Severe asthma: Advances in current management and future therapy

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Effective treatment of severe asthma is a major unmet need because patients’ symptoms are not controlled on maximum treatment with inhaled therapy. Asthma symptoms can be poorly controlled because of poor adherence to controller therapy, and this might be addressed by using combination inhalers that contain a corticosteroid and long-acting β2-agonist as reliever therapy in addition to maintenance treatment. New bronchodilators with a longer duration of action are in development, and recent studies have demonstrated the benefit of a long-acting anticholinergic bronchodilator in addition to β2-agonists in patients with severe asthma. Anti-IgE therapy is beneficial in selected patients with severe asthma. Several new blockers of specific mediators, including prostaglandin D2, IL-5, II-9, and IL-13, are also in clinical trials and might benefit patients with subtypes of severe asthma. Several broad-spectrum anti-inflammatory therapies that target neutrophilic inflammation are in clinical development for the treatment of severe asthma, but adverse effects after oral administration might necessitate inhaled delivery. Macrolides might benefit some patients with infection by atypical bacteria, but recent results are not encouraging, although there could be an effect in patients with predominant neutrophilic asthma. Corticosteroid resistance is a major problem in patients with severe asthma, and several molecular mechanisms have been described that might lead to novel therapeutic approaches, including drugs that could reverse this resistance, such as theophylline and nortriptyline. In selected patients with severe asthma, bronchial thermoplasty might be beneficial, but thus far, clinical studies have not been encouraging. Finally, several subtypes of severe asthma are now recognized, and in the future, it will be necessary to find biomarkers that predict responses to specific forms of therapy. (J Allergy Clin Immunol 2012;129:48-59.)

Key words: Corticosteroids, bronchodilator, cytokine, chemokine, IgE, kinase, p38 mitogen-activated protein kinase, bronchial thermoplasty, corticosteroid resistance, macrolide

Severe asthma is defined by a failure to achieve control with maximum doses of inhaled therapies and represents one of the major unmet therapeutic needs in asthma. Although current management of asthma is highly effective, most patients’ symptoms are well controlled if they take regular inhaled corticosteroids (ICSs) with or without long-acting β2-agonists (LABAs) in combination inhalers. Yet despite the availability of highly effective therapies, more than half of the patients with asthma in the real world have disease that is apparently poorly controlled, largely because of poor adherence to controller therapy.1,2 In patients with difficult-to-treat asthma, more than 80% show poor adherence with regular inhaled therapy.3 Even in the patients with the most severe asthma treated with maintenance oral prednisolone (steroid-dependent asthma), only about half of the patients take the oral steroid based on plasma prednisolone assays. This suggests that poor adherence is a major factor contributing to poor control of asthma. In patients with refractory asthma with persistent sputum eosinophilia despite prescription of high doses of ICSs or maintenance oral steroids, treatment with high-dose intramuscular injection of triamcinolone results in disappearance of sputum eosinophilia in the majority of patients.4 This suggests that poor compliance with inhaled and even oral corticosteroids might be a major factor contributing to difficult-to-treat asthma and that poor compliance with controller therapy is an important determinant of asthma severity.

The reasons for poor compliance with regular therapy, especially in patients with severe asthma, are not well understood, but the lack of immediate symptom relief, as seen with anti-inflammatory treatments, such as corticosteroids, is probably important. Steps need to be taken to more accurately determine adherence to therapy, and strategies to overcome this problem

Abbreviations used

- COPD: Chronic obstructive pulmonary disease
- CRTH2: Chemoattractant homologous receptor expressed on T cell
- 5′-LO: 5′-Lipoxygenase
- HDAC2: Histone deacetylase-2
- ICS: Inhaled corticosteroid
- LABA: Long-acting β2-agonist
- LAMA: Long-acting muscarinic antagonist
- LT: Leukotriene
- MAPK: Mitogen-activated protein kinase
- MIF: Migratory inhibitory factor
- NF-κB: Nuclear factor κB
- Nrf2: Nuclear factor erythroid 2-related factor 2
- PDE: Phosphodiesterase
- PG: Prostaglandin
- PI3K: Phosphoinositide 3-kinase
- PPAR: Peroxisome proliferator–activated receptor
- Syk: Spleen tyrosine kinase
- TSLP: Thymic stromal lymphopoietin

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need to be devised. These findings also indicate that patients with poorly controlled asthma might need additional anti-inflammatory therapy.

This review discusses some of the currently available and developing approaches to the management of severe or refractory asthma. Several new classes of drugs are currently in development for the treatment of severe asthma, but it has proved challenging to find effective and safe therapies. Although severe asthma comprises only approximately 5% to 10% of all asthmatic patients, it accounts for more than half of the health care spending on asthma because patients with severe asthma consume more expensive drugs and are more likely to be hospitalized or require additional medical attention.

