REVIEW

Management of asthma in adults: current therapy and future directions

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Asthma is increasing in prevalence worldwide and results in significant use of healthcare resources. Although most patients with asthma can be adequately treated with inhaled corticosteroids, an important number of patients require additional therapy and an increasing number of options are available. A further minority of patients develop severe persistent asthma which remains difficult to manage despite current pharmacological therapies. This review discusses the various treatment options currently available for each stage of asthma severity, highlights some of the limitations of current management, and outlines directions which may improve the management of asthma in the future.

Asthma is characterised by variable airflow obstruction, airway hyper-responsiveness, and chronic airway inflammation. It is a common disease that can cause considerable morbidity and a significant mortality. Recent national and international asthma management guidelines recommend a stepwise approach, with treatment increased until asthma control is achieved and stepped down once control has been maintained for several months.[1 2] Key factors required for good asthma control are outlined in box 1. Currently available anti-inflammatory and bronchodilator drugs are very effective and good asthma control can be achieved for most patients. A significant minority, however, will have more severe persistent asthma which is difficult to manage and which may necessitate alternative approaches. New drugs which improve control for patients with severe disease, minimise side effects, or improve patient compliance are required. Several new classes of treatment, which may fill these roles, are currently under investigation in asthma. We will review the evidence supporting current asthma therapies including non-pharmacological treatments, suggest alternative approaches where appropriate, and finally discuss novel classes of drugs which may be useful in the future management of asthma. We will discuss the pharmacological options for each category of severity, which are defined in table 1. A summary of the main pharmacological treatments for asthma at each stage of severity is given in box 2.

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MILD INTERMITTENT ASTHMA

As required short acting β_2-agonists

Inhaled short acting β_2-agonists such as salbutamol and terbutaline are effective bronchodilators and should be prescribed to all patients with symptomatic asthma.[1 2] They are also useful in preventing symptoms of exercise induced asthma when given before the start of exercise,[3] and are important in the treatment of acute severe asthma. Their mechanism of action is thought to occur primarily by the relaxation of airway smooth muscle cells, but they also increase mucociliary clearance. They do not have any effective anti-inflammatory activity. Although sympathomimetic agents, short acting β_2-agonists have few side effects when inhaled, but tremor, palpitations, and tachycardia can occur with high doses. They should be used for symptom relief on an as required basis, since studies have shown that their regular use provides no additional benefit[4 5] and may even be harmful. Furthermore, individual patients' requirements for short acting β_2-agonists provides a useful guide to the need for a step-up in treatment: current guidelines suggest that if they are used on a daily basis for symptom control then regular anti-inflammatory agents are indicated.[2] The use of more than one canister of short acting β_2-agonists per month has been particularly associated with poorly controlled disease and should therefore alert the prescriber to the need for increased regular anti-inflammatory treatment.[6] Tolerance to the effects of short acting β_2-agonists can occur, particularly to the protection against bronchoconstriction induced during indirect challenges.[7]

MILD PERSISTENT ASTHMA

Low dose inhaled corticosteroids

Corticosteroids are currently the most effective anti-inflammatory agents for the treatment of asthma and inhaled corticosteroids are currently recommended for all patients with persistent asthma who require short acting β_2-agonists more than once per day[1] or those with intermittent asthma who experience severe exacerbations.[2] They exert their anti-inflammatory effects through a diverse range of mechanisms including the activation of the glucocorticoid receptor leading to the regulation of transcription of target genes, and the direct inhibition of a range of inflammatory cells, particularly eosinophils. Studies have consistently shown that treatment with regular inhaled corticosteroids results in significant improvements in airway inflammation in asthma, an effect demonstrated on bronchial

Abbreviations: FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow

Box 1: Factors required for good asthma control

(1) Minimal (ideally no)
- Day time asthma symptoms.
- Nocturnal wakening due to asthma.
- Asthma exacerbations.
- Emergency general practitioner or hospital visits.
- Time off work or school due to asthma.
- Limitations to everyday activities and exercise.
- Adverse effects of medication.

(2) Peak flow variability <20%
(3) Peak expiratory flow/ forced expiratory volume in one second >80% predicted for age and height

Box 2: Summary of pharmacological treatment for asthma of varying severity

Mild intermittent asthma
- Short acting β_2-agonists as required.

Mild persistent asthma
- Add low dose inhaled corticosteroids.

