



# Care pathways for the selection of a biologic in severe asthma

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Physicians need care pathways to select a biologic in type 2 severe asthma (omalizumab, mepolizumab, reslizumab) <http://ow.ly/pygw30gB7Bv>

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## Introduction

Patients with severe asthma generally benefit from consultations with an asthma specialist to optimise their management, which may include the potential initiation of biologic agents that have made a breakthrough in the treatment of severe disease.

Omalizumab, a monoclonal antibody (mAb) against immunoglobulin E (anti-IgE), was the first biologic developed for the treatment of severe allergic asthma and consistent results of randomised controlled trials (RCTs) [1] or real life trials [2] demonstrated a reduction of severe exacerbations in adults and children [3]. Some nonatopic asthma patients may also benefit from omalizumab [4]. Further investigation is needed to better assess its clinical efficacy in this setting, and to identify predictors of the treatment response.

Eosinophils are important cells in asthma. Mepolizumab or reslizumab, anti-interleukin-5 (anti-IL-5) mAbs or benralizumab, an anti-IL-5 receptor mAb, are effective in reducing exacerbations in patients with severe eosinophilic asthma [5].

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Other biologics targeting different pathways of asthma are in development. Dupilumab, an mAb against IL-4-receptor- $\alpha$  blocking IL-4/IL-13, has promising results [6].

Different biologics targeting IgE and IL-5 are currently available, but physicians have difficulty in prioritising the optimal one for a given patient. This is due to overlaps in patient populations who could qualify for different biologics, since direct comparisons do not exist and meta-analyses of these treatments cannot be conclusive [7, 8]. Care pathways are needed to help physicians stratify their patients with severe asthma [9] to select an appropriate biologic.

### From guidelines to care pathways

Integrated care pathways (ICPs) are structured multidisciplinary care plans detailing essential patient management steps. They promote the translation of guidelines into protocols and their subsequent application to clinical practice. They also empower patients and health and social care professionals. ICPs differ from practice guidelines as they are utilised by a multidisciplinary team and focus on the quality and co-ordination of care. ICPs, the standard of care in oncology or palliative care, have already been proposed for asthma, chronic obstructive pulmonary disease and allergic rhinitis [10] and have been digitalised [11, 12].

TABLE 1 National Institute for Health and Care Excellence, UK (NICE) guidance for omalizumab, mepolizumab and reslizumab

#### Omalizumab for treating severe persistent allergic asthma

Omalizumab (Xolair, Novartis) is a monoclonal antibody that binds to IgE. It has a UK marketing authorisation as add-on therapy to improve control of asthma in adults and adolescents (those aged 12 years and over) and children (those aged 6–11 years) with severe persistent allergic asthma who have:

- A positive skin test or *in vitro* reactivity to a perennial aeroallergen
- Reduced lung function (FEV<sub>1</sub> <80% in adults and adolescents)
- Frequent daytime symptoms or night-time awakenings
- Multiple documented severe exacerbations despite daily high-dose plus LABA

The marketing authorisation states that omalizumab treatment “should only be considered for patients with convincing IgE mediated asthma”.

It also specifies that, 16 weeks after the start of omalizumab, physicians should assess how effective the treatment is, and should continue omalizumab only in patients whose asthma has markedly improved. It also specifies that omalizumab should be initiated and monitored in a specialist centre by a physician experienced in the diagnosis and treatment of severe persistent asthma.

#### Mepolizumab for treating severe refractory eosinophilic asthma

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- The blood eosinophil count is  $\geq 300$  cells per  $\mu\text{L}$  or more in the previous 12 months, and
- The person has agreed to and followed the optimised standard treatment plan, and
  - Has had four or more asthma exacerbations needing systemic corticosteroids in the previous 12 months, or
  - Has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months, and
- The company provides the drug with the discount agreed in the patient access scheme

At 12 months of treatment:

- Stop mepolizumab if the asthma has not responded adequately, or
- Continue treatment if the asthma has responded adequately and assess response each year

An adequate response is defined as:

- At least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with four or more exacerbations in the previous 12 months, or
- A clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control

#### Reslizumab for treating eosinophilic asthma

Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug, only if:

- The blood eosinophil count has been recorded as  $\geq 400$  cells per  $\mu\text{L}$
- The person has had three or more asthma exacerbations in the past 12 months, and
- The company provides reslizumab with the discount agreed in the patient access scheme

At 12 months:

- Stop reslizumab if the asthma has not responded adequately, or
- Continue reslizumab if the asthma has responded adequately and assess response each year

