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Drug Development for Severe Asthma: What Are the Metrics?

Cynthia B. Robinson, MD¹, Joanne Leonard, BS¹, and Reynold A. Panettieri Jr., MD²

¹Epigenesis Pharmaceuticals, Cranbury, New Jersey

²Pulmonary, Allergy and Critical Care Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Although reversible airway obstruction in part defines asthma, lung function as measured by spirometry alone inadequately predicts the value of new therapeutic agents in the treatment of severe asthma.

Our objectives are 1) to review whether pulmonary function and bronchodilator reversibility are endpoints for drug discovery and 2) to identify parameters that predict efficacy in drug development in severe asthma.

An English language literature search using MedLine and PubMed was conducted from 1997 to present concerning pathophysiology, diagnosis and therapy of severe asthma using the terms “severe asthma,” “irreversible asthma,” “difficult asthma,” “airway remodeling,” “fixed airway obstruction,” “reversibility” and “bronchodilator reversibility” as index terms. Eight studies were characterized that encompass 1,424 subjects with asthma.

Our review identified the limitations of using bronchodilator reversibility as a predictor in drug development for severe asthma. Neither improvement in lung function nor bronchodilator reversibility characterized the benefit of new drugs in the treatment of severe asthma. Newly approved drugs in the treatment of severe asthma show decreased asthma exacerbations and improved quality of life associated with steroid-sparing benefits without altering bronchodilator responsiveness or improving lung function.

Although changes in lung function predict asthma control in mild/moderate asthma, lung function alone is inadequate to assess improvement in asthma control in severe asthma manifested by fixed airway obstruction. Endpoints that focus on asthma control, as defined by the Expert Panel Report 3 and GINA guidelines, may predict the value of new therapeutics in the management of severe asthma.

Keywords

Airway remodeling; fixed airway obstruction; irreversible asthma; drug discovery

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Corresponding Author: Reynold A. Panettieri, Jr., MD, Pulmonary, Allergy and Critical Care Division, Department of Medicine, University of Pennsylvania, 125 South 31st Street, TRL Suite 1200, Philadelphia, PA 19104-3413, Phone: 215-573-9860, Fax: 215-746-1224, rap@mail.med.upenn.edu.

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1. Introduction

Asthma, a syndrome characterized by airway hyperresponsiveness (AHR), obstruction and inflammation, remains a substantial financial burden globally due to increasing morbidity and mortality (GINA; National Asthma Education and Prevention Program, 2007). Despite considerable progress in understanding fundamental mechanisms inducing AHR and inflammation, therapeutic approaches to manage severe disease remain a significant unmet need (Jarjour, *et al.*, 2012). Disproportionately, patients with severe persistent asthma have profound decreases in quality of life and frequently require emergency department visits, hospitalizations and unscheduled physician visits (Jarjour, *et al.*, 2012). Further, patients with severe disease also manifest glucocorticoid insensitivity and irreversible airflow obstruction. International programs, such as the Global Initiative for Asthma (GINA) and the National Asthma Education Prevention (NAEP) Program, have focused attention on the characterization of severe asthma as shown in Table 1 (Jarjour, *et al.*, 2012). Compelling evidence suggests that patients with severe disease also represent a heterogeneous group that poses challenges in novel drug discovery (Jarjour, *et al.*, 2012; Lotvall, *et al.*, 2011). Despite attempts to clarify case definitions for severe asthma, few new therapeutics have been developed. The challenges in characterizing severe asthma and the use of metrics or clinical outcomes designed for less severe disease impede progress (Jarjour, *et al.*, 2012). The goals of this review are to summarize case definitions of severe asthma, review outcomes used recently in the approval of therapeutics in severe asthma and address new approaches to characterize the heterogeneity of these patients that may lead to composite metrics for drug discovery.

