Adolescent Asthma Pharmacotherapy in a State of Flux

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Recently, the United States Food and Drug Administration (FDA) elected not to approve a once-daily inhaled corticosteroid/long-acting β_2 agonist combination product in 12–17-year-old patients due to lack of sufficient data, despite approval of previous combination products with similar levels of supporting evidence. As the FDA's stance toward adolescent data is changing, the opportunity to learn about their response to asthma medication has now arisen. A review of the relevant issues pertinent to pharmacotherapy of asthma in the 12–17-year-old population is discussed in this review.

BREO[®] ELLIPTA[®] is a fixed-dose combination containing the inhaled corticosteroid (ICS), fluticasone fuorate (FF), and long-acting β_2 agonist (LABA), vilanterol (VI), administered via the Ellipta[®] dry powder inhaler in two strengths: 100 μ g/25 μ g and 200 μ g/25 μ g. FF/VI 100 μ g/25 μ g was approved by Food and Drug Administration (FDA) in May 2013 for once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The FF component was approved in 2014 for once-daily maintenance dosing for asthma in patients ≥ 12 years old (Arnuity[™] Ellipta[®]). A supplemental new drug application for FF/VI for the once-daily maintenance treatment of asthma in patients ≥ 12 years old was submitted to the FDA in June 2014. An FDA advisory panel of experts, including the Pulmonary-Allergy Drug Advisory Committee (PADAC) and the Drug Safety and Risk Management committee (DSaRM), met in March 2015 and voted 16-4 in favor of approval of FF/VI for use by adults ≥ 18 years old, but voted 18-2 that there was insufficient data to support use in children 12–17 years old. The committee did not feel there was a consistency in the efficacy data, and noted the need for large safety trials to evaluate rate of hospitalization, death, and intubation in this age group.¹ The FDA approved Breo[®] Ellipta[®] in April 2015 for the once-daily treatment of asthma in patients ≥ 18 years old. Outside of the United States, Breo[®] Ellipta[®] has an approved asthma indication for patients ≥ 12 years old in 48 countries. What was the basis for the Committee's decision to recommend not approving Breo[®] Ellipta[®] for 12–17-year-old patients? Was there new information presented regarding the safety of LABAs since the 2007 review of the safety data of LABAs in children by the Pediatric Advisory Panel of the FDA?

The safety of LABAs became a concern with results of SMART study that reported an increase in risk of asthma deaths in adults, with one respiratory-related death in children aged 12–18 years old receiving salmeterol compared with none in the placebo group.² The only significant increased risk in children was for all-cause hospitalization. The details of the study have been discussed elsewhere.³ The FDA did a meta-analysis of 110 asthma clinical trials including 60,954 patients.⁴ In this analysis, the risk of LABA versus no LABA use was compared in patients 4–11, 12–17, 18–64, and >64 years of age. A positive trend toward higher point estimate of differences in risk for the asthma composite outcome (hospitalization, intubation, or death) was seen among all the age groups except patients aged 65 or older. Specifically, 12–17-year-old children had an incidence difference at 11.6 events per 1,000 patient-years (95% confidence interval [CI] –0.5 to 23.7). However, as the 95% CI included zero, it was not significant. In this meta-analysis, the data from four FDA-approved LABA-containing products was included: Serevent[®] metered dose inhaler (MDI), Serevent[®] Diskus, Advair[®] Diskus, Advair[®] HFA, Foradil[®] Aerolizer, Foradil[®] Certihaler, and Symbicort[®]. How did the Breo[®] Ellipta[®] data differ, which resulted in no approval for adolescent patients? Breo went up for approval based on the same standard as previously approved ICS/LABA products with the design of the Phase III trials consulted with and approved by the FDA. When data were presented, the FDA for the first time decided to break out the data for 12–17 year olds. Interestingly, the FDA found the same shift in the point estimate in risk difference in asthma composite outcome, although this was not significant because of insufficient numbers, in favor of the non-LABA group, which lead to the recommendation to obtain

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more data for those aged 12–17 years before use in this age group could be approved.⁵

Currently, five FDA-mandated, large-scale safety clinical trials are ongoing by four manufacturers of LABA-containing products.^{6–11} More than 11,000 patients with asthma aged ≥ 12 years will be enrolled in each of the four adult trials and will be randomly assigned to ICS/LABA or ICS for 6 months. These include a recruiting target of about 12% of patients aged 12–17 years, so that a total of around 1,200 patients per sponsor of 4,800 total will be adolescents, which should allow a more accurate assessment of risk in this age group. One pediatric trial will enroll children with asthma aged 4–11 years. The results of these trials are expected to be available next year.