Moderate persistent asthma: select one of the following options
- Low dose inhaled corticosteroids plus long acting β_2-agonist.
- Higher dose inhaled corticosteroids.
- Low dose inhaled corticosteroids plus leukotriene antagonist.
- Low dose inhaled corticosteroids plus oral theophylline.

Severe persistent asthma
- High dose inhaled corticosteroids plus one or more of the following: long acting β_2 agonist; leukotriene antagonist; oral theophylline; oral β_2-agonist.
- Add oral corticosteroids if control still not achieved.
- Consider corticosteroid sparing agents.

biopsies[8] and also on non-invasive markers of airway inflammation such as the differential eosinophil count in induced sputum or nitric oxide concentrations in exhaled breath.[9] Furthermore, there is evidence that corticosteroid treatment is not helpful in the absence of eosinophilic airway inflammation.[10] In conjunction with these improvements in airway inflammation, inhaled corticosteroids improve symptoms,[11] health status,[12] airway hyper-responsiveness and lung function,[13] and reduce asthma exacerbations.[14] There is also epidemiological evidence from cohort and case-control studies showing that regular low dose inhaled corticosteroids reduce both hospital admissions[15] and asthma deaths.[16] A recent study of patients with mild, apparently well controlled asthma showed that the addition of regular low dose inhaled corticosteroids resulted in significant reductions in asthma exacerbations compared with placebo.[14] These marked benefits, coupled with the low incidence of side effects, have led some to argue that inhaled corticosteroids should be given to all but the mildest patients. It is not yet fully known whether long term treatment with inhaled corticosteroids alters the natural history of the condition and protects against accelerated declines in lung function. A prospective study of the effects of inhaled corticosteroids on pulmonary function showed that children who started inhaled corticosteroid treatment more than five years after the onset of asthma had a significantly lower forced expiratory volume in one second (FEV_1) than children who started treatment within two years of the diagnosis.[17] In a placebo controlled trial in children with mild to moderate asthma, the use of regular inhaled corticosteroids over four to six years resulted in improvements in symptoms, exacerbation rates and airway hyper-responsiveness compared with placebo, but no differences in lung function.[18] Further, long term prospective studies of the effects of regular inhaled corticosteroids on the decline in lung function in adults are needed to address this important issue.

Side effects of inhaled corticosteroids

Patients are often concerned about the possibility of adverse effects of inhaled corticosteroids, and in some parts of the world, notably North America, this has lead to their relative under-use. At low doses, up to 800 μg daily of beclomethasone dipropionate or budesonide or 500 μg daily of fluticasone, systemic side effects are not usually significant, but do become an issue at doses beyond this. Dysphonia commonly occurs due to deposition of inhaled corticosteroid particles locally in the oropharynx[19] and oral candidiasis may also develop.[20] Systemic side effects include bruising and atrophy of the skin[21] and reduced bone mineral density.[22] Suppression of the adrenocortical axis can occur but this is not usually clinically significant.[23] These systemic effects occur partly due to gastrointestinal absorption of swallowed particles and partly due to systemic absorption via the airways. The use of spacer devices, dry powder mechanisms, and mouth rinsing after inhaler use minimise adverse effects.[24 25] Drugs with high first pass metabolism in the liver such as budesonide and fluticasone have fewer systemic side effects than beclomethasone,[26] but at high doses (>800–1000 μg daily of beclomethasone dipropionate/budesonide or >500 μg daily of fluticasone) systemic absorption through the buccal and airway mucosa is an important consideration.

Cromones

The cromones sodium cromoglycate and nedocromil sodium, both given by inhalation, have been used as controller therapies in mild persistent asthma.[2] Their mechanism of action is not fully understood, although they are believed to suppress IgE-mediated inflammatory responses and may inhibit inflammatory cells.[27] Sodium cromoglycate has been shown to reduce symptoms and exacerbation frequency[28] and nedocromil sodium to improve symptoms, lung function, and airway responsiveness.[29] Overall, however, they appear to be rather less effective than low dose inhaled corticosteroids[30] and their long term effects on airway inflammation are unknown. The use of these agents in adults has therefore largely been superseded by the introduction of low doses of inhaled steroids for the majority of patients with persistent asthma.

