

New and future strategies to improve asthma control in children

William C. Anderson III, MD,^{a,b} Stanley J. Szeffler, MD^{b,c}

Aurora, Colo

Symptomatic asthma in childhood has lifelong effects on lung function and disease severity, emphasizing the need for improved pediatric asthma control. Control of pediatric risk and impairment domains can be achieved through increased medication adherence or new therapeutic strategies. Developing electronic monitoring device technology with reminders might be a key noninvasive resource to address poor adherence in children and adolescents in a clinical setting. In patients who have persistently poor control despite optimal medication compliance, newly emerging pharmaceuticals, including inhaled therapies and biologics, might be key to their treatment. However, barriers exist to their development in the pediatric population, and insights must be drawn from adult studies, which has its own unique limitations. Biomarkers to direct the use of such potentially expensive therapies to those patients most likely to benefit are imperative. In this review the current literature regarding strategies to improve pediatric asthma control is addressed with the goal of exploring the potential and pitfalls of strategies that might be available in the near future. (*J Allergy Clin Immunol* 2015;■■■:■■■-■■■.)

Key words: Asthma, asthma control, asthma exacerbations, dupilumab, biomarkers, inhaled corticosteroids, lebrikizumab, long-acting β -adrenergic agonists, mepolizumab, omalizumab, reslizumab, severe asthma, therapeutics

Abbreviations used

ACQ:	Asthma control questionnaire
BADGER:	Best Add-on Therapy Giving Effective Responses
CAMP:	Childhood Asthma Management Program
COPD:	Chronic obstructive pulmonary disease
DREAM:	Dose Ranging, Efficacy, and Safety with Mepolizumab
EMD:	Electronic monitoring device
EPR3:	Expert Panel Report 3
FDA:	US Food and Drug Administration
FENO:	Fraction of exhaled nitric oxide
FVC:	Forced vital capacity
ICATA:	Inner-City Anti-IgE Therapy for Asthma
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
MENSA:	Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma
NHLBI:	National Heart, Lung, and Blood Institute
OCS:	Oral corticosteroid
PEF:	Peak expiratory flow
SARP:	Severe Asthma Research Program
SMART:	Single combination budesonide-formoterol inhaler maintenance and reliever therapy
TALC:	Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid Inadequately Controlled on Lower Dose of Inhaled Corticosteroid
TREXA:	Treating Children to Prevent Exacerbations of Asthma

From ^athe Section of Allergy and Immunology, Department of Pediatrics, Children's Hospital Colorado; ^bthe Department of Pediatrics, University of Colorado School of Medicine; and ^cthe Pediatric Asthma Research Program, Section of Pediatric Pulmonary Medicine, Breathing Institute, Department of Pediatrics, Children's Hospital Colorado, and the Department of Pediatrics, University of Colorado School of Medicine. Supported in part by Public Health Services Research Grant HL-98075 and the Colorado Cancer, Cardiovascular, and Pulmonary Disease Program #13-FLA-48556. Supported in part by Colorado CTSA Grant UL1 RR025780 from the National Center for Research Resources/National Institutes of Health (NIH) and UL1 TR000154 from NIH/National Center for Advancing Translation Sciences.

Disclosure of potential conflict of interest: W. C. Anderson and S. J. Szeffler received writing assistance for this article from Boehringer Ingelheim. S. J. Szeffler has consultant arrangements with Merck, Boehringer Ingelheim, GlaxoSmithKline, Genentech, Novartis, and Roche; has received research support from GlaxoSmithKline; has received payment for lectures from Merck; and has a patent for β -adrenergic receptor polymorphism for the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network.

Received for publication June 23, 2015; revised July 9, 2015; accepted for publication July 9, 2015.

Corresponding author: Stanley J. Szeffler, MD, Research Medical Director and Director, Pediatric Asthma Research Program, The Breathing Institute, Section of Pulmonary Medicine, Children's Hospital Colorado, 13123 E 16th Ave, Box 395, Aurora, CO 80045. E-mail: Stanley.Szeffler@childrenscolorado.org.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.07.007>

Despite advances in care, asthma still imposes a significant burden on the pediatric population. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Asthma Group raised several questions regarding the natural history, diagnostics, outcome measures, and therapeutics of pediatric asthma.¹ They addressed the pressing need to define effective strategies to prevent exacerbations and progression of disease, especially in younger populations.¹ The age of asthma diagnosis is decreasing, from 4.7 years in 1993 to 2.6 years in 2000.² Among children given a diagnosis before age 3 years, by 6 years of age, 35.6% to 45.2% continue to require care for their asthma² and most already have lung function abnormalities,³ suggesting a more persistent disease process. Early-onset asthma has long-lasting effects that can continue throughout childhood into adolescence and adulthood. Patients with mild-to-moderate asthma have an increasing magnitude of airway obstruction over their childhood compared with nonasthmatic subjects.⁴ Persistent pediatric wheezing carries a significant risk for both reduced lung function and FEV₁ growth over adolescence.⁵ Severe childhood asthma is a risk factor for continued active disease as an adult.⁶

Given asthma's lifelong effect, prevention of disease development and progression has been investigated, particularly with inhaled corticosteroids (ICSs). Inhaled fluticasone propionate in preschool children with a positive Asthma Predictive Index result did not change the development of asthma symptoms, exacerbations, or lung function once medication was stopped compared with placebo.⁷ Maintenance inhaled fluticasone propionate in preschool children with multiple-trigger wheezing did not prevent the development of asthma or change in lung function, FEV₁, and airway reactivity compared with placebo by 5 years of age.⁸ To date, no therapy has been able to prevent the development of pediatric asthma. The appropriate time or targets of intervention to prevent pediatric lung remodeling are also unclear.⁹ Given the lack of resources to prevent asthma development, focus should be given to asthma control.

The National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 (EPR3) recommendations focus asthma control on 2 primary domains: impairment and risk.¹⁰ Control in both domains is necessary because pediatric patients with persistent asthma symptoms have an increased risk of exacerbations, hospitalizations, emergency department visits, and oral corticosteroid (OCS) use,¹¹ with exacerbations leading to progressive loss of lung function.¹ Reasons for poor asthma control include controller medication adherence failure, unresponsiveness to available therapies, improper inhalation technique, poor comorbid condition control, psychosocial stressors, and misdiagnosis. In this review we examine current and future approaches of pediatric asthma control, with a focus on adherence and therapeutics in development.

ADHERENCE

Therapeutic adherence should be addressed first when approaching asthma control. Adult and pediatric adherence to controller therapies only ranges from 30% to 70%.¹² In ancillary Childhood Asthma Management Program (CAMP) study data, 75% of children had objective adherence of less than 80%, and 27% of subjects had adherence of less than 50%.¹³ Pediatric adherence specifically to ICSs is only 20% to 33.9%, with only 4.7 to 5.5 prescription refills for inhaled fluticasone over 1 year.¹⁴ The ramifications of poor controller adherence in the pediatric population include an increased risk of severe exacerbations, hospitalizations, emergency department visits, and OCS use.¹⁴ Based on refill data, the risk of an asthma exacerbation was 21% to 68% lower for children who were adherent to controller medications.¹⁴

Even when adherence is assessed, patients are poor self-reporters, with a large discrepancy existing between their reported adherence and their actual medication use.^{13,15-17} Evaluation of CAMP data showed 93.6% self-reported adherence on diary cards but only 60.8% objective adherence based on device actuations in 5- to 12-year-olds.¹³ Diary cards are limited by patients potentially fabricating data or completing it retrospectively. Only 26.2% of patients 6 to 17 years old kept diary cards regularly for at least 6 months in one study.¹⁸ Although regular diary card users had significantly greater use of daily controller therapies, neither the number of asthma exacerbations, emergency department visits, or hospitalizations nor the patient's FEV₁ or Asthma Control Test scores varied between those who completed diary cards and those who did not, regardless of whether they were completed by the patient or parent.¹⁸ Overall, it is unclear how

much symptom diaries or diary cards add to improving asthma control, health care use, or costs.¹⁹

Multiple reasons exist for poor adherence with medications in the pediatric population, including the complexity of treatment regimens, costs of medications, perceived risk of medication-related side effects, insufficient parental health literacy, lack of parental supervision, familial socioeconomic strain, poor patient perception of disease severity, and possible secondary gain from poor asthma control.^{15,20-22} Broadly, this nonadherence can be categorized as either intentional or unintentional.²³

Intentional nonadherence can result from a patient choosing not to take their medication based on their own needs, knowledge base, or perception of the medication.^{15,23} Conversely, unintentional nonadherence can result from the complexity of the treatment regimen or the patient's life, forgetfulness, or understanding of the medication.¹⁵ Nonadherent asthmatic patients are more likely to have unintentional nonadherence and, per the investigators, would likely benefit from reminder systems and patient education.²³

Electronic monitoring devices (EMDs) are a new approach to achieving disease control and adherence in clinical practice and research.^{15,24} EMDs provide accurate, objective, and detailed information on day-to-day patient adherence without significantly disrupting a patient's natural medication-taking behavior.²⁵ The SmartTouch (formerly SmartTrack; Adherium, Auckland, New Zealand) and Propeller (Propeller Health, Madison, Wis) sensors are 2 of the more advanced devices, with date and time recordings of each actuation, real-time uploading to a Web page or smartphone application, and reminders to prompt adherence.²⁵ The Propeller sensor also has a Global Positioning System to monitor location of inhaler use.²⁵ EMDs also overcome the limitation of dose dumping when using remaining doses or canister weight as markers of adherence.^{13,16,24,26} EMDs are not without their limitations, which include their cost,^{15,27,28} time for patient education²⁷ and device testing and data download,²⁸ measurement reliability and potential device failures,^{27,28} identification of patients most likely to benefit from this strategy,^{24,27} and the need to convince patients to use a device that will supervise their behavior.²⁸ As more technologically advanced devices come onto the market, the cost is decreasing.²⁶ Real-world study of the SmartInhaler Tracker (Adherium, Auckland, New Zealand) has demonstrated reliability, with 98.2% of devices passing prestudy checks, only 3.5% being thrown away or lost by patients, and only 1.9% malfunctioning before data upload.²⁹

Adults and adolescents given an EMD with an audiovisual reminder function showed a 19% improvement in ICS adherence compared with control subjects.³⁰ Pediatric and adolescent studies using EMDs with reminders demonstrated a 40% to 54% increase in adherence to controller medications compared with those without reminders.^{25,31} The aforementioned studies showed no difference in asthma outcomes,³¹ school or caregiver work absenteeism, FEV₁ improvement, or emergency department visits.²⁵ One reminder group had significantly fewer asthma exacerbations in the first 2 months but without a persistent difference at 4 and 6 months.²⁵ Possible reasons for lack of improvement include small sample sizes, limited intervention duration, patient awareness of adherence monitoring, or multiple asthma phenotypes requiring different treatment modalities.²⁴ Pediatric patients with poorly controlled asthma who were provided adherence feedback had overall increased adherence, which continued to increase over the course of the study, compared

with those who used an EMD without provider feedback.³² Conversely, in a trial of adolescent and adult asthmatic patients with poorly controlled asthma, although EMDs with reminders increased adherence compared with those with lack of reminders, there was no difference in adherence between those who received additional physician adherence discussions and those who did not.³³ These studies of provider feedback with EMD reminders did not have improved asthma control,³² FEV₁,^{32,33} exacerbation rates,^{32,33} Asthma Control Test scores,³³ or quality of life.³³ For some patients who have optimal adherence but remain symptomatic, additional therapeutics might be warranted. Nonetheless, insurance companies might eventually want to see objective data of adherence, which EMDs can provide, before paying for newer and more expensive medications.

