

REVIEW

Management of Asthma in Adults: Current Trends and Future Directions

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Abstract

Bronchial asthma has witnessed a significant increase in its prevalence in the past decade. Considerable morbidity and significant mortality has been associated with it and this has been matched by increased scientific research into new methods of therapy to supplement or replace the traditionally known treatment modalities. A search for old and new literature on asthma management in adults necessitated forage in the library for old works and an internet search into relevant websites to download several works on asthma from which those relevant to this article were selected. Evidences supporting current asthma therapies including some non-pharmacological measures of intervention and alternative approaches were highlighted. Some novel interventions that may be useful in the future management of asthma were discussed. Some novel therapeutic agents acting on specific components of the inflammatory pathways in asthma are emerging. The future management of asthma may involve the use of these newer agents in combination with more established therapies. For successful management of asthma, patient's education and involvement are essential.

Key words: Bronchial asthma, management, adults

Résumé

L'asthme bronchique a connu une augmentation significative à son fréquence au cours de la décennie passée. On l'avait associée avec une morbidité considérable et une mortalité significative et celles-ci ont été égales avec une recherche scientifique augmentée sur des nouvelles méthodes thérapeutiques pour compléter ou remplacer les modalités du traitement connu traditionnellement. Une recherche pour l'ancienne ou la nouvelle littérature sur la gérance de l'asthme chez les adultes a nécessité un fourrage dans la bibliothèque pour des anciens travaux aussi qu'une recherche sur l'internet aux sites pertinents pour retirer plusieurs travaux sur l'asthme. C'est à partir de ces travaux que ceux qui sont pertinents à cet article sont sélectionnés. Les preuves en faveur des thérapies actuelles de l'asthme y incluent quelques mesures pharmacologiques d'intervention et des autres approches sont soulignées. Quelques interventions nouvelles qui peuvent être utiles dans l'avenir pour la gérance de l'asthme sont aussi discutées. Quelques nouveaux agents thérapeutiques qui agissent sur les composantes spécifiques des chemins inflammatoires en asthme s'émergent. Dans l'avenir la gérance de l'asthme peut entraîner l'emploi de ces nouveaux agents en association avec les thérapies les plus établies. Pour réussir à la gérance de l'asthme, l'éducation et la participation du malade est essentielle.

Mots clés: L'asthme bronchique, la gérance, les adultes

Introduction

The past decades have witnessed a spectacular increase in the prevalence of asthma globally, with associated significant use of healthcare resources. As far back as 1860, Henry Hyde Salter, a Physician at Charing Cross Hospital in London described asthma as paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration in between attacks.¹⁻³

He drew attention to the musical rhonchi that characterised asthmatic bronchoconstriction, and identified its cellular basis, which was only fully elucidated after the development of eosin stain by Paul Ehrlich in 1875.⁴ The pathological basis was further described by Huber and Koessler in 1922.⁵ Similarly, another significant milestone is the characterisation of its trigger factors by Sir William Osler in the early part of the 19th century.⁶

Asthma is associated with variable airflow obstruction, airway hyper-responsiveness, and chronic airway inflammation. It can cause considerable morbidity and a significant mortality. It is defined as reversible airway obstruction associated with inflammation and bronchial hyper-responsiveness.⁷ The airway hyper-responsiveness is induced by a variety of local stimuli involving biochemical pathways of histamine, leukotrienes and prostaglandins. Various risk factors are associated with the development of asthma. These include familial predisposition, maternal smoking, ethnicity, socio-economic status and gender (male sex).^{7,8}

National and international guidelines have developed a stepwise approach to management, with treatment increment until asthma control is achieved and stepped down once control has been maintained for several months.^{7,8} Currently available anti-inflammatory and bronchodilator drugs are very effective and a good asthma control can be achieved for most patients using these agents. A significant minority, however, will have more severe persistent asthma which is difficult to manage and which may require alternative approaches. New drugs which improve control and outcome, with minimal side effects, or improve compliance are therefore needed. Some new classes of drugs, which may fill these roles, are currently under investigation. This review aims to discuss the evidence supporting current asthma therapies including some non-pharmacological measures of intervention, and alternative approaches where appropriate, and finally discuss some novel interventions under development that may be useful in the future management of asthma.

Lifestyle Modification and Other Non-Pharmacological Strategies in the Management of Asthma

Changes in attitude, behaviour and lifestyle may play a significant role in the management of asthma.^{9,10}

Smoking

Cigarette smoking in adults with asthma is associated with an accelerated decline in lung function, increased symptoms severity and exacerbation of frequency of attacks in addition to impaired response to inhaled corticosteroids.¹¹ 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.¹² Appropriate counselling should therefore be given to all patients with asthma who smoke and pharmacological treatments such as nicotine replacement therapy may be relevant.

Patient involvement

Involving patients in their asthma 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 some current guidelines.^{7,8} How this can be applicable in our setting with low literacy rates remain to be determined.