**SMART STRATEGIES**

Several studies have shown that in patients with moderate-to-severe asthma, there is an improvement in asthma control and significant reduction in severe exacerbations if a budesonide/formoterol combination inhaler is used as a reliever instead of a short-acting β2-agonist, whereas maintenance therapy with budesonide/formoterol is administered twice daily as usual. This strategy is now known as single inhaler maintenance and reliever therapy (SMART) and could presumably be used with any combination inhaler containing formoterol, irrespective of the corticosteroid used. However, this strategy is not possible with salmeterol or the once-daily β2-agonists, such as indacaterol and vilanterol, all of which have cumulative side effects. The scientific rationale for SMART is now well understood because the ICS used as rescue therapy has a rapid onset of its anti-inflammatory effect and prevents the build-up of inflammation that precedes an acute exacerbation. The SMART strategy is effective in patients with moderate and severe asthma, although studies confined to severe asthma have not yet been conducted. This strategy might also be effective even when patients forget doses of their maintenance therapy and therefore addresses the key issue of poor adherence with controller therapy discussed above. Indeed, studies are now needed looking at inhaled formoterol/steroid combination inhalers as rescue therapy, even in the absence of the maintenance dose.

**NEW CORTICOSTEROIDS**

Several ICSs are currently available for clinical use, and all have similar clinical efficacy, but there are differences in pharmacodynamic properties so that systemic exposure might differ. Because patients with severe asthma might require higher doses of ICSs, there is an advantage in developing systemic corticosteroids with fewer systemic side effects. Ciclesonide is a recently developed ICS and appears to have the least systemic effects and local side effects because the prodrug is activated in the lungs to the active principle des-ciclesonide by esterases, whereas there is little activation in the oropharynx. This suggests that high doses of ciclesonide might be useful in the treatment of severe asthma. ICSs in pressurized metered-dose inhalers are now administered with hydrofluoralkane 134a rather than chlorofluorocarbon as a propellant, and this results in smaller particle sizes, so that the drugs are more likely to be deposited in the small airways. Theoretically, this should more effectively treat patients with severe asthma in whom there is inflammation of peripheral airways with evidence of small-airway inflammation. More studies are needed on ICSs with hydrofluoralkane 134a propellants in patients with severe asthma.

All currently available ICSs are absorbed from the lungs and thus have the potential for systemic side effects. This has led to a search for safer ICSs with reduced oral bioavailability, reduced absorption from the lungs, or inactivation in the circulation because this would allow higher doses to be administered safely in patients with severe asthma. “Dissociated” steroids attempt to separate the side-effect mechanisms from the anti-inflammatory mechanisms. This is theoretically possible because side effects are largely mediated through transactivation and the binding of glucocorticoid receptors to DNA, whereas anti-inflammatory effects are largely mediated through transrepression of transcription factors through a nongenomic effect. Dissociated steroids are designed to have a greater effect on transactivation than on transrepression and thus might have a better therapeutic ratio and might even be suitable for oral administration. Nonsteroidal selective glucocorticoid receptor activators, such as AL-438 and mapracorat, are in clinical development. However, some of the anti-inflammatory effects of corticosteroids might be due to transactivation of anti-inflammatory genes, and therefore selective glucocorticoid receptor activators might not be as efficacious as existing ICSs. Corticosteroids switch off inflammatory genes by recruiting the nuclear enzyme histone deacetylase-2 (HDAC2) to the activated inflammatory gene initiation site so that activators of this enzyme might also have anti-inflammatory effects or might enhance the anti-inflammatory effects of corticosteroids.

**NEW BRONCHODILATORS**

Bronchodilators play an important role in reducing symptoms in patients with severe asthma, and currently, LABAs are the bronchodilators of choice, usually given in combination with ICSs in a fixed-dose inhaler. Bronchodilators are essential in the management of asthma because they relieve and prevent bronchoconstriction. There have been several advances in the development of bronchodilators for the treatment of severe asthma.

**Once-daily β2-agonists**

β2-Agonists are the most effective bronchodilators because they act as functional antagonists of airway smooth muscle contraction, irrespective of the constricting stimulus. The LABAs salmeterol and formoterol have been a major advance in the management of severe asthma and are usually administered through combination inhalers with corticosteroids. There have been concerns about the safety of LABAs, and there is convincing evidence that LABAs used without a corticosteroid cover increase severe exacerbations and mortality. However, there is no clear evidence that LABAs pose any risk if combined with corticosteroids and therefore should only be used in the form of combination inhalers. Several once-daily β2-agonists (“ultra-LABAs”) are in clinical studies, including indacaterol (already available for chronic obstructive pulmonary disease [COPD] in several countries), carmoterol, vilanterol, and olodaterol. For asthmatic patients, these ultra-LABAs should only be available with a corticosteroid in a fixed combination. Currently, fluticasone furoate/vilanterol and mometasone/indacaterol are in clinical development for asthma as once-daily combination inhalers.
Long-acting muscarinic antagonists

