New Drugs for Asthma

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The goal of asthma therapy is to reduce symptoms to the extent that patients can lead active, unlimited lives and to minimize concern about exacerbations. Unfortunately, despite advances in our understanding of the pathophysiology of asthma and the existence of consensus asthma-management guidelines, patients with asthma still suffer considerable morbidity and, on rare occasions, death. Part of the reason for suboptimal asthma control is poor adherence, by both providers and patients, to the recommended asthma regimens and guidelines. However, even under the ideal circumstances of a motivated patient and a knowledgeable physician, the available asthma drugs are not effective in all patients at all times. The market for asthma drugs has been dynamic; numerous new products have recently been approved for marketing by the Food and Drug Administration. Unfortunately, the products recently approved and those likely to enter the market soon mostly are either reformulations or combinations of established molecules. Developing new drugs to treat asthma, particularly with novel anti-inflammatory properties, should be a priority.
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Introduction

Asthma is characterized by airway inflammation and bronchial hyperresponsiveness. The airway inflammatory response in asthma is complex and involves multiple cell types and mediators.[1] Infiltration of airway walls by eosinophils is found in most but not all patients with asthma. Airway neutrophilia occurs in patients with severe asthma[2] and also in asthma exacerbations.[3] Mast cells and dendritic cells play an important role in processing the inflammatory response to inhaled allergens. Increasing attention is being directed to the role of regulatory T cells in mediating immunodysregulation in allergic diseases such as asthma.[4] Resident airway cells, such as epithelial and smooth-muscle cells, play a role in the airway inflammation in asthma by releasing inflammatory mediators. Numerous mediators have been implicated in the pathogenesis of asthma,

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Table 1. Drugs Currently Approved by the Food and Drug Administration to Treat Asthma

Drug	Formulation	Brand Name
Inhaled Corticosteroids		
Beclomethasone dipropionate	HFA MDI	Qvar
Budesonide	DPI	Pulmicort Flexhaler
Ciclesonide	HFA MDI	Alvesco
Flunisolide	CFC MDI	Aerobid, Aerobid-M
Fluticasone propionate	HFA MDI	Flovent HFA
	DPI	Flovent Diskus
Mometasone furoate	DPI	Asmanex Twisthaler
Triamcinolone acetonide	CFC MDI	Azmacort
Inhaled Short-Acting β_2 Agonists*		
Albuterol	HFA MDI	Proventil HFA, Ventolin HFA, ProAir HFA
	CFC MDI	Generic products
	Nebulized	Generic products
Levalbuterol	HFA MDI	Xopenex HFA
	Nebulized	Xopenex Inhalation Solution
Pirbuterol	CFC MDI	Maxair Autohaler
Metaproterenol	CFC MDI	Alupent
Inhaled Long-Acting β_2 Agonists†		
Salmeterol xinafoate	DPI	Serevent Diskus
Formoterol fumurate	DPI	Foradil Aerolizer
Combination Products		
Salmeterol xinafoate/fluticasone propionate	HFA MDI	Advair HFA
	DPI	Advair Diskus
Formoterol/budesonide	HFA MDI	Symbicort
Miscellaneous Products		
Theophylline	Oral	Uniphyl and generic products
Cromolyn sodium	CFC MDI	Intal
Omalizumab	Subcutaneous injection	Xolair
Montelukast	Oral	Singulair
Zileuton	Oral	Zyflo CR
Zafirlukast	Oral	Accolate

* Inhaled short-acting β_2 agonists generally are not indicated specifically for asthma, but, rather, for the relief of the symptoms of bronchospasm as part of reversible obstructive airways disease and for exercise-induced bronchospasm.
† Nebulizer formulations of formoterol and arformoterol are also commercially available but are not indicated for the treatment of asthma.
HFA = hydrofluoroalkane
MDI = metered-dose inhaler
DPI = dry-powder inhaler
CFC = chlorofluorocarbon

including histamine, chemokines, cytokines, cysteinyl-leukotrienes, nitric oxide, and immunoglobulin E (IgE). Bronchospasm is intimately related to the airway inflammatory response in asthma.

Understanding that the pathophysiology of asthma involves both airway inflammation and bronchial hyperresponsiveness has been fundamental to developing treatment strategies. National[1] and international guidelines[5] recommend anti-inflammatory medications to control airway inflammation as the basic pharmacologic approach to asthma management. In those guidelines, inhaled corticosteroids (ICS) are the preferred anti-inflammatory medication for all patients with persistent asthma. ICSs effectively control airway inflammation,[6-8] improve lung function,[9] reduce respiratory symptoms related to asthma,[9] and decrease both hospitalizations for asthma exacerbation[10] and the risk of death from asthma.[11] Other anti-inflammatory medications useful for treating asthma, but considered secondary to ICSs, are leukotriene-modifying agents and humanized monoclonal antibodies to IgE.[1] In addition to emphasizing controlling airway inflammation, the guidelines recommend that all asthma patients have available inhaled short-acting β_2 agonists to manage symptoms from acute bronchospasm.[1,5] Inhaled long-acting β_2 agonists (LABAs) help control symptoms in patients with more severe asthma.[1,5] Table 1 lists the ICSs and bronchodilators currently available in the United States for treatment of asthma.

