Thomas A. Neff Lecture

Asthma Therapies Revisited
What Have We Learned?

Robert F. Lemanske, Jr.[1]

[1]Department of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Asthma is a heterogenous disorder related to numerous biologic, immunologic, and physiologic components that generate multiple clinical phenotypes. Further, genetic and environmental factors interact in ways that produce variability in both disease onset and severity and differential expression based on both the age and sex of the patient. Thus, the natural history of asthma is complex in terms of disease expression, remission, relapse, and progression. As such, therapy for asthma is complicated and has been approached from the standpoints of primary, secondary, and tertiary prevention. Presently, asthma cannot be cured but can be controlled in most patients, an indication that most of the success clinical research strategies have realized has been in the area of tertiary prevention. Since for many adult patients with asthma their disease had its roots in early life, much recent research has focused on events during early childhood that can be linked to subsequent asthma development with the hopes of creating appropriate interventions to alter its natural history of expression. These research approaches can be categorized into three questions. Who is the right patient to treat? When is the right time to begin treatment? And finally, what is the appropriate treatment to prescribe?

Keywords: asthma; therapy; inhaled corticosteroids; β-agonists

WHO IS THE RIGHT PATIENT?

From epidemiologic observations in birth cohort studies, it has been well established that 20% of all children have at least one episode of a lower respiratory illness associated with wheezing in the first year of life, and 70% of these are associated with viral infections (1). Since viral illnesses contribute significantly to wheezing in early life, it has been of interest to determine which viruses had the greatest potential of not only producing early life wheezing, but possibly to be associated with the subsequent development of asthma as well. In this regard, a number of evaluations in hospitalized infants indicated that respiratory syncytial virus (RSV) infections had this potential (2, 3). However, with the advent of advances in molecular viral technology, it has now been possible to evaluate the contribution of other viruses to asthma development as well. In addition to RSV inpatient infections (4), it has now been clearly established that wheezing illnesses due to rhinoviruses (RV) in early life can be associated with the subsequent development of persistent wheezing (ages 3–5 yr) (5, 6) and ultimately asthma at 6 years of age (7).

(*Received in original form June 24, 2008; accepted in final form November 17, 2008*)

Supported by NIH grants U10 HL074212, U10 HL064305, and P01 HL70831 (to R.F.L.).

Correspondence and requests for reprints should be addressed to Robert F. Lemanske, Jr., M.D., Clinical Science Center, 600 Highland Avenue K4-916, Madison, WI 53792. E-mail: rfl@medicine.wisc.edu

Proc Am Thorac Soc Vol 6. pp 312–315, 2009
DOI: 10.1513/pats.200806-055RM
Internet address: www.atsjournals.org

Thus, children who wheeze in early life with RV and RSV infections appear to be at increased risk of developing asthma, indicating that something is abnormal with either their immune response to the virus or to the pathogenicity of the virus itself. The mechanisms by which RV infections produce wheezing and are associated with asthma development and exacerbations are currently under intense study. Both host (abnormalities in innate immune responses) (8) and viral (strains that may be more virulent or pathogenic) (9) factors are currently being studied. Once these defects can be defined, appropriate therapeutic and vaccine strategies can be designed and evaluated.

Wheezing in the early childhood has been divided into at least four phenotypes: transient, late onset, persistent, and those children who never wheeze (10). As detailed by other authors in this issue, identification of the persistent wheezers is critical in determining which children are most likely to develop asthma and are most likely to benefit from treatment. To this end, an asthma predictive index was developed after prospective observations in a birth cohort study and the subsequent developmental ascertainment of risk factors (Table 1) (11). This index, with subsequent slight modification (12), is helpful in determining "who" may be the right child to treat to reduce symptom burden and exacerbations (13).

WHEN IS THE RIGHT TIME TO TREAT?

