Asthma: second-line therapies

It is important to recognise the inflammatory nature of asthma.

CHARLES FELDMAN, ***MB BCh, PhD, FRCP, FCP (SA)***
Division of Pulmonology, Department of Medicine, Johannesburg Hospital and University of the Witwatersrand, Johannesburg, South Africa

Professor Charles Feldman is Professor of Pulmonology and Chief Physician at the Johannesburg Hospital and University of the Witwatersrand. His clinical research interest is in the field of respiratory tract infections, and his basic research interest is in the field of airway inflammation, both of infective and non-infective origin. He has published extensively on these topics, mainly in international journals.

Asthma is now recognised as an inflammatory condition of the airways.[1,2] The inflammation is responsible for the various manifestations of asthma, namely the symptoms, the airflow limitation and the airway hyper-responsiveness.[2] The majority of asthmatics are therefore treated with so-called controller medications, most of which have well-documented anti-inflammatory activity.[1,2] Reliever medications are used for rescue therapy for the quick relief of symptoms and during acute attacks, although it is recommended that short-acting β_2-agonists (SABA) may be used on their own in truly mild intermittent asthmatics with mild and infrequent symptoms and normal lung function.[1,2] This article describes the second-line medications that may be used in the management of patients with asthma (Table I).

Table I. Alternative agents for the treatment of asthma

Reliever
- Ipratropium bromide

Controller
- Leukotriene receptor antagonist
- Theophylline

Additional
- Omalizumab

Experimental
- Soluble TNFα receptor

Reliever medications

The reliever medications most commonly used in asthmatics are the SABA, which have been considered to be the primary bronchodilator.[1-3] An alternative agent is the short-acting anticholinergic agent ipratropium bromide, which is sometimes used either on its own or in combination with SABA.[3,4] However, a Cochrane Review suggested that there is little additional benefit of adding an anticholinergic to a SABA.[4] Overall it appears that anticholinergics provide less bronchodilatation than the SABA.[4] There does appear to be variability in the anticholinergic response in asthmatics, and patient groups more likely to benefit from anticholinergic agents include older asthmatics, those intolerant of SABA, or those who have nocturnal or intrinsic asthma.[3] In general, adverse effects appear to be more common with β_2-agonists and studies have suggested that these adverse effects occur particularly commonly in patients with a genetic polymorphism in the β_2-receptor (homozygosity for arginine rather than glycine at amino acid residue 16) who would therefore benefit from anticholinergic therapy.[3] Neither SABA nor ipratropium bromide have been shown to have anti-inflammatory activity. The role of long-acting anticholinergics, such as tiotropium bromide, in asthma has not been clarified.[4]

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Controller medications

While inhaled corticosteroids (ICS) are the mainstay controller therapies for the management of asthma and many asthmatic patients can be completely controlled with regular use of low or moderate doses of ICS,[5] some patients with persistent asthma will remain symptomatic on this treatment.[5] Options for the management of these cases are to either increase the dose of ICS or to add in another controller agent, such as a long-acting beta-agonist (LABA), a leukotriene receptor antagonist (LTRA), or a theophylline. Controller agents have been documented to have anti-inflammatory and/or immunomodulatory activity. Most guidelines, including those of the South African Thoracic Society,[2] indicate that LABAs are the preferred additional agents, based on their greater efficacy and lower incidence of side-effects. However, the other agents are potentially suitable alternative options in some cases not controlled on ICS alone.

