CURRENT, NEW, AND EMERGING ASTHMA THERAPIES

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ABSTRACT

Pharmacotherapy remains the most common method for management of asthma. Numerous agents, including inhaled corticosteroids (ICSs), β agonists (short and long acting), leukotriene modulators, cromones, and, more recently, monoclonal antibodies, are used. Of these classes of therapy, ICSs remain the mainstay of treatment for persistent asthma according to various guidelines. This review focuses on the continuing role of ICSs as potent anti-inflammatory agents in the management of asthma. In addition, this article considers new and emerging therapies, including those that target immunoglobulin E/mast cells, cytokine antagonists, novel anti-inflammatory targets, and vaccines. (Adv Stud Med. 2008;8(3):70-78)

Asthma is a heterogeneous inflammatory disease of the airways. Several options are available for the management of asthma. Treatment begins with the identification and elimination of possible environmental inhalant allergens that can trigger symptoms. Substantially reducing exposure to these allergens significantly reduces lung inflammation, improves clinical symptoms, and decreases the need for medications. Allergen immunotherapy is another option that has been shown to provide similar effects. Pharmacotherapy remains the most common method for management of asthma. Numerous agents, including inhaled corticosteroids (ICSs), β agonists (short and long acting), leukotriene modulators, cromones, and, more recently, monoclonal antibodies, are used. Of these classes of therapy, ICSs remain the mainstay of treatment for persistent asthma according to various guidelines.4

This review focuses on the continuing role of ICSs as potent anti-inflammatory agents in the management of asthma. In addition, the paper considers new and emerging therapies, including those that target immunoglobulin (Ig) E/mast cells, cytokine antagonists, novel anti-inflammatory targets, and vaccines.

INHALED CORTICOSTEROIDS

The use of ICSs for the treatment of asthma started in the 1970s with the introduction of beclomethasone dipropionate (BDP) delivered by a metered dose inhaler (MDI). Shortly thereafter, various studies confirmed the effectiveness of these agents and their ability to improve asthma symptoms, reduce bronchial hyperresponsiveness, and decrease morbidity.5-8 As a result of these properties, ICSs are now considered

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first-line therapy in the management of persistent asthma. ICS therapy has been shown to have long-term efficacy in adults as well as children.\(^9,10\)

There are currently 6 ICSs in different preparations that have been approved by the US Food and Drug Administration (FDA) in the United States—BDP, triamcinolone acetonide (TA), flunisolide, budesonide (BUD), fluticasone propionate (FP), and mometasone furoate (MF; Table 1; At press time, ciclesonide was approved by the US FDA). All of these ICSs are effective and safe, although therapeutic profiles differ slightly among ICSs. Ongoing efforts have strived to further reduce side effects, which can occur especially in patients taking high doses.

**SIDE EFFECTS OF INHALED CORTICOSTEROIDS**

Despite recommendations by guidelines advocating the use of ICSs as first-line therapy in persistent asthma, ICSs are still underutilized. One study found that the adherence to therapy is 33.8% of patients in the United States.\(^11\) The reason for this lack of adherence may stem in part from concerns about side effects. Potential side effects of ICS can be categorized as local or systemic. Local side effects occur because of corticosteroid deposition in the oropharyngeal cavity, whereas systemic side effects stem from corticosteroid absorption through the lungs or gastrointestinal tract.\(^12\)

The most common local side effects of ICS are oral candidiasis, dysphonia, and cough.\(^1\) These unwanted effects are usually dose dependent. The incidence of local reactions in most trials has been estimated at 5% to 10%; however, the incidence varies significantly depending on how the local side effects are defined and reported.\(^13\) Oral candidiasis, which results from local immunosuppression, has a variable incidence of 0% to 77%.\(^14,15\) Dysphonia has been reported in 5% to 50% of patients receiving ICS therapy. Dysphonia appears to be a direct effect of the corticosteroid, as dysphonia was absent when the formula was administered without an ICS.\(^16\) Dysphonia is most likely caused by vocal cord muscle myopathy.\(^14\) Cough has been reported in 34% of adults on ICSs.\(^17\) Other reported local side effects include perioral dermatitis, tongue hypertrophy, and a sensation of thirst.\(^13\) Techniques to decrease the deposition of ICSs in the oropharyngeal cavity (eg, using a spacer with an MDI or rinsing the mouth out after use of an ICS) have been shown to decrease the incidence of these local side effects.\(^18\)