Antimuscarinic (anticholinergic) bronchodilators are the preferred first-line therapy in patients with COPD, but in patients with asthma, they are less effective than β2-agonists because they block only the cholinergic component of bronchoconstriction, whereas β2-agonists reverse all bronchoconstrictors, including the direct effects of inflammatory mediators, such as histamine, leukotriene (LT) D₄, and prostaglandin (PG) D₂. Animal studies have recently demonstrated an important role for cholinergic mechanisms in the late response to inhaled allergen in sensitized guinea pigs because the long-acting muscarinic antagonist (LAMA) tiotropium bromide completely blocks the late response in nonanesthetized animals. This response is also blocked by drugs that block TRPA1, an activating ion channel on airway sensory nerves, suggesting that allergens release a mediator (thus far unidentified) that activates TRPA1, leading to cholinergic reflex bronchoconstriction. There is also increasing evidence that muscarinic receptors can be activated by acetylcholine released from nonneuronal cells, such as epithelial and inflammatory cells.20,21 Choline acetyltransferase can be induced in epithelial cells by inflammatory mediators, such as TNF-α, suggesting that acetylcholine synthesis might be increased in the airways of asthmatic patients. In sensitized guinea pigs tiotropium inhibits eosinophilic inflammation in the airways and airway hyperresponsiveness, even in vagotomized animals, suggesting that tiotropium is blocking the effects of nonneurally released acetylcholine on muscarinic M₁ receptors and that tiotropium also blocks eosinophilic inflammatory mechanisms.22 Tiotropium also inhibits TNF-α, cytochrome P450, and leukotriene (LTB₄) release in allergen-exposed sensitized mice and that from human PBMCs.23 It also reduces eosinophilic inflammation, mucin gene expression, and airflow remodeling in a murine model of asthma, possibly through a direct effect on fibroblasts.24 Tiotropium also inhibits neutrophilic inflammation and airway fibrosis after repeated LPS challenge in guinea pigs.25 These experimental studies suggest that tiotropium might have anti-inflammatory effects through antagonism of neurally and extraneurally released acetylcholine on M₃ receptors on inflammatory cells. There is also evidence that blocking M₂ receptors with tiotropium inhibits acetylcholine-induced release of neutrophil chemotactic factors (mainly LTB₄) from human macrophages. These in vitro and experimental studies have paved the way to recent clinical studies of tiotropium in patients with asthma, particularly in those with severe disease. Recent studies have shown that once-daily tiotropium provides useful additional bronchodilatation when added to a LABA in some patients with severe asthma. In one study approximately 30% of patients with severe asthma showed a good additional response when tiotropium was added.27 Addition of tiotropium significantly improves lung function in patients whose symptoms are not controlled by high doses of ICSs and LABAs, although there is no improvement in symptoms or health status.28 Another study showed that tiotropium was comparable with salmeterol in terms of bronchodilator response when added to an ICS in patients who show a good response to a short-acting anticholinergic.29 In asthmatic patients with the Arg16/Arg16 genotype of the β₂-receptor, who have previously been reported to be less responsive to β₂-agonists, once-daily tiotropium was no less effective than twice-daily salmeterol in patients whose symptoms are not controlled with ICSs alone.30 These studies suggest that addition of a LAMA to existing therapy in patients with severe asthma not controlled with ICSs and LABAs is beneficial and might be indicated, particularly in elderly patients with an element of fixed airway obstruction, who have similarities to patients with COPD.

There are several other LAMAs in clinical development for COPD, including once-daily glycopyrrolate and GSK573719 and twice-daily aclidinium bromide.31 There appears to be additivity between LABAs and LAMAs, suggesting that a triple combination of a LABA plus a LAMA plus an ICS might be useful in some patients with severe asthma, although the development of such inhalers might prove difficult technically and for regulatory reasons.32 Several bifunctional molecules that have LABA and LAMA activity are also in development, but it might prove difficult to balance the β₂-agonist and anticholinergic activities.33 It would be logistically easier to combine a bifunctional molecule that has LABA and LAMA activity and an ICS in a combination inhaler to provide triple activity.

Novel classes of bronchodilator

In view of the recent concerns about the long-term safety of LABAs in asthmatic patients, there has been a search for alternative classes of bronchodilator. Novel bronchodilators have proved difficult to develop, and new drugs, such as vasoactive intestinal peptide analogs and potassium-channel openers, have had side effects due to more potent vasodilator than bronchodilator effects. A stable vasoactive intestinal peptide analog, Ro 25-1553, has bronchodilator activity in asthmatic patients but is less effective than inhaled formoterol.34 β₂-Agonists and theophylline relax human airway smooth muscle by activating large-conductance Ca²⁺-activated potassium channels, leading to a search for direct large-conductance Ca²⁺-activated potassium channel activators, but although activating drugs were discovered, they have not been tested in clinical studies in asthma. Rho kinase inhibitors also have potential as bronchodilators but are likely to have significant toxicity. Recently, it has been found that agonists of bitter taste receptors (TAS2Rs), such as quinine, chloroquine, and saccharine, relax human airways in vitro by increasing local Ca²⁺ release, resulting in the opening and hyperpolarization of airway smooth muscle cells.35 In murine models inhaled bitter tastants appear to be more effective than a β₂-agonist, although this species is not very responsive to β₂-agonists. Theophylline relaxes human airway smooth muscle by inhibiting phosphodiesterase (PDE) 3 in airway smooth muscle cells, so that selective PDE3 inhibitors, such as cilostazol and milrinone, are potential bronchodilators. However, there has been concern that PDE3 inhibitors were associated with increased cardiovascular mortality in previous clinical trials. Combined PDE3/4 inhibitors are currently in development as inhaled therapy for asthma and COPD.36 PGE₂ relaxes human airway smooth muscle through EP₃ receptors,37 suggesting that EP₃-selective agonists might be useful bronchodilators and might avoid the coughing induced by PGE₂ through EP₃ receptors on sensory nerve endings.