Ideally, treatment intervention should occur at a time that will prevent the disease process from ever being expressed. Strategies attempting to achieve this outcome have thus far not been successful and remain a laudable goal. To design appropriate strategies, it is important to determine when relevant pathophysiologic elements of the disease begin to be expressed. From the standpoint of airway inflammation, recent work using both bronchoalveolar lavage in wheezing preschool children (14) and bronchial biopsy in infants (15) and young children (16) have demonstrated that both inflammatory cell infiltration and structural alterations (thickening of subepithelial reticular membrane) can be demonstrated by 2 to 3 years of life. Loss of lung function, predominantly noted in the persistent wheezing phenotype, occurs within the first 6 years of life (17). These findings would indicate that any intervention designed to secondarily prevent asthma would need to occur in early life. To this end, treatment of 2- to 4-year old children with a positive asthma predictive index (i.e., those children most likely to develop asthma) for 2 years with an inhaled corticosteroid resulted in a significant improvement in days without symptoms, a reduced risk of exacerbations requiring prednisone, and less demonstrable airflow obstruction while the treatment was being administered compared with those children treated with placebo. Unfortunately, subsequent cessation of treatment resulted in deterioration in asthma control within 3 months that resulted in a level that was comparable to those children previously treated with placebo (13). Thus, while early intervention with inhaled corticosteroids in high-risk chil-

TABLE 1. A CLINICAL INDEX TO DEFINE RISK OF ASTHMA IN YOUNG CHILDREN WITH RECURRENT WHEEZING

Positive index (>3 episodes/yr wheezing in the first 3 yr),
plus one major criterion or two minor criteria
Major criteria
Eczema*
Parental asthma*
+ Aeroallergen skin test*
Minor criteria
+ Food skin test*
Wheezing without upper respiratory infection
Eosinophilia (⩾4%)

* Doctor-diagnosed.
"+" Index: 65% change of asthma by age 6.
"−" Index: 95% chance of asthma by age 6.

dren can clearly reduce symptom burden, it does not appear to alter the ultimate expression of the underlying disease process once the treatment is stopped.

WHAT IS THE RIGHT TREATMENT?

This section will focus briefly on the following areas. First, what is the best first-line therapy and/or treatment strategies for mild persistent asthma? Second, what are some of the controversies regarding the use of β-agonists on a chronic basis? Third, how effective is combination therapy? Fourth, what additional benefits can be derived from the use of therapies targeted at modulating the immune system?

First-line Therapy for Mild Persistent Asthma

This topic has been recently addressed by both the Childhood Asthma Research and Education (CARE) Network and the Asthma Clinical Research Network (ACRN), both funded by the National Heart, Lung, and Blood Institute. The CARE trial was entitled the "Pediatric Asthma Controller Trial" (PACT) and enrolled children 6 to 14 years of age with mild to moderate persistent asthma (18). The children were treated for 48 weeks with one of three therapies: fluticasone monotherapy (100 μg twice daily), combination therapy (PACT combination therapy) (fluticasone 100 μg in the morning and salmeterol 50 μg twice daily), and montelukast (age-appropriate dose once daily). Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percentage of asthma control days, but fluticasone monotherapy was superior for clinic-measured FEV_1/forced vital capacity, maximum bronchodilator response, exhaled nitric oxide, and methacholine PC_{20}. Fluticasone monotherapy was superior to montelukast for asthma control days (64.2% versus 52.5%) and for all other control outcomes. Growth over 48 weeks was not statistically different among the various treatment groups. These results clearly establish inhaled corticosteroids as first-line therapy for children with mild persistent asthma and thus provide solid evidence for the recommendations put forth in the EPR3 asthma guidelines for step 2 care (19).

The IMPACT trial conducted in adult patients with EPR2 guideline defined mild persistent asthma produced controversial results (20). The trial was designed to determine if a 1-year treatment period with an inhaled corticosteroid (budesonide), a leukotriene antagonist (zafirlukast), or placebo would differ in terms of the morning peak expiratory flow (PEF) achieved at the end of the treatment period. This outcome was chosen to confirm previous findings of a potential loss of lung function if appropriate treatment was not started as soon as possible after the diagnosis of asthma (21, 22). Importantly, all three groups were treated with an asthma action plan consisting of limited administration of high-dose inhaled corticosteroids when asthma control was not optimal. Thus, the "placebo" group was really a group of subjects being treated intermittently with high doses of ICS based on symptoms. The three treatments produced similar increases in morning PEF and similar rates of asthma exacerbations, even though the intermittent-treatment group took budesonide, on average, for only 0.5 weeks of the year. As compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in prebronchodilator FEV_1, bronchial reactivity, the percentage of eosinophils in sputum, exhaled nitric oxide levels, scores for asthma control, and the number of symptom-free days, but not in post-bronchodilator FEV_1 or in the quality of life. Daily zafirlukast therapy did not differ significantly from intermittent treatment in any outcome measured. These results indicate that the current definition of mild persistent asthma may define a condition so mild that daily therapy may not be necessary to either adequately control symptom burden or reduce the potential for loss of lung function. Ongoing trials by both the ACRN and CARE networks are designed to determine when daily therapy is clearly warranted to maximize control in both the impairment and risk domains in both children and adults.

