Personalized Medicine in Preschool Children with Asthma

Hengameh Raissy, PharmD,¹ and Kathryn Blake, PharmD, BCPS, FCCP²

A growing body of literature has investigated optimizing asthma management by identifying phenotypes and biomarkers to guide the treatment. In particular, management of asthma in preschool children remains challenging due to different phenotype presentation in early life. The focus of this review is to summarize the recent data on personalized medicine in management of preschool children with wheezing.

Keywords: asthma, preschool children, personalized medicine

PRESCHOOL CHILDREN HAVE their own age criteria for severity and management of asthma in The National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3), Guidelines for the Diagnosis and Management of Asthma¹; long-term controller medication is recommended at step 2 with low-dose inhaled corticosteroids (ICSs) as the preferred choice and cromolyn or montelukast as alternative options. In addition to the EPR3 recommendation, as-needed therapy with ICSs has also been studied in this age group for patients with intermittent wheezing.^{2–4} Asthma, especially in young children has different phenotypic presentations,^{5,6} which may explain a difference in response to controller medications.

A recent publication by Fitzpatrick et al.⁷ (INFANT), investigated the differential responses to asthma medications in young children using clinical biomarkers as predicting tools; the Individualized Therapy for Asthma in Toddlers (INFANT) trial was a multisite, double blind, double-dummy, randomized, crossover trial in children 12–59 months of age. A screening period of 2–8 weeks confirmed guideline-based criteria for step 2 treatment. Qualified children were randomized to a crossover sequence of three 16-week treatment periods with daily ICS (fluticasone propionate 44 µg/puff, 2 puffs twice daily), montelukast (4 mg at bed time) or as-needed ICS (fluticasone propionate 44 µg/puff, 2 puffs twice daily) to be administered with open-label short-acting bronchodilator (albuterol sulfate, 90 µg/puff, 2 inhalations) as needed for symptom release. The primary outcome was the differential response to 3 treatments, including both domains of asthma management (risk and impairment); children were considered as differential responders of 1 treatment than another if the time to an asthma exacerbation was at least 4 weeks longer or if the

number of annualized asthma control days (ACDs) was at least 31 days more. An asthma exacerbation was defined as use of systemic corticosteroids and ACD was defined as full calendar days without use of rescue medications, symptoms, or unscheduled healthcare visits. Nondifferential responders were defined as those children who did not meet any of the 2 criteria. A treatment failure was defined as 2 asthma exacerbations in 1 treatment period; in that case, children proceeded with the next treatment period. A study failure was defined as advancing to 2 treatment periods 2 times during the study, 4 courses of prednisone after randomization or hospitalization for an acute asthma for greater than 24 h. The following biomarkers were measured at the time of randomization: peripheral blood eosinophil count, eosinophil cationic protein (ECP), total serum IgE, specific IgE concentration, specific IgE measurement (ImmunoCAP) for a nationally representative panel of inhalant aeroallergens, and urinary leukotriene E₄ (LTE₄) concentration. Four hundred forty-three patients were enrolled and 300 were randomized; 230 patients completed at least 2 treatment periods and were qualified for assessment of a differential response. Of these, 74% of the patients (170 out of 230 children) had a differential response to the 3 treatments with highest probability of the best response for daily ICS; Aeroallergen sensitization was associated with a differential response in favor of daily ICS. Sex and previous exacerbation were not predictors of differential response to daily ICS. Higher probability to respond to daily ICS was also associated with blood eosinophil counts ≥300/µL, serum ECP levels of ≥10/µL, and dog and/or cat sensitization; the predictive ability was enhanced by both increased eosinophil counts and aeroallergen sensitization. However, the modified Asthma Predictive Index⁸ status, serum IgE levels,

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

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

and urine LTE₄ concentration did not predict a differential response. Daily ICS was associated with more ACDs and fewer exacerbations and use of rescue medications. Interestingly, 26% of the children (60 out of 230) did not have a differential response to any of the treatments; these children had more ACD and lower exacerbation probability compared with the responders. Adherence to medication was self-reported and it was $\geq 96\%$. There was no significant difference in adverse events between treatments with a nonsignificant trend toward decreased linear growth velocity in daily ICS treatment period. Authors concluded that 74% of the children demonstrated a clinically relevant improvement in response to 1 of the 3 treatments with the greatest probability to respond to daily ICS; in addition, clinically accessible biomarkers—aeroallergen sensitization and increased blood eosinophil counts—might be used to predict the best response for children whom ICS offered the most protection for asthma exacerbations and symptoms. It is important to note that considering nondifferential responders, the overall probability of a best response to ICS was 0.40, and many participants did respond to daily montelukast or as-needed ICS. However, the study was able to identify a few predictors with best response to daily ICS. In addition, it was not able to identify clear predictors to other treatments.