Unfortunately, despite advances in our understanding of the pathophysiology of asthma and the existence of consensus asthma-management guidelines,[1,5] patients with asthma still suffer considerable morbidity. Surveys in the United States and around the world document that asthma patients are frequently limited in their ability to perform daily and leisure activities.[12,13] A recent telephone survey of 10,428 asthma patients in Canada revealed that 59% had uncontrolled asthma.[14] Asthma is a frequent cause of emergency-department visits (1.8 million per year) and hospitalizations (489,000 per year) in the United States.[15] Fortunately, deaths from asthma in the United States are relatively low (3,780 deaths attributed to asthma in the United States in 2004, which is an annual mortality rate of 1.3/100,000).[15] A worrisome aspect of asthma mortality, though, is that most asthma-related deaths occur outside the hospital,[16] which suggests that asthma exacerbation still is a serious risk.

The goal of asthma therapy is to reduce symptoms to the extent that patients can lead active, unlimited lives, and to minimize concern about exacerbations.[1,5] As the statistics reviewed above indicate, for many patients these goals are not achieved. There are multiple reasons that asthma control is not more uniformly achieved. Many health care providers do not provide consistent care per the asthma guidelines,[17] and even when appropriate care is provided, many patients do not adhere to the prescribed treatment regimens.[18,19] However, another concern is that available medications might not be effective in all patients. An example of the limitations of guideline-recommended regimens in achieving asthma control can be seen in the results of the Gaining Optimal Asthma Control study.[20] In that 1-year prospective randomized double-blind parallel-group study, 3,421 patients with uncontrolled asthma were assigned to either an ICS or a combination of an ICS and a LABA. The ICS dose was increased if the asthma was not controlled. Both treatment regimens were effective in improving asthma control, but at study end only 77% of the patients who received the combination therapy, and just 68% of those on the ICS alone, had well-controlled asthma (Fig. 1). A smaller percentage had totally controlled asthma. A substantial minority of patients (23% on ICS plus LABA, and 32% on ICS alone) did not have their asthma well-controlled, even though the treatment followed guideline recommendations and was provided under the rigorous conditions of a clinical trial.

The stakes with asthma are high. Asthma is both chronic and common. In the United States, estimates from the 2005 National Health Information Survey suggest that 32.6 million Americans have, at some point in their life, been told they have asthma, and 22.2 million Americans currently suffer from asthma. Besides the human suffering, the economic impact through both direct (eg, medications, health care visits, hospitalizations) and indirect (eg, loss of productivity, work absence) costs are enormous: possibly more than $19.7 billion annually.[15] Limitations in our ability to effectively manage asthma have been well described. Although both health care providers and patients bear responsibility for the poor adherence to the prescribed regimens, it also must be appreciated that, even under the ideal circumstances of a motivated patient and a knowledgeable physician, the asthma drugs currently available will not be effective in all patients at all times. Developing new drugs to treat asthma should be a priority.

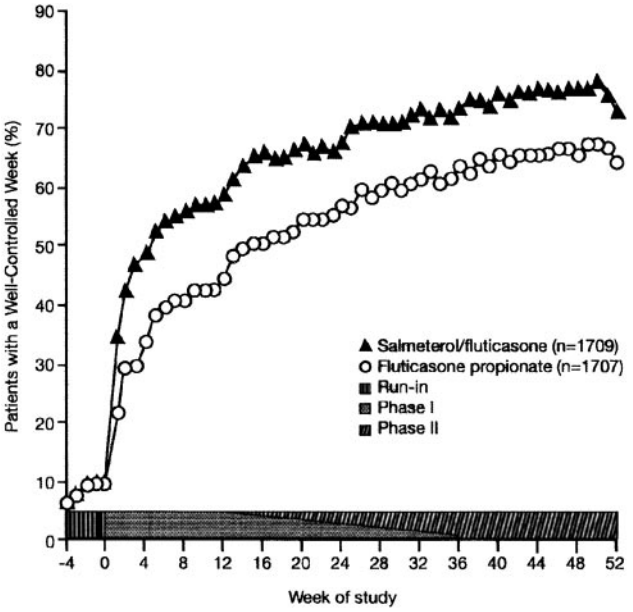

Fig. 1. Proportion of patients in the Gaining Optimal Asthma Control study who achieved a week of well-controlled asthma during the study. The proportion who had a well-controlled week was significantly higher among patients treated with salmeterol plus fluticasone than among those who took fluticasone alone. A substantial minority of the patients did not have a well-controlled week by study end (week 52). (From Reference 20, with permission.)

