Monoclonal antibodies for the treatment of severe asthma

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There are now five monoclonal antibodies licensed as add-on therapy for the treatment of severe asthma. This article provides an overview of their indications, efficacy, safety and place in therapy.

The stepwise approach to asthma treatment advocated in evidence-based management guidelines is generally considered a success for people with mild to moderate asthma. It has not been so for those with severe asthma, which is partly defined by the failure of this strategy. The European Respiratory Society and the American Thoracic Society (ERS/ATS) guidelines define severe asthma as “asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy”. NHS England prefers a stricter definition that includes adherence, exacerbation history and treatment response (see Box 1). This means that access to treatment is determined by both the diagnosis and the failure of optimal treatment strategies.

Epidemiology
Recent European studies estimate that at about 4% of people with asthma in the Netherlands have severe disease, based on patient self-assessment, poor inhaler technique and adherence, increasing to about 6% in Denmark using the ERS/ATS definition of severe asthma (though inhaler technique and adherence had not been fully assessed in many patients). In England, extrapolation from a survey of one asthma centre suggests the prevalence of severe asthma is about 140 per million population, with an estimated 1000 new referrals per year.

Asthma and type 2 inflammation
The central role of airway inflammation in asthma has long been recognised. It is clear from the variation in symptoms, treatment response, impact on lung function and age at onset that the underlying mechanisms, involving many cell types and cytokines, vary between individuals as well as over time. Although these pathways and the interactions of mediators are complex, asthma can be roughly categorised into two types: eosinophilic asthma, the more common, which is associated with a type 2 immune response in which eosinophils and IgE are key contributors; and non-type 2 non-eosinophilic asthma, in which neutrophil airway infiltration is dominant or there is little infiltration.

Among the cytokines that regulate and augment the type 2 immune response are several interleukins (ILs) produced by T helper cells. IL-4 is involved in the regulation of B cells and IgE synthesis; IL-5 is essential for the survival and maturation of eosinophils; and the functions of IL-13 include regulation of IgE.
synthesis and a role in airway hyper-responsiveness. Eosinophils also promote the synthesis and release of these and other cytokines.1,5,7

Multiple phenotypes of severe asthma have been described, emphasising the importance of tailoring treatment to individual need.1,2,8 This includes the use of biomarkers of type 2 inflammation such as serum levels of IgE, peripheral eosinophils and fractional exhaled nitric oxide (FeNO) to identify phenotypes most likely to respond to targeted interventions such as monoclonal antibodies.9

Efficacy of monoclonal antibodies for asthma

Monoclonal antibodies are a relatively new treatment option for severe asthma, targeting different steps in the pathways causing airway inflammation. All have been approved as add-on treatment in patients with inadequately controlled severe asthma (see Table 1 for full details). The first, omalizumab, gained a marketing authorisation in Europe in 2005 and was followed by mepolizumab (2015), reslizumab (2016) and benralizumab (2018). All have been recommended by NICE within their licensed indications subject to other provisos (see below for further details), including patient access schemes that bring their cost effectiveness relative to established treatment below the threshold representing value for money for the NHS.10,13 Dupilumab, which was originally introduced in 2017 for the treatment of atopic eczema, was approved for the treatment of severe asthma in 2019; it is now undergoing appraisal by NICE with final guidance expected in May.14

Omalizumab

Omalizumab is the only monoclonal antibody licensed for severe asthma that directly targets IgE. In 2013, NICE recommended it as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged six years and older who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year).10 NICE reviewed its findings in 2016 and found no evidence to support a change.15

A key efficacy trial in adults with severe asthma was INNOVATE (n=419), for which the primary outcome was the rate of clinically significant asthma exacerbations (i.e., those requiring systemic steroid treatment).16 During 28 weeks of treatment, after adjustment for exacerbation history, there was a significantly lower exacerbation rate with omalizumab compared with placebo (0.68 vs 0.91, p=0.042). In addition, omalizumab halved the rate of severe exacerbations, reduced emergency hospital visits and improved quality of life scores. In children and young people with severe allergic asthma, omalizumab reduced the rate of clinically significant exacerbations (worsening symptoms requiring a doubling of inhaled steroid dose and/or systemic steroids) by 34% compared with placebo over 24 weeks (0.42 vs 0.63, p=0.047); after 52 weeks, the relative reduction was 50%.17

