

PRACTICE OPTIONS BEYOND OUR PAGES

More Work to Do: Differential Responses to Asthma Therapies in Black Patients, Although Not Associated with Percentage of African Ancestry

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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

Wechsler ME, Szeffler SJ, Ortega VE, Pongracic JA, Chinchilli V, Lima JJ, et al. Step-up therapy in black children and adults with poorly controlled asthma. *N Engl J Med* 2019;381:1227-39.

BACKGROUND

The US-based National Heart, Lung, and Blood Institute (NHLBI) and international Global Initiative for Asthma (GINA) asthma treatment guidelines outline stepwise asthma therapy recommendations for children and adults. The current 2020 NHLBI guidelines have shifted to recommend single maintenance as reliever therapy (SMART) with daily and as-needed use of low-dose inhaled corticosteroid (ICS)-formoterol combination therapy as preferred step 3 management for all patients over age 5 years. These differ from the current 2020 GINA guidelines recommending either the addition of a long-acting β_2 -agonist (LABA) to low-dose ICS or an increase to medium-dose ICS in children aged 6 to 11 years, with preference of addition of an LABA in older age groups (age 12 and older).

Notably, primary studies informing these guidelines have included few Black patients despite the disproportionately greater burden of asthma experienced by this patient population.¹ Prior studies reported some racial and ethnic differences in response to asthma therapy, attributed to possible genetic variations affecting responsiveness to β -agonists or ICS²⁻⁷; however, these differences and their implications for asthma therapy approaches are still being elucidated. The original Best Add-on Therapy Giving Effective Responses (BADGER) study by Lemanske et al² and subsequent post hoc analysis of the data demonstrate racial and ethnic differences in asthma therapy response. In asthmatic patients with eczema who were uncontrolled when receiving low-dose ICS therapy, race or ethnic group significantly predicted

differential response to asthma treatments. Black patients with eczema were most likely to have best response to ICS step-up therapy, whereas Hispanic patients were most likely to have best response to the addition of a leukotriene receptor antagonist, and White patients had equivalent responses to added LABA or leukotriene receptor antagonist therapy.^{2,3} Black patients with asthma are disproportionately affected by asthma; they experience more exacerbations, asthma-related urgent care visits, hospitalizations, and deaths from asthma compared with their White counterparts.¹ The population of Black individuals is genetically heterogeneous, and this patient group needs to be studied in greater detail to identify optimal asthma treatment approaches, because it may differ from the population in the most current asthma treatment guidelines.

METHODS

This study was a set of two prospective randomized double-blind trials, one with children aged 5 to 11 years and the other with adolescents and adults aged 12 years and older. Included patients had at least one grandparent who identified as Black, in addition to inadequately controlled asthma despite twice-daily low-dose inhaled glucocorticoids (fluticasone 50 μ g twice daily in children and fluticasone 100 μ g twice daily in adolescents and adults). Diagnosis of asthma was defined by reversibility with β -agonist therapy, positive methacholine challenge, or absolute difference in forced expiratory volume in 1 second (FEV₁) of greater than 12% over two measurements. Patients were excluded if they had more severe asthma features while receiving low-dose ICS therapy, specifically if they required hospitalization for an asthma exacerbation or had three exacerbations requiring oral corticosteroids during the run-in period. Patients with a history of intubation during asthma exacerbation were also excluded.

Pediatric patients were randomized into one of four step-up treatment groups including (1) doubling fluticasone dose to 100 μ g twice daily (double-fluticasone), (2) quintupling fluticasone dose to 250 μ g twice daily (quintuple-fluticasone), (3) doubling fluticasone dose to 100 μ g twice daily with 50 μ g salmeterol twice daily (salmeterol-double fluticasone), and (4) quintupling fluticasone dose to 250 μ g twice daily with 50 μ g salmeterol twice daily (salmeterol-quintuple fluticasone). Adolescent and adult patients were randomized into one of four step-up therapy groups including (1) 2.5 times fluticasone to 250 μ g twice daily (2.5 $\times$ -fluticasone),

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 19, 2021; revised May 10, 2021; accepted for publication May 13, 2021.