An adequate response is defined as:

- A clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids, or
- A clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control

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For omalizumab, data from [17] (published in April 2013 and evidence reviewed again in March 2016 with no changes to the recommendations); for mepolizumab, data sourced from NICE ([www.nice.org.uk/guidance/ta431](http://www.nice.org.uk/guidance/ta431); published January 2017) and for reslizumab, data sourced from NICE ([www.nice.org.uk/guidance/gid-ta10036/documents/final-appraisal-determination-document](http://www.nice.org.uk/guidance/gid-ta10036/documents/final-appraisal-determination-document)). Ig: immunoglobulin; FEV<sub>1</sub>: forced expiratory volume in 1 s; LABA: long-acting inhaled beta-2 agonist; ICS: inhaled corticosteroid.

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## Care pathways in severe asthma

The definition of asthma severity, control and exacerbations was proposed to the World Health Organization (WHO) [13]. The consensus by U-BIOPRED (Unbiased Biomarkers for the Prediction of respiratory disease outcomes) also provides an algorithm for severe asthma based on insufficient therapy, poor treatment adherence and/or multimorbidity [14, 15]. More recently, the American Thoracic Society/European Respiratory Society task force proposed recommendations for severe asthma in developed countries [16].

In patients appropriately diagnosed, severe asthma is defined by the level of current clinical control and risks as: “uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function)” [13]. A stepwise approach for ICPs in severe asthma was proposed to WHO in 2009 [13]. Patients requiring biologics are those with uncontrolled asthma despite optimal pharmacological treatment.

All biologics approved for asthma by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) include stratified patients with severe asthma uncontrolled despite being on a high dose controller therapy including at least inhaled corticosteroids (ICS) and severe exacerbations. In the Global Initiative for Asthma (GINA) strategy, omalizumab, mepolizumab and reslizumab represent the first (and, currently, only) therapies for severe asthma (step 5) (data sourced from GINA: ginasthma.org). The National Institute for Health and Care Excellence, UK (NICE) proposed alternative guidance for omalizumab in 2013 [17], reviewed in 2016, and for mepolizumab and reslizumab in 2017 (table 1).

## Components of care pathways for biologics in asthma

### *Improvement of care pathways understanding the mechanisms*

#### *Mechanisms of action of biologics*

Treatment options for severe asthma are mostly for the type 2 asthma phenotype characterised by a prominent role of type 2 cytokines such as IL-4, IL-5 and IL-13, and IgE [18]. Mechanisms of action of biologics need to be considered since omalizumab is indicated for moderate to severe allergic asthma regardless of baseline eosinophil counts, whereas anti-IL-5 can be effective in both allergic and non-allergic eosinophilic asthma.

Biomarkers are important to help guide individualised therapy in severe asthma, but available ones represent imperfect discriminators for selecting the best option for individual patients [18]. The roles of exhaled nitric oxide fraction ( $F_{\text{eNO}}$ ) and periostin are insufficiently understood while all available biologics are effective in subjects with high eosinophil counts [19]. Furthermore, with current knowledge, the use of existing biomarkers has not been helpful to assess efficacy in either the short or long term.

#### *Anti-viral effects of omalizumab*

Rhinoviruses represent the most common trigger of asthma exacerbations. Escalating ICS dose does not reduce viral-induced wheeze whereas a study in inner city asthma children suggested that omalizumab reduced viral exacerbations [20, 21]. In addition, omalizumab initiated 4–6 weeks before return to school reduced exacerbations in the autumn. Moreover, omalizumab improved interferon- $\alpha$  responses to rhinovirus and, within the omalizumab group, greater interferon- $\alpha$  increases were associated with fewer exacerbations [22]. Finally, omalizumab shortens the frequency and duration of rhinovirus illnesses in asthmatic children. These studies suggest that allergic inflammation is causing increased susceptibility to viral illnesses [23].

#### *Age*

Omalizumab was approved in children above the age of 6 years by the EMA in 2009 and the FDA in 2016 [3]. The other existing biologics are not yet approved in children younger than 12 years.

#### *Adjustment of dosage*

Omalizumab is administered subcutaneously every 2–4 weeks based on baseline total IgE level and body weight. Reslizumab is administered intravenously every 4 weeks based on body weight (3 mg·kg<sup>-1</sup>). Mepolizumab is administered as a fixed dose subcutaneous injection every 4 weeks.

#### *Stopping rules*

Biologics are expensive treatments that should be continued for years when efficacious. It is therefore important to assess whether they should be continued after a short course of treatment (*e.g.* less than 4 months: early stopping rule) and can be discontinued after a longer course of treatment (*e.g.* 3 years: late stopping rule).