A second asthma medication that was recommended for approval by PADAC for adults but not adolescents this year is mepolizumab, Nucala[®]. Mepolizumab is an anti-IL-5 monoclonal antibody for patients with severe eosinophilic asthma, as identified by a blood eosinophil count of at least 150 cells/ μ L at the start of treatment or 300 cells/ μ L in the past 12 months. The FDA Advisory Committee met on June 11, 2015, and voted unanimously in favor of the efficacy and safety of mepolizumab in adults. However, they voted 10–4 against approval for 12–17 year olds due to the limited number of adolescents and inadequate data on efficacy and safety.¹²

This may finally be the time to gain significant information on the treatment of adolescent asthma, an orphan age group that has previously been invested in minimally by the asthma research community. In pharmaceutical clinical trials, adolescents have been grouped with adults, while in National Institutes of Health (NIH)-sponsored networks (Asthma Clinical Research Network and Childhood Asthma Research and Education Network), they were grouped either with adults or with younger children. Previously, data from adolescents may have been assessed by subgroup *post hoc* analyses.^{13,14}

Are adolescents different from younger children? Are they different from adults? Although pubescence induces rather radical changes in growth and development, physiologically, in terms of the ratio of body surface area to body mass and drug biodistribution (absorption, metabolism, and excretion), adolescents (aged ≥ 12 years) are much closer to adults than they are to younger children.¹⁵ This may be why the FDA has historically grouped adolescents with adults, as similarities in drug biodistribution result in similar drug exposures if doses are determined on a weight basis. However, adolescents have shown similarities to younger children as well. The Childhood Asthma Management Program (CAMP) is the largest randomized, placebo-controlled clinical trial involving 1,041 children aged 5–12 years old with mild to moderate persistent asthma.¹⁶ The mean age of patients at enrollment was 9 years old, and patients were randomly assigned to budesonide, nedocromil, or placebo, and followed for a mean of 4.3 years—so into adolescence for many children. The primary outcome, post-bronchodilator FEV1, was controlled for but not separately assessed by age. However, the decrease in growth velocity seen during the first 2 years persisted into adulthood; the effect appeared greater in younger patients, but age at entry was not a significant factor, indicating ICS had an effect in the prepubertal or pubertal stage.¹⁷ In support of this was the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study, a randomized, placebo-controlled clinical

trial involving 7,165 patients aged 5–66 years old with persistent asthma for less than 2 years.¹⁸ Patients were randomly assigned to low-dose budesonide or placebo for 3 years in addition to their usual asthma medication. The data were analyzed for three age groups: 6–11 (28% of the patients), 11–17 (17% of patients), and ≥ 18 years old (55% of the patients) at the time of randomization. The adolescent group had a similar decrease in growth velocity as the younger group. Interestingly, the smallest decline in post-bronchodilator FEV1 and treatment effect as measured by pre-bronchodilator and post-bronchodilator FEV1 of budesonide in 3 years was seen in the adolescent group. The similarities between the first phase of CAMP patients and adolescents in START may provide some insight into this age group of patients.

In the Best Add-on Therapy Giving Effective Responses (BADGER) trial,¹⁴ 182 children aged 6–17 years with uncontrolled asthma on a low dose of ICS were randomly assigned to one of three step-up treatments for 16 weeks: fluticasone 250 μ g twice daily, fluticasone 100 μ g plus 50 μ g of LABA twice daily, or fluticasone 100 μ g twice daily plus a leukotriene receptor antagonist once daily. The patterns of differential response did not differ in 5–11-year-old compared with 12–17-year-old patients.