MODERATE PERSISTENT ASTHMA

An important number of patients with asthma treated with low dose inhaled corticosteroids have sufficient symptoms to justify an increase in treatment.[31] The clinician is faced with an increasing number of treatment options for this important group of patients. Unfortunately data from published placebo controlled studies of the different treatments are not always applicable to everyday clinical practice in this area and important questions remain. We will therefore present the current evidence for each of the major treatment options and briefly discuss some of the outstanding issues.

Long acting β_2-agonists

Long acting β_2-agonists (salmeterol and formoterol) are currently generally recommended as the first choice for patients who have symptoms that persist despite regular inhaled corticosteroids. Salmeterol is a partial agonist of the β_2-receptor while formoterol is a full agonist. Both appear to have similar clinical effects, but formoterol has a more rapid onset of action.[32] Side effects of tachycardia, tremor, and muscle cramps are rarely a problem unless given in high doses. Tolerance to the effects of long acting β_2-agonists with loss of

Table 1 Classification of asthma severity

Severity	Day time symptoms	Night time symptoms	Peak flow
Mild intermittent	Less than once per week	Less than twice per month	⩾80% predicted, variability <20%
Mild persistent	Between once per week and once daily	More than twice per month	⩾80% predicted, variability 20%–30%
Moderate persistent	Daily, attacks affect activity	More than once weekly	60%–80% predicted, variability >30%
Severe persistent	Continuous, limited activity	Frequent	⩽60% predicted, variability >30%

The presence of any of the features of severity is sufficient to place a patient in that category. Patients in any category can have severe exacerbations.[2]

bronchodilator activity after the subsequent administration of both short and long acting β_2-agonists has been reported.[33 34] As with short acting β_2-agonists, these agents work primarily via the relaxation of airway smooth muscle, with additional effects on mast cells and vascular permeability, but without significant anti-inflammatory activity.[35] This lack of anti-inflammatory activity precludes their use as first line agents in asthma[36] and current guidelines recommend that they are only prescribed alongside regular inhaled corticosteroids.[1 2] When used in this way, long acting β_2-agonists have been shown to improve day time and night time symptoms and the need for rescue β_2-agonists.[37 38] In a randomised controlled trial of 852 patients treated with low dose inhaled corticosteroids (the FACET study) the addition of formoterol to inhaled low or high dose budesonide improved symptoms and lung function. In addition, the number of both mild and severe asthma exacerbations was reduced, where mild exacerbations are defined as a fall in peak expiratory flow (PEF) of >20% from baseline on two or more days, increased use of rescue short acting β_2-agonists or nocturnal wakening and severe exacerbations defined as a fall in PEF of >30% from baseline on two or more days or a deterioration in symptoms requiring rescue oral corticosteroids.[39] This study also directly compared the addition of formoterol to the alternative strategy of increasing the dose of inhaled corticosteroids. Compared with a fourfold increase in the dose of inhaled corticosteroids, the addition of formoterol resulted in similar improvements in symptom control but smaller reductions in severe asthma exacerbations. In an uncontrolled study of 429 patients with symptomatic asthma followed over six months, the addition of salmeterol to inhaled beclomethasone dipropionate was shown to result in a greater increases in PEF and greater decreases in symptom scores than a 2.5-fold increase in the dose of inhaled beclomethasone dipropionate, but no differences in exacerbations were seen.[40] More recently, the OPTIMA study in patients with milder disease suggested that the addition of formoterol resulted in greater reductions in exacerbation frequency than doubling the dose of inhaled corticosteroids.[14] One important concern with long acting β_2-agonists is that subjects recruited into many clinical trials are not fully representative of the patients we see in everyday clinical practice. Many of the published studies, for example, only recruited patients who demonstrated acute improvements FEV_1 after inhaled bronchodilators of 15% or more.[39–43] Such degrees of bronchodilator reversibility are distinctly unusual in clinical practice: only 28% of patients with asthma in general practice demonstrated a 15% improvement in FEV_1 after 2.5 mg nebulised salbutamol[44] and only 5%–10% of patients with asthma in our clinic demonstrated similar increases in FEV_1 after 200 μg inhaled salbutamol.[45] Subjects therefore are not only atypical but are particularly likely to respond to bronchodilator therapy. There is a risk that these studies are generalised to wider patient populations when a more reasonable interpretation is that long acting β_2-agonists are particularly helpful for a subgroup of patients who have marked bronchodilator response.