2. Current Metrics for Drug Discovery in Severe Asthma

The World Health Organization, the Global Initiative for Asthma (GINA) and the National Asthma Education Prevention (NAEP) Program recognize that global asthma morbidity and mortality are increasing (GINA; National Asthma Education and Prevention Program, 2007). Despite progress in understanding asthma, there remains an unmet need to develop new therapeutics in the management of the disease. In less severe asthma, long-acting bronchodilators, inhaled corticosteroids (ICS) and leukotriene modifiers have substantially improved asthma care. Today, most guidelines and federal agencies approving drugs have focused on specific domains that encompass asthma control. Accordingly, the development of new therapeutics must address such outcomes that include: objective measures of airflow [peak expiratory flow rate (PEFR) or spirometry], AHR, patient-reported outcomes (PRO) and asthma exacerbations. Although each of these outcomes measures unique aspects of the asthma diathesis, often such domains are interactive. Subjects with more severe airflow obstruction, as measured by objective measures of airflow, tend to have greater symptoms; however, the airway obstruction as measured by spirometry may not reverse as readily as PRO or exacerbation rates as described by the Severe Asthma Research Program (SARP) (Jarjour, *et al.*, 2012). Thus, there can exist a disconnect among symptoms, exacerbation rates and objective measures of airflow obstruction.

2.1. Lung Function

Classically, objective measures of airflow, namely, spirometry or PEFR, served as cornerstones in the approval of therapeutic agents in asthma management. Since asthma manifests as bronchoconstriction and airway inflammation, objective measures of airflow are still frequently used to characterize therapeutic efficacy. Additionally, AHR measured by provocation (cold air inhalation, methacholine, mannitol or adenosine challenges) may also serve as metrics to demonstrate therapeutic efficacy of candidate medications. Although these metrics are well studied in patients with mild asthma who manifest reversible airflow obstruction, most patients with severe asthma may manifest partial reversal of their airflow

obstruction as described in Table 1. Accordingly, FEV₁ and PEFr inadequately reflect the benefit of their medications. Indeed, omalizumab, an anti-IgE therapy, and bronchial thermoplasty were approved by the FDA in subjects with severe asthma with little evidence of improvement in FEV₁. In severe disease, the degree of bronchodilator reversibility in some subjects with asthma can become progressively impaired despite high-dose ICS (Ulrik & Backer, 1999). In a ten-year longitudinal study of asthma, investigators reported that 23% of non-smoking patients developed irreversible airflow obstruction, defined as < 9% acute bronchodilator reversibility and an FEV₁ < 80% predicted. Interestingly, this cohort at study entry also had marked bronchodilator reversibility despite treatment with high-dose ICS (mean doses of ICS 1500 µg) and/or oral steroids. Surprisingly, steroid therapy had little effect on the accelerated loss of pulmonary function (Ulrik & Backer, 1999). Others reported similar findings with longitudinal studies (Rasmussen, *et al.*, 2002). Goleva *et al* studied bronchodilator reversibility and glucocorticoid resistance. Subjects reported that some had no increase in FEV₁ in response to oral steroids and had a lower bronchodilator response than those who responded to steroids (Goleva, *et al.*, 2007). In a cross-sectional study, Hudon *et al* characterized the magnitude of response of bronchodilators in patients with complete and incomplete reversibility of airway obstruction (defined as restoration of the FEV₁% predicted to > 80% with either bronchodilator or corticosteroid therapy). These investigators showed that there exists little difference between absolute increase in FEV₁ after 200 µg of bronchodilator treatment in either group (Hudon, *et al.*, 1997). Collectively, evidence suggests that some patients are insensitive to glucocorticoids and lack bronchodilator responsiveness to β-agonists. As described in Tables 1 and 2, these patients manifest more severe disease. More recent data from the SARP in part challenges the paradigm. Macedo *et al*, using the SARP criteria (Table 1), defined a population of severe and non-severe subjects with asthma who had either a positive methacholine challenge or bronchodilator reversibility. Non-severe patients manifested a significantly lower percentage improvement in FEV₁ after bronchodilator response (9.5%) than those with severe asthma (20.9%). The absolute change (in ml) was not given, however, and patients with severe asthma had a mean FEV₁% predicted of 59% that was significantly lower than patients with non-severe asthma (84% predicted). The patients without severe disease approximate their maximum airway caliber despite lower percentage improvement after bronchodilator (Macedo, *et al.*, 2009). Moore *et al* also showed that the magnitude of the reversibility correlated with the level of baseline airway obstruction as FEV₁% but not with disease severity as shown in Table 2 (Moore, *et al.*, 2007). Severe patients had a lower FEV₁% predicted and a greater response to bronchodilators compared to that of subjects with mild asthma. Significant overlap, however, was observed such that patients with mild or severe disease had the same degree of bronchodilator reversibility. Curiously, bronchodilator response did not predict and may not characterize asthma severity. Collectively, the SARP data suggests that some patients with severe asthma may manifest reduced bronchodilator responsiveness since those patients required between 400-800 µg (twice the recommended dose for testing) of short-acting bronchodilator or β-agonist to achieve maximum bronchodilation. The aforementioned discussion suggests that severe asthma likely includes heterogeneous phenotypes, one of which manifests fixed airway obstruction with reduced bronchodilator response (Moore, *et al.*, 2010). The incidence of such phenotypes may approximate 15% of non-smoking patients with asthma (Jarjour, *et al.*, 2012; Ulrik & Backer, 1999). Taken together, assessment of therapeutic candidates in severe asthma should not solely utilize the objective measures of airflow as the cornerstone in determining efficacy; other metrics may be as important, if not more important, in predicting therapeutic effectiveness.