Pharmacokinetic studies also point out the differences in adolescents compared with other age groups. Plasma concentration of budesonide via a MDI with nebulizer spacer was measured after inhalation of a fixed dose in children 2–6 and adults 20–41 years of age. The systemic absorption was presented as area under the plasma concentration-time curve (AUC) and did not differ between the patients' age groups.¹⁹ Therefore, the authors suggested that the dose did not have to be adjusted for age, as the differences in tidal volumes by age would regulate the dose. The pharmacokinetics of formoterol and active metabolite of beclomethasone dipropionate were evaluated after a single dose via MDI with Aerochamber Plus[™] in three age groups: 200 μ g/24 μ g in 7–11 year old and 400 μ g/24 μ g in 12–17 and ≥ 18 year olds with asthma.²⁰ The systemic exposure as measured by the AUC in the 7–11 age group was halved for active metabolite of beclomethasone and the same for formoterol compared with adolescents and adults. Adolescents and adults had comparable AUC for both components. Interestingly, in a similar study using a combination of beclomethasone/formoterol DPI, the AUC for active metabolite of beclomethasone was the same in children compared to adults, but it was doubled for formoterol.²¹ The AUC for adolescents was about 30% higher for both components compared with adults.

The question remains as to where 12–17 year olds with asthma fit better: should they be grouped with children or adults, or should they have their own age group when it comes to asthma pharmacotherapy. The guidelines²² offer the same recommendations for adolescents as adults, but their recommendation is supported not by studies done in the 12–17 age group, but by how clinical trials have been traditionally—those aged 12 years and older. As pharmaceutical companies direct their efforts to study this age group, one can only hope that more funding opportunities will be available to learn about this patient population. Currently, Boehringer Ingelheim has completed Phase II and III trials with tiotropium in adolescents with asthma in preparation for obtaining FDA approval for asthma indication.^{23–25}

In summary, despite all efforts to offer a comprehensive guideline to manage asthma, there are knowledge gaps as more is learned about the disease and the patient population. The FDA's rules for approval of products for adolescent with asthma seem to be changing. Learning more about this age group is a positive step, as more clinical trials are being required and designed for 12–17-year-old patients with asthma. Meanwhile, providers should be mindful of how the FDA is becoming increasingly rigorous in its evaluation of pediatric data and how it seems to be less inclined to include adolescent age group data as part of the adult data package. This may result in fewer drugs being approved in adolescents at the point that they are approved for the adult population.