THERAPEUTICS IN DEVELOPMENT

In patients whose symptoms remain poorly controlled despite close adherence with optimal current therapy, new therapeutics might be the key to their treatment. However, barriers exist in pharmaceutical development for the pediatric population because the process for drug approval differs somewhat in the United States and Europe, along with other countries (see [Table E1](#) in this article's Online Repository at www.jacionline.org). Traditionally, pediatric drug development is influenced by evidence for dosing, efficacy, and safety from adult studies.³⁴ A large percentage of pediatric medications are used off label based on these adult studies, with asthma medications among the most prescribed off-label drugs in children.³⁵ Extrapolation of new therapeutic advances in adults to children cannot be readily made because of differences in pediatric respiratory function, immunology, and disease pathogenesis.¹ Specific pediatric studies are needed to prevent this inappropriate extrapolation of adult data, especially in the youngest age groups. Although pediatric asthma represents 49.4% of asthma disease burden, only 17.9% of all asthma medication trials from 2006-2011 were in pediatric populations.³⁶

Several unique challenges exist when developing pediatric pharmaceutical trials. The issue of placebo control is more problematic in a vulnerable pediatric population, especially given the benefit of ICSs in the pediatric population.³⁷ The use of a dose or best available practice control might result in a higher threshold for statistical significance or need for a larger sample size compared with adult placebo-controlled studies.^{1,37}

Processes are in place to encourage the development of pediatric medications. The European Union requires every drug in development to have a pediatric investigational plan, with an incentive of an extra 6 months of market exclusivity if followed.³⁸ This intervention has resulted in an overall increase in the number of pediatric trials, subjects, and approved drugs with pediatric indications since its implementation.³⁹ When examining the following drugs, the pediatric literature is highlighted. However, without sufficient studies to date, some conclusions must be drawn from adult data, with the aforementioned limitations, until specific pediatric studies are performed (see [Table E2](#) in this article's Online Repository at www.jacionline.org).

INHALED THERAPIES

NHLBI EPR3 guidelines recognize ICSs as the preferred controller medication for persistent asthma and the addition of a long-acting β -agonist (LABA) at steps 3 and 4, respectively, for

patients 5 years and older and 4 years and younger.¹⁰ The development and introduction of second-generation ICSs and combination ICS/LABAs are likely responsible for the change in course of severe asthma over the last 20 years, including less use of chronic OCSs, with their adverse side effect profiles, and improved asthma control.⁴⁰ However, ICSs and LABAs are not without their own adverse effects and controversy. ICSs are most notably associated with a reduction in growth velocity and adult height^{7,41,42} and potential hypothalamic-pituitary-adrenal axis suppression.^{21,43} Pediatric LABA use is based primarily on data from adults,^{38,44} with studies in pediatric patients, adolescents, and adults conflicting on the added benefit of LABAs compared with higher-dose ICSs in asthma control, exacerbations, and lung function.⁴⁵⁻⁴⁷ The US Food and Drug Administration (FDA) has mandated 5 postmarket clinical trials, including one exclusively in the pediatric population, to investigate the benefits and safety of ICS/LABA combination therapy compared with ICS therapy alone.⁴⁸

New evidence is directing a potential benefit of on-demand dosing of ICSs and ICS/LABAs in the pediatric population. In the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) trial, over 1 year, the use of intermittent 7-day courses of high-dose ICSs did not differ compared with daily low-dose ICSs in children 12 to 53 months old with recurrent wheezing, a positive Asthma Predictive Index score, and at least 1 exacerbation in the previous year.⁴⁹ In the Treating Children to Prevent Exacerbations of Asthma (TREXA) study, both twice-daily and rescue beclomethasone showed a reduction in exacerbation frequency and treatment failure compared with placebo in 5- to 18-year-old patients with mild persistent asthma.⁵⁰ Both studies showed reduced ICS exposure with intermittent treatment, and the TREXA study also showed increased linear growth in this group compared with scheduled dosing.^{49,50}

A similar interest has been raised on the use of an ICS/LABA inhaler both for maintenance and reliever therapy, also known as single combination budesonide-formoterol inhaler maintenance and reliever therapy (SMART), in patients with intermittent to mild asthma to reduce disease burden, limit side effects by titrating the dose according to need, and overcome poor adherence.⁵¹ In patients 4 to 80 years old, a SMART approach prolonged the time to first severe exacerbation and all exacerbations, reduced the risk of a severe exacerbation requiring medical attention, improved symptom control, and improved morning and evening peak expiratory flow (PEF) and FEV₁ compared with budesonide/formoterol or budesonide alone.⁵² A similar study analyzing SMART specifically in patients 4 to 11 years old whose symptoms were uncontrolled on ICSs demonstrated that SMART was superior to budesonide/formoterol and budesonide alone in reducing the rate of asthma exacerbations, prolonging the time to first exacerbation, and reducing the risk of exacerbations requiring medical attention, mild exacerbation days, and nocturnal awakenings but not symptom-free days or asthma control days.⁵³ In both studies children treated with SMART had improved linear growth compared with those treated with fixed-dose budesonide alone.^{52,53}

New ICS-LABA combinations

Three twice-daily ICS/LABA combinations are currently FDA approved for the treatment of asthma, fluticasone propionate/

salmeterol, budesonide/formoterol, and mometasone/formoterol, with only fluticasone propionate/salmeterol approved for patients as young as 4 years old and the other 2 approved for patients as young as 12 years old.⁵⁴⁻⁵⁶ Although LABAs have increased compliance as an add-on controller to ICSs compared with leukotriene receptor antagonists in asthmatic patients 12 years and older,⁵⁷ they still carry the limitation of being a twice-daily medication. A prominent factor associated with poor medication compliance is the treatment regimen complexity.^{15,20,58} Once-daily ICS dosing increases medication adherence and reduces health care costs, irrespective of whether treatment is stepped up or down.⁵⁹ Although new combinations of previously FDA-approved ICSs and LABAs have demonstrated improved asthma control, such as combination fluticasone propionate/formoterol in adolescents and adults,⁶⁰⁻⁶² they still require twice-daily dosing.

Vilanterol is a LABA with 24-hour activity developed as a once-daily treatment in combination with a novel ICS, fluticasone furoate, approved by the FDA for the treatment of chronic obstructive pulmonary disease (COPD) in 2013 and for asthma in patients 18 years and older in 2015.⁶³⁻⁶⁵ In patients 12 years and older with uncontrolled persistent asthma, there was no difference between 100/25 μg daily fluticasone furoate/vilanterol and 250/50 μg twice-daily fluticasone propionate/salmeterol in improvement in FEV₁ and time to onset of bronchodilator effect.⁶³ There was no difference in asthma exacerbations between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol based on adverse event reporting.⁶³ Exclusive pediatric studies of vilanterol/fluticasone furoate are limited. In 5- to 11-year-old patients with well-controlled asthma, fluticasone furoate/vilanterol has a similar tolerability, safety profile, pharmacodynamic effect, and pharmacokinetic profile as fluticasone furoate alone.⁶⁴

Tiotropium

Tiotropium is a long-acting once-daily anticholinergic initially approved for the treatment of COPD in 2004.⁶⁶ Given that tiotropium improves lung function, quality of life, and exacerbations in adults with COPD,⁶⁷ interest emerged in it as a therapeutic in asthmatic patients with incomplete response to standard therapy. Initial studies demonstrated a benefit of tiotropium in adult asthma control. Tiotropium studies were initially conducted with the HandiHaler and then the Respimat device (Boehringer Ingelheim, Ingelheim am Rhine, Germany). In the Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid Inadequately Controlled on Lower Dose of Inhaled Corticosteroid (TALC) trial, addition of tiotropium to an ICS was superior to a doubling dose of ICS and noninferior to the addition of salmeterol in improving morning and evening PEF, asthma control days, and asthma control questionnaire (ACQ) and daily symptom scores in adults with mild-to-moderate asthma.⁶⁶ Tiotropium was superior both to a doubling dose of ICS and to the addition of salmeterol for prebronchodilator and postbronchodilator FEV₁ improvement.⁶⁶ Similar results were demonstrated in adults with poorly controlled asthma receiving medium-dose ICSs⁶⁸ or high-dose ICS/LABA treatment^{69,70} with tiotropium add-on therapy showing an improvement in peak and trough FEV₁,⁶⁸⁻⁷⁰ morning and evening PEF,⁶⁸⁻⁷⁰ ACQ scores,^{68,69} and time to first severe exacerbation.⁶⁹ The addition of tiotropium to ICS/LABA treatment reduced the risk of a severe exacerbation by 21%.⁶⁹

Recent studies demonstrated a benefit of tiotropium in adolescent and pediatric lung function. In studies of symptomatic 6- to

11-year-old⁷¹ and 12- to 17-year-old^{72,73} asthmatic patients receiving at least an ICS, tiotropium improved peak and trough FEV₁ and morning and evening PEF. A potential role exists for tiotropium as add-on therapy to improve FEV₁ in pediatric and adolescent patients with severe asthma and subsequently prevent exacerbations. However, these studies have not yet investigated the effect of tiotropium on asthma exacerbations in pediatric and adolescent patients. Studies in these populations did not show a statistically significant improvement in asthma control with tiotropium.^{71,72} Additional pediatric asthma studies will be needed to compare the addition of tiotropium versus a LABA with an ICS and its addition directly to combined ICS/LABA treatment.