Leukotriene modifiers

Montelukast (Singulair – MSD) and zafirlukast (Accolate – Astra Zeneca) are LTRAs, which are the most recently introduced class of anti-asthma agents.[6] They act through the selective blockade of the cyteinyl leukotriene (cysLT1) receptors, which inhibits both the bronchoconstrictive and inflammatory effects of the leukotrienes.[6,7] In clinical trials of patients with mild asthma, the levels of control of asthma achieved with montelukast have been comparable with those of ICS. As add-on therapy to corticosteroids in the treatment of moderate asthmatics, improvements of asthma control have been achieved with the LTRAs which are comparable with those of LABAs,[8] although a recent Cochrane meta-analysis suggested that LABAs were superior to LTRAs in preventing exacerbations, and for improving lung function, symptoms, and use of rescue therapy.[9] At least some studies clearly demonstrate that allergen-induced airway inflammation, as well as restructural/airway remodelling changes that occur that are not modulated by corticosteroids are reversible by LTRAs.[10] Most national and international asthma treatment guidelines therefore have LTRAs firmly niched in their asthma treatment protocols, most commonly as an alternative adjunctive therapy together with ICS.[1,2] Additional features of the leukotriene antagonists are that they are given orally, thus avoiding any potential patient adherence problems with the use of inhaler devices, but also providing systemic activity and hence suppressing inflammation throughout the airway, including inflammation in the smaller airways.[7] They have a high safety profile.[6] It has been said

that because of their various characteristics, they would be particularly suited for the treatment of asthma in children, for the treatment of asthmatic patients with associated severe allergic rhinitis, for the treatment of exercise-induced bronchospasm and for aspirin-induced asthma.[6,11]

Theophylline

Theophylline has been used for the treatment of patients with asthma for over 6 decades.[12] It remains one of the most commonly prescribed drugs for the treatment of airway disorders, especially in the developing world, because it is inexpensive. In the First World it has largely been relegated to a second- or even third-line choice because of its relatively low efficacy and high frequency of side-effects, and the fact that long-acting bronchodilators and corticosteroids are much more effective anti-inflammatory agents.[12]

Both the Global Initiative for Asthma (GINA) 2006 Guideline[1] and the South African Asthma Guideline (2007)[2] indicate that theophyllines are an alternative add-on therapy in patients with asthma not controlled on low to moderate doses of corticosteroids alone, while indicating that adding LABAs is more effective and associated with fewer side-effects.[13] A number of studies have indicated that adding theophylline to ICS in mild to moderate asthmatics not controlled on low-dose corticosteroids gives equivalent or even better control than doubling the dose of corticosteroids alone.[12,14] However, doubling the dose of ICS itself is associated with very modest benefit. Additional studies have confirmed that theophylline has steroid-sparing effects.[12,15]

Slow-release theophylline has also been shown to be of use in the management of nocturnal asthma, but this has been superceded by use of LABAs.[12] However, theophylline has been shown to be of benefit in patients with severe asthma, with improved control even in cases on high-dose ICS and worsening of asthma with theophylline withdrawal despite continuing use of high-dose inhaled and even oral corticosteroids.[12]

The particular advantage of theophyllines is that they are considerably less expensive than the alternative options and may be the only affordable options when cost considerations are overriding.

Theophylline has been used as a controller therapy in mild persistent asthma but usually with an efficacy less than low-dose ICS alone.[12]

The particular advantage of theophyllines is that they are considerably less expensive than the alternative options and may be the only affordable options when cost considerations are overriding.[12] If a theophylline is being considered for use in an asthmatic, the slow-release formulations are recommended; there is no role for oral short-acting theophyllines in chronic asthma.[2] Side-effects include gastrointestinal effects, palpitations, insomnia, irritability and seizures; it has been suggested that the use of theophylline at concentrations at the lower limit or slightly below the recommended therapeutic range may help limit the adverse effects.[2]

Although theophylline has been traditionally classified as a bronchodilator, its ability to control asthma has been greater than its relatively small degree of bronchodilating activity. In fact, theophylline has been shown to have immunomodulatory, anti-inflammatory and bronchoprotective effects that may well be contributing to its efficacy as an anti-asthma agent (Table II).[12, 16]

A number of studies have been conducted using the PDE4 inhibitors for patients with asthma.[16,17] None of the current PDE4 inhibitors have yet gained regulatory approval in South Africa.

Chromones

According to the Gina Guideline,[1] sodium chromoglycate and nedocromil sodium have a limited role in the long-term management of asthma, having weak anti-inflammatory effects and being less active than even low-dose inhaled glucocorticosteroids.

