrane review in 2016 compared clinical effectiveness and safety of increased versus stable doses of ICSs as part of a patient-initiated action plan for home management of exacerbations in children and adults with persistent asthma.⁶ The review included 3 pediatric^{7–9} and 5 adult

trials^{3,4,10–12}; increasing the dose of ICSs to manage asthma exacerbations was not associated with a significant reduction in the odds of requiring oral corticosteroids in all participants [odds ratio (OR) 0.89; 95% confidence interval (CI) 0.68–1.18; participants=1527] or those who followed the action plan during exacerbations (OR 0.84, 95% CI 0.54–1.30; participants=766). In addition, there was no significant difference in the asthma exacerbation rate between the subgroups based on age (children versus adults), time elapsing before treatment initiation (<48 h versus $\geq$ 48 h), baseline ICS dose, and doubling versus quadrupling ICS dose. Although the report concluded that current evidence does not support increasing the dose of ICSs to manage asthma exacerbations, the wide CIs suggest that potential benefit cannot be completely disregarded. Two recent publications again addressed the issue^{13,14}

The first study evaluated quadrupling the dose of ICSs at the time of asthma deterioration in a pragmatic, unblinded, randomized trial in adolescents and adults with asthma.¹³ Participants had to have at least 1 exacerbation in the previous year and were on ICSs with or without add-on therapy. Participants were randomly assigned to the quadrupling or nonquadrupling groups at the time of asthma deterioration. In the quadrupling group, participants were instructed to quadruple dose of their ICSs when their asthma had deteriorated until symptoms or peak flows were back to normal or up to 14 days. In the nonquadrupling group, participants were instructed to use only their reliever inhalers. The primary outcome was the time to a first severe asthma exacerbation

¹Department of Pediatrics, University of New Mexico, School of Medicine, Albuquerque, New Mexico.

²Biomedical Research Department, Nemours Children’s Clinic, Jacksonville, Florida.

defined as use of oral corticosteroids or an unscheduled healthcare visit for asthma. The trial had 90% power to detect a between-group difference of 30% and the authors considered this degree of reduction as “worthwhile treatment effect.” A total of 1922 participants were randomized of whom 70% were on ICSs and long-acting β_2 -agonist combination inhalers. Forty-five percent of the participants in the quadrupling group had a severe asthma exacerbation compared with 52% of the participants in the non-quadrupling group; the adjusted hazard ratio for the time to a first severe exacerbation was 0.81 (95% CI 0.71–0.92; $P=0.002$). Authors concluded that a temporary quadrupling dose of ICSs at the time of worsening of asthma control resulted in 19% reduction in rate of severe asthma exacerbation compared with using only the reliever inhaler. The pragmatic design of this trial offers a broad inclusion criteria, but it also introduces a few concerns: biased primary outcome because of open-label treatment, different severity of asthma leading to different doses or combination of asthma medications, unconfirmed asthma exacerbation, and undefined duration of temporary increase of ICSs. Interestingly, investigators had considered a 30% reduction in the rate of asthma exacerbation as “worthwhile” or clinically significant; however, the trial only showed 19% reduction.

The second publication, a randomized, double-blinded, parallel group trial in children (Step Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations or STICS trial), was designed to assess the efficacy and safety of increasing the dose of the ICS by 5 times for 7 days during periods of short-term loss of asthma control in children 5–11 years old with mild-to-moderate asthma.¹⁴ All the participants had at least 1 asthma exacerbation in the previous year, and their asthma was controlled on a low dose of ICS. A 4-week run-in period confirmed asthma control as defined by children-asthma control test score of >19 as well as adherence to daily ICS, fluticasone propionate (Flovent, GlaxoSmithKline) at a dose of 44 μg per inhalation, 2 inhalations twice daily, and completion of an electronic diary. As participants continued use of their open-label fluticasone propionate daily, they were instructed to use the blinded inhaler (fluticasone propionate 220 μg per inhalation, 2 inhalations twice daily) for 7 days at the first sign of loss of asthma control. Participants were randomly assigned to the blinded treatment, either low-dose fluticasone propionate (the same as daily dose; fluticasone propionate 44 μg per inhalation, 2 inhalations twice daily) or the high dose for the 7 days. A written asthma action plan was provided, and loss of asthma control—yellow zone—was defined as 1 night awakening due to asthma and use of albuterol, or use of 4 inhalations of albuterol for 6 h, or 6 inhalations in 24 h. Participants were followed for 52 weeks after randomization; the primary outcome was the rate of severe asthma exacerbation treated with oral corticosteroids. Systemic corticosteroids were started after consultation with a trial clinician. Treatment failure was defined as 2 severe asthma exacerbations in 6 months, 3 severe asthma exacerbations in 12 months, or 6 treated yellow-zone episodes. Of the 254 randomized participants, 192 completed the trial, 18 were withdrawn due to treatment failure. A total of 395 yellow-zone episodes were treated: there was no difference in the number of episodes in each treatment arm. The rate of severe asthma exacerbations did not differ between the high-dose (0.48 exacerbations/year, 95% CI 0.33–0.70) and the