2.2. Patient-Reported Outcomes (PROs)

Asthma symptoms manifest as chest tightness, cough and wheezing. In addition, these symptoms will often limit activities of daily living and compromise exercise. Most asthma studies use a variety of valid and reliable PROs to evaluate therapeutic efficacy. Prior to the recent guidelines and the development of such tools, PROs were thought to be somewhat arbitrary and ambiguous. With the development of the Asthma Control Test (ACT), the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ), more systematic approaches to define PROs have been developed (Nathan, *et al.*, 2004). These questionnaires focus on activities of daily living, nocturnal awakenings and albuterol rescue therapy that correlate with severity of disease and asthma control. As shown in Table 1, assessment of new therapeutics in the management of severe asthma has incorporated these questionnaires but, to date, no drug has been approved solely using PROs. In part, assessment of PROs has shown that most subjects with asthma overestimate the control of their asthma (Fuhlbrigge, *et al.*, 2009; Marcus, *et al.*, 2008; Stanford, *et al.*, 2010). Further, physician assessment consistently underestimates asthma severity when compared to standardized tests (Boulet, *et al.*, 2002; Chapman, *et al.*, 2008; Meltzer, 2003). Others have clearly described that specific aspects of patient-reported symptoms improve at faster rates than others. For example, decreasing nocturnal awakenings are maximized after 30 days of ICS and long-acting bronchodilator therapy whereas maximum improvement in daytime symptoms or albuterol rescue use occurred after 150-200 days (Bateman, *et al.*, 2007). Collectively, the use of valid and reliable PROs has improved our understanding of the management of asthma. Regulatory agencies have embraced the use of such tools; however, the heterogeneity of the disease and the variable response to certain aspects of the questionnaires have seemingly limited the ability of such agencies to approve new medications based solely on PROs.

2.3. Asthma Exacerbations

Although asthma is a disease associated with intermittent symptoms, exacerbations of asthma requiring oral corticosteroids, hospitalizations or unscheduled physician visits greatly impact on quality of life, morbidity and mortality. Evidence suggests that risk of future exacerbations is associated with recent exacerbations, and risk of future steroid bursts is associated with recent steroid bursts (Miller, *et al.*, 2007). Surprisingly, despite the approval of a number of new medications to treat asthma from 1998 to 2009, in the United States, there has been little change in hospitalizations, missed work and school days, and emergency room visits over this interval (“Asthma Insight and Management,” 2009). Additionally, most patients do not experience exacerbations, and even those with severe disease may experience two or three asthma flares per year despite having poor quality of life and persistent daily symptoms. Needless to say, exacerbations or oral steroid treatment events have been used as a metric to characterize severe asthma (Jarjour, *et al.*, 2012). Recently, therapeutics including omalizumab and bronchial thermoplasty have used asthma exacerbations as metrics to assess efficacy. The infrequency of these events requires prolonged studies usually of one year’s duration that profoundly impacts on the cost of the drug development. Such challenges will likely hasten discovery of new approaches to “derisk” clinical trials in severe asthma. Further studies are necessary to identify and predict those patients who are more apt to sustain an exacerbation using biomarkers that could serve as surrogates to assess therapeutic value.