Avoidance of allergen

The exposure of patients with atopic asthma to the allergens that they are sensitive to has been shown to increase asthma symptoms and airway hyper-responsiveness and to cause bronchoconstriction. Studies of allergen control measures in infancy have shown reductions in respiratory symptoms, but it remains to be determined if such measures will prevent the development of atopy and asthma in adulthood.¹³

Immunotherapy

Allergy specificity and reaction have been described in asthmatics, and its targeting in management may improve outcome.¹⁴ 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. This has been found to be particularly useful in allergic rhinitis but has also been shown to improve symptoms and airway responsiveness in patients with allergic asthma.¹⁵ Overall the benefits appear to be modest, but desensitisation therapy can be labour intensive, and is associated with life threatening anaphylaxis.

Pharmacological interventions

Most management guidelines have recommended graded interventions of therapy according to severity of symptoms and frequency of attacks.^{7,8}

Mild Asthma

Evidence-based management here revolves around whether the asthma is mild intermittent or persistent. Mild intermittent asthmatics are those in whom symptoms occur less than once a week and have nocturnal symptoms ≤ 2 per month. Their peak expiratory flow rate (PEF) is $\geq 80\%$ of predicted value and shows $< 20\%$ variability. They are asymptomatic and have normal PEF between attacks. In mild intermittent asthma, the mainstay of therapy is still the use of Inhaled short acting β_2 -agonists which are shown to be effective in bronchodilation.^{7,8,16} 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 and should be used for symptom relief when required. Their regular use provides no additional benefit and may even be harmful.¹⁶ The use of more than one canister of short acting β_2 -agonists per month has been associated with poorly controlled disease and should therefore alert the prescriber to the need for increased regular anti-inflammatory treatment.

Mild persistent asthmatics are those in whom symptoms occur more than or equal to once a week but less than once a day. They have nocturnal symptoms more than twice a month while their PEF values are more than or equal to 80% of predicted value and show 20-30% variability. In this group corticosteroids are currently the most effective anti-inflammatory agents for the treatment and inhaled corticosteroids are currently recommended for all patients with persistent asthma who require short acting β_2 -agonists more than once per day or those with intermittent asthma who experience severe exacerbations.^{7, 8} They exert their anti-inflammatory effects through a diverse range of mechanisms including the activation of the glucocorticoid receptors, 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.¹⁷ There is also epidemiological evidence from cohort and case-control studies showing that regular low dose inhaled corticosteroids reduce both hospital admissions and asthma deaths.¹⁸ A recent study of patients with mild, apparently well controlled asthma showed that the addition of regular low dose inhaled corticosteroids resulted in significant reduction in asthma exacerbations compared with the control group.¹⁹ 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 asthma, or protects against decline in lung function. 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.

In-addition, the cromones agents by inhalation, has been used as controller therapies in mild persistent asthma. Though mechanism of action is not fully understood, they are believed to suppress IgE-mediated inflammatory responses and may inhibit inflammatory cells.²⁰ However, they appear to be rather less effective than low dose inhaled corticosteroids 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.²¹

Moderate Persistent Asthma

This refers to patients who use β_2 agonist daily because of daily attacks and who have night time symptoms more than once a week. Their PEF values are more than 60% and less than 80% of predicted value and shows variability of more than 30%. Such patients may have been receiving treatment with low dose inhaled corticosteroids and still have sufficient symptoms to justify a step up along the treatment

ladder. There are an increasing number of treatment options for this group of patients. Long acting β_2 -agonists (e.g. 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 -receptors while formoterol is a full agonist. Both appear to have similar clinical effects, but formoterol has a more rapid onset of action. As with short acting β_2 -agonists, these agents work primarily via the relaxation of airway smooth muscles, with additional effects on mast cells and vascular permeability, but without significant anti-inflammatory activity. This lack of anti-inflammatory activity precludes their use as first line agents in asthma and current guidelines recommend that they are only prescribed alongside regular inhaled corticosteroids.^{7, 8, 22} Long acting β_2 -agonists have been shown to improve day time and night time symptoms and reduce the need for rescue short acting β_2 -agonists. 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 and reduced the rate of acute exacerbations.²³ In-addition, 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.²⁴ One important concern with long acting β_2 -agonists is that subjects recruited into many clinical trials are carefully selected and therefore not fully representative of the patients seen in everyday clinical practice.

The earlier 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,^{23, 25} others have not demonstrated clinically important benefits with moderate or high doses.²⁶ 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.

The next group of agents are the leukotriene receptor antagonists which are capable of markedly inhibiting exercise induced bronchoconstriction and the various responses to inhaled allergen.²⁷⁻²⁹ Moreover, when added to as required short acting β_2 -agonists, clinical trials have shown improvement in lung function.³⁰ Clinical trials have also shown evidence of efficacy in patients taking high doses of inhaled steroids, and the introduction of montelukast has been shown to allow a reduction in the dose of inhaled corticosteroid without loss of asthma control.³¹ 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.

