What's new in asthma treatment?

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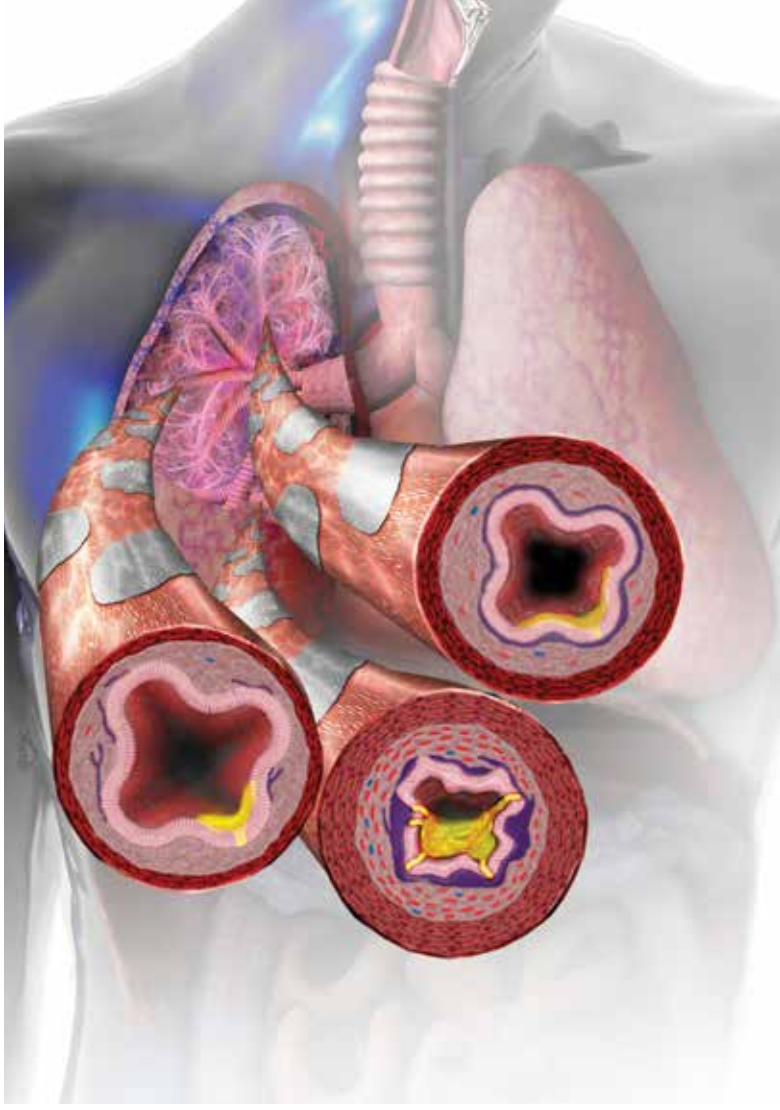
Medical research is redefining asthma as we know it. No longer does one size fit all when it comes to treatment, particularly when asthma is not responsive to standard therapies. There are new inhaled therapies available as well as highly targeted biologic therapies for the allergic and eosinophilic subclasses of asthma.



The development of inhaled corticosteroids (ICSs) to suppress airway inflammation, their use in combination with long-acting beta agonists (LABAs), and a major focus on patient education and prevention of acute exacerbations has led to dramatic improvements in asthma outcomes in Australia over the past two decades.[1] However, not all patients achieve asthma control with standard therapies, and some phenotypes of asthma, such as neutrophilic and obesity-related asthma, remain poorly responsive to ICS plus LABA therapy. Other patients experience suboptimal control of their disease despite taking maximal doses of appropriate inhaled therapies with good technique. New approaches to asthma treatment are being developed as a result of improved understanding of asthma mechanisms.

Key points

- **Large studies in patients with asthma have revealed different patterns of airway inflammation (asthma phenotypes) that suggest the possibility of an individualised approach to asthma management.**
- **Australian doctors and patients now have a wider choice of inhaled corticosteroid (ICS) plus long-acting beta agonist (LABA) combinations and inhaler devices.**
- **Evidence suggests that addition of the long-acting muscarinic antagonist tiotropium to ICS plus LABA therapy may reduce asthma exacerbations while providing modest bronchodilatation.**
- **The monoclonal antibodies omalizumab and mepolizumab were recently licensed in Australia for the management of patients with severe allergic asthma and severe eosinophilic asthma, respectively.**

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Phenotypic categorisation of asthma driving asthma therapy

The past decade has seen a major drive among asthma researchers to better understand the pathophysiology of asthma. Different patterns of airway inflammation have been recognised in large studies of patients with asthma, forming the basis for defining relatively distinct asthma phenotypes, which it is hoped will allow a more tailored approach to management.[2-4] These asthma phenotypes are described in the Table. However, it should be noted that a degree of overlap is often seen in clinical practice, such that some people can have features of more than one phenotype, and some cannot be readily classified into any single phenotype. This reflects the limitations of current phenotyping. Advances in understanding of the molecular mechanisms involved in asthma should allow greater refinement of these phenotypes in the future.