Increasing the dose of inhaled corticosteroids

The traditional approach to patients with persistent symptoms despite low doses of inhaled corticosteroids was to increase the corticosteroid dose, but the evidence for this is somewhat inconsistent. While some studies have demonstrated clear dose related improvements in symptoms and lung function,[39 46 47] others have not demonstrated clinically important benefits with moderate or high doses.[48] Overall the beneficial effects of increasing the dose of inhaled corticosteroids appear to be modest and may be largely outweighed by the increased risk of side effects. As discussed earlier, the comparative studies have suggested that higher doses of inhaled steroids are less effective at controlling symptoms and peak flow variability compared with the addition of long acting β_2-agonists.[39 40] While the relationship between improvement in symptoms and inhaled corticosteroid dose reaches a plateau, control of exacerbation frequency is more closely related to inhaled corticosteroid dose. In the FACET study a fourfold increase in the dose of budesonide resulted in a significantly greater reduction in the number of asthma exacerbations than the addition of formoterol.[39] Conversely, a twofold increase in the dose of budesonide did not result in similar improvements in the rates of exacerbations in milder patients included in the OPTIMA study,[14] suggesting that the higher dose ranges are required for the optimal prevention of exacerbations. There is increasing evidence that asthma exacerbations are associated with eosinophilic airway inflammation,[49 50] and the benefits of the high doses of inhaled corticosteroids on exacerbation frequency are therefore likely to reflect dose related anti-inflammatory effects. Turner and colleagues have shown that a doubling of the dose of beclomethasone in subjects with symptomatic asthma and a persistent sputum eosinophilia despite treatment with inhaled corticosteroids improved symptoms and significantly reduced the sputum eosinophil count, whereas the addition of salmeterol led to improvements in symptoms but no change in the sputum eosinophil count.[50] Similarly, in a study of increasing doses of budesonide in patients with steroid naïve asthma, Jatakanon *et al* demonstrated a dose dependent reduction in the percentage of eosinophils in induced sputum.[9] While low doses of inhaled corticosteroids are therefore probably appropriate for the majority of patients, higher doses of these drugs may be indicated in some patients who experience frequent severe exacerbations of asthma or who have persistent airway inflammation.

Leukotriene antagonists

Montelukast and zafirlukast are both effective cysteinyl leukotriene receptor antagonists capable of markedly inhibiting exercise induced bronchoconstriction[51 52] and the early and late response to inhaled allergen.[53 54] When added to as required β_2-agonists, clinical trials have shown improvement in lung function,[41 42] reduction in the need for rescue bronchodilators,[41 55] and some evidence of a reduction in eosinophilic airway inflammation.[56] In the UK, leukotriene antagonists are currently licensed for use in patients who remain symptomatic despite treatment with inhaled corticosteroids. Clinical trials have shown evidence of efficacy in patients taking high doses of inhaled steroids,[43] and the introduction of montelukast has been shown to allow a reduction in the dose of inhaled corticosteroid without loss of asthma control.[57] The effectiveness of the addition of leukotriene

antagonists compared with increasing the dose of inhaled corticosteroids in patients with persistent symptoms, however, has not yet been fully addressed. Two studies published in abstract form comparing zafirlukast with higher doses of inhaled corticosteroids did not show any important differences between the two treatment strategies.[58] A recent meta-analysis has suggested that the addition of leukotriene antagonists to inhaled corticosteroids does not significantly reduce asthma exacerbations compared with increasing the dose of inhaled corticosteroids,[59] but there is a paucity of adequately powered studies addressing this issue and further work is needed.[60] The relative effectiveness of leukotriene antagonists compared with long acting β_2-agonists as add-on therapy also remains unclear and needs further investigation.[61] Although some studies have shown that the addition of long acting β_2-agonists results in greater improvements in asthma control than the addition of leukotriene antagonists,[62 63] others demonstrate that comparable improvements in symptoms and lung function are seen, with leukotriene antagonists providing additional anti-inflammatory effects that long acting β_2-agonists do not.[64 65] It is possible that subgroups of patients with asthma may be particularly suited to treatment with leukotriene antagonists, perhaps through genetic variations in the cysteinyl-leukotriene pathways (see below).