ANTI-IgE

Omalizumab is the only novel therapy that has specifically been approved for the treatment of severe asthma. Omalizumab is an mAb that binds the Fc portion of IgE and thus prevents activating its high-affinity IgE receptor (FcεRI) on mast cells, basophils, and dendritic cells, as well as a low-affinity receptor
levels are increased in patients with severe asthma. In allergic asthmatic patients with the target total serum IgE concentration of 70 to 300 IU/mL show a good response, and because of the high cost, a trial of therapy over 3 to 4 months is often recommended to identify good responders. Unfortunately, despite extensive analyses, no clinically measurable biomarkers have been found to predict a good response. Patients with non-atopic (intrinsic) asthma are currently excluded, but there is evidence for local IgE production in the airways of at least some of these patients, and therefore future studies should investigate this group of patients who often have difficult-to-control asthma. Similarly, there are patients with severe uncontrolled asthma with total IgE levels of greater than 300 IU/mL who are currently excluded because it is not feasible to give enough antibody to effectively block IgE. In the future, antibodies with a higher affinity for IgE might be developed so that it could be possible to treat patients with very high total IgE levels. An mAb (lumiliximab) directed against FcεRII (CD23) reduces total IgE levels, probably by reducing synthesis by B lymphocytes, but has little clinical benefit, even in patients with mild asthma, and therefore is no longer in clinical development.

TARGETING INFLAMMATORY MEDIATORS

More than 100 mediators are involved in the complex inflammation of asthma, making it unlikely that blocking the synthesis or receptor for a single mediator could be very effective. ICSs are highly effective in suppressing the synthesis of multiple inflammatory mediators, but in patients with severe asthma, they appear to be less effective, making it possible that adding a mediator antagonist to high doses of ICSs might be beneficial. In addition, the inflammation seen in some patients with severe asthma has a different pattern, with a predominance of neutrophils, suggesting that targeting mediators of neutrophilic inflammation might be effective in these patients.

Lipid mediator blockade

The only mediator antagonists currently used in asthma therapy are antileukotrienes, which block cysteinyl leukotriene receptors, but these drugs are much less effective than ICSs and have little place as add-on therapy in patients with severe asthma. LTB₄ is a chemoattractant of neutrophils, mast cells, and T cells, including effector CD8⁺ memory T cells, and its levels are increased in patients with severe asthma. An LTB₄ receptor (BLT₁) antagonist had no effect in patients with mild asthma but has not been tested in patients with more severe disease, in whom it would be more likely to be effective. A low-affinity BLT₂ receptor is expressed on several cell types, including T cells and mast cells, and when inhibited by oligonucleotides, there is a reduction in allergic inflammation in a murine model. BLT₂ receptors are upregulated on mast cells after allergen challenge and mediate the synthesis of T₂2 cytokines. To target both BLT₁ and BLT₂, LTB₄ synthesis can be reduced by an inhibitor of LTA₄ hydrolyase, and such an approach is effective in a murine model of asthma.

Phospholipase A₂ inhibits the generation of all lipid mediators (prostaglandins, leukotrienes, and platelet-activating factor) from membrane phospholipids and therefore theoretically should be effective in patients with severe asthma, although there is uncertainty about whether to block the secretory or cytosolic isoforms of phospholipase A₂, and it has been difficult to discover safe and selective inhibitors.

5'-Lipoxygenase (5'-LO) works through 5'-LO–activating protein, and several novel 5'-LO and 5'-LO–activating protein inhibitors are currently in clinical development. These drugs could be more effective than BLT₁ antagonists because they block production of additional mediators, such as 5-HETE and 5-oxo-ETE, which acts through a specific OXE receptor. Several CRTH2 antagonists are now in clinical development for asthma therapy. Adapted from Barnes.
Cytokine blockade

Cytokines play a key role in orchestrating chronic inflammation and remodeling airway structure and therefore have become important targets for blockade in asthmatic patients, particularly patients with severe disease whose symptoms are not controlled with high doses of ICSs. More than 50 cytokines have been implicated in asthma, and several have already been targeted in clinical studies, often with disappointing results. There is a great redundancy of cytokines, and therefore it might be difficult to inhibit an inflammatory process effectively with a selective blocker. Another problem is the high cost of blocking mAbs, and therefore these drugs are likely to be cost-effective only in patients with severe disease. It is possible that production costs might be reduced by the development of higher-affinity antibodies or the use of fragments, such as domain antibodies, that are cheaper to produce.

Another problem is that there has been a major focus on Th2 cytokines in the belief that Th2 cells drive allergic inflammation. Corticosteroids are very effective in suppressing Th2 cell–driven inflammation, at least in part because they are very potent inhibitors of the Th2 regulating transcription factor GATA3. Animal models of asthma have also been developed that highlight Th2 cell–driven inflammation, and these models might be inappropriate for the development of treatments for severe asthma.

Because different immune mechanisms are likely to operate in many patients with severe asthma, it might be necessary to target different sets of cytokines, such as those involving Th1 and Th17 cells. Th17 cells have been implicated in patients with severe asthma, particularly those patients with a predominantly neutrophilic pattern of inflammation. Interestingly, Th17 cells appear to be corticosteroid resistant and might therefore contribute to the corticosteroid resistance seen in patients with severe asthma.

