ARTICLE

Biologic therapies for severe asthma with persistent type 2 inflammation

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SUMMARY

Asthma is a chronic inflammatory airways disease with reversible airflow obstruction, characterised in the majority by type 2 airway inflammation.

Type 2 inflammation results in secretion of interleukin-4, -5 and -13 in the airways, recruitment of inflammatory cells (especially eosinophils and mast cells), and airway changes such as mucus hypersecretion and increased airway reactivity.

Approximately 5 to 10% of people with asthma, despite optimal therapy and adherence to treatment with inhaled corticosteroids and long-acting beta$_2$ agonists, are unable to obtain good symptom control and continue to experience exacerbations requiring oral corticosteroids; this is known as 'severe asthma'. In many cases, this is associated with persistent type 2 inflammation, indicated by the persistent elevation of blood eosinophils or fractional exhaled nitric oxide.

In people with severe asthma and persistent type 2 inflammation, biologic (monoclonal antibody) therapy is indicated. Biologic therapies currently available in Australia for asthma are benralizumab, dupilumab, mepolizumab and omalizumab. They are administered subcutaneously and are generally well tolerated.

Biologic asthma therapies are very effective in improving symptoms, and reducing the rate of exacerbations and use of oral corticosteroids, in people with severe asthma and persistent type 2 inflammation. Inhaled corticosteroid treatment should be continued in people using a biologic therapy.

Introduction

Our understanding of asthma, in particular the crucial role played by airway inflammation, has advanced considerably in the last 30 years. This has led to treatments that substantially improve outcomes and modify the disease course.

Inhaled corticosteroids (ICS), either alone or in combination with bronchodilators, are effective treatments as they reduce airway inflammation and not just symptoms. While ICS treatment controls asthma in most people, 5 to 10% have refractory disease with poor symptom control and frequent exacerbations ('severe asthma').[1] The development of biologic (monoclonal antibody) therapies that target key inflammatory pathways has improved outcomes for many people with severe asthma and advanced the understanding of asthma pathophysiology.

Asthma is a chronic airways disease

The Australian Bureau of Statistics reports asthma prevalence at 11% of the population.[2] There is a common misconception that asthma is an acute limiting and remitting illness, only present when symptoms are evident, and that relief of symptoms with bronchodilators is sufficient to control the disease. This view is reinforced by the fact that acute severe adverse outcomes for asthma are now fortunately rare – asthma deaths are few and hospital admissions for those greater than 6 years of age continue to decline.[3] Improved asthma awareness and the introduction of effective treatments, that is ICS either alone or in combination with bronchodilators, probably explain these changes, as the prevalence of the disease has not lessened. However, measuring acute asthma events only gives part of the story.

People with asthma report worse quality of life than the general population, and the burden of disease in terms of healthy years of life lost has risen on average at 0.4% per year since 2003.[4] The worst outcomes in terms of burden of illness are seen in remote communities and in the lowest socioeconomic groups. This includes Aboriginal and Torres Strait Islander peoples, in whom asthma is 1.5 times more prevalent and who experience the greatest long-term burden of illness.[4] Misunderstanding asthma as an acute illness alone risks a complacency in approach to management,

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overlooking the importance of optimised maintenance treatment for chronic disease.

There are 2 important aspects to understanding asthma as a chronic disease. First, that poor symptom control inevitably leads to deteriorating disease, and second, that the consequence of this process is increased risk of exacerbations along with the need to use oral corticosteroids to control the disease.[5,6] Oral corticosteroids may be lifesaving in acute asthma; however, repeated courses, or low-dose maintenance treatment, leads to significant toxicity that is cumulative.[7,8] Patients with frequent exacerbations often suffer from regular symptoms, with impaired daily functioning and quality of life.[7] They are also at risk of irreversible loss of lung function, with younger people most at risk.[9] To modify the disease course of asthma, treatment needs to focus on the underlying airway inflammation.