Theophylline

Theophylline has been used for many years in relatively high doses as a bronchodilator, but due to adverse effects it has often been reserved for use in patients with more severe asthma. Gastrointestinal upset is particularly common[66] but tachycardia and arrhythmia can also occur and measurements of serum concentrations are generally advised with high dose treatment.[2] Recent interest has been in the use of theophylline at lower doses where the risk of side effects is minimised. The combination of low dose inhaled corticosteroids and theophylline has been shown to result in comparable asthma control as higher doses of inhaled corticosteroids and may provide slightly greater improvements in lung function.[67–69] A meta-analysis has suggested that long acting β_2-agonists are more effective than theophylline in patients taking low doses of inhaled corticosteroids and result in fewer side effects.[70] Unlike long acting β_2-agonists, however, theophylline has been shown to have possible anti-inflammatory activity and may therefore have a role in some patients.[71]

SEVERE PERSISTENT ASTHMA

A proportion of patients will have persistent symptoms despite appropriate treatment for moderate persistent asthma as outline above. While representing a relatively small minority, these patients experience much morbidity, consume significant healthcare resources,[72] and are probably best managed in specialist settings. Before additional therapeutic measures are considered it is important to accurately confirm the diagnosis, to ensure that persistent symptoms are due to asthma rather than other aggravating factors such as rhinitis or gastro-oesophageal reflux and to assess compliance with existing therapy. Once these issues have been addressed current guidelines advocate a step-up in treatment, usually with high doses of inhaled corticosteroids in combination with long acting β_2-agonists, leukotriene antagonists, theophylline, oral β_2-agonists, or a combination of these agents. There have been no randomised controlled studies comparing these different treatment options in this group of patients and therefore additional therapy should be instituted on a trial basis and discontinued if there is no objective evidence of benefit.[12] Occasionally high doses of inhaled β_2-agonists are needed for optimum symptom control. Though these may be administrated via a nebuliser, metered dose inhalers used in combination with spacer devices have been shown to be equally effective even during acute exacerbations.[73]

Oral corticosteroids and corticosteroid sparing agents

A further group of patients have severe persistent asthma that remains difficult to control despite the measures outlined above. In these circumstances treatment with oral corticosteroids, usually in the form of daily prednisolone, may be required to minimise symptoms and prevent severe asthma exacerbations. While courses of oral corticosteroids are unquestionably a vital part of the management of acute exacerbations, careful consideration should be made before they are administered on a long term basis since there is a high risk of significant adverse effects.[74] Where they are required, the lowest dose which maintains asthma control should be given. Preventative therapy for osteoporosis should be considered and patients should be monitored for the development of hypertension, diabetes, cataracts, glaucoma, and adrenal suppression. Obesity, thinning and bruising of the skin, and myopathy are also important concerns. High doses of inhaled corticosteroids, up to 2 mg daily of beclomethasone or equivalent, should always be continued, as these are likely to allow a reduction in the oral corticosteroid dose.[75] Nebulised corticosteroids have not been shown to reduce systemic toxicity compared with equivalent doses of oral corticosteroids and are not recommended.[2] Other corticosteroid sparing agents include methotrexate, gold, and cyclosporin. Although there is some evidence that these agents have steroid-sparing effects in asthma,[76–78] each have their own safety concerns and their use should be confined to specialist units. The risk of adverse effects from the use of long term oral corticosteroids and the lack of safe alternatives necessitates careful monitoring of the response to treatment. A small minority of patients with severe asthma demonstrate resistance to corticosteroid treatment despite apparently good compliance. The mechanisms for this resistance are not fully understood but may relate to transcriptional regulation of genes associated with steroid responsive inflammation.[79] These patients present a significant therapeutic challenge beyond the scope of this review.

NON-PHARMACOLOGICAL AND ALTERNATIVE THERAPIES IN ASTHMA

Smoking cessation

Cigarette smoking in adults with asthma is associated with an accelerated decline in lung function,[80] increased symptom severity and exacerbation frequency,[81] and an impaired response to inhaled corticosteroids.[82] Although studies confined to populations of patients with asthma have not been done, smoking cessation clearly has a number of important health benefits which are likely to be particularly important to patients with pre-existing respiratory disease. Appropriate advice should therefore be given to all patients with asthma who smoke, and pharmacological treatments such as nicotine replacement therapy or buproprion should also be considered.