Available online ■ ■ ■

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2213-2198

<https://doi.org/10.1016/j.jaip.2021.05.005>

(2) quintupling fluticasone dose to 500 µg twice daily (quintuple-fluticasone), (3) fluticasone 100 µg twice daily with 50 µg salmeterol twice daily (salmeterol-fluticasone), and (4) fluticasone 250 µg twice daily with 50 µg salmeterol twice daily (salmeterol-2.5-fluticasone). Because of the lack of the low-dose ICS-LABA combination, it was not possible to assess the effect of adding salmeterol to the baseline ICS in children, hence there was a difference in the first step-up regimen between the studies. The primary aim in both study groups was to evaluate the superiority of different treatments and the effect of proportion of African ancestry on the composite clinical outcome. Secondary aims included asthma control days, FEV1, and measures of asthma control. Exploratory outcomes included number and type of asthma exacerbations, patient characteristics, and selective biomarkers. These characteristics and biomarkers included sex, baseline measurement of the smallest concentration of a substance required to produce a 20% decrease in FEV1, bronchodilator response, blood eosinophils, sputum neutrophils, sputum eosinophils, IgE, history of eczema, use of systemic corticosteroids during the prior 12 months, asthma exacerbation during the prior 12 months, household education, and household income. Systemic effects of ICS were also studied by comparing baseline ratios of urinary cortisol to creatinine with those after treatment intervals.

A total of 280 children, most of whom were male, and 294 adolescents and adults, most of whom were female, were randomized to step-up treatment sequences in a four-way crossover design, with each treatment period lasting 14 weeks. Clinical responses to each step-up therapy were compared with one another within the pediatric and adolescent/adult populations. Clinical response to therapy was determined by a hierarchical composite asthma measure that sequentially evaluated asthma exacerbations, asthma control days, and percent predicted FEV1. Superiority was defined, sequentially, by the presence of a single asthma exacerbation, differential of 31 annualized asthma control days, or at least 5% increase in FEV1. We analyzed DNA genotyping with HapMap founders to estimate the percentage of African ancestry of each patient to evaluate for an association between ancestry and composite asthma measure outcomes in each treatment group.

RESULTS

In the pediatric group, there was no significant difference in the probability of a superior response between primary outcome groups ($P = .99$). 46% of patients had a superior response in the quintuple-fluticasone group, and 46% had a superior response in the salmeterol-double fluticasone group. This finding indicates that some patients responded best to quintupling ICS dosing whereas others responded to increased ICS dosing with the addition of an LABA. Secondary comparison groups showed varied responses of patients to higher ICS doses and the addition of LABA therapy. Most pediatric patients had a superior response to the higher dose ICS compared with the lower dose; 51% of patients in the quintuple-fluticasone group had a superior clinical response whereas only 37% did in the double-fluticasone group, demonstrating a response to stepped increases of ICS. Moreover, 53% of children in the salmeterol-double-fluticasone group had a superior response, whereas only 41% had a superior response in the double-fluticasone group. In addition, 47% of patients in the quintuple-fluticasone group had a superior response, whereas only 31% in the salmeterol-quintuple-fluticasone group did. In all groups, pediatric clinical responses mostly resulted from increased asthma control days and/or improvement in FEV1 rather than decreased exacerbations.

In the adolescent and adult group, clinical responses were less variable than observed in the pediatric population. More patients had a superior response to the addition of an LABA compared with an increase in ICS dosing; 49% in the salmeterol-fluticasone group had superior responses directly compared with 28% in the 2.5-fluticasone group ($P = .003$). Similarly, 49% of patients in the salmeterol-2.5-fluticasone group had a superior response compared with 31% in the quintuple-fluticasone group ($P = .02$). There was no difference in responses when the 2.5-fluticasone and quintuple-fluticasone groups or salmeterol-fluticasone and salmeterol-2.5-fluticasone groups were compared.

Genetic ancestry studies showed a broad distribution of percentage of African ancestry (2% to 100%; $\mu = 81\%$ children and $\mu = 82\%$ adolescents and adults), which was similar to Black populations from previous studies. The percentage of African ancestry did not predict a superior response to specific treatments in any of the studied patients, and no cutoff of percentage African ancestry was identified that was predictive of therapeutic response.

No studied biomarker or patient characteristic, including eczema, was found to identify specific patient subgroups who were more likely to respond to a specific treatment group. Regarding safety, the highest dose of ICS (250 µg twice daily) was associated with a decrease in the ratio of urinary cortisol to creatinine, but only in children aged less than 8 years.