Asthma is caused by chronic airway inflammation

The majority of people with asthma show evidence of type 2 (T2) inflammation.[10] This is an inflammatory pathway driven by T helper 2 (Th2) CD4+ lymphocytes. It results in secretion of the cytokines interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13) in the airways. This leads to recruitment of inflammatory cells, especially eosinophils and mast cells, along with airway changes such as mucus hypersecretion and increased airway reactivity.[11]

Asthma that is driven by the T2 inflammatory cascade can be further subdivided into **allergic asthma** and **eosinophilic non-allergic asthma**. Patients with an allergic phenotype are characterised by an elevated serum immunoglobulin E (IgE) concentration and demonstrate allergen-specific IgE. People with allergic asthma typically experience disease onset in childhood and often have concurrent atopic dermatitis or allergic rhinitis. Eosinophilic asthma occurs independently of allergy, usually in those with asthma onset in adulthood.

The presence of airway inflammation in asthma can be measured directly by readily available clinical tests, such as an elevation in blood eosinophils or fractional exhaled nitric oxide (FeNO).[12] FeNO can be measured using a point-of-care test, most often available in Australia in lung function laboratories.

Understanding that airway inflammation is present in people with asthma is crucial, as asthma control can only be achieved through the use of anti-inflammatory treatment. Relief of symptoms and airflow obstruction is not enough, in those with asthma of all severities, including mild and severe disease.

Inhaled corticosteroids are first-line treatment for asthma

In people with asthma confirmed on spirometry, that have symptoms more than once a month, or a history of acute asthma triggered by virus infection, allergies or exercise, treatment with a short-acting beta$_2$ agonist alone is associated with worse clinical outcomes and should always be avoided.[13]

Even in mild asthma, where symptoms are intermittent, recent evidence strongly demonstrates that people do better with regular low-dose ICS or ICS+formoterol as needed.[14] This benefit is seen for everyone with asthma that has been demonstrated by reversible airflow obstruction, though the benefits are highest in those with demonstrable asthma-related inflammation, as measured by blood eosinophils more than 0.3×10^9 cells/L (300 cells/microlitre) or an elevated FeNO.[15,16] This emphasises the crucial role of airway inflammation even in mild asthma.

In most people with asthma, control of airway inflammation can be achieved with low to moderate doses of ICS.[17] In those with persistent poor control or exacerbations, the addition of a long-acting beta$_2$ agonist (LABA), such as formoterol, to a low- to moderate-dose ICS is as effective as high-dose ICS.[18] ICS+formoterol can be used as both maintenance and reliever therapy, and is arguably more efficacious in terms of reducing exacerbations. It can achieve equivalent symptom control but has the added benefit of enhancing flexibility of ICS dosing at a time of increased disease activity without the need to always resort to oral corticosteroids.[19]

Severe asthma is disease that is not responsive to inhaled corticosteroids

While ICS regimens, with or without a LABA, are usually effective, in a proportion of people asthma control remains elusive and exacerbations continue.[20] This is known as **'difficult asthma'**. The first step should always be to ensure the patient is taking their medication as prescribed and using their inhaler device correctly, as these are the most common reasons for difficult asthma.[21]

'Severe asthma' is a subset of difficult asthma, where there is continuing poor symptom control and ongoing exacerbations requiring oral corticosteroids despite optimised ICS and LABA use, adherence and device technique, and management of comorbid conditions.[1,22] In the past, guidelines have suggested ever-increasing doses of ICS, but this approach has been shown to be ineffective, exposing people to higher risk of asthma exacerbations and oral corticosteroid courses compared with lower ICS doses.[23] The question then is what to do instead?

Severe asthma with evidence of persistent type 2 inflammation is an indication for biologic therapy

People with severe asthma and evidence of persistent T2 airway inflammation are indicated for treatment with a biologic (monoclonal antibody). There is something about the airway inflammation in these individuals that makes it refractory to even high doses of ICS and relatively refractory to oral corticosteroids.[24] Heightened T2 inflammation despite ICS therapy is associated with poor symptom control and increased airway reactivity.[25]

A meta-analysis of the control arms from 7 trials of biologic therapies in severe allergic and eosinophilic asthma demonstrated that persistent T2 airway inflammation (elevated FeNO or blood eosinophils throughout the treatment period) was an independent risk factor for future exacerbations.[26] Greater inflammation was associated with greater risk. Key comorbidities, especially chronic rhinosinusitis with nasal polyposis, were identified as markers of treatment-refractory disease.