There have since been many clinical trials and systematic reviews of omalizumab. A 2014 Cochrane review used data from 10 studies to show that omalizumab reduced the proportion of patients experiencing an exacerbation compared with placebo from 26% to 16% over a period of 16–60 weeks. Treatment was also associated with fewer hospital admissions and a reduction in use of inhaled steroids. However, the efficacy analysis combined patients with moderate and severe asthma and there was no difference from placebo in withdrawal from oral steroids.18 A 2019 review of 42 ‘real-world’ studies (co-authored by the licence holder) involving adults with severe asthma published between 2008 and 2018 found that omalizumab reduced annual exacerbation rates (compared with pretreatment rates) by 62% after 12 months and 84% after 23–32 months.19 It was also associated with improvements in asthma symptoms and quality of life scores, and reductions in medication use, health resource use and hospital visits.

Mepolizumab

Mepolizumab binds to IL-5, preventing its interaction with its receptor, thus reducing the production and survival of eosinophils. Mepolizumab is administered by subcutaneous injection (though the licence holder says this should be given only by a healthcare professional).

In its 2017 guidance (currently under review), NICE recommended mepolizumab as an add-on to optimised standard therapy in adults with severe refractory eosinophilic asthma, only if the blood eosinophil count is ≥300 cells per μL in the previous 12 months, the patient has followed their optimised standard treatment plan, and they have had four or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or have had continuous oral corticosteroids at the level of at least the equivalent of prednisolone 5mg per day over the previous six months.11

In the MENSIA trial, 576 patients with severe eosinophilic asthma were randomised to treatment with mepolizumab 75mg intravenously or 100mg subcutaneously, or to receive placebo every four weeks. The primary outcome was the annualised rate of clinically significant exacerbations (worsening asthma requiring systemic steroids for at least three days, emergency hospital visit or admission).20 After 32 weeks, subcutaneous mepolizumab significantly reduced the annual rate of exacerbations per patient compared with placebo (0.83 vs 1.74, p<0.001). This was associated with fewer patients requiring an emergency visit (6% vs 13%) and improvements in lung function, quality of life score and symptom control.

The SIRIUS trial (n=135) demonstrated that patients treated with mepolizumab 100mg subcutaneously reduced their steroid dose compared with those assigned to placebo (mean dose reduction 50% vs 0%, p=0.007) after 20 weeks’ treatment.21 They also experienced a 32% reduction in the annual exacerbation rate and an improvement in asthma symptoms.