Systemic side effects have also been associated with the use of ICSs. A systematic review using evidence published through the year 2000 was conducted to determine the systemic side effects of ICSs.\(^19\) Overall, there was good evidence to suggest that skin thinning and bruising can occur with higher doses of ICSs.\(^19\) In elderly patients, bone mineral density can be reduced with long-term, high-dose ICS therapy.\(^19\) Finally, the risk of cataracts and glaucoma may be increased although the evidence on this point was not conclusive.\(^19\) A significant concern in the pediatric population is the use of ICSs and growth suppression. According to the National Asthma Education and Prevention Program guidelines updated in 2007, ICSs have the potential to decrease growth velocity, but there was no evidence that low to medium doses of ICS therapy affected final adult height.\(^1\)

**THE IDEAL INHALED CORTICOSTEROID**

There is a need to develop an ICS that would allow for maximum clinical efficacy with minimal adverse

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**Table 1. Inhaled Corticosteroids Currently Available in the United States**

<table>
<thead>
<tr>
<th>Medication</th>
<th>US FDA Approved, y</th>
<th>Devices</th>
<th>Ages</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>2000</td>
<td>MDI-HFA</td>
<td>&gt;5</td>
<td>B</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>1984</td>
<td>MDI-CFC</td>
<td>&gt;6</td>
<td>C</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>1982</td>
<td>MDI-CFC</td>
<td>&gt;6</td>
<td>C</td>
</tr>
<tr>
<td>Budesonide</td>
<td>1997</td>
<td>DPI, Nebulizer</td>
<td>&gt;1</td>
<td>B</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>1996</td>
<td>MDI-HFA, DPI</td>
<td>&gt;12</td>
<td>C</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>2005</td>
<td>DPI</td>
<td>&gt;12</td>
<td>C</td>
</tr>
<tr>
<td>Fluticasone propionate/salmeterol</td>
<td>2000</td>
<td>DPI, MDI-HFA</td>
<td>&gt;12</td>
<td>C</td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>2006</td>
<td>DPI</td>
<td>&gt;12</td>
<td>C</td>
</tr>
</tbody>
</table>

\(^*\) At press time, ciclesonide was approved by the US FDA.

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered dose inhaler; US FDA = US Food and Drug Administration.
reactions. Several pharmacokinetic and pharmacodynamic properties of previous ICSs should be considered when developing an ideal ICS (Table 2).

First, the drug and delivery device should deliver high pulmonary deposition and low local (pharyngeal) deposition to maximize the anti-inflammatory activity in the lungs and minimize the local effects. It has been estimated that pulmonary depositions of FP and BUD using an MDI are 12% and 18%, respectively. The remainder of the dose is deposited in the device or in the gastrointestinal tract. Depending on the oral bioavailability of the steroid, gastrointestinal deposition can contribute to the absorbed drug that produces systemic side effects. FP and MF have particularly low oral bioavailability among the currently available ICSs.

Second, the ICS should have high glucocorticoid receptor (GR) affinity in order to target activity in the lung with the local concentrations achieved. BDP is converted into an active metabolite, BMP, with approximately a 25-fold increase in affinity for the GR. Unfortunately, BMP has a relatively high oral bioavailability. BMP is further metabolized into another active metabolite, beclomethasone, which has similar affinity to the GR as BDP.

A third factor to consider is the systemic protein binding of the ICS. Only free ICSs can bind GRs in peripheral tissues when absorbed through the lungs or gastrointestinal tract. Approximately 10% to 13% of BDP, BUD, and FP are free and unbound in the systemic circulation, whereas MF is 99% protein bound.