*Early stopping rule*

The early stopping rule was investigated for omalizumab [24]. Baseline characteristics did not reliably predict benefit with omalizumab. The global evaluation of treatment effectiveness by physicians after 16 weeks of treatment is the most meaningful measure of response to therapy. This was confirmed in all RCTs or real life studies [25]. There are no data supporting a validated stopping rule for anti-IL-5 mAbs. However, NICE has proposed guidance for a 12 month stopping rule for anti-IL-5 mAbs (table 1).

*Late stopping rule*

Few data are available to assist clinicians with decisions regarding long-term use of asthma biologics. A prospective study evaluated the benefit and persistence of response in subjects continuing or withdrawing from long-term omalizumab treatment [26]. More subjects in the omalizumab group (67%) had no exacerbation compared to the placebo group (47.7%). Time to first exacerbation was also longer in the omalizumab treated patients, and subjects continuing omalizumab had significantly better asthma control than those who stopped. No late stopping rule study is available for anti-IL-5 mAbs.

**Care pathways for a biologic in severe asthma**

*Patient stratification for biologics*

Patient stratification for available biologic therapies is based mainly on clinical end points, allergy tests, IgE levels and blood eosinophils (table 2). There are insufficient data for other biomarkers such as periostin or FeNO. The optimal cut off level of eosinophils for initiation of anti-IL-5 is still subject to debate. A minimal level of 150 per mm<sup>3</sup> is often utilised for mepolizumab based on pivotal trials [27] but NICE has proposed a higher level (table 1). A blood eosinophil count of 400 per mm<sup>3</sup> is considered to be the threshold for initiation of reslizumab [28].

*Care pathway for biologics in severe asthma*

Based on current knowledge, we propose an ICP for biologics in severe asthma to help physicians distinguish patients eligible for omalizumab or anti-IL-5 mAbs using a simple stepwise approach (box 1). This is based not only on efficacy and safety of the mAbs, but also on the availability of early stopping rules and age (figure 1).

**Conclusion**

This manuscript deals with a rapidly changing field, and thus the proposals made should be regularly updated [31]. A high level evidence for comparative efficacy and effectiveness of biologics in severe asthma is lacking, since there are no head-to-head RCTs comparing anti-IgE and anti-IL5. There is a need for platform trials in severe asthma comparing different biologics with each other, but also comparing other pharmacological (e.g. long-acting muscarinic antagonists, azithromycin, oral prostaglandin D<sub>2</sub> antagonists (CRTH2 antagonists)) and non-pharmacological treatments (e.g. bronchial thermoplasty; pulmonary rehabilitation; weight reduction) as an add-on or replacement of mAbs.

TABLE 2 Stratification of patients for biologics

	Omalizumab	Anti-IL-5 mAb
<b>Primary mechanisms of action</b>	Anti-IgE	Anti-IL-5
<b>Other potential mechanisms of action</b>	Anti-rhinovirus	
<b>Biomarker for patient selection</b>	IgE to indoor aeroallergen	Eosinophils
<b>Stratification of the patient</b>	Severe asthma plus high dose controller (ICS) plus exacerbations	
<b>Efficacy</b>	RCTs and real life	RCTs
<b>Children</b>	≥6 years	≥12 years
<b>Patient selection</b>	Total IgE and BMI	BMI for reslizumab
<b>Administration</b>	Subcutaneous	Mepolizumab: subcutaneous Reslizumab: intravenous
<b>Clinically relevant outcome</b>		Severe exacerbation
<b>Safety</b>		10 years of post-marketing surveillance; safe in phase III studies
<b>Biomarker of efficacy</b>		Eosinophils
<b>Demonstrated early stopping rule</b>	GETE (4 months)	Unclear (12 months)
<b>Late stopping rule</b>		Unclear

IL: interleukin; Ig: immunoglobulin; ICS: inhaled corticosteroid; RCT: randomised controlled trial; BMI: body mass index; GETE: global evaluation of treatment effectiveness.

**BOX 1** Integrated care pathway to help physicians distinguish which severe asthma patients are eligible for omalizumab or anti-interleukin-5 monoclonal antibodies (anti-IL-5 mAbs)

**Step 1**

There are some simple situations:

For patients who are allergic but not eosinophilic (level <300 per mm<sup>3</sup>), omalizumab should be the first choice.

For patients who are not allergic and have a high blood eosinophil count (mepolizumab ≥300 per mm<sup>3</sup>, reslizumab ≥400 per mm<sup>3</sup>), anti-IL-5 mAbs should be considered first line [29].