3. Lessons Learned

Since the formulation of improved case definitions of asthma by the World Health Organization, GINA and NAEP, therapeutic agents have recently been approved or reviewed by federal agencies in the treatment of severe asthma. Accordingly, we reviewed

the publicly available English literature from 1997 and surveyed using search terms for “severe asthma,” “asthma pathophysiology,” “airway hyperresponsiveness,” “bronchodilator,” “irreversible asthma,” “fixed airway obstruction,” “difficult asthma,” “reversibility,” “tumor necrosis factor,” “omalizumab,” “bronchial thermoplasty,” “irreversible airflow obstruction,” “non-reversible airflow obstruction,” “steroid-resistant asthma,” “length adaptation” and “airway remodeling.” All studies that addressed the diagnosis, pathology, physiology or treatment of severe asthma were reviewed for inclusion. Since the definitions of severe asthma were globally redefined in 1997, studies prior to 1997 were excluded. Given our search criteria, we examined eight studies with a combined subject recruitment of 1,424.

Although reversible airflow obstruction and improvement in FEV₁ have served as primary outcomes in the development of new therapeutics in mild to moderate asthma, such targets have not predicted clinical success or agency approval in severe asthma. New therapeutics aimed at improving severe asthma will be discussed within the context of responsiveness to β -agonists as measured by the FEV₁ or peak flow as well as review criteria used to approve the therapeutics for severe asthma (Table 3).

3.1. Anti-IgE Therapy

Omalizumab was the first agent approved for severe asthma on the basis of reduction in exacerbations and not on improvement in FEV₁. Omalizumab (Xolair®), which decreases the incidence of asthma exacerbations, is indicated for patients with moderate to severe disease whose symptoms persist despite corticosteroids (“Omalizumab Summary Basis of Approval,”). Although the pivotal trials were conducted in patients who demonstrated bronchodilator reversibility at the time of screening, omalizumab had little effect on spirometry in asthma. Challenge studies with omalizumab also failed to reduce BHR to methacholine (Djukanovic, *et al.*, 2004) but did show a reduction to an adenosine monophosphate (AMP) challenge (Prieto, *et al.*, 2006) (Table 3). Thus, the experience with omalizumab reveals a disconnect between effectiveness in reducing exacerbations and improvement in FEV₁ or other spirometric measures. Surprisingly, the lack of effect on FEV₁ occurred in the clinical cohort with known bronchodilator reversibility.

3.2. Anti-TNF α Therapy

The role of TNF α in severe asthma was recently reviewed, and several anti-TNF α monoclonal antibodies are in development for severe asthma (Brightling, *et al.*, 2008). A clinical study of an anti-TNF α monoclonal antibody reported improvement in symptoms, BHR, pulmonary function and symptoms (Howarth, *et al.*, 2005); however, a larger study in mild asthma failed to show improvement in BHR or airway inflammation biomarkers (Erin, *et al.*, 2006). A pivotal study was conducted in 309 patients with severe asthma who were treated with high-dose ICS with long-acting β -agonists (LABA) and/or oral steroids. The coprimary endpoints were trough FEV₁ and severe exacerbations (defined as the need for increased corticosteroids) (Wenzel, *et al.*, 2009). Entry criteria include at least one of the following measures within five years of the screening visit: bronchodilator reversibility, positive BHR to methacholine challenge or a 30% PEFR variability. The study was terminated early because of increased incidence of serious infections and malignancies (Wenzel, *et al.*, 2009) (Table 3). The study also did not meet either of the co-primary endpoints: improvement in trough FEV₁ or reduction in severe exacerbations defined as the need for an increase in oral steroids. Post hoc analysis revealed that select subgroups responded to the anti-TNF α therapy with a reduction in exacerbations but not with an increase in trough FEV₁. These responsive subgroups included: older patients, patients with later onset of disease, patients with FEV₁% predicted < the median value of 60.5 and patients with reversible disease. Interestingly, no effect was observed in FEV₁ in the highly

reversible severe asthma population. This trial again illustrated that the endpoint (FEV₁ or exacerbation) must fit both the target (TNF α) and the specific patient phenotype. If TNF α is a target for severe asthma, then either the endpoints or the patient population must be further refined since the broader population (“severe asthma”) and the chosen endpoints (FEV₁ and exacerbation) showed little benefit.