Drugs Recently Approved to Treat Asthma

The market for asthma drugs has been dynamic: numerous new products have recently been approved for marketing by the Food and Drug Administration (FDA). The combination product budesonide plus formoterol in a metered-dose inhaler (MDI) (Symbicort, AstraZeneca, Wilmington, Delaware) was approved in 2006 but only became commercially available for use in the long-term maintenance treatment of asthma in 2007. There are several advantages to this ICS plus LABA combination. It more effectively controls asthma symptoms and reduces the risk of asthma exacerbation than does a higher dose of ICS alone.[21] Although formoterol does not confer additional anti-inflammatory benefits to budesonide,[22] formoterol is an effective bronchodilator, with both a rapid onset

of action (within minutes, similar to albuterol) and a prolonged effect (approximately 12 h, similar to salmeterol).[23] In the United States this combination is approved only for maintenance therapy in asthma, but in Europe there has been considerable interest in using this combination as both a maintenance and a reliever therapy. In large clinical trials that lasted 6–12 months, asthma patients randomized to treatment with the budesonide plus formoterol combination as maintenance therapy and also allowed to use it as needed for rescue therapy had fewer asthma exacerbations, more effective symptom control, and better lung function than those who used a traditional treatment regimen that included a short-acting β_2 agonist for symptom control.[24-26] The FDA-approved label for this product includes a black box warning, though, about risks related to LABA. A worldwide safety trial, which randomized 18,124 asthma patients to either formoterol or albuterol for rescue relief, provided reassuring data on the safety profile of formoterol used as rescue medication. In that study the safety profile of formoterol was similar to that of albuterol, and formoterol-treated patients had fewer asthma exacerbations.[27]

Ciclesonide (Alvesco, Sepracor, Marlborough, Massachusetts), an ICS formulated as a small-particle solution aerosol with a hydrofluoroalkane (HFA) propellant MDI, was approved in 2008 for the prophylactic treatment of asthma. With regular use, ciclesonide effectively controls asthma symptoms and improves lung function.[28,29] Interestingly, ciclesonide was administered once daily in those studies, but only twice-daily dosing has been approved by the FDA. In patients with severe asthma who required oral corticosteroids, high-dose twice-daily ciclesonide facilitates oral corticosteroid tapering.[30] The intriguing aspect of ciclesonide is its potentially advantageous safety profile. It has low oral bioavailability and high intravascular protein binding. These 2 features result in a much lower level of free ciclesonide in the systemic circulation and, thus, less systemic adverse effect.[31] Rigorous studies designed to evaluate the systemic effects of ciclesonide found no evidence of hypothalamic-pituitary-adrenal axis suppression in adults[32] and no growth suppression in children.[33] Unfortunately, ciclesonide has not been approved by the FDA for use in children.

Remarkable changes in the portfolio of inhalable asthma drugs have occurred through reformulation of established molecules. Because of environmental concerns about chlorofluorocarbon (CFC), the FDA mandated that all albuterol MDI products with CFC propellant be withdrawn from the market by December 2008.[34] Three new HFA-propelled albuterol products have been approved by the FDA and will replace generic CFC albuterol. Another formulation that recently became available is an HFA-propelled levalbuterol MDI (Xopenex, Sepracor, Marlborough, Massachusetts). The HFA-propelled albuterol products have comparable efficacy and similar safety profiles to the CFC albuterol MDIs they are replacing. However, there are differences in the taste and feel of the aerosol spray between the HFA and CFC albuterol MDIs. The HFA albuterol MDIs emit a softer, warmer aerosol spray than the CFC albuterol MDIs (Fig. 2). Patients may notice this difference when they begin using an HFA albuterol MDI. As with all MDIs, patients should be advised to regularly clean the actuator of an HFA MDI.

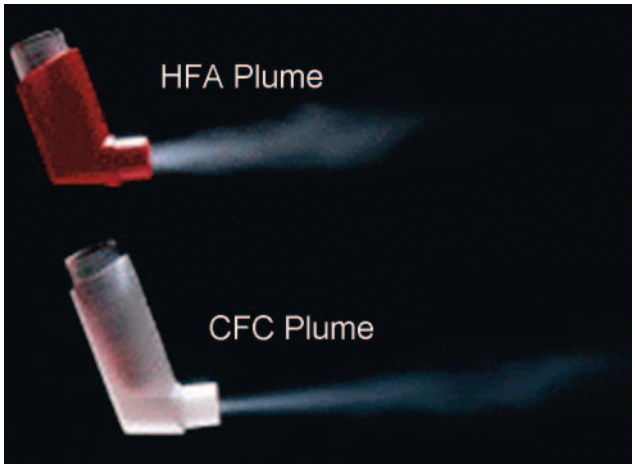

Fig. 2. Aerosol plumes from albuterol metered-dose inhalers propelled by hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC). The HFA-propelled plume is smaller and less jet-like. Patients may notice a reduced spray force, different taste, and warmer spray with HFA albuterol. (Courtesy of Teva Specialty Pharmaceuticals, Jerusalem, Israel.)