Biomarkers for additional ICSs

Biomarkers and patients' characteristics can provide guidance into the optimal add-on therapy to ICSs, including LABAs and tiotropium, in patients with poorly controlled asthma. The Best Add-On Therapy Giving Effective Responses (BADGER) study demonstrated considerable response variability to step 3 therapy, with 44.1% of subjects responding best to the addition of a LABA, 29.2% responding best to the addition of a leukotriene receptor antagonist, and 26.7% responding best to a medium-dose ICS.⁴⁷ Improved response to LABA step-up therapy in the BADGER study was associated with lower prebronchodilator FEV₁/forced vital capacity (FVC) ratio, higher prebronchodilator impulse oscillometry with resistance at 5 Hz, and higher prebronchodilator impulse oscillometry reactance area, suggesting a response in children with low lung function related primarily to peripheral airway obstruction.⁷⁴ *Post hoc* BADGER data analysis demonstrated phenotypically that patients without eczema responded best to LABA step-up therapy to an ICS irrespective of race, whereas those with eczema varied in preferred best treatment option by race and ethnicity.⁷⁵ The upcoming Best African-American Response to Asthma Drug (BARD) study will examine the role of step-up therapy specifically in African Americans by comparing an increased dose of ICS versus the addition of a LABA on asthma control in uncontrolled African American asthmatic patients aged 5 years and older on low-dose ICSs, with separate analysis of patients 5 to 11 years old and those older than 12 years.^{37,76}

Clinical characteristics predicting a response to tiotropium have been derived from adult studies only. TALC data showed tiotropium improved FEV₁ and PEF in patients with a response to albuterol, decreased FEV₁/FVC ratio, and higher cholinergic tone, as reflected by a lower resting heart rate.⁷⁷ Adults less than 42 years old had greater improvement in asthma control days than older patients with the addition of tiotropium.⁷⁷ Improvements in FEV₁ with the addition of tiotropium to ICS/LABA treatment tended to be greater in patients with a lower percent predicted FEV₁, men, and former smokers with less than a 10 pack year history.⁶⁹ Tiotropium studies have not shown a response association with allergic markers, including atopy,⁶⁹ IgE level, sputum eosinophil count, or fraction of exhaled nitric oxide (FENO).⁷⁷ Extrapolation of these tiotropium response predictors to pediatric patients is conflicting because the response in younger patients with reversible airway obstruction would suggest a benefit in a pediatric population. Additional independent prospective studies are needed to identify treatment response markers in children and adolescents.

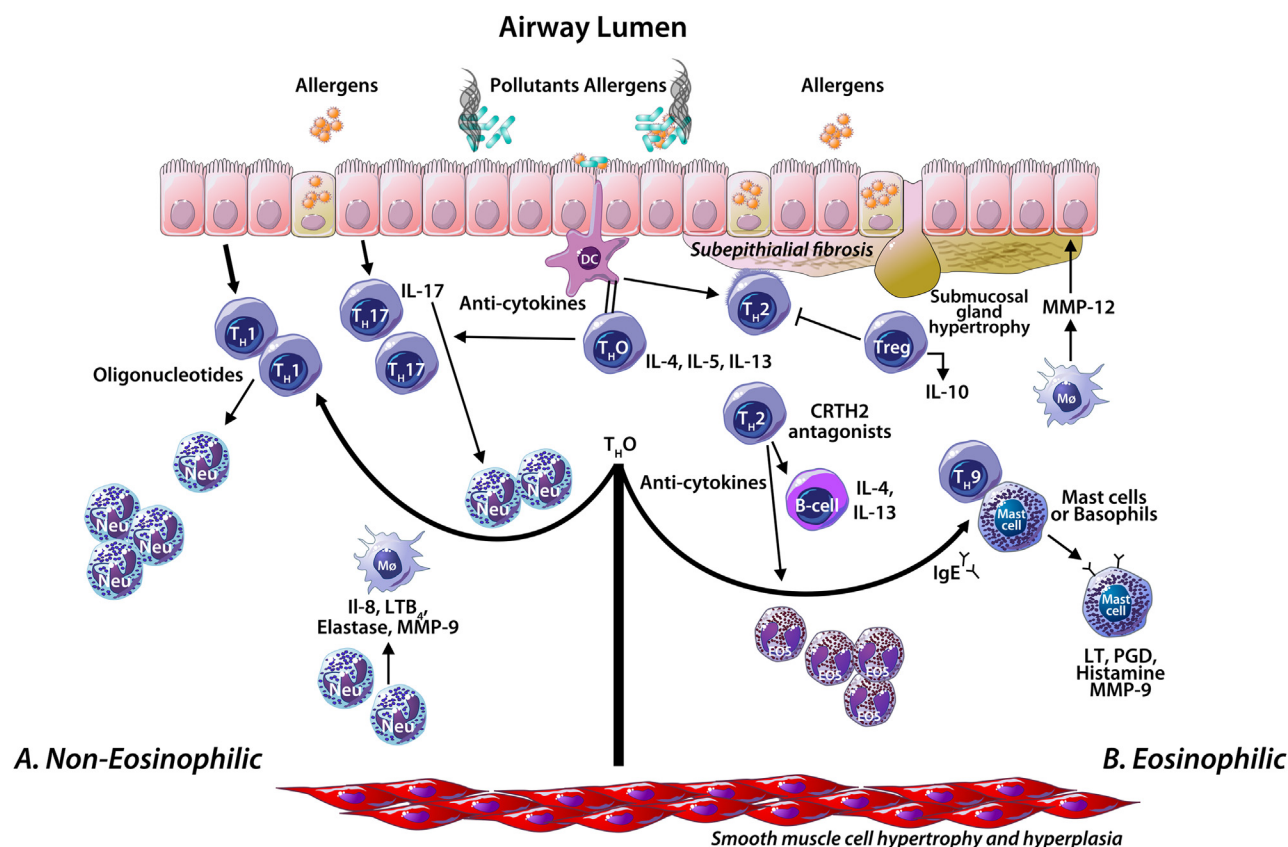


FIG 1. Modified from Szeftler et al¹ to show potential intervention sites of new therapies. Airway inflammation in the setting of asthma. DC, Dendritic cell; LT, leukotriene; MBP, major basic protein; MF, macrophage; MMP, matrix metalloproteinase; PGD, prostaglandin; Treg, regulatory T cell.

BIOLOGICS

Phenotypes, endotypes, and biomarkers

Biologics, also known as immunomodulators, are directed against a specific determinant, such as an immunoglobulin, cytokine, or cytokine receptor,⁷⁸ placing them at the forefront of personalized medicine. Asthma is a complex disease with multiple phenotypes representing several heterogeneous underlying immunologic endotypes. Thus for these biologics to be successful in personalized asthma management, 2 goals must be achieved. First, they must be developed in light of a greater understanding of both asthma clinical phenotypes and molecular and cellular endotypes.^{20,79,80} Second, they must be used with biomarkers that identify which patients would benefit most from their therapy.⁸⁰

Adult asthmatic phenotypes have previously been explored by using data from the Severe Asthma Research Program (SARP).⁸¹ Similarly, a cluster analysis of SARP patients 6 to 17 years old identified 4 phenotypic clusters, 3 of which were atopic, with differentiation based on their level of lung function.⁸² These same SARP clusters could be replicated in 6- to 18-year-olds from 3 Childhood Asthma Research and Education Network clinical trials.⁸³ Spectral clustering of children from the CAMP study identified 5 clusters distinguished based on atopic burden, degree of airway obstruction, and exacerbation rates.⁸⁴ Four of the 5 CAMP clusters were moderately to highly atopic.⁸⁵ Most pediatric patients with atopic asthma, especially those with severe asthma, are characterized by a younger presentation,

less-controlled disease with increased symptoms and exacerbations, increased atopy, and increased airway hyperresponsiveness and reversibility compared with other phenotypes.^{20,86-90}

Immunologically, most pediatric patients with atopic asthma, including those with severe asthma, have an eosinophilic or T_H2 profile. An eosinophilic profile includes peripheral eosinophilia^{20,85,91} compared with nonallergic asthmatic patients. A T_H2 profile is characterized by the cytokines IL-4, IL-5, IL-9, IL-13, IL-25, and IL-31, which favor antibody class-switching to IgE and the presence of eosinophils, basophils, and mast cells.⁷⁸ Recent studies with anti-IL-5 modulators are questioning whether an eosinophilic phenotype and an allergic phenotype might be fundamentally different.⁹² Most biologics to date in adults have focused on these T_H2 cytokines (Fig 1), including anti-IL-4-, anti-IL-5-, and anti-IL-13-based therapies.⁷⁸ In the Childhood Allergy Study birth cohort, patients with allergic asthma had higher mean IL-5 and IL-13 levels in stimulated peripheral blood samples and lower ratios of IFN- γ and IL-12 to IL-4, IL-5, and IL-13.⁹³ Conversely, bronchoalveolar lavage of pediatric patients with severe therapy-resistant asthma has shown increased eosinophil counts compared with those in control subjects but no increase in IL-4, IL-5, or IL-13 levels.⁹⁴ This suggests that the new immunomodulators directed toward these T_H2 cytokines might not be effective in pediatric patients with severe asthma.⁹⁵ These studies illustrate the heterogeneity of treatment-resistant pediatric phenotypes alone and the need for further identification of appropriate biomarkers.

Omalizumab

Omalizumab was the first FDA-approved biologic for the treatment of asthma in 2003.⁹⁶ Omalizumab is a humanized IgG₁ anti-IgE mAb that binds the Cε3 domain of circulating free IgE.^{22,96,97} Omalizumab decreases free IgE levels, inhibits binding of IgE with its high- and low-affinity receptors (FcεRI and CD23), and downregulates these receptors on mast cells, basophils, and circulating dendritic cells.⁹⁸⁻¹⁰⁰ Overall, this inhibits IgE-induced inflammatory mediator release and reduces allergen presentation.^{96,98} Omalizumab can be a prototype for the development of additional immunomodulators in both adults and children.