3.3. Bronchial Thermoplasty

Bronchial thermoplasty, a bronchoscopic intervention for severe asthma, purportedly targets smooth muscle function. The procedure involves the application of controlled thermal energy delivered to the airway wall via bronchoscopy to reduce smooth muscle mass. Despite the fact that all enrolled patients demonstrated BHR (methacholine PC₂₀ < 8 mg/mL) and that the therapy targets airway smooth muscle, there was no improvement in FEV₁ demonstrated in a pivotal trial (Castro, *et al.*, 2010). Instead, improvements in the asthma quality of life questionnaire (AQLQ), reductions in severe exacerbations and in health care utilization were noted during the follow-up period after active treatment (Castro, *et al.*, 2010). These results are consistent with the position that even when a therapy targeted a specific cell type that regulates bronchomotor tone, the FEV₁ did not predict the therapeutic benefit in severe asthma.

4. New Approaches

Asthma remains a complex, heterogeneous syndrome whose pathogenesis likely encompasses different etiologies and pathophysiologies. Many phenotypes exist as defined by physiology, triggers and inflammatory parameters (Lotvall, *et al.*, 2011). The majority of patients with asthma are atopic; however, 30% to 40% are non-atopic patients who are often overrepresented in severe asthma (Arbes, *et al.*, 2007; Jarjour, *et al.*, 2012; Moore, *et al.*, 2007). Over the past five years, SARP demonstrated specific clusters of patients that identify unique severe asthma cohorts. These disease clusters include older onset patients, variable allergic asthma and severe fixed airflow obstruction characterized by both eosinophilia and neutrophilia (Jarjour, *et al.*, 2012). Greater delineation of the specific cohorts using novel biomarkers found in sputum or in serum may prospectively identify such cohorts that will predict responsiveness to new therapeutics (Moore, *et al.*, 2010). Interestingly, current medication responses to ICS or bronchodilators do not necessarily correlate with such specific phenotypes (Moore, *et al.*, 2010). Conceptually, categorizing severe asthma by endotype, a subtype of a condition defined by a distinct functional or pathophysiologic mechanism, may have improved value in predicting therapeutic efficacy or disease progression (Holgate, 2011; Lotvall, *et al.*, 2011). Examples of such endotypes include aspirin-sensitive asthma, allergic bronchopulmonary mycosis and late-onset asthma. In each endotype, the asthma appears to be severe and relatively insensitive to current therapies. One of the major unmet needs in asthma lies with delivering personalized therapy via mechanism-specific approaches that are highly effective in specific endotypes of asthma. An understanding of severe asthma endotypes will likely guide federal agencies in predicting the efficacy of new therapeutics. Such strategies will be advantageous both in clinical study design and for the development of future targeted therapies.

5. Conclusions

Development of therapeutics in severe asthma has focused on inclusion of patients with bronchodilator reversibility and improvement in baseline pulmonary function. Until the Food and Drug Administration approval of omalizumab in 2003, the only approvable primary endpoint for asthma drugs in the US was change in FEV₁. Other symptomatic endpoints could be co-primary endpoints but superiority of the active over placebo required improvement in the FEV₁. Omalizumab was approved by showing a significant reduction in