Other recently approved reformulated drugs include budesonide and a combination product of salmeterol xinafoate plus fluticasone propionate (Advair, GlaxoSmithKline, Research Triangle Park, North Carolina). Budesonide had been available in the Turbuhaler (AstraZeneca, Wilmington, Delaware), but that product was withdrawn from the market and replaced with the Flexhaler. With that transition from one type of powder inhaler to another, there was a notable change in the dosing recommendation for budesonide: once-daily dosing is no longer approved. The combination salmeterol xinafoate plus fluticasone propionate product is now available in both a powder inhaler (Diskus) and an HFA-propelled MDI. There are 3 different strengths of each formulation, which correspond so that 2 puffs of the MDI formulation of a given strength will provide similar drug content to one inhalation of the powder formulation.

Two drugs have been approved in 2007 that, although not specifically indicated for the treatment of asthma, might be used in asthma patients. Formoterol fumarate, formulated for nebulization (Perforomist, Dey, Napa, California), is indicated in chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It

is an effective bronchodilator, with both a rapid onset of action (substantial effects are detectable at 5 min after administration) and a prolonged duration (substantial effects for 12 h).[35] No cardiac safety concerns were found in a study of older (mean age 62.8 y) patients with COPD, who received nebulized formoterol furoate twice daily for 12 weeks.[36]

Arformoterol tartrate (Brovana, Sepracor, Marlborough, Massachusetts), which is the (R,R) isomer of formoterol, was also approved in 2007 for use in patients with COPD. It is administered via nebulization, and its bronchodilating properties are similar to those of formoterol fumarate.[37,38] Interestingly, an in vitro study found that arformoterol tartrate is physically compatible with 3 other commercially available nebulized drugs: acetylcysteine, ipratropium bromide, and budesonide.[39] Although combining nebulized drugs might be convenient, the authors of that study pointed out that the impact of co-administration of various nebulized drugs on clinical safety and efficacy is uncertain.

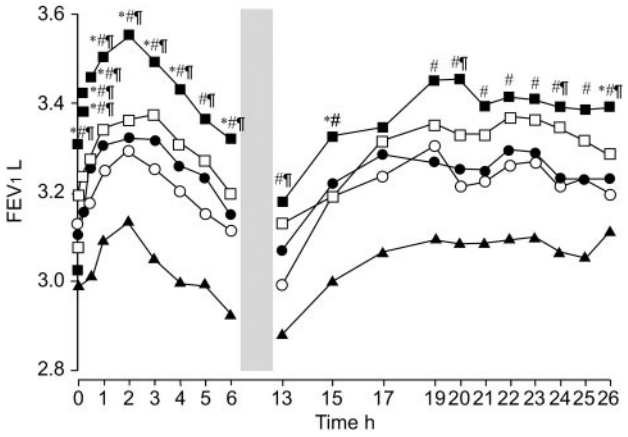

Fig. 3. The effects of a single dose of indacaterol on forced expiratory volume in the first second (FEV_1, a standard measure of bronchodilation) over 26 hours.[41] The shaded portion of the graph indicates sleep. ▲ = placebo. ○ = indacaterol 50 μg. ● = indacaterol 100 μg. □ = indacaterol 200 μg. ■ = indacaterol 400 μg. * $p < 0.05$ vs 200 μg. # $p < 0.05$ vs 100 μg. ¶ $p < 0.05$ vs 50 μg. (From Reference 41, with permission.)

Drugs Most Likely to Be Approved in the Near Future for Asthma

The pharmaceutical industry is intensely interested in developing new drugs for the asthma market. Multiple products are currently in late-phase development. Unfortunately, the products likely to enter the market in the near future are mostly combinations of established molecules, particularly combinations of ICS and LABA. The preferred LABA is formoterol because of its rapid onset of action. Clinical development projects are in process with formoterol plus fluticasone propionate (Abbott/Skye Pharma/Mundipharma collaborative effort), mometasone (Novartis/Schering-Plough collaborative effort), and ciclesonide (Sepracor/Nycomed collaborative effort). The formoterol-fluticasone propionate and formoterol-mometasone products might be commercially available as early as 2009. The formoterol-ciclesonide combination will probably not be available until at least 2013.