The risk of asthma exacerbations can be predicted based on asthma severity, a history of exacerbations and by measuring blood eosinophils and FeNO.[27] Similarly to the use of established biomarkers for cardiovascular disease (such as serum total cholesterol:high-density lipoprotein cholesterol [HDL-C] ratio), biomarkers of T2 inflammation predict patients who are most at risk of asthma exacerbations and most likely to benefit from biologic therapy.[28]

The biologic therapies for asthma target key aspects of T2 inflammation. In Australia, the available therapies and their targets are omalizumab (anti-IgE), mepolizumab and benralizumab (anti-IL-5), and dupilumab (anti-IL-4 and anti-IL-13).

Robust clinical trial evidence has demonstrated that for appropriately selected patients, the addition of a biologic asthma therapy to a patient's existing moderate-dose ICS and LABA regimen results in significant reductions in exacerbations and use of oral corticosteroids, and improved asthma symptom control and quality of life, though there are only modest improvements in lung function.[29-33]

Table 1 provides a comparison of biologic therapies for severe asthma, including efficacy data.

Biologic asthma therapies need to be prescribed by a specialist

For a biologic asthma therapy to be supplied under the Pharmaceutical Benefits Scheme (PBS) in Australia, it must be prescribed by a respiratory physician, immunologist, allergist or general physician experienced in the management of patients with severe asthma. The patient must have a diagnosis of asthma, and persistent suboptimal symptom control and exacerbations requiring oral corticosteroids, despite the use of high-dose ICS and LABA. They must have evidence of allergy (for dupilumab and omalizumab) or elevated blood eosinophils (for dupilumab, benralizumab or mepolizumab).

When referring a patient to an asthma specialist, the following information should be included to help guide and progress investigations and management decisions:

- the patient's onset of asthma
- frequency and severity of exacerbations
- current inhaler therapy
- history of oral corticosteroid use
- previous lung function testing
- investigation results, including blood eosinophils (full blood count), evidence of allergy (radioallergosorbent test [RAST] or skin prick test) and total serum IgE.

There are no direct head-to-head comparisons of the biologic therapies for severe asthma that can guide the choice of which therapy to use. The initial biologic choice is often dependent upon physician preference and the approved PBS-subsidised indications for each therapy. Patients with childhood-onset asthma and evidence of allergy may be offered omalizumab or dupilumab first, while those with adult-onset eosinophilic asthma are often treated with anti-IL5 therapies (mepolizumab and benralizumab). Some biologic asthma therapies have been shown to improve outcomes in other allergic or T2 inflammatory diseases, such as atopic dermatitis and chronic rhinosinusitis with nasal polyposis, so the presence of these may also inform the choice of biologic therapy (Table 1).

Biologic therapies for asthma are administered subcutaneously, most often by self-administration, or they can be administered in primary care.

Biologic asthma therapies are well tolerated

It is important to note that biologic therapies used in asthma specifically target mediators of T2 inflammation, rather than the inflammatory response as a whole and, unlike oral corticosteroids or biologic therapies used for rheumatoid arthritis or inflammatory bowel disease, asthma biologics are not conventionally immunosuppressive. Consequently, asthma biologics are generally not discontinued or withheld in the context of intercurrent infection. It has been advised that dupilumab be withheld before live attenuated vaccination, but this is based on consensus opinion.[50]

Table 1 Comparison of biologic therapies for severe asthma with persistent type 2 inflammation