asthma exacerbations defined as “a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose.” To support the registration of Advair® 500/50 in the US for severe asthma, improvement in PEFR (another expiratory pulmonary function endpoint) was also required. Both Advair® and Xolair® included only patients with bronchodilator reversibility, relying on bronchodilator reversibility as a diagnostic criterion for asthma and to exclude patients with COPD. The focus on reversibility to diagnose asthma excludes a distinct population of patients with severe asthma whose airways are unresponsive to bronchodilators. Longitudinal studies show that nearly 25% of non-smoking asthmatics who lack bronchodilator responsiveness may develop an accelerated loss of pulmonary function. This discrete asthma endotype differs in its response to current therapy, and the metric to study clinical drug development in these patients is challenging. Experience with severe asthma patients has also shown that, even with effective therapy, bronchodilator reversibility poorly correlates with improvements in FEV₁ over time. Importantly, no asthma therapy to date re-establishes bronchodilator responsiveness in patients with irreversible airway obstruction.

International treatment guidelines (GINA and Expert Panel Report 3) strongly recommend that asthma should be managed to maximize control; yet little information is available on the correlation between any measure of asthma control and the basic pathophysiology in severe asthma. Measures of asthma control, such as AQLQ or ACT (Juniper, *et al.*, 2006) may offer more value in predicting efficacy in patients with fixed airway disease. Asthma exacerbations, a suitable endpoint for studies in severe disease, offer opportunity; however, the large numbers of research subjects and study duration pose substantial financial hurdles for drug approval (Reddel, *et al.*, 2009).

Limited clinical drug trials in severe asthma exist, hindering our ability to match the fixed airway cohort of severe asthma to the most appropriate outcome measure. Today, researchers face a conundrum in which only reversible patients are chosen for study, and only patients with improvements in FEV₁ are considered to have a therapeutic response. Significant portions of patients with severe asthma have little bronchodilator reversibility, and even those that can improve FEV₁ do not show improvement in exacerbation rates. We postulate that composite outcomes using PROs and surrogates for predicting asthma exacerbation rather than objective measures of airflow will foster more rapid drug approval to meet a profound unmet need in improving the management of severe asthma. Further, our understanding of the basic pathophysiology of severe asthma remains incomplete. Studies of severe asthma endotypes will engender a personalized medicine approach that may expedite clinical trials in severe asthma by better defining subjects with unique pathophysiology.

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Abbreviations

ACT	Asthma Control Test
AHR	Airway hyperresponsiveness
AMP	Adenosine monophosphate
AQLQ	Asthma Quality of Life Questionnaire
BHR	Bronchial hyperresponsiveness
COPD	Chronic obstructive pulmonary disease

FEV₁	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
LABA	Long-acting β -agonist
PEFR	Peak expiratory flow rate
SARP	Severe Asthma Research Program
TNFα	Tumor necrosis factor-alpha

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Table 1**Criteria for the Diagnosis of Severe Asthma (SARP)**

Major Criteria: Need 1
Treatment with continuous or near continuous (50% of year) oral corticosteroids
Requirement for treatment with high-dose inhaled corticosteroids
Minor Criteria: Need 2
Requirement for additional daily treatment with a controller medication (e.g., LABA, theophylline or leukotriene antagonist)
Asthma symptoms requiring short-acting β -agonist use on a daily or near-daily basis
Persistent airway obstruction ($FEV_1 < 80\%$ predicted, diurnal peak expiratory flow variability $> 20\%$)
One or more urgent care visits for asthma per year
Three or more oral steroid bursts per year
Prompt deterioration with a 25% reduction in oral or inhaled corticosteroid dose
Near-fatal asthma event in the past

Table 2

Lung Function Characteristics of SARP Cohort (Moore *et al.*, 2007)

Baseline Lung Function	Mild	N	Moderate	N	Severe	N	P value*
FEV ₁ % predicted	94 ± 11	164	66 ± 11	70	62 ± 22	204	<0.0001
FVC % predicted	100 ± 12		81 ± 13		77 ± 20		<0.0001
FEV ₁ /FVC (%)	80 ± 7		67 ± 10		65 ± 13		<0.0001
Best lung function		157		60		185	
FEV ₁ % predicted	102 ± 11		79 ± 12		77 ± 21		<0.0001
FVC % predicted	103 ± 13		91 ± 14		91 ± 18		<0.0001
Maximal % change in FEV ₁	9 ± 7		20 ± 16		20 ± 24		<0.0001
Methacholine PC 20 (log mg/mL)	0.24 ± 0.62	133	-0.11 ± 0.54	46	-0.06 ± 0.7	87	0.002

Three way comparison, significant because of differences between mild vs. moderate and severe. The magnitude of bronchodilator reversibility (9% vs. 20% and 20%, for mild vs. moderate and severe, respectively) correlated with the level of FEV₁ % predicted, P < 0.0001 (94% vs. 66% and 62% for mild vs. moderate and severe, respectively) but not with disease severity classification (mild, moderate or severe).