There is also interest in developing bronchodilators with a prolonged duration of effect. Inhalable ultra-long-acting β_2 agonists are particularly attractive for use in asthma.[40] Of the molecules in this class the most advanced in terms of clinical development seems to be indacaterol. In a dose-response study that included 42 patients with stable asthma, single doses of 200 μg and 400 μg of indacaterol via an HFA MDI significantly increased the forced expiratory volume in the first second (FEV_1) within 5 min.[41] The bronchodilator effect of both doses was maintained throughout 24 hours (Fig. 3). The increase in FEV_1 was numerically, but not significantly, greater with the 400-μg dose than with the 200-μg dose throughout 24 hours. Both doses were well-tolerated and there were no obvious safety concerns. A subsequent clinical trial confirmed that indacaterol provides statistically significant and clinically meaningful bronchodilation for 24 hours with repeated dosing for over 7 days, and suggested that the 200 μg dose in patients with asthma provided the best safety-efficacy profile.[42] Interestingly, in patients with COPD, indacaterol doses up to 800 μg are well-tolerated with repetitive dosing for 28 days.[43] Indacaterol could be available in the United States by 2011.

Asthma Drugs and Products With an Uncertain Future

Clinical trials have been performed with various novel compounds for the treatment of asthma, but the results have not been convincing. There has been considerable speculation that interleukin-5 (IL-5) plays a fundamentally important role in mediating the airway eosinophilic inflammation and remodeling in asthma. For instance, an IL-5-deficient mouse had significantly less peribronchial fibrosis and smooth-muscle thickness after sensitization to ovalbumin, which is a standard animal model of induced asthma.[44] Consequently, several companies developed humanized monoclonal antibodies (SCH55700 [Schering-Plough, Kenilworth, New Jersey] and mepolizumab [GlaxoSmithKline, Research Triangle Park, North Carolina]), which block the binding of human IL-5 to the α chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Unfortunately, initial studies in humans with monoclonal antibodies to IL-5 showed only partial efficacy. In atopic asthmatics, 3 infusions of this product decreased eosinophils in bronchoalveolar lavage fluid and deposition

of proteins in the bronchial subepithelial basement membrane.[45] However, a study in patients with mild asthma showed only a partial effect from monoclonal IL-5 antibodies on airway eosinophils, and no corresponding improvement in lung function.[46] Similarly, a single infusion of monoclonal IL-5 antibodies to patients with mild asthma lowered blood and sputum eosinophilia but did not improve airway hyperresponsiveness.[47] In a small study with patients with severe persistent asthma, a single dose of monoclonal IL-5 antibodies reduced blood eosinophil count, but caused only small and inconsistent effects on FEV_1.[48] In a more definitive study, the effects of 3 monthly infusions of monoclonal IL-5 antibody were assessed in 362 asthma patients with persistent symptoms despite use of ICS. Treatment significantly reduced blood and sputum eosinophilia, but there was no clinically relevant improvement in asthma symptoms, lung function, or exacerbation rate.[49] Future clinical development of a monoclonal antibody against IL-5 seems unlikely.

Another cytokine thought to play a critical role in mediating the allergic inflammation in asthma is IL-4. This cytokine enhances IgE-mediated immune responses, promotes inflammatory cell migration into the asthmatic lung, and plays a role in the differentiation of T helper 2 (Th2) cells, which drive the allergic phenotype.[50] Several products were developed to interfere with IL-4 activity, including a soluble decoy receptor (nuvance, Immunex), and a humanized anti-IL-4 monoclonal antibody (pascolizumab, Protein Design Labs/GlaxoSmithKline). Unfortunately, numerous clinical trials with these IL-4 products found no clinical benefit. Development of an IL-4 inhibitor seems unlikely, although there is interest in designing drugs that inhibit multiple cytokines, including IL-4.

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that has been implicated as a possible important mediator of airway inflammation in asthma.[51] Currently available products that block the effect of TNF-α are etanercept (Enbrel, Wyeth, Berkshire, United Kingdom), which is a TNF-α receptor-immunoglobulin G Fc fusion protein, and infliximab (Remicade, Centocor, Malvern, Pennsylvania), which is a recombinant human-murine chimeric monoclonal antibody directed against the soluble TNF-α homotrimer and its membrane-bound precursor. Small clinical trials have suggested that either etanercept or infliximab might provide clinically meaningful improvement in patients with moderate-to-severe asthma. In 15 patients with severe asthma and substantially elevated airway TNF-α, etanercept was given via subcutaneous injection twice weekly for 12 weeks, as additional therapy to ICS.[52] At study end the patients were less often bothered by asthma symptoms, FEV_1 significantly improved, and bronchial hyperresponsiveness decreased. Three infusions of infliximab were given over 6 weeks to 17 patients with moderate-to-severe asthma already on ICS.[53] Infliximab significantly reduced sputum TNF-α. There was no improvement in morning peak expiratory flow with infliximab treatment over the 12-week study, but the infliximab-treated patients, compared to control patients who received placebo, had significantly fewer moderate asthma exacerbations. In 10 patients with mild-to-moderate asthma on ICS, treatment with etanercept for 10 weeks decreased peripheral-blood monocyte-membrane-bound TNF-α and improved FEV_1, asthma symptoms, and bronchial hyperresponsiveness.[54] The results from these small studies are encouraging, but large clinical trials are needed for confirmation. Most important in these larger clinical trials will be determining whether only patients with elevated TNF-α benefit. If clinical trials do confirm the safety and efficacy of these products, the earliest they could become commercially available in the United States would be 2011.