Similar result has been reported in children 6 to 18 years of age with mild persistent asthma (TREXA⁹); the details of this study are presented elsewhere.¹⁰ In this study, children with positive skin test or more burdensome asthma showed more benefit from daily ICS.¹¹

The optimal strategy for management of asthma in preschool children is not clear. There is a body of evidence supporting the use of daily ICS in children with persistent symptoms to prevent asthma exacerbation (castro).^{1,12} However, there are still concerns about ICS's effect on linear growth especially at early ages as well as lack of benefit in improving lung function after discontinuation of ICSs.^{1,13} Children with episodic viral wheezing or severe intermittent wheezing present a different phenotype^{14,15} with other alternative options, including early initiation of oral corticosteroids and episodic use of ICS or montelukast during respiratory tract illness.^{16,17} A recent meta-analysis,¹⁷ including 4756 preschool children with recurrent wheezing confirmed superiority of daily ICS to placebo and montelukast by reducing exacerbations. A subgroup analysis of children with intermittent wheezing showed reduced exacerbation rate with use of intermittent ICS compared with placebo; the same benefit was not reported with montelukast. The meta-analysis did not identify the phenotype of the patients responding to each treatment option.

The question remains as what the characteristic of preschool children who respond to each treatment strategy are; and as different strategies are investigated, it is important to note the dose and duration of ICS to identify optimal dose. INFANT⁷ trial was the first trial in preschool children to investigate different phenotypes and biomarkers to predict response to a treatment; preschool children with persistent asthma requiring step 2 treatment would benefit more from daily ICS if they have evidence of aeroallergen sensitivity and/or blood eosinophil count $\geq 300/\mu\text{L}$. If the child does not have the specified biomarkers or has not responded to daily ICS, other alternative step 2 treatment may be considered. That being said,

treatment should not be held if the biomarker information is not readily available.

More clinical trials are warranted to allow clinicians practice personalized medicine and offer a tailored treatment based on phenotypes. Although there have been many advances to our appreciation and understanding of individualized treatments, early and clear description of disease pattern, baseline risk, and easy to assess and measure biomarkers in the clinical trials are still needed.

Author Disclosure Statement

Dr. Raissy is the principal investigator for AsthmaNet, NHLBI-funded network at the University of New Mexico. No other competing financial interests exist.

References

1. National Asthma Education and Prevention Program. Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda, MD: US Department of Health and Human Services, 2007.
2. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr, et al.; CARE Network of the National Heart, Lung, and Blood Institute. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365:1990–2001.
3. Raissy HH, Blake K. Management of wheezing in preschool children. *Pediatr Allergy Immunol Pulmonol* 2012; 25:172–173.
4. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus induced wheezing in young children. *N Engl J Med* 2009; 360:339–353.
5. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvärinen A, Kaulek V, et al.; PASTURE Study Group. Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med* 2014; 189:129–138.
6. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011; 127:1505–1512.
7. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, et al.; NIH/NHLBI AsthmaNet. Individualized therapy for persistent asthma in young children INFANT. *J Allergy Clin Immunol* 2016; 138:1608–1618.
8. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162(4 Pt 1):1403–1406.
9. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 650–657.
10. Raissy HH, Blake K. As needed use of inhaled corticosteroids for management of mild persistent asthma in children. *Pediatr Allergy Immunol Pulmonol* 2011; 24: 231–233.
11. Gerald JK, Gerald LB, Vasquez MM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, et al. Markers of differential response to inhaled corticosteroid treatment among children with mild persistent asthma. *J Allergy Clin Immunol Pract* 2015; 3:540–546.

12. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123:e519–e525.
13. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985–1997.
14. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32:1096–1110.
15. Bacharier LB, Phillips BR, Bloomberg GR, Zeiger RS, Paul IM, Krawiec M, et al.; Childhood Asthma Research and Education network, National Heart, Lung, and Blood Institute. Severe intermittent wheezing in preschool children: a distinct phenotype. *J Allergy Clin Immunol* 2007; 119: 604–610.
16. Horner CC, Bacharier LB. Management approaches to intermittent wheezing in young children. *Curr Opin Allergy Clin Immunol* 2007; 7:180–184.
17. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016; 137:e20154496.

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

E-mail: hraissy@salud.unm.edu

Received for publication September 29, 2017; accepted after revision October 29, 2017.