A post hoc analysis of the MENSIA and DREAM studies (DREAM evaluated intravenous mepolizumab) found that the reduction in exacerbation rate during treatment with mepolizumab vs placebo increased with baseline eosinophil count, rising from 52% at ≥150 cells per μL to 70% at ≥500 cells per μL.22 As noted.
<table>
<thead>
<tr>
<th>Monoclonal</th>
<th>Target</th>
<th>Indication*</th>
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<th>Other information</th>
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<tr>
<td>Omalizumab</td>
<td>Binds to IgE, preventing it from binding to high-affinity IgE receptor on basophils and mast cells; down-regulates IgE receptor expression</td>
<td>Add-on therapy in patients aged 6 to &lt;12 years with severe persistent allergic asthma who have: • A positive skin test or in vitro reactivity to a perennial aeroallergen and • Frequent daytime symptoms or night-time awakenings and • Who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta₂ agonist Add-on therapy in over-12s and adults with all the above, plus: • Reduced lung function (FEV₁ &lt;80%)</td>
<td>Dose depends on baseline IgE level and bodyweight. Ranges from 75mg to 600mg given by subcutaneous injection every 2 or 4 weeks Doses &gt;150mg should be divided between two or more sites</td>
<td>Benefit less likely if baseline IgE &lt;76IU/ml Therapeutic effect seen in 12–16 weeks; review benefit of treatment at 16 weeks Only available as prefilled syringe</td>
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<tr>
<td>Benralizumab</td>
<td>Binds to IL-5 receptor on eosinophils and basophils, leading to apoptosis</td>
<td>Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists</td>
<td>30mg by subcutaneous injection every 4 weeks for the first 3 doses then every 8 weeks thereafter</td>
<td>Available as prefilled pen or syringe Review benefit of treatment annually</td>
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<tr>
<td>Mepolizumab</td>
<td>Binds to IL-5, preventing interaction with receptor on surface of eosinophils</td>
<td>Add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older</td>
<td>Child 6–11 years: 40mg ≥12s and adults: 100mg Both by subcutaneous injection every 4 weeks</td>
<td>Available in vials for reconstitution, or as a prefilled pen or syringe Review benefit of treatment annually</td>
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<tr>
<td>Reslizumab</td>
<td>Binds to IL-5, preventing interaction with receptor on surface of eosinophils</td>
<td>Add-on therapy in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment Dose depends on bodyweight Administered by intravenous infusion over 20–50 minutes once every 4 weeks</td>
<td>Available in vials for reconstitution Review benefit of treatment annually</td>
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<tr>
<td>Dupilumab</td>
<td>Inhibits IL-4 and IL-13 signalling, decreasing type 2 inflammation</td>
<td>Adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO inadequately controlled with high-dose inhaled corticosteroids plus another maintenance treatment Initially 400mg (two 200mg injections) then 200mg every other week by subcutaneous injection For patients with severe asthma taking an oral steroid, or with co-morbid moderate to severe atopic dermatitis/severe rhinosinusitis: initially 600mg (two 300mg injections) then 300mg every other week by subcutaneous injection</td>
<td>Available as prefilled pen or syringe Review benefit of treatment annually</td>
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*Indication reflects recruitment criteria in key clinical trials

Table 1. Currently approved monoclonal antibodies for severe asthma
above, NICE recommends mepolizumab only for patients in whom the eosinophil count is ≥300 cells per μL, pointing out that a level of ≥150 cells per μL is within the normal range.11

Reslizumab
Like mepolizumab, reslizumab works by binding to IL-5. It is administered by intravenous infusion. NICE recommended reslizumab as an add-on therapy for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if the blood eosinophil count has been recorded as ≥400 cells per μL and the person has had three or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months.12

Two identical randomised phase 3 trials provide evidence for the efficacy of reslizumab in a population with an eosinophil count consistent with the NICE recommendation.23 Eligible patients (asthma with an eosinophil count of ≥400 cells per μL not controlled by medium-to-high doses of inhaled steroids, and one or more exacerbations in the previous year) were randomised to treatment with reslizumab 3mg/kg IV every four weeks or placebo. The primary outcome was the annual frequency of clinical asthma exacerbation.

Of 953 patients randomised, 763 had severe asthma (taking medium to high doses of inhaled steroid plus another controller, with or without maintenance oral steroids). In a pooled analysis, reslizumab reduced the rate of exacerbations after one year by 56% compared with placebo (0.85 vs 1.95). This was associated with improvements in lung function, asthma control and quality of life scores. In another study, there was no evidence of a difference in response to reslizumab according to baseline blood eosinophil count of 400 to <500 cells per μL vs ≥500 cells per μL, though there was a trend to a greater response at ≥700 cells per μL.24

Benralizumab
Benralizumab targets the IL-5 receptor on eosinophils and basophils. It is given by subcutaneous injection and, like omalizumab and dupilumab, is suitable for self-administration, but it is not licensed for use in children or adolescents.