Self management plans (personalised asthma action plans)

Combined with regular medical review, asthma self management plans, particularly those that include written advice for patients to follow should symptoms and/or peak flow readings deteriorate, have been shown to reduce hospital admissions for asthma and are recommended in current guidelines.[1 83] Despite this, there have been some suggestions that neither patients nor primary health care professionals are convinced of their benefits and they may be particularly suited to those patients with poor symptom perception or recurrent asthma exacerbations.[84]

Breathing retraining, Buteyko techniques, and physical training

There is increasing interest in breathing retraining techniques in asthma, particularly among patients and the lay press. The Buteyko technique, for example, which uses hypoventilation in an attempt to raise the partial pressure of carbon dioxide in the blood, has been advocated as a method to allow reductions in, or even withdrawal of, asthma medication. Unfortunately rigorous trials of these methods have not yet been published and they should therefore be viewed with caution. It has recently been recognised, however, that many patients treated for asthma in primary care also have symptoms suggestive of dysfunctional breathing patterns.[85] Results of a physiotherapy based breathing retraining programme in such patients suggested significant improvements in health status in the short term,[86] and more work in this area is clearly needed. It is likely that retraining techniques may improve symptoms and health status where there is dysfunctional breathing, either in the context of mild asthma or where asthma has been misdiagnosed. Physical training methods have been shown to improve cardiovascular fitness but not lung function in patients with asthma but effects on symptoms and quality of life have not been assessed.[87]

Allergen avoidance

The exposure of patients with atopic asthma to the allergens that they are sensitised to has been shown to increase asthma symptoms and airway hyper-responsiveness and to cause bronchoconstriction.[88] Studies of measures that aim to control the exposure of house dust mite and pet allergens, however, have not conclusively been shown to improve asthma outcomes and larger trials have been advocated.[89] Studies of allergen control measures in infancy have shown reductions in respiratory symptoms,[90 91] but it remains to be seen if such measures will prevent the development of atopy and asthma in later life.

Immunotherapy

Allergen specific immunotherapy, or desensitisation, involves the administration of specific allergen extracts via subcutaneous injections of increasing concentration with the aim of inducing immunological tolerance. The process may work by generating interleukin-10 producing regulatory T-cells. Immunotherapy appears to be particularly useful in allergic rhinitis but has also been shown to improve symptoms and airway responsiveness in patients with allergic asthma.[92] Overall the benefits appear to be modest, the technique is labour intensive, and major concerns about its safety remain since life threatening anaphylactic reactions can occur. Thus, while some patients may gain dramatic benefits immunotherapy for asthma is not recommended in the UK.[93]

FUTURE DEVELOPMENTS IN THE MANAGEMENT OF ASTHMA

It is likely that new therapies will become available over the next 5–10 years. Some of the more promising agents are discussed below. We also feel that there will be increasing interest in the heterogeneous nature of asthma in the future, specifically the heterogeneity of treatment response. Identification of factors predicting a response to treatment will enable therapy to be targeted, may improve outcomes and result in more rational, economical use of treatment. This is likely to be particularly important with the introduction of novel agents which are likely to be expensive, effective against only specific components of a complex inflammatory cascade, and therefore best reserved for subgroups of patients most likely to respond. New developments in the pharmacogenetics of asthma are likely to play a key role in this area.

(1) Novel pharmacological therapies

Anti-IgE monoclonal antibody

IgE has an important role in the development of allergic diseases in atopic subjects and suppression of IgE is therefore a potential target in the management of atopic asthma. A monoclonal anti-IgE antibody, omalizumab, which blocks the interaction of IgE with mast cells and basophils, has been developed. This has now been studied in patients with moderate and severe allergic asthma treated with inhaled corticosteroids. Compared with placebo omalizumab, given as a subcutaneous injection at doses titrated to serum IgE levels, it resulted in improved symptom control,[94] fewer exacerbations, and greater reductions in inhaled corticosteroid doses with no apparent adverse effects.[94 95] It therefore appears to be a potentially useful anti-inflammatory agent in patients with atopic asthma.

Monoclonal antibody to interleukin-5

Interleukin-5 is a very selective cytokine, which is responsible for the maturation and release of eosinophils in the bone marrow. Since eosinophils are a characteristic pathological feature of asthma, inhibition of interleukin-5 represents another potential treatment and two monoclonal antibodies to interleukin-5 are currently under investigation. The first published study showed that the humanised anti-interleukin-5 monoclonal antibody SB-240563 was able to reduce the sputum eosinophilia after allergen challenge when given intravenously, but had no effect on the early or late fall in FEV_1, or on airway responsiveness.[96] Since eosinophilic airway inflammation appears to be related more closely to asthma exacerbations than hyper-responsiveness,[97] it is possible that agents such as anti-interleukin-5 will be more useful in preventing asthma exacerbations than minimising day to day symptoms.