For children aged 6 and <12 years of age that meet prescribing criteria, omalizumab is the only choice.

For patients who are both allergic and eosinophilic, and meet prescribing criteria for any of these agents, no direct comparative data exist, meta-analyses are not informative and either of these classes of therapy may be considered as first line therapy. However, when making the decision, clinicians should take into account the ability to stop omalizumab after 16 weeks, in combination with a large body of real life data and over a decade of post marketing surveillance confirming its safety.

**Step 2**

For omalizumab-treated patients, after 16 weeks, global evaluation of treatment effectiveness should be assessed in omalizumab-treated patients and a switch to anti-IL-5 mAb is proposed for those who did not respond and have a high blood eosinophil count. This is possible since mepolizumab may be effective in patients previously treated by omalizumab [30].

For anti-IL-5 mAbs-treated patients, a relatively vague stopping rule is provided by NICE (table 1) at 12 months.

Importantly, there are no data examining combination therapy with different biologics for those who are partial responders.

There is a significant unmet need for therapies for individuals who have low eosinophil counts and who are not allergic. Bronchial thermoplasty may be considered in this non-type 2 patient population and substantive workup should be undertaken to evaluate for compliance to treatment, other asthma multimorbidities (e.g. acid reflux, rhinosinusitis), risk factors (e.g. smoking, allergen exposure) or differential diagnosis (e.g. chronic obstructive pulmonary disease, aspiration, vocal cord dysfunction).

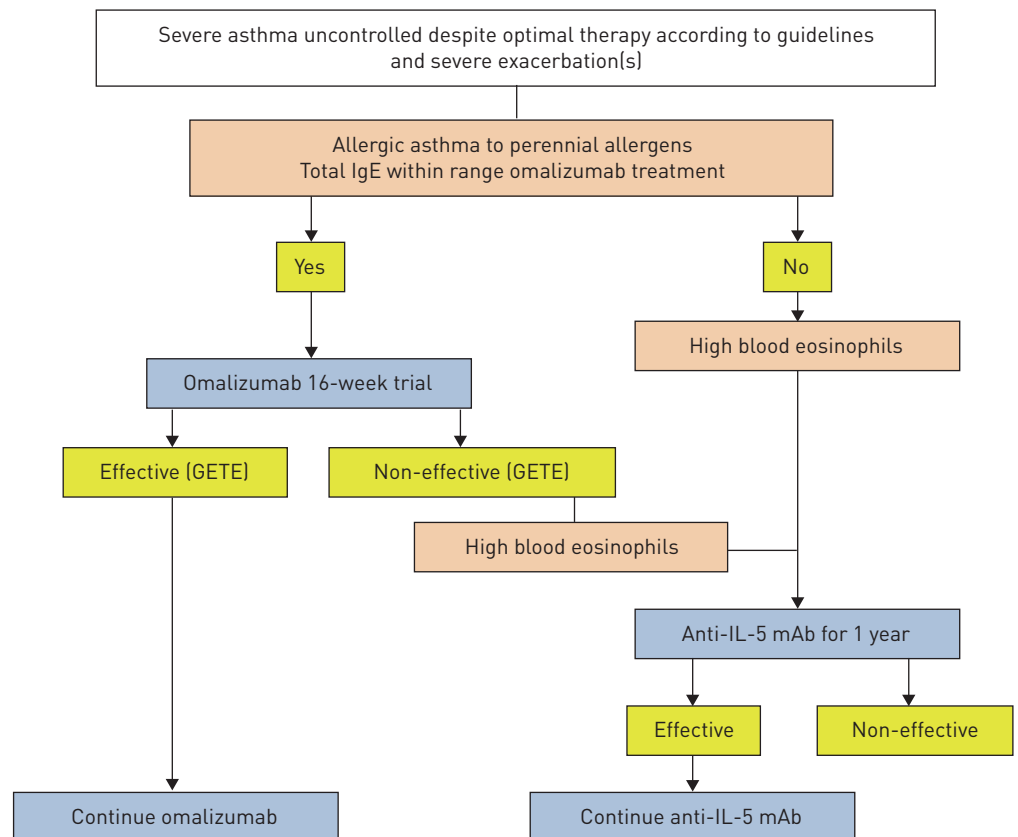


FIGURE 1 Care pathways for biologics in asthma. Ig: immunoglobulin; GETE: global evaluation of treatment effectiveness; IL: interleukin; mAb: monoclonal antibody.

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