A fascinating nonpharmacologic approach to asthma therapy is also being evaluated. Bronchial thermoplasty (Alair System, Asthmatx, Mountain View, California) delivers controlled radiofrequency energy to the airways, which essentially heats the bronchial tissue and damages the airway smooth muscle. Pilot studies in humans confirmed that controlled application of radiofrequency energy to airway walls reduces airway smooth muscle in a limited area without damaging surrounding lung.[55,56] Early clinical trials have been encouraging, reporting clinically meaningful improvements in asthma symptoms, lung function, and bronchial hyperresponsiveness.[57,58] Follow-up of patients through 2 years after the procedure found no delayed safety concerns, but there were potentially important safety issues during the immediate post-procedure period. For up to a week after the procedure the patients reported various respiratory-related adverse events. In one recent study, hospitalization for respiratory-related adverse events was reported in 4 of 15 patients (27%) within 1–2 days of bronchial thermoplasty.[59] Further clinical development of bronchial thermoplasty will require a careful exploration of its risks and benefits.

Potential Future Drugs for Asthma Treatment

As scientific advances in our understanding of the pathophysiology of asthma continue, the pharmaceutical industry has an increasing number and variety of targets to address in developing new compounds to treat asthma.[60-63] These compounds fall into 4 domains of pharmacologic activity (Table 2). The domain with the largest number of drugs in clinical trials is intracellular signal trafficking, which includes bronchodilators (muscarinic antagonists or β_2-receptor agonists), corticosteroids (especially molecules that are dissociated in effect [ie, effective anti-inflammatories that have lower systemic activity]), and phosphodiesterase inhibitors. Another domain includes drugs that

Table 2. Domains of Pharmaceutical Activity in Developing New Drugs for Asthma

Intracellular Signal Trafficking
Muscarinic antagonists
β_2 receptor antagonists
Novel corticosteroids
Phosphodiester inhibitors
Lipoxygenase inhibitors
Nuclear factor kappa β inhibitors
Syk kinase inhibitors
STAT-6 inhibitors
Cell Trafficking
E-selectin, p-selectin, and L-selectin mediated cell adhesion inhibitors
Very late antigen 4 antagonists
Mediator Inhibition
Interleukin inhibitors (IL-4, IL-5, IL-9, and IL-13)
Prostaglandin antagonists (D_2, LTD_4, LTC_4, and TxA_2)
Adenosine, neurokinin, histamine, and bradykinin antagonists
Elastase and tryptase inhibitors
Antigen Processing
Immunomodulatory oligonucleotides
T helper 2 cytokine inhibitors
Chemoattractant receptor homologous molecule on T helper 2 cells receptor antagonist

STAT = signal transducers and activator of transcription proteins

inhibit the effect of inflammatory mediators (eg, leukotriene modifiers), primarily by acting as antagonists but also potentially by inhibiting mediator production or release. Included within a third domain are drugs that affect cell trafficking, particularly the movement of inflammatory cells from the intravascular space to the lungs and airways. A particularly fascinating domain is drugs that act as immunomodulators by influencing antigen processing.

The domain of immunomodulatory drugs includes some truly novel products. Bacterial and viral genomes, unlike vertebrate genomes, contain high levels of unmethylated cytosine-guanine oligodeoxynucleotides, which are strongly immunoreactive.[64,65] The cytosine-guanine deoxyribonucleic acid interacts with toll-like receptor 9, which is constitutively expressed on B lymphocytes and plasmacytoid dendritic cells. The cytosine-guanine complex with toll-like receptor 9 may have various immunomodulatory effects, including inducing interferon production from plasmacytoid dendritic cells, activating B cells, and generally stimulating a Th1-type immune response. These effects may be important in treating asthma, because the allergic inflammatory process reflects a Th2-type pattern. Switching the Th2-type inflammatory response to a Th1-type process may interrupt the allergic cascade. Oligodeoxynucleotides have become well-established as potent vaccine adjuvants,[65] which may mean that they could play a role in developing improved immunotherapy approaches for patients with allergies.[66] In animal models of asthma, immunomodulatory oligodeoxynucleotides reduce airway inflammation, bronchial hyperresponsiveness, and airway remodeling.[67-69] There are other exciting products within the domain of immunomodulatory drugs. Suplatast tosilate is an orally administered inhibitor of IL-4 and IL-5 release from Th2 cells.[70,71] Antisense oligonucleotides induce functional gene ablation by degenerating the template activity of specific target messenger ribonucleic acid.[72] A respirable antisense oligonucleotide has been developed that is directed against adenosine receptors.[73] It will be extremely exciting to see how effective immunomodulators are in treating asthma in upcoming clinical trials.