Chronic β-Agonist Therapy

In the early 1990s, the use of inhaled β-agonists on a regular basis was controversial in terms of its potential to produce adverse consequences: some maintained that this method of use could result in increased morbidity and mortality (23), while others did not (24). To address this controversy, the ACRN conducted a number of studies using both short- and long-acting β-agonists on a regularly scheduled basis in subjects with both mild and moderate persistent asthma. In patients with mild asthma taking albuterol four times daily for 16 weeks followed by a 4-week washout period, they found that this therapy was neither harmful nor beneficial (25). With the discovery of the existence of β-adrenergic receptor polymorphisms, they subsequently performed a retrospective analysis of these same patients and found that individuals who were homozygous Arg/Arg at codon 16 for the receptor had significant worsening of AM PEF when albuterol was taken on a regularly scheduled basis as compared with the opposite genotype, Gly/Gly (26). Genotype-attributable adverse effects in Arg/Arg subjects were subsequently confirmed in a prospective trial that was unique in that subjects were randomized on the basis of their genotype (Arg/Arg versus Gly/Gly) (27).

These findings in trials using short-acting β-agonists were conducted at the same time long-acting β agonists (LABAs) were approved in the United States. As a result, the ACRN began addressing the proper use of LABAs in a series of clinical trials. The first trial used a common run-in period in patients with mild to moderate asthma receiving a moderate dose of inhaled corticosteroids (ICS) to subsequently allocate the population into two groups based on pulmonary function and symptom control. The SOCS (Salmeterol or Corticosteroids) trial (28) involved those with more mild asthma, and its objective was to determine if patients adequately controlled on monotherapy with ICS could stop this therapy and use only the LABA salmeterol as monotherapy. The results clearly demonstrated that asthma control significantly worsened in subjects randomized into this form of therapy. The companion SLIC (Salmeterol ± Inhaled Corticosteroids) (29) trial was designed to evaluate the next step in treatment in subjects who were inadequately controlled on low-dose ICS and whose control was improved after the addition of salmeterol (30, 31). The results of this trial confirmed that salmeterol should not be used as monotherapy, but its use had the potential of permitting significant reductions in ICS doses in the majority of patients.

The concerns regarding β-adrenergic receptor polymorphisms and their influence on chronic β-agonist therapy have also been evaluated in patients using long-acting β-agonists. In retrospective analyses, adverse consequences based on genotype have not been observed (32).

Combination Therapy

Recent therapeutic recommendations by both the GINA and EPR3 committees have focused on asthma "control" as the endpoint that should be the focus of various intervention strategies. To this end, clinical trials have used levels of control (e.g., well-controlled and total control) as outcomes to evaluate response to ICS and ICS + LABA (i.e., combination therapy) therapy. In this regard, the "GOAL" (Gaining Optimal Control) study has achieved much attention due to its design and the results observed (33). Both well-controlled and total control status could be achieved with either therapy, but both outcomes were significantly more likely to occur in subjects receiving combination therapy.