Table 3

Severe Asthma Clinical Studies Examined

Author	Design	Key Inclusion	Key Exclusion	N	Demographics	Major Findings
(Holgate, <i>et al.</i> , 2006)	R, DB, PC, 32-week steroid stable phase, 16-week steroid reduction phase	<ol style="list-style-type: none"> 1 1000 µg fluticasone ± LABA 2 + skin test 3 IgE 30-700 IU/mL 	<ol style="list-style-type: none"> 1 Other asthma meds 2 History (hx) of anaphylaxis 3 Hx of infection within 4 weeks 	246	<ol style="list-style-type: none"> 1 FEV₁ % predicted 62.9-66% 2 Mean BD reversibility 18.6-20.6% 	<ol style="list-style-type: none"> 1 Significant reduction in fluticasone dose active vs. placebo, p = 0.003 2 Significant percentage of patients with 50% reduction in fluticasone dose, p=0.001 3 Insignificant change in FEV₁
Djukanovic, <i>et al.</i> , 2004	R, DB, PC, 16 weeks, airway hyperresponsiveness Sputum induction, bronchoscopy	<ol style="list-style-type: none"> 1 Steroid naïve 2 IgE 30-700 IU/mL 3 Sputum eosinophilia of 2% 4 PC₂₀ methacholine < 8 mg/mL 		45	<ol style="list-style-type: none"> 1 FEV₁ % predicted 84%-86% 2 Geometric Mean MCh PC₂₀ mg/mL Active 1.01 Placebo 0.54 	<ol style="list-style-type: none"> 1 Significant reduction in sputum eosinophilia active vs. placebo, p<0.05 2 Insignificant change in AHR active vs. placebo, p=0.14
Prieto, <i>et al.</i> , 2006	R, DB, PC, 12-week treatment, AMP challenge at weeks 4 and 12	<ol style="list-style-type: none"> 1 Mild-moderate asthma on low-med ICS treatment 2 FEV₁ % predicted 80% 3 IgE 30-700 IU/mL 4 + AMP 5 + MCh challenge studies 	<ol style="list-style-type: none"> 1 Smoking hx 2 Hx of infection within 4 weeks 	34	<ol style="list-style-type: none"> 1 FEV₁ % predicted 100-101.4 2 Geometric Mean PC₂₀ for MCh 1.27-2.13 3 PC₂₀ for AMP 14.32-31.20 	<ol style="list-style-type: none"> 1 Changes in AMP doubling concentrations were significantly different at 4 weeks (p=0.02) but not 12 weeks (p=0.24) between active and placebo 2 Insignificant difference in change in MCh doubling concentrations at 4 or 12 weeks between active and placebo 3 Insignificant increase in FEV₁
Howarth, <i>et al.</i> , 2005	Open label, uncontrolled, 12-week treatment, ACQ, PEFR, FEV ₁ , MCh challenge, sputum induction, biopsy	<ol style="list-style-type: none"> 1 Severe asthma, treatment with high dose ICS + prednisone 2 Hx of bronchodilator reversibility 	<ol style="list-style-type: none"> 1 Smoking hx 2 Hx of TB 3 Hx of autoimmune diseases 	17	<ol style="list-style-type: none"> 1 Severe asthma 2 FEV₁ % predicted 68.3 3 Treatment with high dose ICS, prednisone, LABA, LTRA, theophylline 	<ol style="list-style-type: none"> 1 Significant reduction in ACQ from 3.71 to 1.57, p<0.001 2 Significant increase in trough FEV₁, p=0.01 3 Significant increase in doubling concentration MCh, p=0.033