	Omalizumab [30,34-37]	Mepolizumab [31,38-41]	Benralizumab [31,42-44]	Dupilumab [33,45-48]
Indications and dosing for asthma				
Approved indication [NB1]	allergic asthma	eosinophilic asthma	eosinophilic asthma	asthma with type 2 inflammation
Approved age for use [NB1]	6 years and older	12 years and older	12 years and older	6 years and older
Approved dose (via subcutaneous injection) [NB1]	6 years and older: 75 to 375 mg every 2 to 4 weeks dose and interval determined by weight and baseline total serum IgE concentration maximum 150 mg per injection site	12 years and older: 100 mg every 4 weeks	12 years and older: 30 mg every 4 weeks for the first 3 doses, then 30 mg every 8 weeks	12 years and older: 400 mg initially, then 200 mg every 2 weeks if maintenance oral corticosteroid therapy required or comorbid atopic dermatitis: 600 mg initially, then 300 mg every 2 weeks 6 to 11 years: refer to approved product information maximum 300 mg per injection site
Biomarkers				
Elevated blood eosinophils (>0.15 × 10^9 cells/L or 150 cells/microlitre)	predicts better response	needed for response	needed for response	predicts better response
Elevated FeNO (≥20 ppB)	predicts better response	not applicable	not applicable	predicts better response
IgE sensitisation or allergy	needed for response	not applicable	not applicable	response independent of the presence of atopy
Efficacy at 16 to 30 weeks of treatment				
Mean reduction in ACQ from baseline compared with placebo (95% CI) [NB2]	data from observational trials (compared with baseline): 1.56 (1.66 to 1.45) (ACQ5)[30]	data from a meta-analysis of RCTs: 0.38 (0.50 to 0.26) (ACQ5)[31]	data from a meta-analysis of RCTs: 0.26 (0.34 to 0.17) (ACQ6)[31]	data from an RCT: 0.35 (0.48 to 0.21) (ACQ5)[46]
Relative reduction (95% CI) in rate of asthma exacerbations that require treatment with an oral corticosteroid for at least 3 days compared with placebo	data from observational trials (compared with baseline): risk ratio 0.19 (0.09 to 0.41) or 81% reduction[30]	data from a meta-analysis of RCTs: rate ratio 0.45 (0.36 to 0.55) or 55% reduction[31]	data from a meta-analysis of RCTs: rate ratio 0.59 (0.52 to 0.66) or 41% reduction[31]	data from a meta-analysis of RCTs: rate ratio 0.44 (0.35 to 0.055) or 56% reduction[33]
Pre-bronchodilator FEV_1 mean increase L/second (95% CI) from baseline compared with placebo	data from observational trials (compared with baseline): 0.22 (0.08 to 0.36)[30]	data from a meta-analysis of RCTs: 0.09 (0.05 to 0.14)[31]	data from a meta-analysis of RCTs: 0.11 (0.08 to 0.15)[31]	data from a meta-analysis of RCTs: 0.14 (0.12 to 0.17)[33]
Proportion of patients on maintenance oral corticosteroid who achieved a reduction in their maintenance oral corticosteroid dose from baseline	data from observational trials: 43% achieved at least a 20% reduction[30]	planned oral corticosteroid reduction RCT: 54% achieved at least a 50% reduction (compared with 33% in the placebo group)[40]	planned oral corticosteroid reduction RCT: 66% achieved at least a 50% reduction (compared with 37% in the placebo group)[42]	planned oral corticosteroid reduction RCT: 80% achieved at least a 50% reduction (compared with 50% in the placebo group)[45]
Use in other allergic disease associated with type 2 inflammation				
Other approved indications [NB1]	chronic rhinosinusitis, chronic spontaneous urticaria	chronic rhinosinusitis, eosinophilic granulomatosis with polyangiitis	none	chronic rhinosinusitis, atopic dermatitis, prurigo nodularis

ACQ = asthma control questionnaire; CI = confidence interval; FeNO = fractional exhaled nitric oxide, measured as parts per billion (ppB); FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; RCT = randomised controlled trial

NB1: These are the Therapeutic Goods Administration (TGA) approved indications and doses. See TGA approved Australian product information for more details, and refer to the Pharmaceutical Benefits Scheme website for indications that are subsidised in Australia.