Combination therapy has also been evaluated to determine its efficacy as both a maintenance and reliever medication. In a double-blind, randomized, parallel-group study, 2,760 patients with asthma aged 4 to 80 years (FEV_1, 60–100% predicted) received either terbutaline 0.4 mg as short-acting β-agonist (SABA) with budesonide/formoterol 80/4.5 μg combination twice a day, budesonide 320 μg twice a day + SABA as rescue, or budesonide/formoterol 80/4.5 μg twice a day with this same formulation used as-needed for rescue/relief. The use of combination medication as both maintenance and reliever therapy significantly prolonged the time to first exacerbation, resulting in a 45 to 47% reduction in risk compared with the other two treatment approaches. In addition, many of the secondary outcomes evaluating lung function and symptom control were also most consistently the best in the group receiving combination therapy as both maintenance and reliever medication. Interestingly, one investigative group has demonstrated that the benefit of combination therapy can be attributable to both the ICS and LABA components (34); another group has demonstrated that in more mild persistent asthma, significant clinical benefit can be observed with the concomitant use of ICS + SABA (albuterol) used only on an as-needed basis (35). Taken together, these findings indicate that the periodic use of ICS along with some form of β-agonist as relief medication has the potential for reducing exacerbation risk in both mild and moderate persistent asthma.

Immunomodulators

In more moderate to severe asthma, a number of therapies targeted at modulating the immune system (immunomodulators) have been evaluated. The agent most widely studied and currently approved for use in the United States is omalizumab (anti-IgE antibody). This is a humanized mouse monoclonal antibody that is directed toward a portion of the IgE molecule that binds to the receptor. As such, it leads to a significant reduction in the concentration of circulating IgE antibody and ultimately to decreased cell surface binding as well. To date, four trials have been completed in patients receiving various doses of ICS: three in patients receiving low to moderate (168–1,200 μg/d) doses of ICS, and one in patients with more severe asthma receiving higher doses of ICS ($\geq$ 1,000 μg/d of fluticasone). In the three trials in patients receiving low to moderate doses (one was done in children), dose reduction of ICS was achieved, as was a reduction in exacerbation rates. In the patients with more severe asthma, ICS dose reduction did not cause any significant alteration in symptom control, but exacerbation rates were not reduced. In a fifth trial in patients receiving ICS + LABA combination therapy, an effect on exacerbation rates was noted only after *post hoc* stratification based on pretreatment exacerbation rates was performed (recently reviewed by Strunk and Bloomberg [36]).

The role of the eosinophil in the pathobiology of asthma has been of great interest for decades (37). Interleukin-5 (IL-5) is a cytokine important for eosinophilopoeisis, migration, and survival. Recently, two monoclonal antibodies have been developed directed against IL-5 (SCH 55700 and mepolizumab), and their efficacy in asthma models and patients have been evaluated. In an allergen challenge model, the prior administration of SCH 55700 has been demonstrated to reduce both peripheral blood and sputum eosinophils while having little effect on alterations in pulmonary function (38). Mepolizumab was administered to over 300 patients with asthma who were still symptomatic despite receiving 400 to 1,000 μg/day of beclomethasone or equivalent. Despite a significant decrease in both blood and sputum eosinophil counts, treatment did not influence any of the clinical endpoints evaluated. There was a trend, however, for exacerbations to be reduced with the highest dose of mepolizumab that was administered (39). The lack of clinical benefit may be related to the fact that anti–IL-5 therapy only partially depletes airway eosinophils (40).

Finally, recent work has evaluated the ability of compounds directed against tumor necrosis factor α (TNF-α) to be of benefit in asthma (41–43). Since TNF-α has multiple biologic effects that influence asthma pathogenesis, it is plausible to consider this cytokine as a logical therapeutic target (44). When the TNF receptor etarnecept was administered to subjects with refractory asthma, significant benefit was noted in the following outcome measures: asthma quality of life, lung function, and airway hyperresponsiveness; a reduction in exacerbations was also observed (42). Unfortunately, there was a notable heterogeneity of response to the treatment, which suggests that there may be subgroups of patients who could derive significant benefit. The ability to define responsive populations will be important, since the risks involved with treatment are not inconsequential: pneumonia and malignancy (44).

CONCLUSIONS

In the past two to three decades, much has been learned regarding answers to the questions regarding the right patients to treat, the right times to treat, and what treatment approaches are appropriate in individualizing asthma care. However, many issues remain unresolved. Although asthma can be controlled in many patients, a cure still appears to be in the distant future. Since asthma begins in early life in many individuals, much more insight into mechanisms of disease inception, expression, and progression must be gained before appropriate new strategies targeted at primary, secondary, and tertiary prevention can be realized.