Humanised recombinant interleukin-12

Interleukin-12 is another potential treatment for asthma. It is a macrophage-derived cytokine that is able to suppress eosinophilic inflammation via modulation of T-lymphocyte responses. A trial of subcutaneous humanised recombinant interleukin-12 given to patients with mild asthma was somewhat disappointing. As with anti-interleukin-5, suppression of eosinophilic inflammation occurred but was not associated with improvements in airway hyper-responsiveness.[98] Additionally, significant side effects developed in a number of subjects and this is likely to limit its usefulness.

Interleukin-4 receptor antagonists

Interleukin-4 is another key cytokine in the development of airway inflammation that has been targeted in the search for novel asthma therapies. A nebulised soluble interleukin-4 receptor which acts as an interleukin-4 antagonist is under investigation. Initial studies have shown that this drug is well tolerated and may reverse the deterioration in symptoms and lung function that occur after withdrawal of inhaled corticosteroids.[99] Study withdrawal due to asthma exacerbations after corticosteroid withdrawal were not prevented, however, and larger studies of longer duration are required.[100]

(2) Targeting the appropriate therapy for individual patients

It is becoming clear that the key features of asthma: symptoms, disordered airway function, airway inflammation, exacerbations and long term decline in lung function, are not closely related to each other within patients and might have a different pathophysiological basis. Recent studies have questioned a direct causal association between eosinophilic airway inflammation and airway hyper-responsiveness,[96 97] and have suggested that infiltration of airway smooth muscle by mast

Table 2 Evidence for the efficacy of each class of treatment on the four major features of asthma

Treatment class	Symptoms/VAO	Exacerbations	Inflammation	Decline in FEV_1
Short acting β_2-agonists	+	–	–	?
Long acting β_2-agonists	++	+	–	?
Inhaled corticosteroids	++	++	++	+
Leukotriene antagonists	+	+	+	?
Theophylline	+	?	+	?

VAO, variable airflow obstruction.

cells might be more important.[101] In contrast, asthma exacerbations are more closely related to eosinophilic airway inflammation, such that the induced sputum eosinophil count has emerged as a good surrogate marker of exacerbation frequency.[97] There is increasing evidence that some patients with asthma do not have eosinophilic airway inflammation and might not respond to inhaled corticosteroids.[10 97 102]

Taken together, these findings suggest that targeting of treatment, based on assessments of the predominant feature of disease in individual patients, might result in more effective use of treatment (table 2). It might also result in more economical use of treatment compared with ad hoc treatment trials that are currently recommended. In a recent study we compared a management strategy that aimed to normalise the induced sputum eosinophil count as well as minimise symptoms.[97] We found that the sputum management strategy achieved significantly better control of eosinophilic airway inflammation and a marked reduction in severe asthma exacerbations than the traditional management strategy (35 *v* 109, p=0.01). Furthermore, significantly fewer patients in the sputum management strategy were admitted to hospital with asthma (1 *v* 6, p=0.047). There were no significant differences in the average daily dose of inhaled or oral corticosteroids between the two groups, since monitoring airway inflammation in the sputum management strategy identified a group of patients whose sputum eosinophil count was predominantly within the normal range. In these subjects we were able to markedly reduce the dose of corticosteroids without evidence of deterioration in control. We have therefore shown that the use of induced sputum in targeting anti-inflammatory treatment is feasible and results in significantly improved patient outcomes. In patients with moderate to severe asthma at least, we believe that regular monitoring of airway inflammation in this way is required for optimal treatment.

(3) Recent advances in the pharmacogenetics of asthma

Pharmacogenetics, the study of how genetic differences influence the variability of individual patient responses to drugs, aims to distinguish responders from non-responders and thus lead to rationalised drug therapy. The clinical heterogeneity of asthma has lead to increasing interest in the study of the genetic variability of this disease. There has been particular interest in the pharmacogenetics of β_2-agonists and modifiers of the cysteinyl-leukotriene pathway.