Approach to patients who appear poorly responsive to ICS plus LABA therapy

The first steps in assessing patients with a poor response to standard asthma treatments involve basic principles of good medicine. More often, improving asthma control involves addressing the issues outlined below rather than prescribing a new medication.

- Is the diagnosis of asthma correct? Asthma is defined by airflow obstruction that varies spontaneously or in response to therapy.
  - Has spirometry been performed before and after bronchodilator treatment?
  - Has peak flow monitoring been undertaken over a period of time to confirm variable airflow obstruction? This is a useful strategy if the diagnosis is unclear or an occupational trigger is suspected.
- Has inhaler technique and adherence to treatment been reviewed? Problems in these two areas are common causes of failure to achieve good asthma control.
- Have other issues such as smoking cessation, avoidance of trigger factors and management of comorbidities been addressed?

If all these considerations have been addressed and the patient's asthma remains poorly controlled then consider specialist referral. A respiratory physician will usually initiate and guide the addition of inhaled LAMAs or other medications.

New ICS plus LABA combinations

ICS plus LABA combinations such as budesonide plus formoterol (eformoterol) (Symbicort) and fluticasone propionate plus salmeterol (Seretide, Airzate and Evocair) have been a well-established component of asthma management for many years. New combination products are now available for use in asthma, including fluticasone propionate plus formoterol (Flutiform) and fluticasone furoate plus vilanterol (Breo Ellipta).[5] Both Flutiform and Breo Ellipta are available under the PBS for people aged 12 years or over experiencing frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. Flutiform offers the advantage of a relatively small particle size, and may therefore achieve greater drug deposition in small to medium airways. Breo has the advantage of once-daily use. Neither has been evaluated for use as a single maintenance and reliever inhaler.

Australian doctors and patients now have a wide choice of different inhaler devices, but this carries with it a greater risk of errors. Good patient education and regular review of technique have never been more important. The potency of the different ICSs varies and dose adjustments need to be closely reviewed, particularly when switching between inhalers.

New therapies in asthma – LAMAs

The Global Initiative for Asthma (GINA) met in 2016 to reformulate their guidelines based on the new concept of phenotypic asthma variants and its implications for targeted therapies. New to this version of the guidelines was the addition of long-acting muscarinic antagonist (LAMA) therapy in step 4 (initial therapy) of the stepwise asthma management algorithm.[6] Acetylcholine causes smooth muscle constriction, and LAMAs have long been used for patients with chronic obstructive pulmonary disease (COPD) but have not until recently been licensed in Australia for use in patients with asthma.

A growing body of evidence consistently demonstrates the beneficial effects of combining the LAMA tiotropium with ICS plus LABA therapy in patients with asthma who are prone to exacerbations and have persistent airflow obstruction, defined as a postbronchodilator forced expiratory volume in 1 second (FEV_1) of 80% or less of the predicted value.[7] Addition of tiotropium to ICS plus LABA therapy reduces asthma exacerbations while providing modest bronchodilatation.[8] Tiotropium is TGA approved (but not PBS listed) for adults with asthma treated with maximal ICS plus LABA therapy who experienced one or more severe exacerbations in the previous year. There is currently no evidence base on which to recommend use of other LAMAs in asthma.

New targeted therapies

Omalizumab

Omalizumab, a recombinant humanised monoclonal antibody targeting the Fc region of IgE, is licensed in Australia for the management of patients with severe allergic asthma. By reducing free circulating IgE, omalizumab decreases the early and late phases of the asthmatic response to inhaled allergens. The downstream effects are vast and include a reduction in the number of eosinophils in sputum, downregulation of the high affinity IgE receptor on basophils and mast cells, and reduced allergen processing and presentation. There is good clinical trial evidence showing that omalizumab can reduce asthma exacerbations and improve asthma control when added to maximal inhaled ICS plus LABA therapy.[9,10]

Like all monoclonal antibodies, omalizumab is expensive, and its use is therefore restricted to patients with uncontrolled severe allergic asthma despite maximal conventional therapy (step 5 of the GINA guidelines – higher level care and/or add-on treatment).[6] Prescription of omalizumab requires written application to the Department of Human Services, which must be initiated by a respiratory physician,

Table. Characteristics and suggested treatments for currently accepted asthma phenotypes

Phenotype	Natural history	Pathophysiology	Clinical features	Biomarkers	Suggested treatments
Early-onset allergic	• Onset in childhood • Severity ranges from mild to very severe	• T helper type 2 (Th2) dominant physiology with elevated IgE	• Prominent allergic symptoms and history	• Increased total IgE and allergen-specific IgE	ICS, LABA, oral corticosteroids, omalizumab
Late-onset eosinophilic	• Onset in adulthood, usually >40 years • Often severe	• Th2 dominant physiology, with markedly elevated interleukin 5 (IL-5)	• Minimal/no atopic history • Sinus disease	• Peripheral eosinophilia • Total IgE may be normal	ICS, LABA, mepolizumab
Exercise-induced	• Intermittent, exercise induced • Usually mild	• Local mast cell activation	• Exertion/exercise history	• Nil	Leukotriene receptor antagonists, short-acting bronchodilators
Obesity-related	• Usually adult onset • More likely in women than men • Symptoms disproportionate to spirometry and bronchial hyper-responsiveness	• Mechanical factors, breathing at low lung volumes • Elevated adipokines and inflammatory mediators	• Obesity • Exercise-naïve	• High BMI, distribution of obesity	Weight loss, pulmonary rehabilitation
Neutrophilic	• Usually adult onset • Absence of the above factors	• Th17 dominant physiology	• Often heavily treated with corticosteroids despite being poorly responsive	• Sputum neutrophilia	Possibly macrolide antibiotics
Asthma with persistent airflow obstruction	• Unknown	• May involve structural airway changes (airway wall remodelling)	• FEV_1 <80% persistently	• Nil	ICS, LABA, consider adding tiotropium

Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta agonist.

clinical immunologist, allergist or general physician with experience in managing patients with severe asthma. The criteria for initiation of omalizumab include the following (further details are available on the PBS website):

- a proven diagnosis of asthma for over one year
- an FEV_1 less than or equal to 80% predicted, documented on three or more occasions in the previous 12 months
- elevated IgE and evidence of allergic sensitisation
- failure to achieve asthma control with optimal inhaled therapy (ICS plus LABA), despite formal assessment of and adherence to correct inhaler technique
- significant asthma exacerbations requiring either daily oral corticosteroids for at least six weeks, or a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months.

Omalizumab is administered by subcutaneous injection given fortnightly or monthly. Dosage charts based on weight and serum IgE concentration determine the required dose, which is capped at 750 mg every four weeks. Local skin reactions are the more common adverse effect, but anaphylaxis is possible and occurs at a frequency of approximately 1 in 1000.[11] Omalizumab binds to free IgE only, rather than IgE bound to mast cells, and therefore is not inherently anaphylactogenic. Although this monoclonal antibody carries the lowest risk of anaphylaxis of all the antibodies currently on the market in Australia, most patients are also prescribed an adrenaline (epinephrine) autoinjector because of the risk of delayed anaphylaxis.

The aim of therapy is to reduce the frequency of asthma exacerbations, minimise the need for oral corticosteroids and improve quality of life. All these endpoints have been clearly demonstrated in trials of patients with severe allergic asthma. After omalizumab

is started, clinical improvement is not immediate but is usually seen by three to four months. If no response is seen by six months then it is very unlikely that the individual will respond. Not surprisingly, patients with severe atopic skin disease often find that this also improves significantly with omalizumab therapy.

Mepolizumab

Recently approved in Australia for patients with severe asthma is mepolizumab, a humanised anti-interleukin-5 monoclonal antibody that is being investigated for the management of severe asthma, atopic dermatitis, hypereosinophilic syndromes and eosinophilic vasculitides. Mepolizumab is targeted at severe eosinophilic asthma, another of the asthma phenotypes. The DREAM and MENSA studies demonstrated its efficacy in patients with eosinophilia and severe asthma.[12,13] Exacerbation reductions of 40 to 50% relative to high-dose ICS plus LABA therapy have been reported.[14] Other effects include reducing the need for oral corticosteroids and reducing blood and sputum eosinophil counts.

Mepolizumab is TGA approved as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over and was recently recommended for listing on the PBS. At the time of writing, the PBS criteria for initiation of mepolizumab have not been finalised but are likely to include evidence of severe asthma, failure to achieve asthma control despite optimal inhaled therapy and a history of frequent exacerbations and blood eosinophilia. Given that mepolizumab targets a different asthma phenotype (eosinophilic asthma) to omalizumab (allergic asthma), it is likely that mepolizumab and other agents targeting eosinophils will become more widely used in the future. Although specialists will be the only practitioners initiating mepolizumab and other biologic therapies in the foreseeable future, GPs are likely to see a small number of their patients with severe asthma treated with these agents, and GP practice nurses may be increasingly involved in their administration.

Bronchial thermoplasty

Bronchial thermoplasty appears to have promise as a new treatment for severe refractory asthma. The procedure involves the controlled application of local heat to the airways during three sequential bronchoscopy sessions. The mechanism of action is meant to involve disruption of smooth muscle bundles in the airway walls, but surprisingly there is no consistent improvement in airflow obstruction. Benefits of the procedure appear to include improvements in asthma symptoms and quality of life.[15,16] More research is needed to guide practitioners in choosing which patients are likely to benefit or not benefit from this procedure.

Conclusion

Increasing scientific understanding of the pathophysiology of asthma is fundamental to the development of tangible therapeutic targets. As we learn more about the different phenotypes of asthma, we are better able to direct therapies to the most appropriate patient group. Monoclonal antibody therapies are being developed in all fields of medicine and are likely to play a major role in patients with severe asthma. The vast majority (more than 95%) of patients with asthma do not require these therapies but can be successfully managed with ICS and LABA therapy. However, the frequency of severe asthma (currently estimated at 5 to 10% of those with asthma) means that more and more GPs are likely to encounter patients who already use or will require referral for consideration of these agents. This will increase the complexity of managing these patients. **RMT**

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