Conflict of Interest Statement: R.F.L. has been reimbursed by Merck for speaker honoraria in the amount of $29,000 in 2005, $31,000 in 2006, and $15,000 in 2007. He has also served as a consultant and speaker for other companies (GlaxoSmithKline, Aventis, AstraZeneca, and Novartis), but none of this activity resulted in compensation over $10,000 in any one year. He has also received compensation in the form of speaker honoraria from the following organizations: Oregon Health Sciences, Medical College of Wisconsin, LA Allergy Society, Pennsylvania Allergy Society, Michigan Allergy Society, American College of Allergy, Asthma and Immunology, Discovery International, and the University of Washington (all under $10,000 in any one year).

References

1. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study: II. Lower respiratory tract illness in the first year oflife. *Am J Epidemiol* 1989;129:1232–1246.
2. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171:137–141.

3. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy–the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66–71.
4. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–545.
5. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, Kirk CJ, Reisdorf E, Roberg KA, Anderson EL, *et al.* Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571–577.
6. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105–1110.
7. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E, *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high risk children. *Am J Respir Crit Care Med* 2008;178:667–672.
8. Johnston SL. Innate immunity in the pathogenesis of virus-induced asthma exacerbations. *Proc Am Thorac Soc* 2007;4:267–270.
9. Lee WM, Kiesner C, Pappas T, Lee I, Grindle K, Jartti T, Jakiela B, Lemanske RF, Shult PA, Gern JE. A diverse group of previously unrecognized human rhinoviruses are common causes of respiratory illnesses in infants. *PLoS One* 2007;2:e966.
10. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.
11. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403–1406.
12. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ, Larsen G, Spahn JD, Zeiger RS, Heldt G, *et al.* The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials* 2004;25:286–310.
13. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF, Jr., Strunk RC, Allen DB, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985–1997.
14. Krawiec ME, Westcott JY, Chu HW, Balzar S, Trudeau JB, Schwartz LB, Wenzel SE. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1338–1343.
15. Saglani S, Malmstrom K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M, Turpeinen M, Rogers AV, Payne DN, Bush A, *et al.* Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171:722–727.
16. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, Jeffery PK. *et al.* Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007; 176:858–864.
17. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253–1258.
18. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, *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.
19. Busse WW, Lemanske RF Jr. Expert Panel Report 3: moving forward to improve asthma care. *J Allergy Clin Immunol* 2007;120:1012–1014.
20. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, Dimango EA, Deykin A, *et al.* Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519–1528.
21. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–381.
22. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Selroos O, Sovijarvi A, *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700–705.
23. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, Yates DM, Lucas MK, Herbison GP. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391–1396.
24. McFadden ER Jr. Perspectives in beta-2-agonist therapy: vox clamantis in deserto vel lux in tenebris? *J Allergy Clin Immunol* 1995;95:641–651.
25. Drazen JM, Israel E, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, Lazarus SC, Lemanske RF, Jr., Martin RJ, Peters SP, *et al.* Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med* 1996;335:841–847.
26. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, Cooper DM, Fahy JV, Fish JE, Ford JG, *et al.* The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162:75–80.
27. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364:1505–1512.
28. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, *et al.* Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583–2593.
29. Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, *et al.* Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285:2594–2603.
30. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481–1488.
31. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 1994;344:219–224.
32. Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, Dorinsky PM. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol* 2006;118:809–816.
33. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE. Can guideline-defined asthma control be achieved? the Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836–844.
34. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744–753.
35. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, *et al.* Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;356:2040–2052.
36. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med* 2006;354:2689–2695.
37. O'Byrne PM. The demise of anti IL-5 for asthma, or not. *Am J Respir Crit Care Med* 2007;176:1059–1060.
38. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, Danzig M, Cuss F, Pauwels RA. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167:1655–1659.
39. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, Robinson D, Wenzel S, Busse W, Hansel TT, *et al.* A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062–1071.
40. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167: 199–204.
41. Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, Zacharasiewicz AS, Turner J, Barnathan ES, Kon OM, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor-α in asthma. *Am J Respir Crit Care Med* 2006;174:753–762.
42. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006;354:697–708.
43. Erzurum SC. Inhibition of tumor necrosis factor alpha for refractory asthma. *N Engl J Med* 2006;354:754–758.
44. Brightling C, Berry M, Amrani Y. Targeting TNF-alpha: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008;121: 5–10.