Inhibiting Th2 cytokines

Inhibition of IL-4 by using inhaled soluble receptors proved to be disappointing, but there is continued interest in blocking IL-13, a related cytokine that regulates IgE formation, particularly in patients with severe asthma. IL-13 can also induce corticosteroid resistance and therefore appears to be an appropriate target for patients with severe asthma. Pitrakinra is a mutated form of IL-4 that blocks IL-4 receptor α, the common receptor for IL-4 and IL-13, and significantly reduces the late response to inhaled allergen in patients with mild asthma when administered subcutaneously or by means of nebulization, and larger clinical trials are currently in progress with this protein. Several IL-13 and IL-4 receptor α blocking antibodies are also in clinical development, but thus far, clinical studies in patients with severe asthma have been disappointing. A blocking mAb to IL-13, lebrikizumab, has been studied in asthmatic patients whose symptoms are not controlled with high doses of ICSs and showed a small increase in FEV1 (approximately 5%) compared with placebo after 12 weeks but no significant effect at 24 weeks. There are no significant improvements in symptoms or asthma-related health status and no reduction in exacerbations. Interestingly, increased concentrations of the plasma biomarker periostin, which was discovered by means of proteomic analysis of IL-13–stimulated epithelial cells, showed a slightly better response (approximately 8%) than low concentrations, suggesting that it can be used as a biomarker to predict greater responses. An mAb targeting IL-4 receptor α (AMG317), which therefore blocks the effects of IL-4 and IL-13, has been ineffective in controlling asthma symptoms or lung function in 3 different doses over a 12-week period in patients with mild asthma.

One question about the poor efficacy of anti–IL-13 strategies might be whether the dose is sufficient to block endogenous IL-13 in the airways. In a recent study a blocking anti–IL-13 mAb profoundly suppressed IL-13 in nasal secretions after local allergen challenge, yet there was no significant reduction in eosinophil numbers or nasal symptoms. IL-4 and IL-13 signal through the transcription factor signal transducer and activator of transcription 6, and small-molecule inhibitors, such as AS1517499, have now been developed that are active in a murine model of asthma but have yet to be developed clinically.

IL-5 is of critical importance for eosinophilic inflammation, and a blocking antibody to IL-5 (mepolizumab) depletes eosinophils from the circulation and sputum of asthmatic patients but disappointingly has no effect on the response to inhaled allergen, airway hyperresponsiveness, symptoms, lung function, or exacerbation frequency in asthmatic patients. However, more recent studies show that mepolizumab reduces exacerbations in highly selected patients who have persistent sputum eosinophilia despite high doses of ICSs, although there is no improvement in symptoms, lung function, or airway hyperresponsiveness.

Another IL-5 blocking antibody, reslizumab, failed to improve asthma control over 12 weeks in patients with sputum eosinophilia despite high doses of ICSs, but there was some reduction in symptoms and sputum eosinophils. An antibody against the IL-5 receptor α (benralizumab, MEDI-563) might more effectively deplete airway eosinophils than blocking IL-5 itself through antibody-dependent cytotoxicity of eosinophils and is currently being studied in clinical trials. Inhaled antisense oligonucleotides that block the common β chain of IL-5 and GM-CSF receptors together with the chemokine receptor CCR3 (TPI ASM8) have a small effect in reducing allergen responses and airway inflammation. Overall, blocking IL-5, although effective in reducing eosinophilic inflammation, has been disappointing, although it might be effective in highly selected patients, as well as in patients with other hypereosinophilic diseases, such as Churg-Strauss syndrome and eosinophilic esophagitis.

Another Th2 cytokine that is currently being targeted is IL-9, which plays a role in mast cell proliferation, although there is recent evidence that it is produced particularly by a subset of CD4+ T cells designated Th9 cells. Clinical studies have been encouraged by animal studies showing that inhibition of IL-9 leads to reduced allergic inflammation and mucus hypersecretion, and a blocking IL-9 antibody (MEDI-528) has been shown to be safe after weekly subcutaneous injections, with a trend toward reduction in exercise-induced asthma, which is mediated through mast cell activation. Larger clinical trials are now in progress.

There has been considerable interest in thymic stromal lymphopoeitin (TSLP), an IL-7–related cytokine that is secreted by airway epithelial cells, because it instructs dendritic cells to secrete chemokines that attract Th2 cells into the airways and potentiates the activation of these cells. TSLP expression by airway epithelial cells is increased in a subset of patients with severe asthma treated with high doses of ICSs, suggesting that
this might be a good target, especially because it acts as an up-stream cytokine. Several pharmaceutical companies are developing antibodies to TSLP and its receptor, as well as to OX40 and OX40 ligand, which act as costimulatory molecules to TSLP, although bronchial OX40/OX40 ligand expression is not increased in patients with severe asthma compared with those in patients with mild asthma.

Other cytokines

Another cytokine targeted in asthmatic patients is TNF-α, which might play a significant role in those with severe asthma. Several uncontrolled or small studies suggested that anti-TNF therapies (TNF blocking antibodies infliximab or soluble receptor etanercept) might be useful in reducing symptoms, exacerbations, and airway hyperresponsiveness in patients with severe asthma, but a recent large multicenter trial with the humanized antibody golimumab showed no beneficial effect on lung function, symptoms, or exacerbations, and there were increased reports of pneumonia and cancer. A study of etanercept over 4 weeks in patients with moderate-to-severe asthma showed no clinical efficacy, but there were no safety problems.

Several other cytokine blockers are currently being targeted in asthmatic patients, including IL-17, IL-25, IL-33, GM-CSF, and stem cell factor, but thus far, no clinical studies in patients with severe asthma have been reported.

