Monoclonal antibody therapy for severe asthma

National Asthma Council AUSTRALIA

Information paper for primary care health professionals

Key points:

- Monoclonal antibody therapy is the most effective add-on treatment for patients with severe allergic or eosinophilic asthma that does not respond adequately to treatment with high-dose inhaled corticosteroids (ICS) in combination with long-acting beta$_2$ agonists (LABAs).
- In patients with severe asthma and persistent type 2 airway inflammation (see Airway inflammation in severe asthma), monoclonal antibodies ('biologic' agents) markedly reduce the rate of severe asthma exacerbations, improve symptom control, and can reduce the use of systemic corticosteroids.
- The monoclonal antibody therapies currently available in Australia for severe asthma treatment are generally well tolerated and are not associated with clinically significant unwanted immunosuppression. Injection site reactions are common but systemic reactions, including anaphylaxis, are rare.

Practice points

- Guidelines recommend against prolonged treatment with high-dose ICS, or other medicines added to medium-dose ICS in combination with a LABA, if they are ineffective for reducing an individual's symptoms and exacerbations.
- When asthma symptoms are poorly controlled, confirm that the diagnosis of asthma is correct and that the symptoms are due to asthma. Check for and manage common causes such as incorrect inhaler technique, suboptimal adherence, and comorbidities. Adjust treatment as necessary, update the patient's asthma action plan, and optimise self-management. If asthma symptoms are still not well controlled with treatment that includes at least a medium maintenance dose of ICS-LABA, the patient may benefit from monoclonal antibody therapy.
- Primary care clinicians can fast-track patients' access to monoclonal antibody therapy through early identification of patients with type 2 airway inflammation that is non-responsive to ICS, and prompt referral to an appropriate specialist – do not wait until the patient needs maintenance treatment with oral corticosteroids or frequent short courses of oral corticosteroids.
- When referring a patient for investigation of severe asthma, provide the following information, if possible: age at onset of asthma, information about frequency and severity of exacerbations requiring use of oral corticosteroids, current asthma treatment, records of lung function testing (spirometry with bronchodilator responsiveness test), results of fractional exhaled nitric oxide (FeNO) test, if available, and results of other investigations including full blood count, total serum immunoglobulin (Ig)E, and allergy tests (skin-prick testing or radioallergosorbent test).
- Patients using monoclonal antibody therapy must keep taking maintenance ICS-LABA treatment and need an up-to-date written asthma action plan.

Monoclonal antibody therapy is an add-on treatment option for reducing severe exacerbations, improving symptom control, and reducing systemic corticosteroid use in patients with severe allergic or eosinophilic asthma that remains uncontrolled (persistent symptoms, exacerbations or both) despite treatment with high-dose ICS-LABA. These treatments target inflammatory pathways that activate type 2 immune responses leading to airway inflammation.

Monoclonal antibody therapies for asthma are subsidised by the Pharmaceutical Benefits Scheme (PBS) for patients in specialist care who meet specified criteria. They are prescribed by specialists and can be administered in primary care or by the patient or carer.

Severe asthma – uncommon but challenging

In most adults and adolescents, asthma can be effectively treated with regimens based on low doses of inhaled corticosteroids, such as low-dose budesonide-formoterol taken as needed for symptom relief, or maintenance and reliever therapy with low-dose budesonide-formoterol or beclometasone-formoterol.

Among people with persisting asthma symptoms, low lung function, or exacerbations despite ICS-containing treatment, only a small proportion have severe asthma. The most common reasons for failure to achieve good asthma control (few symptoms and few exacerbations) are suboptimal adherence, poor inhaler technique, continued exposure to environmental triggers (e.g. smoking), and untreated comorbid medical conditions such as chronic rhinosinusitis. When these problems are identified and corrected, asthma control improves for many people.

ICS dose escalation should prompt a rethink

Severe asthma has been defined as asthma that remains uncontrolled despite high-dose ICS-LABA (with correct inhaler technique and good adherence) or maintenance oral corticosteroids, or that requires such treatment to prevent it becoming uncontrolled.[1] However, these are not recommended long-term treatments.

Long-term high-dose ICS is indicated for very few patients. Asthma that fails to respond to medium doses of ICS should be investigated by a specialist as soon as possible, to avoid futile dose escalation and delay to effective treatment.