β_2-Agonist pharmacogenetics

The cell surface β_2-adrenergic receptor, via which β_2-agonists exert their effects, contains a number of genetic variants. Single nucleotide polymorphisms resulting in amino acid substitutions at positions 16 and 27 of the receptor and at position 19 of its upstream peptide are particularly common in white populations and are related to each other.[103 104] The role of these genetic polymorphisms in β_2-agonist treatment response remains unclear, however. Some studies, for example, have suggested that the β_2-adrenergic receptor position 16 genotype is associated with the response to β_2-agonist treatment with Gly16 homozygotes having diminished and Arg16 homozygotes exaggerated treatment responses.[105–107] Other studies, however have failed to demonstrate such an association.[108 109] It is possible that combinations of different alleles (haplotypes) rather than single nucleotide polymorphisms are important in determining treatment responses.

Leukotriene pharmacogenetics

Cysteinyl leukotrienes are important mediators in the inflammatory response in asthma. They are derived from arachidonic acid via the 5-lipoxygenase pathway. The study of the pharmacogenetics of the leukotrienes has concentrated on two key enzymes of this leukotriene synthesis pathway, 5-lipoxygenase and leukotriene-C_4 synthase. 5-Lipoxygenase catalyses the conversion of arachidonic acid to leukotriene-A_4 and is blocked by the drug Zileuton, which is not licensed in the UK.

An early study suggested that the response to a Zileuton derivative exhibited considerable genetically determined variability, with patients who have two mutant alleles at the promoter sequence of the 5-lipoxygenase gene being resistant to treatment.[110] The second key enzyme, leukotriene-C_4 synthase is involved in the conversion of leukotriene-A_4 to leukotriene-C_4, which subsequently forms leukotriene-D_4 and leukotriene-E_4. The leukotriene receptor antagonists montelukast and zafirlukat inhibit the binding of these cysteinyl leukotrienes to their receptor. Again, genetic polymorphisms of the leukotriene-C_4 synthase gene may relate to variations in clinical response, with one study suggesting that patients with C/C and C/A variants of the leukotriene-C_4 synthase promoter respond particularly well to treatment with zafirlukast.[111]

Although clearly much more work is needed in this field, the study of pharmacogenetics offers great potential in furthering our understanding of the heterogeneous nature of asthma and improving our use of existing asthma therapies. Such advancements, which may enable the use of genotyping to tailor therapy for individual patients, are eagerly awaited.

CONCLUSIONS

Inhaled corticosteroids remain the cornerstone of treatment for patients with chronic asthma. While they effectively improve eosinophilic airway inflammation and lung function and control asthma symptoms in most patients, a number will require additional therapy. There is currently a range of effective additional treatments available for these patients. To rationalise the future management of asthma it will be important to target treatments to those patients who are most likely to respond by identifying individual treatment goals and carefully assessing the likely underlying pathophysiology. In patients with more severe asthma close monitoring of airway inflammation is required for optimal management. Novel therapeutic agents which act on specific components of the inflammatory pathway in asthma are emerging. The future management of patients with asthma may well involve the use of these newer agents in combination with more established therapies.

QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

Q1. Long acting β_2-agonists:

(A) Are equally as effective as inhaled corticosteroids as monotherapy in asthma

(B) Reduce mild exacerbations of asthma

(C) Effectively suppress eosinophilic airway inflammation

(D) Improve asthma symptoms when given to patients who remain uncontrolled despite regular inhaled corticosteroids

(E) Are unsuitable for the majority of patients due to a poor side effect profile

Q2. Leukotriene antagonists:

(A) May be given as an alternative to inhaled corticosteroids in mild asthma

(B) May allow a reduction in the dose of inhaled corticosteroid

(C) Have less anti-inflammatory action than long acting β_2-agonists

(D) May prevent exercise induced bronchoconstriction

(E) Are less effective in patients with a polymorphism of the promoter sequence of the 5- lipoxygenase gene

Q3. Novel pharmacological asthma treatments:

(A) The antibody to IgE, omalizumab, must be given by intravenous injection

(B) Omalizumab reduces exacerbations in patients with allergic asthma

(C) Humanised anti-interleukin-5 has been shown to reduce airway responsiveness in asthma

(D) Recombinant interleukin-12 is associated with significant side effects

(E) A soluble interleukin-4 receptor may improve lung function when given orally

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ANSWERS

Q1. F, T, F, T, F; Q2. F, T, F, T, T; Q3. F, T, F, T, F.