In-addition, high up the ladder is theophylline which has been in use for many years as

a bronchodilator, but due to adverse effects, it has often been reserved for use in patients with more severe asthma. 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.³² Following a meta-analysis, long acting β_2 -agonists are shown to be superior to theophylline in patients taking low doses of inhaled corticosteroids and result in fewer side effects as well.³³ However, unlike long acting β_2 -agonists, theophylline has been shown to have anti-inflammatory activity and may therefore be more beneficial in some patients.

Severe Persistent Asthma

This refers to patients with limited physical activity due to continuous symptoms. Night time symptoms are frequent and their PEF values are less than or equal to 60% of predicted values with a variability of more than 30%. This group of patients have persistent symptoms despite appropriate treatment for moderate persistent asthma. It is imperative in this group of patients to ensure that the 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 resolved, current guidelines recommend 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.^{7, 8} 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.³⁴

A further group of patients continue to 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. When needed, the lowest dose which maintains asthma control should be given. Prophylactic therapy for osteoporosis should be considered and patients should be monitored for the development of hypertension, diabetes, cataracts, glaucoma, and adrenal suppression. Similarly, obesity, thinning and bruising of the skin, and myopathy are also important concerns. Other corticosteroid sparing agents that include methotrexate, gold, and cyclosporine can be used in some instances. Although

there is some evidence that these agents have steroid-sparing effects in asthma each has its own safety concerns and their use should be limited to specialist units.^{35, 36}

There is also need for individualised treatment plans, required for different settings due to differences in circumstances regarding clinical presentation, and even in terms of personnel and resources. For instance, the severity of symptoms in asthma differs in pattern across the globe in epidemiology, risk profile and manifestations.³⁷ Relevant guidelines have evolved to suit different settings even in some developing countries as South Africa.³⁹

Future Therapies

This involves the use of such agents as Anti-IgE monoclonal antibody. The hypersensitivity type 1 immunoglobulin, IgE has a significant role in the development of allergic diseases in atopic subjects, and particularly asthma.¹⁴ Its suppression 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 agent given as subcutaneous injection at doses titrated to serum IgE levels, resulted in improved symptom control in a series of patients with resultant fewer exacerbations, and even a greater reduction in inhaled corticosteroid doses with no apparent adverse effects.⁴⁰ This is an important future treatment of patients with atopic asthma.

The development of monoclonal antibodies to interleukin-5 has been widely acknowledged. This is based on the principle that the eosinophils are a characteristic inflammatory response cells in asthma. The inhibition of the cytokine interleukin-5, responsible for the maturation and release of this group of cells in the bone marrow represents another potential treatment. It has been shown that the humanised anti-interleukin-5 monoclonal antibody SB-240563 was able to reduce the sputum eosinophilia after allergen challenge when given intravenously, though without effect on the early or late fall in FEV₁, or on airway responsiveness.⁴¹

More recently, the role of human recombinant interleukin-12 and interleukin-4 receptor antagonists in the armamentarium of management of asthma are being investigated. Interleukin-12 is a macrophage-derived cytokine that can suppress eosinophilic inflammation by modulating T-lymphocyte responses. In several studies it has been shown to suppress eosinophilic inflammation with no associated improvements in airway hyper-responsiveness.⁴² It awaits further characterisation and development.

Interleukin-4 is another key cytokine in the development of airway inflammation that has been targeted in the search for novel asthma therapies by the use of its antagonists. Some initial reports have shown that this drug may reduce the deterioration in symptoms and the reduced lung function that follows after withdrawal of inhaled corticosteroids.⁴³

Conclusion

Despite the recent advancement in understanding of the pathophysiology and targets for therapeutic interventions in asthma, the use of inhaled corticosteroids is still the cornerstone of treatment in chronic asthma. Steroids are effective in improving eosinophilic airway inflammation, lung function and also control asthma symptoms in most patients. But some patients will still require additional therapy. There is a range of effective additional treatments available. It is vital to target treatments to patients who are most likely to respond through identification of individual treatment goals and careful assessment of likely underlying pathophysiology. In patients with more severe asthma, close monitoring of airway inflammation is required for optimal management.

Currently, some novel therapeutic agents acting on specific components of the inflammatory pathways in asthma are emerging as discussed. The future management of asthma may well involve the use of these newer agents in combination with more established therapies, after their further development and establishment of efficacy. In another but equally important dimension, patient education and involvement is an essential component of successful asthma management.⁴⁴ Current management approaches require patients and families to effectively carry on with complex pharmacologic regimens, institute environmental control strategies, detect and self-treat most asthma exacerbations, and communicate appropriately with health care providers. Doctors should train patients to gain the motivation, skill, and confidence to control their asthma. Research shows that asthma education can be cost-effective and can reduce morbidity for both adults and children, especially among the high-risk patients, with appropriate lifestyle intervention.^{44, 45}

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