To further limit adverse effects, the ideal ICS should have limited oral deposition and low oral bioavailability. FP and MF have less than 1% oral bioavailability. BUD, flunisolide, and TA have more than 10% oral bioavailability. The apparently low oral bioavailability of BDP is probably due to conversion to BMP, which has a high availability.

Another important factor in determining success of ICS is the duration of time that they remain in the lungs, which is in turn determined by lipophilicity. BUD, and probably TA and flunisolide, are converted to fatty acid esters that are highly lipophilic and slowly reconverted to active drug and released from the lungs. The once-a-day indication for BUD probably reflects the function of this depot.

Finally, the route of administration and dosing should allow for maximum adherence and clinical efficacy. ICSs are currently delivered by 1 of 3 methods: MDI, dry powder inhaler, or nebulizer. Each method has advantages and disadvantages. The ideal ICS would allow for once-daily dosing to increase adherence to therapy.

### Hydrofluoroalkane Formulations

Traditional MDIs use chlorofluorocarbon (CFC) as propellants. Given the detrimental effects of CFC on the ozone in the upper atmosphere, they are increasingly being replaced by hydrofluoroalkane...
In addition to being environmentally safe, HFA formulations have the advantage of allowing for smaller particle size, which is realized in greater lung deposition and lower oropharyngeal deposition. Vanden Burgt et al showed greater than 50% lung deposition with the use of HFA-BDP when measured by gamma scintigraphy. The increased pulmonary deposition equates to improved clinical efficacy as demonstrated in a study comparing CFC-BDP to HFA-BPD. Another benefit of the smaller particle size is better control of small airway inflammation. Smaller particle size and improved delivery also increase the amount of ICS absorbed and the risk of systemic side effects.

Ciclesonide (CIC) is a new ICS that is not currently approved for use in the United States (At press time, ciclesonide was approved by the US FDA). It has many features that make it desirable (Table 2). It has been developed as an MDI with HFA as the propellant. Fifty-two percent of the dose is deposited in the lung. Ciclesonide is a prodrug that is activated in the lungs to produce the active metabolite desisobutyryl-ciclesonide (des-CIC). des-CIC has 100-fold greater affinity for the GR than CIC. This selective tissue activation allows for greater activity at the site of inflammation. Similar to BUD, CIC undergoes reversible lipid conjugation, allowing it to remain in the lungs longer. This feature allows for once-daily dosing, which may translate into better adherence. Once in the circulation, more than 99% of CIC is protein bound, a property that limits the potential for interaction with systemic receptors. CIC undergoes extensive first-pass metabolism with more than 99% metabolized by the liver. The absolute bioavailability of CIC is less than 1%. These features allow for limited systemic exposure of CIC. The pharmacokinetic and pharmacodynamic properties of CIC described earlier in this article have translated into an attractive clinical profile in several studies. At doses that control asthma, CIC does not affect serum cortisol levels and has an incidence of local side effects (pharyngitis, candidiasis, or dysphonia) similar to or less than placebo. CIC is currently under development in the United States and has been approved for use in the United Kingdom and Australia.

**Combination Therapy: Inhaled Corticosteroid and Long-Acting β Agonists**

Patients on ICS therapy should be on the lowest possible dose that provides control of their asthma. An effective alternative to increasing the ICS dose for patients with uncontrolled asthma is the use of combined ICS and long-acting β2 agonists (LABA). Combination of the ICS and LABA in 1 inhaler has simplified therapy and improved adherence. Currently, 2 combinations of an ICS and LABA in 1 inhaler are available for use in asthma—fluticasone/salmeterol and budesonide/formoterol. Only fluticasone/salmeterol is currently available in the United States. Several studies have shown the superior efficacy of adding a LABA to ICS therapy over increasing the dose of an ICS to improve symptoms and lung function. As a result, guidelines recommend the addition of LABA to an ICS for the management of patients with moderate-to-severe asthma. Budesonide/formoterol offers the advantage of once-daily dosing without loss of clinical efficacy.