Anti-immunoglobulin e (anti-IgE)

It is well known that IgE is a key mediator of the allergic response in humans and that it also plays a major role in allergic conditions such as asthma and allergic rhinitis.[18] Because of this, therapies based on blocking IgE by antibodies directed against the IgE molecule were developed.[18] Omalizumab is a humanised monocolonal anti-IgE antibody that works by binding free IgE and thus preventing the interaction between free IgE and both the high and low affinity IgE receptors on inflammatory cells, such as basophils and mast cells.[18,19] Also, by removing free IgE from the circulation omalizumab downregulates the expression of high-affinity IgE receptors on these cells.[18] This therapy has been particularly recommended for patients with severe persistent asthma, in whom a number of studies have suggested that omalizumab decreases exacerbations and improves symptom control, lung function and quality of life.[18-20] It has also been shown to reduce airway inflammation and to have a steroid-sparing effect.[19,20] It has been shown to be particularly effective in poorly controlled patients with severe persistent asthma, and has been recommended as a possible second-line agent in patients with moderate to severe persistent allergic asthma not controlled on standard therapy.[18,21] However, it has been suggested that its benefits need to be balanced against its high cost, as well as the relative inconvenience of its use, since it needs to be administered subcutaneously every 2 or 4 weeks.[19]

Anti-TNF therapy

Patients with refractory asthma have been clearly shown to have an upregulation of the TNF-α pathway. Recently investigators have studied the effects of soluble TNF receptor (etanercept) in patients with mild to moderate asthma and documented decreased methacholine hyper-responsiveness, an improvement in asthma quality of life and a significant increase in post-bronchodilator FEV_1.[22]This represents an interesting, potentially new approach to the management of asthma for the future.

Table II. Proposed mechanisms of action of theophylline[12]

Phosphodiesterase inhibition (non-selective)
Adenosine receptor antagonism (A_1-, A_{2A}-, A_{2B}- receptors)
Increased interleukin-10 release
Stimulation of catecholamine (epinephrine) release
Mediator inhibition (prostaglandins, tumor necrosis factor-α)
Inhibition of intracellular calcium release
Inhibition of nuclear factor-$_k$B (↓ nuclear translocation)
Increased apoptosis
↑ Histone deacetylase activity (↑ efficacy of corticosteroids)

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Other therapies

According to the South African Asthma Guidelines:[2]

- antihistamines have no role in adults for the treatment of asthma itself
- immunosuppressive agents such as methotrexate have a limited benefit and patients considered for this treatment should be referred for specialist opinion
- there is little scientific evidence that ionisers, oxygen therapy, acupuncture, homeopathy, and exclusion diets are useful in the treatment of asthma
- desensitisation using immunotherapy is not routinely recommended, but patients with refractory asthma sensitised to one allergen may be referred to a specialist for immunotherapy.

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In a nutshell

- Asthma is an inflammatory condition of the airway.
- The inflammation is responsible for the manifestations of asthma, namely the symptoms, the airflow limitation and the airway hyper-responsiveness.
- The majority of asthmatics are treated with a controller medication of which the inhaled corticosteroids (ICS) are the mainstay of therapy.
- In patients not controlled on ICS alone, it is recommended that an additional controller medication is added, rather than simply increasing the ICS dose, and the long-acting beta-agonists are the preferred option.
- Leukotriene receptor antagonists (LTRAs) are suitable options that are given orally
- LTRAs appear to be particularly useful for the treatment of asthma in children, for asthmatic patients with allergic rhinitis, for the treatment of exercise-induced asthma and for aspirin-induced asthma.
- Sustained release theophylline is an alternative additional controller therapy, which although very cheap, is associated with low efficacy and a high frequency of side-effects.
- Chromones have limited value in the long-term management of asthma.
- Anti-immunoglobulin E therapy is the most recently introduced therapy which is recommended for use as a second-line agent in patients with moderate to severe allergic asthma not controlled on standard recommended therapy.
- For reliever therapy, the primary bronchodilators are the short-acting beta-agonists (SABA), although anticholinergic agents may be suitable for older adults, for those intolerant of SABA, and for patients with nocturnal or intrinsic asthma.