Chemokine receptor antagonists

Chemokines are small cytokines that attract inflammatory cells, including mast cells, eosinophils, and T12 cells, into the airways and are therefore appropriate targets for therapy, particularly because they signal through G protein–coupled receptors for which small-molecule antagonists can be developed. The major focus of interest in asthmatic patients has been the chemokine receptor CCR3, which is predominantly expressed on eosinophils and mediates the chemotactic response to CXCL11 (eotaxin), which is secreted in asthma. CCR3 is also expressed on mast cells and some T12 cells. Several small-molecule inhibitors of CCR3 have been in clinical development, but their effects in asthmatic patients have not yet been reported because they have usually been discontinued because of toxicology problems. An inhaled antisense oligonucleotide that targets CCR3 has some effect in reducing sputum eosinophils, but results are difficult to interpret because IL-5 and GM-CSF β-chain antisense were coadministered. Other chemokine receptors that are targeted for asthma therapy are CCR2 on monocytes and T cells and CCR4, CCR8, and CXCR4 on T12 cells. A defucosylated antibody to CCR4 (mogamulizumab, also known as KW-0761 and AMG-761) results in prolonged cytotoxic effects on T12 cells, marked and prolonged depletion of T12 cells, and reduced lung inflammation in animal models. This antibody is now in early clinical trials for asthma and adult T-cell leukemia-lymphoma. CXCR2 is expressed on neutrophils and monocytes and might be involved in the recruitment of neutrophils into the airways of patients with severe (neutrophilic) asthma. Several small-molecule inhibitors of CXCR2 are now in clinical development. An oral CXCR1/CXCR2 antagonist, navarixin (SCH-527123), is effective in blocking ozone-induced sputum neutrophilia in healthy subjects and is currently in clinical trials in patients with severe asthma.

BROAD-SPECTRUM ANTI-INFLAMMATORY TREATMENTS

The fact that the symptoms of patients with severe asthma might not be controlled by high doses of ICSs plus LABAs and sometimes even oral corticosteroids has prompted a search for alternative anti-inflammatory therapies that can be added to existing therapies to provide additional control. In addition, inflammation in some patients with severe asthma is predominantly neutrophilic so that inhibitors of neutrophilic inflammation are needed, and corticosteroids are poorly effective against neutrophilic inflammation. Several approaches to treating neutrophilic inflammation might be applicable to the treatment of severe asthma. Although several classes of broad-spectrum noncorticosteroid anti-inflammatory treatments have been in development, there have usually been problems with side effects when the drugs are administered orally, and this has had limited clinical development. This suggests that it might be necessary to develop potent topically active anti-inflammatory treatments that avoid systemic exposure, but thus far, this has proved to be a major challenge.

PDE4 inhibitors

The most advanced of the anti-inflammatory therapies are PDE4 inhibitors, which have a wide spectrum of anti-inflammatory effects that are relevant to severe asthma, inhibiting T cells, eosinophils, neutrophils, mast cells, airway smooth muscle, epithelial cells, and nerves and are highly effective in animal models of asthma. PDE4 inhibitors are effective against neutrophilic inflammation, making them an attractive potential therapy for severe asthma when there is neutrophilic inflammation. An oral PDE4 inhibitor, roflumilast, has an inhibitory effect on allergen-induced responses in patients with mild asthma and also reduces symptoms and lung function similar to a low dose of ICS. Roflumilast is currently licensed for use in patients with severe COPD, and therefore there has been increased interest in its potential for the treatment of severe asthma. However, a major limitation to this class of drug is the mechanism-based side-effect profile, including nausea, headaches, and diarrhea, which is dose limiting. On the basis of animal models, the anti-inflammatory effects appear to be mediated by inhibition of PDE4B, whereas nausea and vomiting are mediated through PDE4D inhibition, suggesting that PDE4B-selective inhibitors might be better tolerated. Another approach is to deliver PDE4 inhibitors by means of inhalation, but thus far, these drugs have had no efficacy. Inhaled PDE3/4 inhibitors are also in development and might have the advantage of bronchodilatation through PDE3 inhibition.

Kinase inhibitors

Kinases play a key role in regulating the expression of inflammatory genes in asthmatic patients and might amplify inflammation in patients with severe asthma. There are now several kinase inhibitors that might be useful in the treatment of severe asthma (Fig 2). The transcription factor nuclear factor κB (NF-κB) regulates many of the inflammatory genes that are abundantly expressed in asthmatic patients and is activated in asthmatic airways. Small-molecule inhibitors of the key enzyme IKK2/IKKβ (inhibitor of κB kinase) block inflammation induced by NF-κB activation and are now in preclinical testing.
p38 mitogen-activated protein kinase (MAPK) activates similar inflammatory genes to NF-κB, is activated in cells from patients with severe asthma, and has been linked to corticosteroid resistance. A p38 MAPK inhibitor appears to improve corticosteroid responsiveness in cells from patients with severe asthma. p38 MAPK also plays a key role in activation of GATA3, a transcription factor that regulates T1/2 cell differentiation and expression of T1/2 cytokines. Corticosteroids block GATA3 activation and are mimicked by p38 MAPK inhibitors. An antisense that blocks p38 MAPK demonstrated efficacy in a murine asthma model. Several small-molecule p38 inhibitors are now in clinical development for the treatment of inflammatory diseases, but side effects after systemic administration have proved to be a major problem.