Summary

The pharmaceutical industry is extremely interested in developing new asthma drugs. The clinical need and the size of the potential market represent a large financial incentive. Near-term prospects for novel asthma treatments, however, are limited. Most asthma pharmaceutical development activity has been and still is focused on reformulating established molecules in new devices and combinations. Advances in our understanding of the pathophysiology of airway inflammation in asthma has produced new targets for developing anti-inflammatory drugs. Initial work with drugs that act as anti-inflammatory medications in novel ways is encouraging, but the requirements for successful clinical development of these products are rigorous, and commercialization of these novel anti-inflammatory drugs will take time.

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Discussion

Sorkness: You seem optimistic that ciclesonide could hit the market as a single entity. The rumblings I've been hearing at meetings and by participating in some of the trials are that, overall, the safety profile is comparable to other low doses of ICS. The restoration of Flovent Diskus low-dose for children provides an option that has had some very good safety data related to growth in kids. The marketplace is really about combination therapy. Do you think ciclesonide will make it as a monotherapy?

Colice: I have to be careful what I say, because I've been involved in that program from its inception. The information they have now is adequate to support approval. If the company wanted the drug to be approved today, it would be approved today. The limiting factor is not approval, but getting the labeling they want, because that's where the commercial advantage will be. Two factors influence that: one is the growth issue, and the other is the once-a-day issue. They have a study in now that, I think it's fair for me to say, is positive for once-a-day, and they have a study that is very favorable on growth, and if those 2 studies get them the labeling they want it will be a very attractive product. The labeling they want would say that there's no growth effect, which would clearly differentiate them from every other ICS on the market. The limiting factor is the labeling, not the approval.

Sorkness: I agree that we need new therapies. I'm a bit skeptical about the value of the TNF-α agents. Though there is some positive signal from the data, I think it's mixed. In some of our trial experience in asthma and COPD we found these are tough drugs to use; they have toxicities. This is a class of drugs being applied to more severe disease, where we're going to sort out the phenotypes and determine which phenotypes benefit.

Colice: I agree. There is also another important factor. Xolair paved the way, because it was the first asthma drug that was approved based on a non-FEV_1 indication. I've interacted with the FDA quite a few times recently, so I can tell you from personal experience that they are now much more flexible about entertaining non-FEV_1 end points. If Xolair had had the problems with anaphylaxis that they're experiencing now, I'm not sure it would have been approved the first time around. But the FDA has expressed a willingness to approve a drug based on exacerbations. The FDA is also making a big effort to decide on the definition of an exacerbation.

Moores: I want to follow up what Christine said about phenotypes. When you look at the studies on TNF-α blockers, I think the reason they're so far ahead in their progress is that they're available for other diseases and we use them frequently. You're looking at a new indication for a drug that's already FDA-approved for other things. TNF-α is related to neutrophilic inflammation, and yet the studies with a lot of outcome data looked at eosinophil numbers and exhaled nitric oxide. I'm not sure those are the end points they want to be looking at. FEV_1 may be one, and you did see an improvement there. I think the key is to figure out, as Christine said, which patients have more of a neutrophilic component, and that may be the group that you need to target with TNF-α blockers. It's not going to be a magic bullet, because TNF-α may not play a major role in other patients with asthma.

Colice: I disagree with you a little bit, because the FDA knows the adverse effects and complications of those drugs, so imagine how big a study the FDA is going to ask these companies to do to make sure there's no extra risk for, say, tuberculosis in these patients. This is a big problem for the companies developing this, with regard to providing a large enough safety database in a population that might be more uniquely at risk for developing some of these respiratory diseases. So it's an advantage in one sense, but I think it's also a big disadvantage in another.

Moores: You're right. Although we've learned a lot about how to avoid that particular complication, there may be others we're not aware of.

Colice: The FDA is very scared about safety. So if you're a consultant for the company, and the FDA said, "Reassure us about the safety of this product," how big of a study would you have to do, and how long would you have to do it?

Moores: I am certainly not an expert on the approval process, but I'm curious about these studies that you're showing and saying they're a little further along. I think there's a reason why they might be, but I'm not sure they're looking at the right end points for that particular drug.

Colice: They've gotten a big buzz in the pharmaceutical industry and on Wall Street.

Donohue: Regarding monoclonal antibodies, as you know, in the omalizumab (Xolair) program there initially seemed to be a signal of increased malignancy, but ultimately that was pretty much put to rest. Atopic people seem to have fewer malignancies, and if you look at cancer registries, you find fewer atopic people. In the initial omalizumab data there was a slight increase, but once you control, there's no signal. But Steve Rennard did a study[1] that exposed 238 patients with COPD to infliximab, and they had 9 malignancies in the exposed arm and 1 in the control arm, so we really have to be careful with these biologics. Gene, is there any future in IL-4 to IL-5 monoclonal antibodies? I think those have not been put to rest.