low-dose groups (0.37/year exacerbations, 95% CI 0.25–0.55) with relative rate of 1.3 (95% CI 0.8–2.1; $P=0.30$). There was no difference between the groups with regard to the time to the first severe asthma exacerbation, rate of emergency department or urgent care visits for asthma, the rate of treatment failure, and the total symptom burden during yellow-zone episodes. With regard to safety outcomes, the growth rate was 0.23 cm/year less in the high-dose than in low-dose ICS groups (5.43 cm versus 5.65 cm per year accordingly, $P=0.06$). Interestingly, a dose-response relationship in the high-dose group (0.12 cm per year lower growth per yellow-zone episode, $P=0.02$ for the comparison with the low-dose group) was only seen in children younger than 8 years of age; furthermore, this finding was noted in children who had >2 treated yellow zones. Comparing the treated yellow zones, 32% in the high-dose and 19% in the low-dose-treated groups resulted in severe asthma exacerbation. The authors concluded that increasing the low dose of ICS by a factor of 5 for 7 days for yellow-zone episodes did not reduce the rate of severe asthma exacerbations, leading to treatment with systemic glucocorticoids. This strategy resulted in a greater total exposure to corticosteroids, leading to a slightly lower linear growth rate.

This trial is a reminder of importance of placebo controlled and randomized clinical trials; as it was pointed out by the authors, 80% of the yellow zones in the low-dose ICS group did not result in severe asthma exacerbation. This low rate of exacerbation may have contributed to the perception of positive result of escalating doses of ICSs in practice. It is also important to point out that the conclusion of this trial is only applicable to school children with mild-to-moderate asthma on low dose of ICS and the result cannot be extrapolated to other age groups or different severities of asthma.

One consideration for conflicting results and lack of support to increase dose of ICS during yellow-zone episodes may be the efficacy of daily ICSs; ICSs remain the cornerstone of asthma management and they may just be the most effective treatment in preventing asthma exacerbations.¹ That being said, clinicians agree and recognize that taking action at early signs of loss of asthma control is the best potential strategy to manage asthma exacerbations; a written asthma action plan with instruction to increase use of rescue medication is supported by current evidence.^{1,2,5} Future well-designed studies are needed to determine whether an increase in dose of ICSs or any other add-on asthma therapy may be beneficial to prevent severe asthma exacerbations. These trials should precisely define patient population, severity of asthma, intervention, yellow zone/asthma exacerbation, the timing to start the intervention, adherence, and duration of intervention; the outcomes should consider both efficacy and safety of the intervention such as use of systemic corticosteroids, duration and severity of exacerbations, cumulative dose of ICS, and last but not least safety reports. In addition, it is important to investigate and identify the phenotypes of asthma exacerbation that may respond to the proposed intervention. Evidence-based best practice is evolving, and for now, the current well-designed trials do not support temporarily increasing the dose of ICSs during yellow-zone episodes to prevent asthma exacerbation.

Author Disclosure Statement

Dr. Raissy is the Principal Investigator for AsthmaNet at the University of New Mexico.

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Address correspondence to:
 Hengameh Raissy, PharmD
 Department of Pediatrics
 University of New Mexico, School of Medicine
 MSC10 5590
 1 University of New Mexico
 Albuquerque, NM 87131-0001

E-mail: hraissy@salud.unm.edu

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