Omalizumab was approved for the treatment of moderate-to-severe persistent asthma in patients 12 years of age and older whose disease is not adequately controlled with ICSs alone.¹⁰¹ Omalizumab is indicated as an additional controller medication in steps 5 and 6 of the NHLBI EPR3 guidelines for patients aged 12 years and older.¹⁰ Omalizumab in adolescents and adults decreases rates of asthma exacerbations,^{99,102,103} annualized rates of hospital admission,⁹⁹ total emergency department visits,^{99,103} unscheduled doctor's office visits,⁹⁹ rescue therapy use,¹⁰² and ICS dose.¹⁰⁰ It also improves symptom scores, quality of life, and time to first asthma exacerbation.¹⁰²

Although currently not FDA approved for patients less than 12 years old, omalizumab has been demonstrated to improve asthma control and decrease medication use in this pediatric population¹⁰⁴⁻¹⁰⁷ similar to that seen in adolescents and adults. In the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial of 6- to 20-year-olds with predominantly moderate-to-severe persistent or uncontrolled asthma, the use of omalizumab resulted in absolute reductions in exacerbations, symptom days, and hospitalizations compared with placebo.¹⁰⁴ Most notably, omalizumab was found to nearly eliminate the seasonal variability of exacerbations in the fall and spring.¹⁰⁴ Omalizumab has been found to reduce both OCS and ICS use in pediatric patients. In the ICATA trial omalizumab was able to reduce the ICS dose by 109 μg/d.¹⁰⁴ Separate trials of 6- to 12-year-old patients with moderate-to-severe asthma¹⁰⁵ and patients with severe asthma who are less than 12 years old¹⁰⁶ have demonstrated a reduction in ICS use while still reducing asthma exacerbation rates. In the aforementioned trial of 6- to 12-year-olds, 55% of patients had complete withdrawal of ICSs, and there was an overall reduction in urgent physician's office visits, missed school days, and daily rescue medication use compared with control subjects.¹⁰⁵ In a small trial of 5- to 16-year-olds with severe asthma requiring daily maintenance OCS, omalizumab was able to reduce 85% of the patients' OCS doses, with a median reduction of 15 mg/d.¹⁰⁷ Given its proved benefit and only twice-weekly or monthly dosing, omalizumab theoretically could be used to provide control in a noncompliant population. In a small trial of 6- to 26-year-old poorly compliant symptomatic asthmatic patients requiring ICSs with or without LABAs, the addition of omalizumab resulted in fewer exacerbations requiring OCSs than placebo, despite continued noncompliance with inhaled controllers.¹⁰⁸

Patients 12 to 75 years old in the EXTRA study had greater reductions in asthma exacerbations with omalizumab if they had "high" baseline levels, based on median split, of the type 2 inflammatory markers FENO, peripheral eosinophil count, and periostin compared with those with "low" levels.^{102,109,110} Similarly, in the ICATA trial patients with a FENO value of 20 ppb or greater, a peripheral eosinophil count of 2% or greater,

and a body mass index of 25 kg/m² or greater had a significantly lower number of exacerbations with omalizumab compared with those with lower values of these parameters.¹¹¹ In subgroup analysis of 12- to 75-year-old patients with uncontrolled asthma with normal lung function treated with omalizumab, a peripheral eosinophil count of 300/μL or more was associated with a reduction in asthma exacerbations versus placebo, whereas those with low eosinophil counts at baseline had no improvement versus placebo in exacerbations.¹¹² Although larger prospective, randomized, placebo-controlled studies are needed to validate biomarkers for omalizumab, FENO values and peripheral eosinophil counts could be readily available, reproducible, and cost-effective measures to identify those patients most likely to respond to omalizumab.

Mepolizumab

Mepolizumab is a humanized mAb directed against IL-5. Given that IL-5 induces the maturation, activation, and recruitment of eosinophils,⁷⁸ it is a logical target for the treatment of asthma. Several studies have demonstrated a decrease in eosinophil counts in asthmatic patients treated with mepolizumab.¹¹³⁻¹¹⁷ Much like omalizumab development, initial mepolizumab studies showed a reduction in asthma exacerbations in adults,^{113,114} with only recent studies enrolling patients as young as 12 years old.¹¹⁶⁻¹¹⁸ Specific pediatric studies must be performed, and insights thus far can only be extrapolated from these adolescent and adult studies.

In the Dose Ranging, Efficacy, and Safety with Mepolizumab (DREAM) study of patients 12 to 75 years old maintained on high-dose ICSs with at least 2 exacerbations in the previous year and evidence of eosinophilic inflammation, mepolizumab reduced the number of clinically significant exacerbations per patient per year, delayed the time to first exacerbation, and decreased the number of exacerbations requiring hospital admission or an emergency department visit.¹¹⁶ Even though patients from 12 years old were eligible, demographics suggest that no pediatric subjects were actually enrolled.²²

Although the DREAM study did not show improvement in FEV₁ or ACQ scores,¹¹⁶ the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trial demonstrated improvements in both of these parameters, as well as rates of both all exacerbations and exacerbations requiring a hospitalization or emergency department visit.¹¹⁷ As such, although earlier studies might have pointed to a benefit in control only in the risk domain,⁹² newer studies suggest prevention in both risk and impairment domains with mepolizumab.

In the Steroid Reduction with Mepolizumab (SIRIUS) trial of asthmatic patients at least 12 years old requiring maintenance OCSs for at least 6 months and with serum eosinophilia, mepolizumab reduced OCSs compared with placebo, with a 50% median reduction in daily OCS use from baseline.¹¹⁸ Furthermore, this same population had a reduction in asthma exacerbations, improved FEV₁, and improved ACQ scores despite the reduction in OCS dose.¹¹⁸

Previous studies of mepolizumab that did not use biomarkers to guide treatment did not find a clinical benefit in exacerbation rates, FEV₁, symptom scores, or quality-of-life measures.¹¹⁵ In the DREAM trial eosinophilic inflammation was defined as a sputum eosinophil count of 3% or greater, FENO value of 50 ppb or greater, or peripheral eosinophil count of $0.3 \times 10^9/L$ or greater.¹¹⁶ FENO values have been found to correlate with lung

eosinophilia but are independent of IL-5 levels.^{110,113,119} Reductions in the rate of clinically significant exacerbations with mepolizumab in the DREAM study correlated with baseline patient blood eosinophil counts and numbers of exacerbations in the year but not atopic status, IgE concentrations, FEV₁, or bronchodilator response.¹¹⁶ An eosinophil count of 300/ μ L or greater could be a feasible biomarker for mepolizumab treatment. This difference in response to atopic markers might differentiate it as a treatment from omalizumab.¹¹⁶

Reslizumab

Reslizumab is an IgG_{4k} humanized mAb that binds human IL-5.^{120,121} As seen with anti-IL-5 treatment with mepolizumab, reslizumab decreases eosinophilia in asthmatic patients.^{120,121} Also like mepolizumab, early reslizumab studies focused on adults,¹²⁰ with only recently published studies involving adolescents older than 12 years.¹²¹ Initial study of reslizumab in adults with poorly controlled asthma and sputum eosinophilia of 3% or greater receiving ICSs and another controller agent resulted in improved FEV₁ and FVC but not asthma exacerbations.¹²⁰ Most recently, a study of 12- to 75-year-old patients with poorly controlled asthma maintained on ICSs with a peripheral eosinophil count of 400/ μ L or greater demonstrated a reduction in asthma exacerbation rates with reslizumab comparable with that seen in the DREAM and MENSA studies with mepolizumab.¹²¹ In addition, there was improvement in time to first exacerbation, FEV₁, ACQ, and quality-of-life scores.¹²¹ Although the study authors noted that the improvements in asthma control and lung measures were more striking than seen in the DREAM or MENSA studies, this reslizumab study had a higher eosinophil cutoff of 400/ μ L or greater¹²¹ compared with 300/ μ L or greater in the mepolizumab studies.^{116,117} Although the eosinophil count can be once again used as a biomarker, it raises interest about whether the level of eosinophilia itself can act as a biomarker to distinguish response to 2 therapies that both target IL-5. Additional studies, including a pediatric population, are warranted.

Lebrikizumab

Lebrikizumab is a humanized anti-IL-13 IgG₄ mAb.¹²² IL-13 mediates its effects through downstream production of periostin by bronchial epithelial cells acting on fibroblasts, ultimately resulting in mucus production, goblet cell hyperplasia, myeloblast differentiation, smooth muscle cells contraction, airway remodeling, and airway hyperresponsiveness.^{78,123,124} In conjunction with IL-4, IL-13 is responsible for generating IgE production.⁷⁸ Published lebrikizumab clinical trials to date have focused only on adults,¹²² highlighting the need for additional research in adolescent and pediatric populations.

The importance of biomarkers in assessing treatment response is demonstrated with lebrikizumab. Patients with inadequately controlled asthma despite treatment with medium-to high-dose ICSs were classified based on median split according to periostin level and T_H2 signature, as defined by an IgE level of greater than 100 IU/mL and a peripheral eosinophil count of greater than 0.14×10^9 cells/L.¹²² The population treated with lebrikizumab had an improvement in prebronchodilator FEV₁ but not asthma exacerbation rates compared with placebo.¹²² When examining biomarkers, patients with high periostin levels had a more marked

improvement in FEV₁, and those with a high T_H2 signature had a significant improvement in exacerbation rates.¹²² Additional analysis revealed that a high baseline FENO value and periostin level correlated with improved FEV₁ with lebrikizumab, but the T_H2 signature did not.^{122,125} This might be explained immunologically by IL-13's ability to strongly induce FENO^{110,119,126} and clinically by those patients with a high periostin level demonstrating a greater decrease in FENO values with lebrikizumab.¹²²

A study of adults with stable asthma not receiving ICSs who were similarly classified based on periostin and T_H2 signature did not show a significant change in FEV₁ either in the total treatment group or in the high periostin arm with lebrikizumab.¹²⁷ This suggests that the interaction of IL-13 with ICS itself might contribute to lebrikizumab response. This study was limited by insufficient power to detect a difference between periostin groups and attainment of periostin levels only before unblinding.¹²⁷

Potential questions also exist for periostin as a biomarker specifically in the pediatric population. Periostin is a product of bone turnover, which would suggest higher baseline levels in growing children compared with adults, thereby limiting its use. Childhood Origins of Asthma (COAST) data revealed that although periostin levels are 2- to 3-fold higher in children than in adults, those patients with asthma by 6 years of age had significantly higher periostin levels than children who did not have asthma by that age.¹²⁸ A study of 6- to 15-year-olds demonstrated significantly higher periostin levels in asthmatic patients than healthy control subjects, with the periostin level correlating with both methacholine PC₂₀ and mannitol PD₁₅ values.¹²⁹ Although these studies show a relationship between periostin levels and development of pediatric asthma, additional studies examining periostin levels in relation to IL-13 and lebrikizumab in children are needed.