Oral corticosteroid use must be minimised

Maintenance treatment with oral corticosteroids is a last resort, considered only when no other option is available to prevent severe exacerbations. Monoclonal antibody therapies can reduce or eliminate the need for maintenance systemic corticosteroids to suppress airway inflammation,[2] and this approach is rarely necessary.[3]

Short courses of oral corticosteroids are necessary to manage asthma exacerbations, but there is increasing evidence that each course adds to lifetime risk of osteoporosis, pneumonia, cardiovascular or cerebrovascular diseases, cataract, sleep apnoea, renal impairment, depression/anxiety, type 2 diabetes, and weight gain.[4] A cumulative dose of more than 1000 mg prednisolone significantly increases the risk of type 2 diabetes, cerebrovascular accidents, heart failure, and cardiovascular or cerebrovascular disease, compared with cumulative doses below 500 mg.[4] A cumulative dose of only 500 mg to <1000 mg increases the risk of type 2 diabetes, compared with lower use.[4] Prevention of exacerbations is therefore the goal.

Fast-tracking patients to effective treatment

When asthma is poorly controlled, first confirm the diagnosis and check for common causes (e.g. incorrect inhaler technique and suboptimal adherence, comorbidities, self-management difficulties) and correct these. Consider specialist referral for patients with uncontrolled asthma (persistent symptoms, recurrent exacerbations or both) despite medium-dose ICS-LABA. Those with type 2 airway inflammation are at highest risk and most likely to benefit from monoclonal antibody therapy – refer these patients as soon as possible.

Airway inflammation in severe asthma

Type 2 inflammation of the airways represents multiple inflammatory pathways involving recruitment of eosinophils and resulting in mucus hypersecretion and airway hyperresponsiveness.[5] Clinical tests for type 2 airway inflammation include blood eosinophil count, sputum eosinophil count (less common), and FeNO, a non-invasive test available in lung function laboratories.

Most people with asthma have type 2 inflammation,[6] which typically responds well to low-dose ICS. However, a small proportion of patients have type 2 inflammation that does not respond to high-dose ICS and is relatively non-responsive to oral corticosteroids.[6] Despite ICS treatment, these patients show persistently raised blood eosinophil count, raised FeNO or both, with or without atopy and elevated serum total IgE.[6]

Persistent type 2 airway inflammation is a strong predictor of exacerbations.[6] The risk of severe exacerbations is very high among adults with asthma that is uncontrolled despite treatment with medium- or high-dose ICS plus LABA, a history of exacerbations in the previous year, elevated blood eosinophil count and elevated FeNO.[7]

Targeting airway inflammation with monoclonal antibody therapy

Monoclonal antibody therapies are designed to block the clinical effects of type 2 inflammation by targeting either IgE[8] or interleukin (IL) cytokines in the inflammatory pathway.[9-11]

For patients with severe eosinophilic or allergic asthma, monoclonal antibody therapies added to ICS-LABA significantly lower the rate of severe exacerbations requiring systemic corticosteroids, emergency department visits or hospitalisation, and may allow patients to reduce or stop oral corticosteroid treatment.[2] Some patients with previously uncontrolled severe asthma experience complete or near-complete asthma symptom control during monoclonal antibody therapy.[12]

Four monoclonal antibody therapies are available in Australia: benralizumab (anti-IL-5Rα),[10] mepolizumab (anti-IL-5),[9] dupilumab (anti-IL-4Rα),[11] and omalizumab (anti-IgE).[8] Indications approved by the Therapeutic Goods Administration (TGA) are shown in Table 1.

For PBS subsidy, patients must also meet strict criteria for uncontrolled asthma despite optimised treatment, criteria for allergic status (omalizumab and dupilumab) and/or for eosinophilia (benralizumab, mepolizumab, dupilumab), and must be treated by a specialist (respiratory physician, clinical immunologist, allergist, or general physician experienced in the management of patients with severe asthma). Unless the diagnosis of severe asthma was made by a multidisciplinary severe asthma clinic team, the patient must be under the care of the same specialist for at least 6 months before becoming eligible for PBS subsidy. Measurement of biomarkers is required to guide selection, to determine doses and to demonstrate PBS eligibility.