Author Disclosure Statement

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References

1. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Summary minutes of the joint pulmonary-allergy drug advisory committee and the drug safety and risk management drugs advisory committee meeting. (sNDA) 204275-S001, for fluticasone furoate and vilanterol inhalation powder (tradename Breo Ellipta) submitted by GlaxoSmithKline for the once daily maintenance treatment of asthma in patients 12 years of age and older. March 19, 2015.
2. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15–26.
3. Kelly HW. The U.S. Food and Drug Administration (FDA) and the safety of Salmeterol in Children. *Pediatr Asthma Allergy Immunol* 2008;21:105–108.
4. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics* 2011;128:e1147–1154.
5. US Food and Drug Administration. Center for Drug Evaluation and Research. FDA advisory committee briefing document, presented to Pulmonary-Allergy Drug Advisory Committee. BREO[®] ELLIPTA[®] (Fluticasone Furoate/Vilanterol Inhalation Powder) For Treatment of Asthma NDA 204275/S-001. March 19, 2015.
6. Chowdhury BA1, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med* 2011;364:2473–2475.
7. ClinicalTrials.gov. A 6-month study to assess the safety and benefit of inhaled fluticasone propionate/salmeterol combination compared with inhaled fluticasone propionate in the treatment of adolescents and adults (12 years of age and older) with asthma. (AUSTRI). NCT01475721. Available at <https://clinicaltrials.gov/ct2/show/NCT01475721?term=NCT01475721&rank=1>. Accessed July 13, 2015.
8. ClinicalTrials.gov. A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort[®], a fixed combination of inhaled corticosteroid (ICS) (Budesonide) and a long acting β_2 -agonist (LABA) (Formoterol) as compared to treatment with ICS (Budesonide) alone in adult and adolescent (≥ 12 years of age) patients with asthma. NCT01444430. Available at <https://clinicaltrials.gov/ct2/show/NCT01444430>. Accessed July 13, 2015.
9. ClinicalTrials.gov. A 26-week randomized, double-blinded, active controlled study comparing the safety of mometasone furoate/formoterol fumarate mdi fixed dose combination versus mometasone furoate MDI monotherapy in adolescents and adults with persistent asthma (Protocol No. P06241 Also Known as P202). NCT01471340. Available at <https://clinicaltrials.gov/ct2/show/NCT01471340?term=NCT01471340.&rank=1>. Accessed July 13, 2015.
10. ClinicalTrials.gov. A 26 week, randomized, active-controlled safety study of double-blind formoterol fumarate in free combination with an inhaled corticosteroid versus an inhaled corticosteroid in adolescent and adult patients with persistent asthma. NCT01845025. Available at <https://clinicaltrials.gov/ct2/show/NCT01845025?term=NCT01845025&rank=1>. Accessed July 13, 2015.
11. ClinicalTrials.gov. A 6-month safety and benefit study of inhaled fluticasone propionate/salmeterol combination versus inhaled fluticasone propionate in the treatment of 6,200 pediatric subjects 4–11 years old with persistent asthma. (VESTRI). NCT01462344. Available at <https://clinicaltrials.gov/ct2/show/NCT01462344?term=NCT01462344.&rank=1>. Accessed July 13, 2015.
12. Mepolizumab. US Food and Drug Administration. Center for Drug Evaluation and Research. FDA Advisory committee Briefing document. Presented to Pulmonary-Allergy Drug Advisory committee meeting. NUCALA[®] (mepolizumab) for Treatment of Patients with Severe Asthma with Eosinophilic Inflammation BLA125526. June 11, 2015.
13. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650–657.
14. Lemanske RF Jr, Mauger DT, Sorkness CA, 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;362:975–985.
15. Kauffman RE. Drug action and therapy in the infant and child. In Yaffe SJ, Aranda JV eds: *Neonatal and Pediatric Pharmacology; Therapeutic Principles and Practice*, fourth ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2011:20–30.
16. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054–1063.
17. Kelly HW, Sternberg AL, Lescher R, et al. CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904–912.
18. O'Byrne PM, Pedersen S, Busse WW, et al. START Investigators Group. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest* 2006;129:1478–1485.
19. Onhøj J, Thorsson L, Bisgaard H. Lung deposition of inhaled drugs increases with age. *Am J Respir Crit Care Med* 2000;162:1819–1822.
20. Govoni M, Piccinno A, Lucci G, et al. The systemic exposure to inhaled beclomethasone/formoterol pMDI with valved holding chamber is independent of age and body size. *Pulm Pharmacol Ther* 2015;30:102–109.
21. Chawes BL, Govoni M, Kreiner-Møller E, et al. Systemic exposure to inhaled beclomethasone/formoterol DPI is age and body size dependent. *Respir Med* 2014;108:1108–1116.

22. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, 2007. Available at www.nhlbi.nih.gov/guidelines/asthma. Accessed July 13, 2015.
23. ClinicalTrials.gov. Efficacy and safety of 3 doses of tiotropium compared to placebo in adolescents (12 to 17 yrs) with moderate asthma. NCT01122680. Available at <https://clinicaltrials.gov/ct2/show/NCT01122680>. Accessed July 13, 2015.
24. ClinicalTrials.gov. Efficacy and safety of 2 doses of tiotropium respimat compared to placebo in adolescents with severe persistent asthma. NCT01277523. Available at <https://clinicaltrials.gov/ct2/show/NCT01277523?term=NCT01277523&rank=1>. Accessed July 13, 2015.
25. ClinicalTrials.gov. Efficacy and safety of 2 doses of tiotropium via respimat compared to placebo in adolescents with moderate persistent asthma. NCT01257230. Available

at <https://clinicaltrials.gov/ct2/show/NCT01257230?term=NCT01257230&rank=1>. Accessed July 13, 2015.

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