Dupilumab

Dupilumab is a fully human mAb to the IL-4 receptor α subunit, which is shared by both the IL-4 and IL-13 receptors.^{78,92,130} IL-4 is key to the polarization and maintenance of T_H2 cells.⁷⁸ Inhibition of the IL-4 receptor α subunit would theoretically inhibit the downstream actions of both cytokines. Published studies to date have only examined dupilumab in adults with moderate-to-severe persistent asthma whose symptoms are not well controlled with medium-to high-dose ICS/LABA combined therapy with serum or sputum eosinophilia.¹³⁰ Dupilumab reduced asthma exacerbations and improved time to first exacerbation, asthma symptoms, and FEV₁.¹³⁰ In this proof-of-concept trial, LABAs were discontinued, and the dose of ICS was tapered throughout the study.¹³⁰ The improvement in FEV₁ occurred as early as week 2 and was maintained throughout despite the reduction and removal of background therapy.¹³⁰ Although specific biomarkers for dupilumab need to be explored, FENO values were inversely correlated with the change in FEV₁.¹¹⁰ Additional adolescent and pediatric dupilumab studies to investigate a benefit in asthma control and the use of therapy-guiding biomarkers are warranted.

CONCLUSION

Improved pediatric asthma control is imperative to prevent potential adverse disease sequelae later in life. Interventions should be made on a global level to make up for the lag in pediatric asthma drug development (see Table E1). While we wait

TABLE I. Timeline for emerging pharmacologic therapies in pediatric patients with asthma*

Agent	Trial	Summary	Sponsor	Phase	Current status	Start date	End date/estimated completion date
Fluticasone furoate/vilanterol	NCT01134042	24-wk trial in adolescent and adult patients (aged >12 y) with persistent asthma	GlaxoSmithKline	III	Completed	June 2010	October 2011
	NCT01147848	24-wk trial in adolescent and adult patients (aged >12 y) with persistent asthma	GlaxoSmithKline	III	Completed	June 2010	July 2011
	NCT01165138	12-wk trial in adolescent and adult patients (aged >12 y) with persistent asthma	GlaxoSmithKline	III	Completed	August 2010	October 2011
	NCT01453023	Two-period trial in children (aged 5-11 y) with persistent asthma	GlaxoSmithKline	II	Completed	October 2011	June 2012
	NCT01498653	12-wk trial in adolescent adult patients (aged >12 y) of Asian ancestry despite high-strength ICS or midstrength ICS/LABA combination therapy	GlaxoSmithKline	III	Completed	January 2012	March 2013
	NCT01498679	12-wk trial in adolescent and adult patients (>12 y) of Asian ancestry despite low-to middle-strength ICS or low-strength combination therapy	GlaxoSmithKline	III	Completed	January 2012	July 2013
	NCT01686633	12-wk trial in adolescent and adult patients (aged >12 y) with persistent asthma	GlaxoSmithKline	III	Completed	September 2012	October 2013
	NCT02301975	24-wk trial in adolescent and adult patients (>12 y) with persistent asthma despite middle-dose ICS/LABA combination therapy	GlaxoSmithKline	III	Recruiting	March 2015	August 2016
Tiotropium bromide	NCT01122680	Trial with 4-week treatment periods in adolescent patients (aged 12-17 y) with moderate persistent asthma	Boehringer Ingelheim	II	Completed	May 2010	April 2011
	NCT01257230	48-wk trial in adolescent patients (aged 12-17 y) with moderate persistent asthma	Boehringer Ingelheim	III	Completed	December 2010	December 2013
	NCT01277523	12-wk trial in adolescent patients (aged 12-17 y) with severe persistent asthma	Boehringer Ingelheim	III	Completed	January 2011	October 2013
	NCT01383499	Trial with 4-wk treatment periods in children (aged 6-11 y) with moderate persistent asthma	Boehringer Ingelheim	II	Completed	August 2011	September 2012
	NCT01634113	12-wk trial in children (aged 1-5 y) with persistent asthma	Boehringer Ingelheim	II	Completed	July 2012	December 2014
	NCT01634139	48-wk trial in children (aged 6-11 y) with moderate persistent asthma	Boehringer Ingelheim	III	Ongoing	July 2012	December 2015
	NCT01634152	12-wk trial in children (aged 6-11 y) with severe persistent asthma	Boehringer Ingelheim	III	Ongoing	July 2012	May 2015
Mepolizumab	NCT01000506	52-wk trial in adolescent and adult patients (aged 12-65 y) with severe uncontrolled refractory asthma	GlaxoSmithKline	II	Completed	November 2009	March 2012
	NCT01691508	24-wk trial in adolescent and adult patients (>12 y) with severe refractory asthma	GlaxoSmithKline	III	Completed	October 2012	December 2013
	NCT01691521	32-wk trial in adolescent and adult patients (aged >12 y) with severe refractory asthma	GlaxoSmithKline	III	Completed	October 2012	January 2014
	NCT01842607	12-mo trial in adolescent and adult patients (>12 y) with severe refractory asthma	GlaxoSmithKline	III	Completed	May 2013	March 2015
	NCT02135692	Trial of up to 128 wk in adolescent and adult patients (>12 y) with seriously debilitating asthma	GlaxoSmithKline	III	Recruiting	May 2014	October 2017
	NCT02281318	24-wk trial in adolescent and adult patients (aged >12 y) with severe eosinophilic asthma	GlaxoSmithKline	III	Recruiting	December 2014	May 2016
	NCT02377427	12-wk trial in children (aged 6-11 y) with severe eosinophilic asthma	GlaxoSmithKline	II	Planned	April 2015	August 2016
Reslizumab	NCT01270464	16-wk trial in adolescent and adults patients (aged 12-75 y) with eosinophilic asthma	Cephalon (Teva)	III	Completed	December 2010	December 2013
	NCT01285323	12-mo trial in adolescent and adult patients (aged 12-75 y) with eosinophilic asthma	Teva	III	Completed	March 2011	May 2014
	NCT01287039	12-mo trial in adolescent and adult patients (aged 12-75 y) with eosinophilic asthma	Cephalon (Teva)	III	Completed	March 2011	April 2014

(Continued)

TABLE I. (Continued)

Agent	Trial	Summary	Sponsor	Phase	Current status	Start date	End date/estimated completion date
Lebrikizumab	NCT01875003	104-wk trial in adolescent patients (aged 12-17 y) with uncontrolled asthma despite ICS and a second controller medication	F. Hoffmann-La Roche	III	Recruiting	August 2013	August 2019
	NCT01987492	44-wk trial in adolescent and adult patients (aged 12-75 y) with severe corticosteroid-dependent asthma	F. Hoffmann-La Roche	II	Recruiting	March 2014	August 2018
Dupilumab	NCT02414854	1-y trial in adolescent and adult patients (>12 y) with persistent asthma	Sanofi	III	Recruiting	April 2015	August 2017

*ClinicalTrials.gov was accessed on May 15, 2015, using the search terms “agent” AND “asthma.” The results were then manually filtered for trials involving pediatric patients.

for these pharmaceuticals to gain FDA approval, focus should be directed toward medication adherence. EMDs can be a tool to generate discussion of adherence and provide reminders to patients. Real-world studies are needed to consistently demonstrate that such technology ultimately leads to prevention of exacerbations and improved symptom control. Inhaled therapeutics, including tiotropium, might be more readily available alternatives as add-on therapy to achieve asthma control. Developing immunomodulators (Fig 1) are already showing promise for control of both risk and impairment domains in adolescents and adults. Given the difference in adult and pediatric lung function and asthma phenotypes, specific studies are warranted to assess their benefit in children (Table I). Concurrently, appropriate pediatric clinical biomarkers need to be explored to guide immunomodulator use. The coming years will see a wealth of options available to provide control of pediatric asthma, but this will ultimately rely on a joint venture between patients, clinicians, and researchers to find the appropriate personalized strategies to gain success.

Editorial assistance was provided by Denise Bonen, PhD, at Complete HealthVizion, which was supported by Boehringer Ingelheim Pharmaceuticals for these services. Drs Anderson and Szefer would like to thank Gretchen Hugen for assistance with manuscript preparation.

REFERENCES

- Szefer SJ, Chmiel JF, Fitzpatrick AM, Giacoia G, Green TP, Jackson DJ, et al. Asthma across the ages: knowledge gaps in childhood asthma. *J Allergy Clin Immunol* 2014;133:3-14.
- Radhakrishnan DK, Dell SD, Guttman A, Shariff SZ, Liu K, To T. Trends in the age of diagnosis of childhood asthma. *J Allergy Clin Immunol* 2014;134:1057-62.e5.
- Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.
- Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefer SJ, et al. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 2006;118:1040-7.
- Lodge CJ, Lowe AJ, Allen KJ, Zaloumis S, Gurrin LC, Matheson MC, et al. Childhood wheeze phenotypes show less than expected growth in FEV1 across adolescence. *Am J Respir Crit Care Med* 2014;189:1351-8.
- Tai A, Tran H, Roberts M, Clarke N, Gibson AM, Vidmar S, et al. Outcomes of childhood asthma to the age of 50 years. *J Allergy Clin Immunol* 2014;133:1572-8.e3.
- Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
- Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;368:754-62.
- Szefer SJ. Advances in pediatric asthma in 2011: moving forward. *J Allergy Clin Immunol* 2012;129:60-8.
- EPR. Guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- Haselkorn T, Fish JE, Zeiger RS, Szefer SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124:895-902, e1-4.
- Eakin MN, Rand CS. Improving patient adherence with asthma self-management practices: what works? *Ann Allergy Asthma Immunol* 2012;109:90-2.
- Krishnan JA, Bender BG, Wamboldt FS, Szefer SJ, Adkinson NF Jr, Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol* 2012;129:112-8.
- Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015;45:396-407.
- Weinstein AG. Asthma adherence management for the clinician. *J Allergy Clin Immunol Pract* 2013;1:123-8.
- Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefer S, Milgrom H, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol* 2000;85:416-21.
- Patel M, Perrin K, Pritchard A, Williams M, Wijesinghe M, Weatherall M, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology* 2013;18:546-52.
- Arga M, Sahbaz H, Bakirtas A, Turktas I, Demirsoy MS. Does self-monitoring by means of symptom diaries improve asthma control in children? *J Asthma* 2014;51:299-305.
- Krishnan JA, Lemanske RF Jr, Canino GJ, Elward KS, Kattan M, Matsui EC, et al. Asthma outcomes: symptoms. *J Allergy Clin Immunol* 2012;129(suppl):S124-35.
- Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Pract* 2014;2:489-500.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
- Robinson PD, Van Asperen P. Newer treatments in the management of pediatric asthma. *Paediatr Drugs* 2013;15:291-302.
- Lee JX, Wojtczak HA, Wachter AM, Lee ML, Burns L, Chen D, et al. Understanding asthma medical nonadherence in an adult and pediatric population. *J Allergy Clin Immunol Pract* 2015;3:436-7.
- Chan AH, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. *J Allergy Clin Immunol Pract* 2013;1:446-54.
- Chan AH, Stewart AW, Harrison J, Camargo CA Jr, Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015;3:210-9.
- Chan AH, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract* 2015;3:335-49.e5.
- Szefer SJ. Monitoring and adherence in asthma management. *Lancet Respir Med* 2015;3:175-6.