Budesonide/formoterol has been used not only as maintenance therapy but also as reliever therapy. This combination has been shown to reduce exacerbations and improve asthma control compared to traditional fixed-dose regimens. Combination therapy with an ICS and LABA continues to play a key role in the management of patients with moderate-to-severe persistent asthma.

**Novel Inhaled Corticosteroids**

Dissociated steroids are being developed based on the premise that corticosteroid-associated side effects are mediated by transactivation of gene expression via binding of GR to DNA, whereas the anti-inflammatory effects are mediated by inhibition of transcription ("transrepression") through other GR-mediated effects. Another approach is development of “soft” steroids. These unique steroids are pharmacologically active at the desired site, but their distribution away from the site results in a prompt metabolic deactivation that prevents toxicity. Two examples of soft corticosteroids include loteprednol etabonate, which has been approved for use as an ophthalmic preparation, and etiprednol dicloacetate. Thus far, soft steroids developed for asthma have not demonstrated adequate efficacy, probably because of local rapid metabolism in
the lungs. With the discovery of GR isoforms that mediate different effects of glucocorticoids in diverse cell types and tissues, the possibility of developing isoform-selective glucocorticoids that have anti-inflammatory effects but not side effects is raised. Further studies are needed to maximize the therapeutic potential of ICSs in the management of asthma.

NEW AND EMERGING THERAPEUTICS

Asthma is a complex inflammatory disease of the airways involving mast cells, eosinophils, basophils, T cells, and structural cells, including smooth muscle and epithelium. An advanced understanding of the immunobiology and pathophysiology that drives this process has led to the emergence of novel therapeutic targets (Table 3).

IMMUNOGLOBULIN E AND MAST CELL TARGETS

Immunoglobulin E plays a key role in the pathophysiology of asthma. After sensitization to allergens has occurred, B cells secrete IgE that binds to the high-affinity IgE receptors (FcεRI) found on the surface of mast cells and basophils. On re-exposure, the sensitizing allergens bind and crosslink IgE to cause degranulation of mediators from mast cells and basophils. These mediators, including histamine, prostaglandins, leukotrienes, and cytokines, cause an immediate response of bronchospasm in patients with asthma. A late-phase response with infiltration of inflammatory leukocytes ensues with continued release of mediators that cause inflammation, airway hyperresponsiveness, and bronchospasm. Blocking IgE potentially stops this cascade of events from occurring.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody approved for clinical use in patients with asthma. It binds circulating IgE and thereby prevents it from attaching to FcεRI on mast cells and basophils. Because omalizumab does not interact with bound IgE, anaphylaxis does not occur. Although free IgE levels are significantly reduced after a single injection of omalizumab, it can take weeks to months for IgE bound to mast cells to disappear. Omalizumab also decreases the expression of IgE receptors on mast cells and reduces IgE synthesis by B cells. Clinical studies support the use of omalizumab in the treatment of patients with moderate-to-severe asthma by showing decreased use of an ICS, reduced asthma exacerbations, and improved lung function. Furthermore, an unexpected anti-inflammatory effect was seen in the airways of patients with asthma. The cost of this agent has limited its use in clinical medicine.

The low-affinity IgE receptor FcεRII (or CD23) is thought to regulate IgE-mediated inflammatory