Phosphoinositide 3-kinase (PI3K) also regulates inflammation and has several isoforms, but nonselective inhibitors are likely to be toxic. The isoenzyme PI3Kγ is important in chemotactic responses, and selective inhibitors are in development, whereas PI3Kδ activation results in reduced corticosteroid responsiveness through reduced HDAC2 activity, so that PI3Kδ inhibitors might potentially reverse corticosteroid resistance in patients with severe asthma. Theophylline is a selective inhibitor of PI3Kδ, and theophylline derivatives that lack PDE inhibition or selective PI3Kδ inhibitors might therefore be of therapeutic value. A general concern about novel kinase inhibitors is that they might have side effects because they target mechanisms that are found in many cell types. Therefore it might be necessary to develop inhaled formulations for use in asthmatic patients in the future, as proved necessary for corticosteroids.

Spleen tyrosine kinase (Syk) is involved in activation of mast cells and other immune cells, and several small-molecule Syk kinase inhibitors are in development, particularly for patients with severe asthma. An antisense inhibitor of Syk kinase is effective in an animal model of asthma, and the small-molecule inhibitor R112 administered nasally reduces nasal symptoms in patients with hay fever. More potent inhibitors, such as R343 and Bay 61-3606, are in development for inhalation in asthmatic patients. Because Syk is widely distributed in immune and neuronal cells, there are concerns about side effects. As with other kinase inhibitors, there can be side effects with systemic administration, and therefore inhalation might be preferred.

**Peroxisome proliferator–activated receptor γ agonists**

Peroxisome proliferator–activated receptor (PPAR) γ agonists have a wide spectrum of anti-inflammatory effects, including inhibitory effects on macrophages and T cells and neutrophilic inflammation, and polymorphisms of the PPARγ gene have been linked to increased risk of asthma. The PPARγ agonist rosiglitazone produced a small improvement in lung function in smoking asthmatic patients in whom ICs were ineffective and a modest (15%) reduction in late response to inhaled allergen in patients with mild asthma. This suggests that PPARγ agonists, such as thiazolidinediones, have little therapeutic potential in asthma therapy.

**MAST CELL INHIBITORS**

 Mast cell activation is important as a driving mechanism in some patients with severe asthma. There are several approaches to inhibiting mast cell activation (Fig 3), and anti-IgE has already been shown to be of value in the treatment of some patients with severe asthma. Stem cell factor is a key regulator of mast cell survival in the airways and acts through the receptor c-Kit on mast cells. Plasma concentrations of stem cell factor are increased in patients with severe asthma. Blockade of stem cell factor or c-Kit is effective in animal models of asthma, suggesting that this pathway might be a good target for new asthma therapies. Mastinib is a potent tyrosine kinase inhibitor that blocks c-Kit (as well as platelet-derived growth factor receptors) and provides some symptomatic benefit in patients with severe asthma. More selective c-Kit inhibitors are in development.

Cromones (cromolyn sodium and nedocromil sodium) inhibit the activation of human mucosal mast cells and are very effective against allergen and other indirect challenges that involve mast cell activation. The effects of cromones are closely mimicked
by the diuretic furosemide, suggesting that they might act through ion channels. However, the molecular target for cromones was never identified, although recent studies suggest that an orphan G protein–coupled receptor called GPR35 might be a target.114

THE PROBLEM OF CORTICOSTEROID RESISTANCE

Resistance to the anti-inflammatory effects of corticosteroids might be an important factor in determining asthma severity. Several molecular mechanisms have now been described to account for corticosteroid resistance in asthmatic patients, including activation of p38 MAPK activity (as described above), increased expression of an alternatively spliced variant of the glucocorticoid receptor GRβ, increased production of macrophage migratory inhibitory factor (MIF), and reduced expression of HDAC2.115 This suggests that there might be therapies that could potentially reverse corticosteroid resistance and that there might be different phenotypes of corticosteroid resistance in asthma that could require different therapeutic approaches. p38 MAPK inhibitors have been shown to increase the anti-inflammatory responses to corticosteroids in PBMCs from patients with severe asthma,98 and as discussed above, p38 MAPK inhibitors are in clinical development for the treatment of severe asthma. MIF is reported to be increased in patients with severe asthma and block the anti-inflammatory effects of corticosteroids,116 but the molecular mechanisms are poorly understood, and it has been difficult to find drugs that block its actions.117 MIF can signal and cause corticosteroid resistance through the activation of p38 MAPK.118

HDAC2 activation

There is increasing evidence that corticosteroid resistance in patients with COPD is due to a reduction in HDAC2 activity and expression as a result of oxidative and nitrative stress.119 This results in increased acetylation of the glucocorticoid receptor, which prevents it from inhibiting NF-κB–driven inflammation.120 There is evidence that a similar mechanism might underlie corticosteroid resistance in patients with severe asthma, in whom there is increased oxidative stress from endogenously generated oxidants.121,122 A novel therapeutic strategy is reversal of this corticosteroid resistance by increasing the expression and activity of HDAC2, and this can be achieved in several ways (Fig 4).