1. Rennard SI, Fogarty C, Kelsen S. The safety and efficacy of infliximab in moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; 175(9):926-34.

Colice: I don't think they've stopped at all, Jim. There's a huge interest in IL-4, IL-5, IL-13, et cetera. They have products that have multiple antagonistic effects against multiple interleukins, and there's still a lot of interest there. It's just a question of how effective they can be. How low do you have to go to get these things to really work? The Xolair experience is very instructive, because Xolair gets it down, but probably not down far enough.

Donohue: There's a second generation of omalizumab in clinical development that is now in Phase 3 clinical trials. You may not have to be limited to using it for those with IGE levels in the range of 30-700 as you are with the present formulation. The smaller volumes should allow its use in those with higher IGE levels. Also, it is premixed and will be easier to use.

Colice: Xolair is an interesting example for the pharmaceutical industry, because it's a drug, and it's a revolutionary concept, but the benefit is marginal. And yet I think it's selling more than $450 million a year. So people are grasping at straws to get effective therapy for these patients.

Donohue: Gene, there is a new cross-FDA effort on exacerbations because of the problem with the noninferiority designs in prior antibiotic trials. Laurie Burke developed guidance for patient-reported outcomes,[1] and Nancy Clyde Leidy is the leader of the EXACT-PRO initiative to develop a tool to study exacerbations.[2] There are now the longitudinal studies to validate those instruments. With the patient-reported outcomes we'll be able to look at other variables, such as the area under the curve of an exacerbation, the on signal, the off signal, and the interval, so a lot of things might come from this if they're validated, and it will give us more things to look at when we assess biologicals and interventions that are directed at FEV_1.

1. Sloan JA, Halyard MY, Frost MH, Dueck AC, Teschendorf B, Rothman ML; the Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group. The Mayo Clinic manuscript series relative to the discussion, dissemination, and operationalization of the Food and Drug Administration guidance on patient-reported outcomes. Value Health 2007;10 Suppl 2:S59-S63.
2. EXACT-PRO Initiative: the exacerbations of chronic pulmonary disease tool: a patient reported outcome initiative. United Biosource Corporation. http://www.exactinitiative.com. *Accessed April 1, 2008.*

Medoff: My primary academic pursuit is lung immunology and the basic mechanisms of asthma. The available therapies and the anti-IgE therapy really hit "downstream" mediators, of which there are multitudes. You can hit IL-5, but you still have to hit IL-4 and IL-13. We've shifted our focus to "upstream" mediators, such as STAT-6 [signal transducer and activator of transcription protein] and Xanef kappa β, which are much more attractive, because if you hit just those signal agents, you basically cut off the entire downstream cascade that results. Thymextremal lymphopoiten is another very interesting potential upstream mediator. It's made by epithelial cells in response to these antigens, which are extremely important, and it probably turns on the entire Th2 polarity in the lungs.

Colice: Yes, there are about 50 that I did not mention.

Enright: I liked your emphasis that the "glass is half empty." There's one therapy that I think would fill a tremendous gap for a large population and much improve the asthma control in the United States. It has been available in other countries, and it has low adverse effect. And that is a low-dose, low-cost, generic ICS, which is such an important unmet need in the poor and underinsured population. Can you comment on why that's not going to happen in the United States any time soon?

Colice: A low-dose, low-cost generic ICS? I'm trying to think of all the patent protection issues involved. There are big patent issues. The HFA issue is very complicated, and there are a lot of deals that are, unfortunately, off the books. They're not transparent, so how these things have worked themselves out I'm unfortunately not allowed to tell you. I'm sorry I can't.

Enright: It's pretty obvious to many poor people who have to go to Canada or Mexico or elsewhere to get an affordable ICS that the FDA and pharmaceutical industry have colluded during the current administration to prevent low-cost drugs and extend the 15-year patents. And I think it's ludicrous to claim that the miniscule amount of CFC emitted by CFC MDIs has any measurable effect on the ozone layer.

Colice: The government is in a very interesting situation, and it recently did something that might not jibe with what you just said, which is that CMS [Centers for Medicare and Medicaid Services] decided to pay the same price for levalbuterol as for albuterol. In Europe they have a 2-step process. The first step is regulatory approval of the drug to be marketed. The second step is an extensive pricing evaluation. The company has to demonstrate that their new drug has advantages or is cheaper or something to get a price advantage. If they can't do that, they're approved to market it, but they can't get a price advantage. That's why in Europe HFA albuterol is essentially the same cost as CFC albuterol.

In the United States that's never been the case; the FDA's mandate has been to evaluate safety and efficacy, and that's it. Now for the first time CMS has asked, "Why are we paying more for a drug that has no other advantages?" Now we may see CMS say, "Unless you demonstrate better efficacy, we're only going to pay you what we pay everybody else."