Table 3. New and Emerging Therapeutics*

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICSs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Local activation, depot formation, low protein binding Transrepression without transactivation (see text)</td>
<td></td>
</tr>
<tr>
<td>Dissociated steroids</td>
<td></td>
<td>Drug inactivated when not in lungs</td>
</tr>
<tr>
<td>Soft steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE and Mast Cell Targets</td>
<td>Omalizumab</td>
<td>Anti-IgE therapy</td>
</tr>
<tr>
<td></td>
<td>Lumiliximab</td>
<td>Anti-CD23 antibody</td>
</tr>
<tr>
<td></td>
<td>Syk inhibitors</td>
<td>Target mast cell signaling</td>
</tr>
<tr>
<td>Cytokine Inhibitors</td>
<td>Soluble IL-4 receptor</td>
<td>IL-4 antagonist</td>
</tr>
<tr>
<td></td>
<td>Mepoluzimab</td>
<td>IL-5 antagonist</td>
</tr>
<tr>
<td></td>
<td>Suplatast tosilate</td>
<td>Suppresses IL-4 and IL-5</td>
</tr>
<tr>
<td></td>
<td>Daciluzumab</td>
<td>IL-2α receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>TNF antagonist</td>
</tr>
<tr>
<td></td>
<td>Inflimab</td>
<td>TNF antagonist</td>
</tr>
<tr>
<td>Novel Anti-Inflammatory Agents</td>
<td>Roflumilast</td>
<td>PDE4 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Efaluzimab</td>
<td>Adhesion molecule antagonist</td>
</tr>
<tr>
<td></td>
<td>VEGF inhibitors</td>
<td>Disrupt angiogenesis</td>
</tr>
<tr>
<td>Vaccines</td>
<td>AIC vaccine</td>
<td>Toll-like receptor 9 agonists</td>
</tr>
</tbody>
</table>

*At press time, ciclesonide was approved by the US Food and Drug Administration.
AIC = Amb a 1-immunostimulatory oligodeoxynucleotide conjugate; ICSs = inhaled corticosteroids; Ig = immunoglobulin; IL = interleukin; PDE = phosphodiesterase; Syk = spleen tyrosine kinase; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.
processes. Lumiliximab, an anti-CD23 antibody, has been shown to be well tolerated and reduces IgE concentrations in patients with mild asthma. Its clinical efficacy has yet to be reported.

The enzyme spleen tyrosine kinase (Syk) is involved in the activation of mast cells through an IgE-dependent pathway. Therefore, blocking this key enzyme could prevent production and release of mediators upon allergen binding to IgE on mast cells. R112, a novel small molecule inhibitor of Syk, has been shown to decrease nasal symptoms in patients with allergic rhinitis when given intranasally. More clinical studies are warranted to test the value of Syk as a target for development of inhibitors for allergic asthma.

Cytokine Inhibitors

Cytokines, pleiotropic proteins secreted from a variety of cells, help to regulate the immune response. Th2 cells are a subset of helper T cells that produce cytokines, such as interleukin (IL)-4, IL-5, and IL-13, all of which are important in the inflammation associated with asthma and other allergic diseases. Novel therapeutics targeting such products may provide clinical benefit in these patients.

Interleukin-4 is a major stimulus for the production of IgE antibodies and the development of Th2 cells. Borish et al studied the effects of a recombinant human soluble IL-4 receptor administered by nebulization. This molecule neutralized free IL-4 to prevent its effects. This study was disappointing in that it showed minimal efficacy. Further studies using this molecule have been abandoned.

Interleukin-5 is a cytokine that promotes the growth, recruitment, and differentiation of eosinophils. Eosinophils are thought to contribute to the inflammation associated with asthma. Targeting IL-5 may help to control this inflammation. Mepolizumab is a humanized monoclonal antibody (mAb) that targets IL-5. Leckie et al showed that mepolizumab is safe and that it effectively reduced eosinophil levels in blood and sputum; however, it only lowered airway eosinophils by 55%. In addition, there was no effect on the late asthmatic response, airway hyperresponsiveness, or other asthma clinical outcomes. Other Th2 cytokines that have been pursued as potential targets in asthma include IL-13. In addition, Th2-skewing cytokines, such as IL-9, IL-25, and thymic stromal lymphopoietin (TLSP), a novel IL-7–like cytokine that is highly expressed in airways of patients with asthma, are also attractive candidates.

Suplatast tosilate is a unique agent that suppresses the synthesis of IL-4 and IL-5. Studies using this compound have shown that patients experience an increase in forced expiratory volume in 1 second (FEV₁) and morning peak expiratory flow while having a decrease in serum IgE, asthma symptoms, and rescue inhaler use compared to placebo. The success of suplatast tosilate in treating patients with asthma may stem from its ability to block more than 1 cytokine at a time.