Low doses of oral theophylline increase HDAC2 expression in alveolar macrophages from patients with COPD and thereby restore steroid responsiveness.123,124 It has previously been shown that addition of low-dose theophylline to moderate doses of ICSs is more effective in patients with severe asthma than increasing the dose of ICS to the maximum tolerated dose125 and that withdrawal of low-dose theophylline causes a loss of asthma control in patients with severe asthma.126 In smoking asthmatic patients who become refractory to corticosteroids, low-dose theophylline is effective when added to a dose of ICS, which is ineffective alone.127 The molecular mechanism of action of theophylline in increasing HDAC2 levels is independent of PDE inhibition and appears to be mediated by inhibition of oxidant-activated PI3Kδ.103,128 The tricyclic antidepressant nortriptyline also reverses corticosteroid resistance by inhibiting PI3Kδ and therefore might have clinical benefit as an add-on therapy, although clinical trials have not yet been done in patients with severe asthma.129 Selective PI3Kδ inhibitors might be of potential value in patients with severe asthma in combination with ICSs. Selective PI3Kδ inhibitors are now in clinical development for the treatment of B-cell leukemia but might also be useful in patients with severe asthma, especially if administered by means of inhalation to avoid any hematologic side effects.

Antioxidants

Oxidative stress is increased in patients with severe asthma,130 particularly during exacerbations, and reactive oxygen species are likely to amplify inflammation and contribute to its...
Oxidative stress also reduces steroid responsiveness through a reduction in HDAC2 activity and expression. This suggests that antioxidants might reverse corticosteroid resistance and also reduce inflammation. Unfortunately, currently available antioxidants based on glutathione are relatively weak and are inactivated by oxidative stress, and therefore new and more potent and stable antioxidants are needed, such as superoxide dismutase mimics and NADPH oxidase inhibitors.  

The transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) plays a key role in the regulation of endogenous antioxidant genes and might be dysfunctional in patients with severe asthma. Several Nrf2 activators, such as sulforaphane (which occurs naturally in broccoli) and the synthetic triterpenoid 1-(2-cyano-3-, 12-dioxooleana-1,9-dien-28-oyl)imidazole-methyl ester, have now been identified, and Nrf2 activators are now in clinical development.

Macrolides have long been recognized that macrolides have anti-inflammatory effects that might be independent of their antibiotic effects. Macrolides appear to inhibit inflammation by inhibiting NF-κB and other transcription factors, but the precise molecular mechanisms have not yet been determined. In patients with severe neutrophilic asthma, a course of azithromycin significantly reduced sputum neutrophil numbers and CXCL8 concentrations, with some improvement in symptoms. This suggests that it might be worth using a therapeutic trial of macrolide antibiotics in patients with severe asthma who have predominantly neutrophilic inflammation. A nonantibiotic macrolide (EM-703) reverses corticosteroid resistance caused by oxidative stress by increasing HDAC2 activity. Several nonantibiotic macrolides are now in development as anti-inflammatory therapies.

Bronchial thermoplasty delivers controlled thermal energy to the bronchial wall to selectively reduce the amount of airway smooth muscle and has been studied in patients with severe asthma. It is usually administered as 3 outpatient bronchoscopic procedures separated by 3 weeks. In a large controlled trial of almost 200 patients with severe asthma, bronchial thermoplasty compared with a sham procedure produced a small improvement in asthma-specific quality-of-life scores (although this was far less than the minimal clinically significant difference for this test) and a small reduction in exacerbations after treatment. However, significantly more patients were hospitalized, and therefore it is uncertain whether the small clinical benefit is justifiable. In another study asthma control was improved compared with that seen in a control group in patients taking ICSs in whom long-acting β2-agonists were withdrawn, suggesting that it would provide no greater benefit than a bronchodilator. The safety of the procedure has been followed for up to 5 years with no loss of lung function, suggesting that there are no structural changes as a consequence of the therapy. It is still unclear how much benefit this procedure provides in patients with severe asthma, and the clinical outcomes show little change and might not even be apparent when patients are treated with long-acting bronchodilators. It is possible that this procedure is indicated in carefully selected patients in whom airway smooth muscle hypertrophy is predominant, as evidenced by pronounced airway hyperresponsiveness. The mechanism of action of bronchial thermoplasty has been determined from studies in normal dogs, and it is uncertain how the procedure affects the airways of asthmatic patients or whether it leads to reduced inflammation by reducing airway smooth muscle cell secretion of inflammatory mediators in the airways of asthmatic patients.

Future Directions

It is now becoming clear that there are several distinct phenotypes of severe asthma and that these might require different therapeutic approaches. For example, patients whose symptoms were not controlled on maximal inhaled therapies that have high sputum eosinophilia and frequent exacerbations might benefit from anti–IL-5 therapy with mepolizumab or reslizumab. By contrast, neutrophilic asthma might respond to anti-inflammatory therapies that target neutrophilic inflammation, including PDE4 inhibitors, p38 MAPK inhibitors, CXCR2 antagonists, or macrolides. Corticosteroid resistance is likely to be an important mechanism contributing to poor treatment control in patients with severe asthma and might respond to therapies that target the molecular mechanisms of corticosteroid resistance, such as p38 MAPK inhibitors in some patients, or treatments that increase HDAC2 levels, such as theophylline, nortriptyline, and PI3K抑制 inhibitors among others. Analysis of large datasets of adults and children with severe asthma is now beginning to recognize distinct phenotypes. It will be important to identify biomarkers that predict response to identify therapeutic subphenotypes of asthma, and this area requires more research so that therapy can be personalized, particularly for therapies that target specific mediators or mechanisms, because only a small proportion of patients with severe asthma are likely to respond adequately.
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