28. Bender BG. Advancing the science of adherence measurement: implications for the clinician. *J Allergy Clin Immunol Pract* 2013;1:92-3.
29. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol Pract* 2013;1:83-91.
30. Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. *J Allergy Clin Immunol* 2007;119:811-6.
31. Black P, Garratt E, Noonan L, Arandjus C, Salmon B, Sutherland G. An inhaler with ringtones improves compliance with inhaled steroids in childhood asthma. *Am J Respir Crit Care Med* 2008;117:A615.
32. Burgess SW, Sly PD, Devadason SG. Providing feedback on adherence increases use of preventive medication by asthmatic children. *J Asthma* 2010;47:198-201.
33. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014;134:1260-8.e3.
34. Zajicek A, Barrett JS. The grand challenges in obstetric and pediatric pharmacology. *Front Pharmacol* 2013;4:170.
35. Silva D, Ansotegui I, Morais-Almeida M. Off-label prescribing for allergic diseases in children. *World Allergy Organ J* 2014;7:4.
36. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JP, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. *Pediatrics* 2012;130:285-92.
37. Cabana MD, Kunselman SJ, Nyenhuis SM, Wechsler ME. Researching asthma across the ages: insights from the National Heart, Lung, and Blood Institute's Asthma Network. *J Allergy Clin Immunol* 2014;133:27-33.
38. Smyth AR, Barbato A, Beydon N, Bisgaard H, de Boeck K, Brand P, et al. Respiratory medicines for children: current evidence, unlicensed use and research priorities. *Eur Respir J* 2010;35:247-65.
39. Winzenburg G. More than 5 years of European Paediatric regulation: statistics and industrial experience. *Int J Pharm* 2014;469:260-2.
40. Reddy MB, Doshi J, Covar R, Spahn JD. The changing face of severe childhood asthma: a comparison of two cohorts of children evaluated at National Jewish Health over the past 20 years. *Allergy Asthma Proc* 2014;35:119-25.
41. Guilbert TW, Mauger DT, Allen DB, Zeiger RS, Lemanske RF Jr, Szeffler SJ, et al. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. *J Allergy Clin Immunol* 2011;128:956-63, e1-7.
42. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904-12.
43. Martin RJ, Szeffler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165:1377-83.
44. Bisgaard H, Szeffler S. Long-acting beta2 agonists and paediatric asthma. *Lancet* 2006;367:286-8.
45. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119:64-72.
46. Wells KE, Peterson EL, Ahmedani BK, Severson RK, Gleason-Comstock J, Williams LK. The relationship between combination inhaled corticosteroid and long-acting beta-agonist use and severe asthma exacerbations in a diverse population. *J Allergy Clin Immunol* 2012;129:1274-9.e2.
47. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
48. Communication FDS. FDA requires post-market safety trials for long-acting beta-agonists (LABAs) 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm>. Accessed May 20, 2015.
49. 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.
50. 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 randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650-7.
51. Beasley R, Weatherall M, Shirlcliffe P, Hancox R, Reddel HK. Combination corticosteroid/beta-agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? *J Allergy Clin Immunol* 2014;133:39-41.
52. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
53. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
54. GlaxoSmithKline. Advair: FDA Prescribing Information. Updated April 2008. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021077s029lbl.pdf. Accessed May 20, 2015.
55. AstraZeneca. Symbicort: FDA Prescribing Information 2006. Available at: <http://www1.astrazeneca-us.com/pi/symbicort.pdf>. Accessed May 20, 2015.
56. Merck. Dulera: FDA Prescribing Information. Updated January 2015. Available at: https://www.merck.com/product/usa/pi_circulars/d/dulera/dulera_pi.pdf. Accessed May 20, 2015.
57. Sadatsafavi M, Lynd L, Marra C, Bedouch P, Fitzgerald M. Comparative outcomes of leukotriene receptor antagonists and long-acting beta-agonists as add-on therapy in asthmatic patients: a population-based study. *J Allergy Clin Immunol* 2013;132:63-9.
58. Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. *Pediatrics* 2002;110:e6.
59. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J* 2005;14:88-98.
60. Nathan RA, D'Urzo A, Blazhko V, Kaiser K. Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial. *BMC Pulm Med* 2012;12:67.
61. Bodzenta-Lukaszyk A, Buhl R, Balint B, Lomax M, Spooner K, Dissanayake S. Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomized, controlled, non-inferiority trial of efficacy and safety. *J Asthma* 2012;49:1060-70.
62. Corren J, Mansfield LE, Pertseva T, Blahzko V, Kaiser K. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. *Respir Med* 2013;107:180-95.
63. Woodcock A, Bleecker ER, Lotvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013;144:1222-9.
64. Oliver A, VanBuren S, Allen A, Hamilton M, Tombs L, Inamdar A, et al. Tolerability of fluticasone furoate/vilanterol combination therapy in children aged 5 to 11 years with persistent asthma. *Clin Ther* 2014;36:928-39.e1.
65. GlaxoSmithKline. Breo Ellipta: FDA Prescribing Information. Updated April 2015. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Breo_Ellipta/pdf/BREO-ELLIPTA-PI-MG.PDF. Accessed May 20, 2015.
66. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.
67. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543-54.
68. Kerstjens HA, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med* 2015;3:367-76.
69. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
70. Kerstjens HA, Disse B, Schroder-Babo W, Bantje TA, Gahlemann M, Sigmund R, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011;128:308-14.
71. Vogelberg C, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Hamelmann E, Engel M, et al. A randomised dose-ranging study of tiotropium Respimat(R) in children with symptomatic asthma despite inhaled corticosteroids. *Respir Res* 2015;16:20.
72. Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, et al. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med* 2014;108:1268-76.
73. Hamelmann E, Boner A, Bernstein J, Moroni-Zentgraf P, Engel M, Avis M, Unsel A, et al. 1-year efficacy and safety study of tiotropium Respimat add-on to ICS in adolescent patients with symptomatic asthma. *Eur Respir J* 2014;44(suppl 58):1889.
74. Rabinovitch N, Mauger DT, Reisdorph N, Covar R, Malka J, Lemanske RF Jr, et al. Predictors of asthma control and lung function responsiveness to step 3 therapy in children with uncontrolled asthma. *J Allergy Clin Immunol* 2014;133:350-6.

75. 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.
76. Sutherland ER, Busse WW. National Heart, Lung, and Blood Institute's AsthmaNet. Designing clinical trials to address the needs of childhood and adult asthma: the National Heart, Lung, and Blood Institute's AsthmaNet. *J Allergy Clin Immunol* 2014;133:34-8.e1.
77. Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013;132:1068-74.e1.
78. Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A, et al. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders. *Allergy* 2015;70:727-54.
79. Holgate ST. Pathophysiology of asthma: what has our current understanding taught us about new therapeutic approaches? *J Allergy Clin Immunol* 2011;128:495-505.
80. Szeffler SJ. Advances in pediatric asthma in 2014: Moving toward a population health perspective. *J Allergy Clin Immunol* 2015;135:644-52.
81. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
82. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382-9, e1-13.
83. Chang TS, Lemanske RF Jr, Mauger DT, Fitzpatrick AM, Sorkness CA, Szeffler SJ, et al. Childhood asthma clusters and response to therapy in clinical trials. *J Allergy Clin Immunol* 2014;133:363-9.
84. Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA, et al. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol* 2014;133:1289-300, e1-12.
85. Schatz M, Rosenwasser L. The allergic asthma phenotype. *J Allergy Clin Immunol Pract* 2014;2:645-9.
86. Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D. EGEA Cooperative Group. Allergic vs nonallergic asthma: what makes the difference? *Allergy* 2002;57:607-13.
87. Fitzpatrick AM, Teague WG. Severe asthma in children: insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy Immunol Pulmonol* 2010;23:131-8.
88. Paton J. Severe asthma in children. Symposium: respiratory medicine. *J Paediatr Child Health* 2007;17:180-7.
89. Gibson PG, Simpson JL, Hankin R, Powell H, Henry RL. Relationship between induced sputum eosinophils and the clinical pattern of childhood asthma. *Thorax* 2003;58:116-21.
90. He XY, Simpson JL, Wang F. Inflammatory phenotypes in stable and acute childhood asthma. *Paediatr Respir Rev* 2011;12:165-9.
91. Fitzpatrick AM, Gaston BM, Erzurm SC, Teague WG. National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol* 2006;118:1218-25.
92. Darveaux J, Busse WW. Biologics in asthma—the next step toward personalized treatment. *J Allergy Clin Immunol Pract* 2015;3:152-61.
93. Zoratti E, Havstad S, Wegienka G, Nicholas C, Bobbitt KR, Woodcroft KJ, et al. Differentiating asthma phenotypes in young adults through polyclonal cytokine profiles. *Ann Allergy Asthma Immunol* 2014;113:25-30.
94. Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. *J Allergy Clin Immunol* 2012;129:974, 982.e13.
95. Szeffler SJ. Advances in pediatric asthma in 2012: moving toward asthma prevention. *J Allergy Clin Immunol* 2013;131:36-46.
96. Humbert M, Busse W, Hanania NA, Lowe PJ, Canvin J, Erpenbeck VJ, et al. Omalizumab in asthma: an update on recent developments. *J Allergy Clin Immunol Pract* 2014;2:525-36.e1.
97. Bonini M, Di Maria G, Paggiaro P, Rossi A, Senna G, Triggiani M, et al. Potential benefit of omalizumab in respiratory diseases. *Ann Allergy Asthma Immunol* 2014;113:513-9.
98. Kuhl K, Hanania NA. Targeting IgE in asthma. *Curr Opin Pulm Med* 2012;18:1-5.
99. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60:302-8.
100. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632-8.
101. Genentech I. Xolair: FDA prescribing information. Updated September 2014. Available at: http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed May 6, 2015.
102. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573-82.
103. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
104. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005-15.
105. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108:E36.
106. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;124:1210-6.
107. Brodrie M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. *Arch Dis Child* 2012;97:604-9.
108. Hendeles L, Khan YR, Shuster JJ, Chesrown SE, Abu-Hasan M. Omalizumab therapy for asthma patients with poor adherence to inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol* 2015;114:58-62.e2.
109. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
110. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol* 2015;135:299-311.
111. Sorkness CA, Wildfire JJ, Calatroni A, Mitchell HE, Busse WW, O'Connor GT, et al. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. *J Allergy Clin Immunol Pract* 2013;1:163-71.
112. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol* 2013;132:485-6.e11.
113. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
114. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
115. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71.
116. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
117. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
118. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
119. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. *Am J Respir Crit Care Med* 2010;181:1033-41.
120. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011;184:1125-32.
121. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
122. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.

123. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180:388-95.
124. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, Solberg OD, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol* 2012;130:647-54.e10.
125. Zeskind B. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:2432, author reply 2433-4.
126. Chibana K, Trudeau JB, Mustovich AT, Hu H, Zhao J, Balzar S, et al. IL-13 induced increases in nitrite levels are primarily driven by increases in inducible nitric oxide synthase as compared with effects on arginases in human primary bronchial epithelial cells. *Clin Exp Allergy* 2008;38:936-46.
127. Noonan M, Korenblat P, Mosesova S, Scheerens H, Arron JR, Zheng Y, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol* 2013;132:567-74.e12.
128. Anderson HM, Lemanske RF Jr, Arron JR, Holweg C, Rajamanickam V, Gern JE, Jackson DJ. Developmental assessment of serum periostin as an asthma biomarker in children. *J Allergy Clin Immunol* 2014;133(suppl):AB85.
129. Song JS, You JS, Jeong SI, Yang S, Hwang IT, Im YG, et al. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. *Allergy* 2015;70:674-81.
130. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66.

Supplemental Table 1. Global Pediatric Asthma Drug Development¹⁻⁴

Comparisons	EU	US
Knowledge gaps	Historically, drugs have been used in the treatment of children without the same level of evidence as has been obtained in the treatment of adults	
	• Strategies to prevent exacerbations • Diagnostic criteria for all ages • Validated control tests for all ages • Clinical trials in children ≤ 5 years • Phenotype/genotype stratification • Criterion to start LABA therapy • Long term follow-up depending on MOA • SIT in allergic asthma • Surrogate endpoints/biomarkers • Exercise induced asthma • Age appropriate devices • Validated PD parameter for dose finding	• Strategies to prevent exacerbations • Primary prevention • Disease modification • Treatment of wheezing and mild asthma • Identification of optimal strategies for ICS or ICS+LABA step-down therapy • Outcomes measures for children • AEs as a function of development • Personalization of asthma therapies • Identify age-appropriate medication delivery, especially in the hospital setting • Varying bioavailability and dose finding
Regulatory legislation	EMA	FDA
	• Current EU legislation, in place since 2007 combined with US legislation drives pediatric asthma product development • One pediatric process: – Study incentives and requirements are unified under one legislation • In the EU, mandatory pediatric product development is discussed earlier in the regulatory process compared with the US	• Current US regulations/legislation, in place since 1997 drives pediatric asthma product development • 2 separate pediatric processes were both made permanent under FDASIA in 2012: – BPCA incentive process; studies are voluntary, applies to drugs only – PREA mandatory requirement; studies are required, applies to drug and biologic asthma products

	Pediatric Collaboration: FDA & EMA • Legislation passed in 2012 to move EU and US closer, regarding the requirements for timing of discussion of pediatric plans to avoid exposing children to unnecessary trials • Both have agreed on the importance of age appropriate formulations, validated endpoints, and long term follow-up to permit accurate and safe dosing, assessment of efficacy and effects of chronic therapy, including effects on growth	
Pediatric development	End of Phase II	End of Phase II
Document used	Pediatric Investigation Plan	Pediatric Study Plan
Age classifications	Term newborn infants: 0 to 27 days	Neonate: birth to 1 month
	Infants/toddlers: 28 days to 23 months	Infant: 1 months to 2 years
	Children: 2 to 11 years	Children: 2 to 12 years
	Adolescents: 12 to 16-18 years	Adolescents 12 to <16 years
Types of studies required	• Grade of asthma severity • Efficacy • Safety • PK and PD • Non clinical • Quality	• Grade of asthma severity • Efficacy • Safety • PK and PD

BPCA = Best Pharmaceuticals for Children Act; EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; FDASIA = Food and Drug Administration Safety and Innovation Act; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists; MOA = mechanism of action; PD = pharmacodynamics; PK = pharmacokinetics; PREA = Pediatric Research Equity Act; SIT = specific immunotherapy; US = United States

1. European Medicines Agency. Report of the expert meeting on paediatric asthma. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/11/WC500135121.pdf. Last updated 2012. Accessed 16 September 2014.
2. Smyth AR, Barbato A, Beydon N, Bisgaard H, de BK, Brand P, Bush A, Fauroux B, de JJ, Korppi M, O'Callaghan C, Pijnenburg M, Ratjen F, Southern K, Spencer D, Thomson A, Vyas H, Warris A, Merkus PJ. Respiratory medicines for children: current evidence, unlicensed use and research priorities. *Eur Respir J* 2010; 35: 247-265.
3. Sutherland ER, Busse WW. Designing clinical trials to address the needs of childhood and adult asthma: the National Heart, Lung, and Blood Institute's AsthmaNet. *J Allergy Clin Immunol* 2014; 133: 34-38.
4. European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Last updated 2001. Accessed 16 September 2014.

Supplemental Table 2. Emerging pharmacological therapies for asthma¹

Classification	Agent	Mechanism	Efficacy	Potential predictors of response	Mode of administration	Development Phase
Bronchodilator: Long-acting anticholinergic	Tiotropium bromide Boehringer Ingelheim 1-11	Relaxes airway smooth muscle cells	Improves FEV ₁ , FVC, PEF, ACQ, AQLQ and reduces exacerbation rate in adult patients Improves FEV ₁ , PEF and ACQ in adolescent patients (12-17 years) Improves FEV ₁ , FVC, PEF, ACQ, PAQLQ[S] in children (6-11 years)	FEV ₁ , FVC, PEF, ACQ, AQLQ, exacerbations	Inhaled QD	Phase III
Bronchodilator: Inhaled corticosteroids/ long-acting β_2 -agonists	Fluticasone propionate /formoterol fumarate SkyePharma AG 12-24	Suppresses airway inflammation or relaxation effect on airway smooth muscle	Improves FEV ₁ , PEF, ACQ, AQLQ and reduces exacerbation rate in adolescent (>12 years) and adult patients	FEV ₁ , PEF, ACQ, AQLQ, exacerbations	Inhaled BID	Phase III
	Fluticasone furoate/vilanterol GlaxoSmithKline 25-30		Improves FEV ₁ and PEF in adolescent (>12 years) and adult patients The PK and PD profile were comparable with fluticasone furoate in children (6-11 years)	FEV ₁ , PEF	Inhaled QD	Phase III
	Indacaterol maleate/mometasone furoate Novartis 31		Improves FEV ₁ , FVC, PEF, ACQ and reduces exacerbation rate in adolescent (>12 years) and adult patients	FEV ₁ , FVC, PEF, ACQ, exacerbations	Inhaled QD	Phase II
	Fluticasone furoate/umeclidinium bromide GlaxoSmithKline 32		Improves FEV ₁ and PEF in adult patients	FEV ₁ , PEF	Inhaled QD	Phase II
Anti-IL-4/IL-13 monoclonal antibody	Dupilumab Sanofi and Regeneron 33	Modulates IL-4 and IL-13 signaling, drivers of a T _H 2 immune response	Improves FEV ₁ and ACQ and reduces exacerbation rate in adult patients	FEV ₁ , ACQ, exacerbations	Subcutaneous QW	Phase III
Anti-IL-5	Reslizumab	Reduces	Improves FEV ₁ , ACQ, AQLQ and	FEV ₁ , ACQ,	Intravenous	Phase III

monoclonal antibodies	Teva and Cephalon 34,35	production, activation, and proliferation of eosinophils	reduces exacerbation rate in adolescent (>12 years) and adult patients	AQLQ, exacerbations	QW	
	Benralizumab AstraZeneca, MedImmune LLC and Kyowa Hakko Kirin Company 36-38		Reduces eosinophil counts and exacerbation rate in adult patients	Eosinophils, exacerbations	Intravenous QW	Phase III
	Mepolizumab GlaxoSmithKline 39-44		Improves PEF, ACQ, AQLQ, reduces exacerbation rate and eosinophil counts in adolescent (>12 years) and adult patients	PEF, ACQ, AQLQ, exacerbations, eosinophils	Intravenous Q4W	Phase III
Anti-IL-13 monoclonal antibodies	Tralokinumab AstraZeneca and MedImmune 45	Theoretically blocks airway hyperresponsive ness, eosinophilic inflammation, and mucus production	Improves FEV ₁ in adult patients	FEV ₁	Subcutaneous Q2W	Phase III
	Lebrikizumab F. Hoffmann-La Roche and Genentech 46-48		Improves FEV ₁ in adult patients	FEV ₁	Subcutaneous QMT	Phase III
	QAX576 Novartis		No results reported		Intravenous Q3W	Phase II
Anti IL-17 monoclonal antibody	Brodalumab Amgen 49	Blocks IL-17 inflammatory signaling	No treatment differences observed in adult patients		Subcutaneous	Phase II
CRT _H 2 antagonists	OC000459 Oxagen 50-52	Reduces PGD2/CRT _H 2 effect on inflammation	Improves FEV ₁ , ACQ, AQLQ and reduces eosinophil counts in adult patients	FEV ₁ , ACQ, AQLQ, eosinophils	Oral QD	Phase II
	MK1029 Merck Sharp & Dohme Corp		No results reported		Oral QD	Phase II
	ARRY-502 Array BioPharma		No results reported		Oral QD	Phase II
	ADC3680 Pulmagen Therapeutics		No results reported		Oral QD	Phase II
	QAW039 Novartis		No results reported		Oral QD	Phase II
Oligonucleotide	ASM8	Promotes T _H 1	Decreases eosinophil counts in	Eosinophils	Inhaled BID	Phase II

agents	Pharmaxis 53	over T _H 2 response	adult patients			
TLR7 agonist	GSK2245035 GlaxoSmithKline	Blocks T _H 2- mediated airway inflammation	No results reported		Nasal spray QW	Phase II