Dacizumab is a humanized mAb targeted against the IL-2 receptor α-chain (CD25). It is currently approved for use in renal allograft rejection. Recent studies have shown it to be useful for improving asthma control in some patients with refractory asthma. Furthermore, dacizumab has been shown to inhibit expression of IL-4, IL-5, and IL-13 in vitro.

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine produced by many cell types. Etanercept is a recombinant TNF receptor-IgG fusion protein that is commonly used in rheumatic conditions to block the effects of TNF. In a recent study by Berry et al, patients with severe refractory asthma given etanercept twice weekly had a decrease in bronchial hyperresponsiveness to methacholine, an improvement in asthma-related quality of life, and an increase in postbronchodilator FEV₁ compared to placebo. Another study using infliximab, a mAb to TNF-α, found a decrease in the number of patients with exacerbations in symptomatic moderate asthma. Further studies are warranted to determine which patients can benefit the most from these agents.

The limited success of blocking the actions of single cytokines may reflect the redundancy of multiple cytokines. Based on the currently available studies, none of these novel agents seem to be curative for asthma. Further studies are warranted with mAbs.

Novel Anti-Inflammatory Therapies

Theophylline, the prototypical phosphodiesterase inhibitor, was commonly used in the management of asthma in the past. Because of its side effect profile and narrow therapeutic window, it is not commonly used any more. Recent studies have shown resurgence of interest in phosphodiesterase inhibitors, particularly type 4 phosphodiesterase (PDE4) inhibitors. These
Compounds inhibit T cells, eosinophils, mast cells, airway smooth muscle, and epithelial cells. Roflumilast, a novel PDE4 inhibitor given orally, reduced symptoms and improved lung function in patients with asthma to an extent comparable to low doses of inhaled steroids. The utility of this agent is limited by its side effects of nausea, vomiting, headaches, and gastrointestinal disturbances. These side effects may constitute class effects that could prevent further development.

Adhesion molecules are important in the migration of cells into areas of inflammation. Blocking cell adhesion molecules represents another approach to disrupting inflammation. Efaluzimab, an mAb targeting lymphocyte function-associated antigen-1, reduced inflammatory cells in the sputum of patients with asthma. However, there were no clinical effects on lung function. Another target currently under clinical investigation is very late antigen-4. Further studies are warranted to determine whether adhesion molecule blockers can be efficacious in the treatment of asthma.

Angiogenesis, an important part of the inflammatory response, constitutes another potential target in the treatment of asthma. Vascular endothelial growth factor (VEGF) is increased in patients with asthma and correlates with disease severity. Clinical studies are needed to determine whether blocking this target can provide another therapeutic option in asthma. Because many companies have been targeting VEGF for treatment of cancer, there are many compounds that can be tested in asthma.

VACCINES

There is no treatment currently available that can cure asthma. Inhaled corticosteroids are potent anti-inflammatory medications. However, once they are stopped, asthma symptoms usually return. Allergen immunotherapy represents the only disease-modifying treatment that can potentially alter the natural course of asthma. A new form of immunotherapy using Amb a1 (a ragweed-pollen antigen) conjugated to a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA (AIC) was shown to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis. Whether similar outcomes will be observed in patients with asthma remains to be seen. It should be noted that immunotherapy has generally been found to be more effective for allergic rhinitis than for asthma.

CONCLUSIONS

There are several agents available for the treatment of asthma. ICSs are presently considered the mainstay of therapy. There is a need for development of new treatment options for patients with asthma. Extensive research has been conducted in the past decade to identify novel targets that may play a role in asthma. Given the complexity of asthma and new information on pharmacogenetics, the future of asthma treatment may well include steps taken to tailor treatments offered to subsets of patients based on genotype. It also seems likely that cocktails of agents that provide maximum benefit for management of asthma will be designed.

REFERENCES