Table 1. Monoclonal antibody therapies for asthma in Australia

	Omalizumab (Xolair)	Mepolizumab (Nucala)	Benralizumab (Fasenra)	Dupilumab (Dupixent)
Target	IgE	IL-5	IL-5Rα on surface of eosinophils and basophils	IL-4Rα subunit of IL-4 and IL-13 receptor complexes
Approved* asthma indication	≥ 12 years: moderate-to-severe allergic asthma 6 to < 12 years: severe allergic asthma with exacerbations despite daily high-dose ICS Serum IgE levels within specified ranges	Severe eosinophilic asthma	Severe eosinophilic asthma (blood eosinophil count 300 cells/microL or 150 cells/microL while on oral corticosteroid treatment)	Moderate-to-severe asthma with type 2 inflammation (elevated eosinophils or elevated FeNO) inadequately controlled despite other maintenance treatment
Age	≥6 years	≥12 years	≥12 years	≥6 years
Route of administration	SC injection (powder for injection, pre-filled auto-injector, pre-filled safety syringe)	SC injection (pre-filled auto-injector)	SC injection (pre-filled auto-injector)	SC injection (pre-filled auto-injector, pre-filled safety syringe)
Dose (asthma)	Based on body weight and serum IgE	100 mg every 4 weeks	30 mg every 4 weeks (first 3 doses) then every 8 weeks	≥ 12 years: 400 mg (first injection) then 200 mg every 2 weeks (higher dose if OCS-dependent or comorbidity)† Children < 12 years: based on bodyweight
Other approved* indications	Chronic rhinosinusitis with nasal polyps Chronic spontaneous urticaria	Chronic rhinosinusitis with nasal polyps Relapsing or refractory EGPA	Not applicable	Chronic rhinosinusitis with nasal polyposis Atopic dermatitis Prurigo nodularis
PBS links	Omalizumab Authority criteria	Mepolizumab Authority criteria	Benralizumab Authority criteria	Dupilumab Authority criteria

EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; IL: interleukin; ICS: inhaled corticosteroids; PBS: Pharmaceutical Benefits Scheme; * Approved by Therapeutic Goods Administration; separate criteria apply for PBS reimbursement; †comorbid moderate-to-severe atopic dermatitis or comorbid severe chronic rhinosinusitis with nasal polyposis

Safety

All the monoclonal antibody therapies currently available in Australia for severe asthma are generally well tolerated.[13] Common adverse events include injection site reactions, headache, and pharyngitis, but these are usually mild.[13] Systemic reactions, including anaphylaxis, have been reported with all the available monoclonal antibody therapies for severe asthma, but are rare.[8-11,13,14]

Monoclonal antibody therapies used in asthma are not conventional immunosuppressants and can be continued during most infections.[13]

For detailed safety information refer to TGA-approved product information and TGA safety updates.

Use in pregnancy

TGA-approved product information advises that if clinically needed, the use of omalizumab may be considered during pregnancy or breast-feeding.[8] Product information for benralizumab,[10] mepolizumab,[9] and dupilumab[11] advises that treatment should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, and advises against breastfeeding during treatment.

A recent international consensus panel[15] agreed that monoclonal antibody therapy for women with severe asthma can be started during pregnancy or before planned conception, if clinically indicated and the woman agrees, after discussion of risks and benefits. Panellists agreed that a hospital admission or intensive care admission due to an asthma exacerbation would lower the threshold for initiating an asthma biologic during pregnancy, as would the presence of steroid-related adverse effects such as including gestational diabetes reduced bone density. The panel emphasised that women of child-bearing age should have documented discussions with their specialist team about the use of asthma monoclonal antibody therapy in pregnancy, before starting treatment.

Ongoing care of patients receiving monoclonal antibody therapy

When administering monoclonal antibody therapies, follow instructions for storing, preparing and administering doses.

Advise patients who have been prescribed a monoclonal antibody therapy that they should keep taking their ICS-containing treatment. Continue to check adherence and inhaler technique regularly and at every opportunity.

Ensure that each patient has an up-to-date written asthma action plan: review it at least yearly or whenever the medication regimen is changed. Remind patients taking monoclonal antibody therapy to follow their written asthma action plan when symptoms worsen.

Make sure that patients understand that they must attend all scheduled specialist visits to remain eligible for access to monoclonal antibody therapy through the PBS.

Most patients who require monoclonal antibody therapy would be eligible for a GP Management Plan and Team Care Arrangements and may benefit from a MedsCheck by a community pharmacist, or Home Medicines Review by a credentialed pharmacist to assess adherence and inhaler technique.

For some patients relying on oral corticosteroids to control their asthma, it may be possible to reduce the dose or stop after gradually reducing the dose. Patients should be warned against abruptly stopping corticosteroids at any time, including after starting monoclonal antibody therapy. Any reduction in the dose of oral corticosteroid should be carefully considered and the patients should be monitored carefully because of the risk of adrenal suppression.

The optimal approach to reducing the maintenance ICS-LABA dose after a good response is under investigation. Research is also currently underway to guide switching between classes of monoclonal antibody therapy if a good response not achieved, and whether the dose or dosing interval can be decreased in patients with very good response.

Resources and support

Severe Asthma Toolkit toolkit.severeasthma.org.au

Australian Asthma Handbook asthmahandbook.org.au

NUYOU Nurse Support Program for patients prescribed mepolizumab (Nucala) nuyousupport.com.au

Connect 360 – Patient support program for patients prescribed benralizumab (Fasenra) connect360asthma.com.au

Monoclonal Antibody Therapy for Severe Asthma wall chart nationalasthma.org.au/living-with-asthma/resources/health-professionals/charts/monoclonal-antibody-therapy-for-severe-asthma-chart

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