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BID, twice daily; CRT_H2, chemoattractant receptor-homologous molecules expressed on T helper lymphocytes; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IL, interleukin; NO₂, nitric oxide; PEF, peak expiratory flow; PGD2, prostaglandin D2; PAQLQ[S], Standardised Paediatric Asthma Quality of Life Questionnaire; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily; QMT, once monthly; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; TLR, toll-like receptor

1. PubMed search performed using the Boolean string: (Agent [Title/Abstract]) AND asthma[Title/Abstract]) in May 2015. ClinicalTrials.gov accessed on May 14, 2015 using the search terms: “agent” AND “asthma”

References

1. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger L, Engle LL, DiMango EA, Fahy JV, Israel E, Jarjour N, Kazani SD, Kraft M, Lazarus SC et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363: 1715-1726.
2. Kerstjens HAM, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, Engel M, van Noord JA. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128: 308-314.
3. Bateman ED, Kornmann O, Schmidt P, Pivovarov A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011; 128: 315-322.
4. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367: 1198-1207.
5. Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger LC, Engle LL, DiMango EA, Israel E, Kraft M, Lazarus SC, Lemanske RF, Jr., Lugogo N et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132: 1068-1074.e1.
6. Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, Korn S. Tiotropium Respimat[®] in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. *Respir Res* 2014; 15: 61.

7. Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, Nething K, Vevere V, Vandewalker M. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med* 2014; 108: 1268-1276.
8. Timmer W, Moroni-Zentgraf P, Cornelissen P, Unseld A, Pizzichini E, Buhl R. Once-daily tiotropium Respimat[®] 5 µg is an efficacious 24-hour bronchodilator in adults with symptomatic asthma. *Respir Med* 2015; 109: 329-338.
9. Kerstjens HAM, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, Engel M, Bour L, Verkleij CB, Moroni-Zentgraf P, Bateman ED. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med* 2015; [Epub ahead of print].
10. Vogelberg C, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Hamelmann E, Engel M, Szeffler S. A randomised dose-ranging study of tiotropium Respimat[®] in children with symptomatic asthma despite inhaled corticosteroids. *Respir Res* 2015; 16: 20.
11. Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, Sakamoto W, Adachi M. Long-term once-daily tiotropium Respimat[®] is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. *PLoS One* 2015; 10: e0124109.
12. Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulm Med* 2011; 11: 28.

13. Bodzenta-Lukaszyk A, Pulka G, Dymek A, Bumbacea D, McIver T, Schwab B, Mansikka H. Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. *Respir Med* 2011; 105: 674-682.
14. Bodzenta-Lukaszyk A, Buhl R, Balint B, Lomax M, Spooner K, Dissanayake S. Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomized, controlled, non-inferiority trial of efficacy and safety. *J Asthma* 2012; 49: 1060-1070.
15. Aalbers R, Brusselle G, McIver T, Grothe B, Bodzenta-Lukaszyk A. Onset of bronchodilation with fluticasone/formoterol combination versus fluticasone/salmeterol in an open-label, randomized study. *Adv Ther* 2012; 29: 958-969.
16. Nathan RA, D'Urzo A, Blazhko V, Kaiser K. Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial. *BMC Pulm Med* 2012; 12: 67.
17. Cukier A, Jacob CM, Rosario Filho NA, Fiterman J, Vianna EO, Hetzel JL, Neis MA, Fiss E, Castro FF, Fernandes AL, Stirbulov R, Pizzichini E. Fluticasone/formoterol dry powder versus budesonide/formoterol in adults and adolescents with uncontrolled or partly controlled asthma. *Respir Med* 2013; 107: 1330-1338.
18. Bodzenta-Lukaszyk A, van Noord J, Schröder-Babo W, McAulay K, McIver T. Efficacy and safety profile of fluticasone/formoterol combination therapy compared to its individual components administered concurrently in asthma: a randomised controlled trial. *Curr Med Res Opin* 2013; 29: 579-588.
19. Corren J, Mansfield LE, Pertseva T, Blahzko V, Kaiser K. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. *Respir Med* 2013; 107: 180-195.

20. Pearlman DS, LaForce CF, Kaiser K. Fluticasone/Formoterol combination therapy compared with monotherapy in adolescent and adult patients with mild to moderate asthma. *Clin Ther* 2013; 35: 950-966.
21. Pertseva T, Dissanayake S, Kaiser K. Superiority of fluticasone propionate/formoterol fumarate versus fluticasone propionate alone in patients with moderate-to-severe asthma: a randomised controlled trial. *Curr Med Res Opin* 2013; 29: 1357-1369.
22. Mansur AH, Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. *J Aerosol Med Pulm Drug Deliv* 2013; 26: 190-199.
23. Antilla M, Castro F, Cruz A, Rubin A, Rosario N, Stelmach R. Efficacy and safety of the single-capsule combination of fluticasone/formoterol in patients with persistent asthma: a non-inferiority trial. *J Bras Pneumol* 2014; 40: 599-608.
24. Papi A, Price D, Sastre J, Kaiser K, Lomax M, McIver T, Dissanayake S. Efficacy of fluticasone propionate/formoterol fumarate in the treatment of asthma: a pooled analysis. *Respir Med* 2015; 109: 208-217.
25. Oliver A, Quinn D, Goldfrad C, van Hecke B, Ayer J, Boyce M. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomised, controlled trial. *Clin Transl Allergy* 2012; 2: 11.
26. Kempsford RD, Oliver A, Bal J, Tombs L, Quinn D. The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing. *Respir Med* 2013; 107: 1873-1880.

27. Allen A, Schenkenberger I, Trivedi R, Cole J, Hicks W, Gul N, Jacques L. Inhaled fluticasone furoate/vilanterol does not affect hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomised, double-blind, placebo-controlled study. *Clin Respir J* 2013; 7: 397-406.
28. Woodcock A, Bleecker ER, Lotvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013; 144: 1222-1229.
29. Oliver A, VanBuren S, Allen A, Hamilton M, Tombs L, Inamdar A, Kemsford R. Tolerability of fluticasone furoate/vilanterol combination therapy in children aged 5 to 11 years with persistent asthma. *Clin Ther* 2014; 36: 928-939.
30. Lin J, Kang J, Lee SH, Wang C, Zhou X, Crawford J, Jacques L, Stone S. Fluticasone furoate/vilanterol 200/25 mcg in Asian asthma patients: a randomized trial. *Respir Med* 2015; 109: 44-53.
31. Beasley RW, Donohue JF, Mehta R, Nelson HS, Clay M, Moton A, Kim HJ, Hederer BM. Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk in adolescent and adult asthma: a double-blind randomised controlled trial. *BMJ Open* 2015; 5: e006131.
32. Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. *Respir Med* 2015; 109: 54-62.
33. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, Pirozzi G. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368: 2455-2466.

34. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P, for the Res-5-0010 Study Group. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125-1132.
35. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; [Epub ahead of print].
36. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013; 132: 1086-1096.
37. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, van der Merwe R, Kolbeck R, Molfino NA, Raible DG. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; 2: 879-890.
38. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F, Fiening JP, Kim K, Molfino NA. A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015; 33: 14-20.
39. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, Robinson D, Wenzel S, Busse W, Hansel TT, Barnes NC, on behalf of the International Mepolizumab Study Group. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; 176: 1062-1071.

40. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973-984.
41. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985-993.
42. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651-659.
43. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189-1197.
44. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *N Engl J Med* 2014; 371: 1198-1207.
45. Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, She D, Kell C, May RD, Geba GP, Molfino NA. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J* 2013; 41: 330-338.
46. Corren J, Lemanske RF, Jr., Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, Mosesova S, Eisner MD, Bohen SP, Matthews JG. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; 365: 1088-1098.

47. Noonan M, Korenblat P, Mosesova S, Scheerens H, Arron JR, Zheng Y, Putnam WS, Parsey MV, Bohen SP, Matthews JG. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol* 2013; 132: 567-574.
48. Scheerens H, Arron JR, Zheng Y, Putnam WS, Erickson RW, Choy DF, Harris JM, Lee J, Jarjour NN, Matthews JG. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. *Clin Exp Allergy* 2014; 44: 38-46.
49. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, Lin SL. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013; 188: 1294-1302.
50. Barnes N, Pavord I, Chuchalin A, Bell J, Hunter M, Lewis T, Parker D, Payton M, Collins LP, Pettipher R, Steiner J, Perkins CM. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin Exp Allergy* 2012; 42: 38-48.
51. Singh D, Cadden P, Hunter M, Pearce Collins L, Perkins M, Pettipher R, Townsend E, Vinall S, O'Connor B. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. *Eur Respir J* 2013; 41: 46-52.
52. Pettipher R, Hunter MG, Perkins CM, Collins LP, Lewis T, Baillet M, Steiner J, Bell J, Payton MA. Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. *Allergy* 2014; 69: 1223-1232.
53. Gauvreau GM, Pageau R, Seguin R, Carballo D, Gauthier J, D'Anjou H, Campbell H, Watson R, Mistry M, Parry-Billings M, Killian K, Renzi PM. Dose-response effects of TPI ASM8 in asthmatics after allergen. *Allergy* 2011; 66: 1242-1248.