CRITICAL APPRAISAL

A few limitations of this study have been identified. First, there was a larger dropout rate than expected among included children (25% vs 20%); thus, the study may be underpowered to detect differences in treatment responses in the studied pediatric population. Second, because of the lack of low-dose ICS-salmeterol combination in pediatric populations, the study could not compare 50 µg fluticasone alone versus 50 µg fluticasone plus 50 µg salmeterol. Thus, comparisons made in the pediatric population in this study have the inherent added effect of increased corticosteroids dosing when adding an LABA. Further studies could compare these two groups with alternative ICS-LABA combinations to evaluate the effect of LABA addition alone versus increased ICS dose in the Black pediatric population. Third, adherence to asthma medications is challenging to enforce, and it is important to quantify and control for this in a randomized controlled trial. In this study, medication adherence of 75% or greater was required for randomization; however, this may not reflect real-life use of prescribed daily low-dose ICS in this patient population. Despite a large enrolled population, 10% of pediatric patients and 9% of adult patients were nonadherent according to the identified guidelines, and subsequently were not included in randomization; additional nonadherence was identified later in the randomized groups. Finally, the study was not designed to address linear growth effects of increased doses of ICS in this population, which should be explored in further studies.

In contrast to prior studies exploring racial or ethnic differences in step-up asthma therapy responses, this study was dedicated entirely to the population of asthmatic patients with at least one family member who identified as Black, yielding a large patient population to be studied in their own right. Other studies, including the BADGER study, included only pediatric patients, with Black patients accounting for only 27% of the

entire cohort (49 of 182 patients). In contrast to the findings of the post hoc analysis of the BADGER study, this study did not identify differences in responses to step-up therapy between Black patients with different biomarkers including a history of eczema, although it may have been underpowered in this particular subgroup. The findings of this study do not support a unified approach of increasing ICS over adding an LABA in Black pediatric patients with eczema, given their variable findings in a large cohort.

The responses to therapy were varied in the pediatric population. However, Black adults responded more often to the addition of an LABA compared with increasing the ICS dose. This study is in line with current GINA guidelines that recommend adding an LABA to low-dose ICS for step 3 therapy for those aged 12 years and older. The NHLBI guidelines recommend SMART therapy as preferred treatment, which was not addressed in this study.

Using ancestral genotyping data, this publication supported current understanding of the genetic heterogeneity in the Black population. Uniquely, the results found no treatment response differences in association with patients' percentage African ancestry.

RECOMMENDATION

Updated NHLBI asthma treatment guidelines recommend daily and as-needed use of ICS-formoterol SMART therapy as preferred step 3 treatment for patients aged greater than 5 years. This study highlights the variability to which Black pediatric patients respond to varying doses of ICS and the addition of salmeterol. Appreciating the variability to which Black pediatric patients respond to asthma treatments, clinicians in practice should consider a more personalized approach to asthma treatment. Specifically, if first-line therapy recommended by national and international guidelines is ineffective in a patient, alternative approaches to treatment should be tried, such as increasing ICS dosing. Owing to the timing of publication,

SMART therapy with ICS-formoterol was not addressed in this particular study, but we anticipate that SMART therapy may not be the universal best choice for all Black pediatric patients compared with increasing ICS dosing. Formal comparisons between increased ICS doses and SMART therapy with ICS-formoterol in Black children should be pursued to determine whether SMART therapy remains the best first step in the treatment of Black pediatric asthma. In Black adults, addition of LABA therapy likely remains the most effective step-up option, although SMART therapy also was not addressed in this age group. This work has highlighted the continued need for inclusion of diverse populations in future asthma treatment trials, such that national and international guidelines can more appropriately represent the patients we serve with this condition.

REFERENCES

1. Wechsler ME, Szefer SJ, Ortega VE, Pongracic JA, Chinchilli V, Lima JJ, et al. Step-up therapy in black children and adults with poorly controlled asthma. *N Engl J Med* 2019;381:1227-39.
2. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
3. Malka J, Mauger DT, Covar R, Rabinovitch N, Lemanske RF Jr, Spahn JD, et al. Eczema and race as combined determinants for differential response to step-up asthma therapy. *J Allergy Clin Immunol* 2014;134:483-5.
4. Naqvi M, Thyne S, Choudhry S, Tsai HJ, Navarro D, Castro RA, et al. Ethnic-specific differences in bronchodilator responsiveness among African Americans, Puerto Ricans, and Mexicans with asthma. *J Asthma* 2007;44:639-48.
5. Naqvi M, Tcheurekdjian H, DeBoard JA, Williams LK, Navarro D, Castro RA, et al. Inhaled corticosteroids and augmented bronchodilator responsiveness in Latino and African American asthmatic patients. *Ann Allergy Asthma Immunol* 2008;100:551-7.
6. Federico M, Covar R, Brown E, Leung DY, Spahn JD. Racial differences in T-lymphocyte response to glucocorticoids. *Chest* 2005;127:571-8.
7. Chan MTS, Leung DY, Szefer SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol* 1998;101:594-601.