Two studies, identical but for their duration, evaluated its impact on exacerbations in patients with uncontrolled severe eosinophilic asthma; both included a treatment arm using a subsequently non-licensed dose. The primary endpoint was the annual rate of exacerbations in patients using high-dose inhaled steroids plus a long-acting bronchodilator with baseline blood eosinophils ≥300 cells per μL. In CALIMA (n=881 excluding patients assigned to the non-licensed dose), benralizumab reduced the exacerbation rate by 28% over 52 weeks compared with placebo (0.66 vs 0.93, p=0.0188).25 In SIROCCO (n=805), benralizumab reduced the annual asthma exacerbation rate by 51% over 48 weeks compared with placebo (0.74 vs 1.52, p<0·0001).26 In both studies, benralizumab also improved lung function and asthma symptom scores.

In recommending benralizumab as a treatment option, NICE concluded that it is cost effective compared with mepolizumab and reslizumab and recommends it with the same eligibility criteria as for these two agents.13

Overview of anti-IL-5 therapies
A Cochrane systematic review included 13 studies of mepolizumab, reslizumab and benralizumab involving a total of about 6000 patients with severe eosinophilic asthma.27 All lowered the blood eosinophil count but depletion was almost complete with benralizumab. The review concluded that all agents approximately halved the rate of clinically severe exacerbations compared with standard care, with small improvements in peak expiratory flow rates. Quality of life scores were improved but not to a clinically significant extent. No head-to-head trials have been reported; indirect comparisons have produced different conclusions about relative efficacy.28-30

Dupilumab
Dupilumab inhibits IL-4 and IL-13 signaling. It is licensed as add-on treatment in adults and adolescents aged >12 years with severe, inadequately controlled eosinophilic asthma diagnosed either by raised blood eosinophil count or FeNO. It has a fortnightly dose regimen but can be self-administered using a pen.

Two trials provide the key evidence for dupilumab. Patients with uncontrolled moderate to severe asthma (medium to high dose inhaled steroids plus a bronchodilator and an exacerbation requiring intervention within the previous year; n=1902) were randomised to treatment with dupilumab 200mg or 300mg fortnightly (after a loading dose) or to receive...
placebo. The primary endpoints were the annualised rate of severe asthma exacerbations and the absolute change in forced expiratory volume in 1 second (FEV₁) at 12 weeks. Both doses of dupilumab almost halved the rate of severe exacerbations from a mean baseline of about two per year and significantly increased FEV₁ compared with placebo. There was a greater effect in patients with higher baseline blood eosinophil count (≥150 cells per μL), and higher baseline FeNO (≥25ppb).

A second study in 210 patients with severe steroid-dependent asthma reporting about two exacerbations in the previous year evaluated the steroid-sparing effect of dupilumab 300mg fortnightly (after a loading dose). Mean steroid dose at baseline was 11–12mg daily prednisolone or equivalent. After 24 weeks, the mean steroid dose was reduced by 70% among patients treated with dupilumab and 42% with placebo (p<0.001), with at least a 50% reduction in dose in 80% and 50% of patients respectively. The effect was greater among patients with baseline blood eosinophil count of ≥300 cells per μL. There was also an associated reduction in the rate of severe exacerbations and improved lung function with dupilumab compared with placebo.

**Safety**

Reviews of clinical trials have reported no significant excess of adverse events in patients with moderate to severe asthma with omalizumab, mepolizumab, reslizumab or benralizumab, other than injection-site reactions, compared with placebo. To date, there appears to be no evidence of an increased risk of infection, although dupilumab may cause eosinophilia (<2% of patients vs 0.5% with placebo in clinical trials). Clinical experience has been longest with omalizumab and small studies report generally good tolerability in patients who continue treatment for up to nine years (though others stopped treatment sooner due to adverse effects). Anti-drug antibodies may occur but do not appear to affect efficacy. Anaphylaxis has been reported rarely.

**Summary**

Severe asthma poses a challenge to patients and clinicians alike but monoclonal antibodies, as adjuncts to inhaled steroid and bronchodilator therapy, have improved the outlook for many people. Clinical trials were designed primarily to demonstrate a reduction in exacerbations but they have also been shown to reduce steroid use and improve symptoms. Progress will depend on further research on their role in children and on refining the use of biomarkers to personalise treatment, to assess therapeutic response and to determine relative effectiveness.

**References**


Declaration of interests None to declare.

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