Author	Design	Key Inclusion	Key Exclusion	N	Demographics	Significant Findings
Erin, <i>et al.</i> , 2006	R, DB, PC, 6 weeks, PEFR, eNO, FEV ₁ , sputum induction	<ol style="list-style-type: none"> 1 FEV₁ % predicted between 40%-90% 2 Bronchodilator reversibility 3 Treatment with ICS 	<ol style="list-style-type: none"> 1. Treatment with other asthma medications except short-acting bronchodilators 	38	<ol style="list-style-type: none"> 1 FEV₁ % predicted 66.4%-69.9% 2 Bronchodilator reversibility 23%-26% 3 ICS dose ~ 600-750 µg/day 	<ol style="list-style-type: none"> 1 Insignificant change in AM/PM PEFR, p=0.09 and 0.14, respectively 2 Significant worsening in diurnal variation in PEFR, active vs. placebo, p=0.02 3 Insignificant change in FEV₁ from baseline in active group, p=0.88 4 Insignificant change in eNO 5 Insignificant change in sputum cell counts
Wenzel, <i>et al.</i> , 2009	R, DB, PC, dose-ranging, 52-week study, trough FEV ₁ , number of severe exacerbations	<ol style="list-style-type: none"> 1 Severe asthma 2 Treatment with high dose ICS + LABA 3 2 exacerbations in past year 4 Bronchodilator reversibility within 5 years or AHR or 30% diurnal PEFR variability 	<ol style="list-style-type: none"> 1. Smoking hx 	309	<ol style="list-style-type: none"> 1 FEV₁ % predicted 58.9%-60.9% 2 Bronchodilator reversibility 15.6%-17.8% 3 ACQ 2.9-3.1 	<ol style="list-style-type: none"> 1 Insignificant change in postbronchodilator FEV₁ % predicted, p values range from 0.357 to 0.945 2 Insignificant change in exacerbations, p values range from 0.256 to 0.779
Castro, <i>et al.</i> , 2010	R, DB, sham-controlled, 3 treatments 3 weeks apart; treatment with radiofrequency ablation of airway smooth muscle	<ol style="list-style-type: none"> 1 Treatment with high dose ICS + LABA 2 Other asthma medications allowed 3 AQLQ score 6.25 4 FEV₁ % pred >60% 5 PC₂₀ to methacholine < 8 mg/mL 	<ol style="list-style-type: none"> 1 Smoking hx 2 3 lower respiratory infections 3 4 pulses of oral steroids 4 3 hospitalizations for asthma in past year 	297	<ol style="list-style-type: none"> 1 FEV₁ % pred 77.8%-79.7% 2 PC₂₀ mg/mL Geometric mean 0.27-0.31 	<ol style="list-style-type: none"> 1. Insignificant difference between treatment and sham in change from baseline in integrated AQLQ measured at 6, 9 and 12 months where treatment baseline went from 5.71 to 5.80 at 12 months and sham baseline went from 5.49 to 5.56 at 12 months

Abbreviations Used in Table 3

ACQ: Asthma Control Questionnaire, a validated instrument to assess asthma stability, developed by E.F. Juniper (*Juniper, et al., 2006*)

AHR: Airway hyperresponsiveness, also known as bronchial hyperresponsiveness or BHR

AMP: Adenosine monophosphate, an agent used to provoke airway constriction/inflammation

AQLQ: Asthma Quality of Life Questionnaire, a validated instrument to assess changes in quality of life, developed by E.F. Juniper (*Juniper, et al., 2006*)

BD: Bronchodilator

DB: Double blind

eNO: Exhaled nitric oxide, a biomarker of airway inflammation

Hx: History

ICS: Inhaled corticosteroid

LABA: Long-acting β -agonist

LTRA: Leukotriene receptor antagonist

MCh: Methacholine challenge, a measure of BHR

PC: Placebo-controlled

PEFR: Peak expiratory flow rate, the greatest velocity of air flow achieved during a maximal expiratory effort

R: Randomized

TB: Tuberculosis