NB2: The asthma control questionnaires, ACQ5 and ACQ6, are 5-item and 6-item questionnaires, respectively, regarding asthma symptoms with a lower score indicating better control. Score reductions of 0.5 or more points are considered to be clinically meaningful.[49]

Local injection-site reactions, headache and pharyngitis may occur, but are usually mild.

More severe systemic adverse events, such as anaphylaxis, are rare. Dupilumab should, however, be used with caution in patients with baseline hypereosinophilia (more than 1.5 × 10^9 cells/L [1500 cells/microlitre]) because of the risk of precipitating a hypereosinophilic syndrome, such as eosinophilic granulomatosis with polyangiitis.[51]

There are theoretical concerns that the biologic therapies used for asthma may increase the risk of parasitic infections but, even in areas with endemic parasitic infections, there is little evidence of increased risk.[52] In Australia, it would be reasonable to ask about whether people have lived in areas of northern Australia and, in those at clinical risk, screen for infections such as *Strongyloides*.

Long-term oral corticosteroid use should be reduced once stabilised on biologic therapy

An attempt should be made to taper oral corticosteroid use once a patient has been established on biologic therapy. There is good evidence that biologic therapies allow a reduction in the use of oral corticosteroids without loss of asthma control, even in people on long-term maintenance oral corticosteroid therapy. In some cases, oral corticosteroids may be ceased.[42,45]

In those on long-term oral corticosteroid therapy, caution needs to be exercised when reducing oral corticosteroid use as some patients will have developed secondary adrenal insufficiency.[53]

Inhaled corticosteroid treatment should be continued

Regular treatment with a combination ICS and LABA regimen remains a mainstay of asthma therapy and should be continued in those on biologic therapy.

There is currently a paucity of data regarding the safety of ICS dose down-titration in the setting of biologic use. ICS nonadherence has been shown to increase oral corticosteroid requirements and the risk of acute exacerbations in a population treated with mepolizumab.[54] In practice, clinicians should down-titrate the ICS dose for patients who achieve complete control with a biologic, monitoring for a return of asthma symptoms, or loss of lung function.

Biologic asthma therapy is usually long term

The clinical response to biologic therapy varies, with some responding better than others. Overall those with more active baseline T2 inflammation are more likely to benefit from biologic therapy.[26] Registry trials support these findings, suggesting success is more limited in those without a strong T2 signature and multiple comorbidities.[55]

Investigators are now starting to discuss what is meant by asthma remission in those who respond well to biologic therapy, with definitions including the achievement of very good asthma control and absence of exacerbations requiring oral corticosteroids.[56] However, it is not clear whether these people will achieve lasting remission or whether biologic therapy could be successfully withdrawn.

At this stage, with the current treatment selection criteria applied, the majority of people with severe asthma treated with biologic therapies remain on them long term, with only 13% stopping them and 16% switching to a different biologic.[57] An attempt to stop mepolizumab in people with severe asthma who had achieved a clinical response resulted in a return of blood eosinophilia and increased exacerbations.[58] At this stage, treatment with biologic therapies should be regarded as long term.

Conclusion

Biologic treatments for asthma are highly effective for people with inadequately controlled asthma symptoms and recurrent exacerbations, despite optimised inhaled asthma therapy and evidence of persistent T2 inflammation. They improve asthma symptoms, reduce exacerbations and reduce exposure to oral corticosteroids. They are well tolerated, with few adverse events. Potentially eligible patients with severe asthma should be referred to a respiratory physician or immunologist for consideration of a biologic therapy. <

Conflicts of interest: Peter Wark has received funding for an investigator-initiated trial from GlaxoSmithKline to compare effectiveness of omalizumab and mepolizumab in severe asthma. He has received honoraria to speak about severe asthma from AstraZeneca, Sanofi/Regeneron, GlaxoSmithKline and Novartis.

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