Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

Value-based prescribing

Biological medicines for severe uncontrolled asthma

September 2022

(October 2022 – Estimates for numbers of eligible patients have been removed)

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1.0 Biological medicines for severe uncontrolled asthma

This paper details the inclusion of biological medicines for severe uncontrolled asthma within the "Optimal prescribing for higher health gain" domain of the value-based prescribing programme.

1.1 Background and rationale

In 2017–2018 there were over 3,500 hospital admissions in Wales for asthma[1]. In the ten year period up to this (2009 to 2018) the number of deaths related to asthma in Wales increased by 43% with the average probability of death related to asthma being estimated at 0.78% per hospital admission[2,3].

The *All Wales Adult Asthma Management and Prescribing Guideline* places treatment with biological medicines towards the end of the treatment pathway, for consideration in patients with severe difficult to treat asthma[4]. Difficult to treat asthma is asthma that is uncontrolled despite high-dose inhaled corticosteroids and an additional controller agent, or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. In many cases, asthma may be difficult to treat due to modifiable factors such as incorrect inhaler technique, poor adherence, smoking, comorbidities, or because the diagnosis is incorrect[5]. Severe asthma is confirmed asthma that remains uncontrolled despite adherence with maximal optimised therapy and treatment of contributary factors, or that worsens when high-dose treatment is reduced[5]. Patients with severe asthma have historically often needed short-term courses of oral steroids for exacerbations, or have required long-term maintenance therapy. Long-term treatment with oral steroids is associated with a number of potentially significant adverse effects[6]. These adverse effects often require additional medications to treat them and can have a significant effect on a patient's quality of life.

A 2017 Cochrane review concluded that treatment with biological medicines roughly halves the rate of asthma exacerbations[7]. In addition to decreasing hospital admissions, a decrease in exacerbations is associated with decreased oral steroid use, with reduced morbidity and social isolation; therefore improving a patient's quality of life[8,9]. The biological medicines are thought to be currently underused in the treatment of severe asthma with estimates in England suggesting only around 20% of eligible patients are currently receiving these biological medicines[10]. Data for Wales indicate a similar rate of prescribing[11]. In England, this underutilisation has led to the inclusion of these medicines within the accelerated access collaborative programme[12].

The first biological medicine given a positive recommendation for use in severe asthma was omalizumab; it was recommended by NICE in 2013 for use in severe persistent allergic asthma[13]. Allergic asthma results from excess immunoglobulin E (IgE) produced in response to environmental allergens such as house dust mites, pollen and moulds[13]. Omalizumab selectively targets and binds to IgE[14]. Since 2013, NICE have recommended a further four biological medicines for use in severe asthma. Three of these are specifically indicated for severe eosinophilic asthma. Eosinophilic asthma, is a subtype of type 2 (Th2) asthma, and is associated with severe symptoms which are triggered by higher levels of eosinophil cells[15,16]. Benralizumab, mepolizumab and reslizumab all target interleukin-5 (IL-5)[12]. IL-5 induces, maintains and amplifies eosinophilic inflammation[17]. Mepolizumab and reslizumab inhibit IL-5, whilst benralizumab targets its receptor[17]. All are considered to be 'add-on options' to standard therapies within the severe asthma treatment

pathway, with eligibility based around blood eosinophil count, number of exacerbations and the use of maintenance oral steroids[2,8,9]. NICE has concluded there is enough evidence to state that these three medicines have comparable efficacy[2,8,9].

NICE recommends that benralizumab, mepolizumab and reslizumab are reviewed after 12 months of treatment and stopped if the asthma has not responded adequately[2,8,9]. An adequate response is defined as a clinically meaningful reduction in the number of severe exacerbations needing systemic steroids, or a clinically significant reduction in continuous oral steroid use whilst maintaining or improving asthma control[2,8,9].

Dupilumab is the most recently recommended biological medicine by NICE for severe asthma; with use being recommended for patients with severe Th2 asthma[18]. Dupilumab binds to the interleukin-4-Rα receptor, inhibiting interleukin-4 and interleukin-13 signalling[19]. Patients suitable for treatment with dupilumab will be made up of two main groups. The first group will be made up of patients who will be ineligible for benralizumab, mepolizumab and reslizumab as they will not meet the anti-IL-5 prescribing criteria, but may be eligible for dupilumab[18,20]. The second group will be made up of patients who may not respond adequately to benralizumab, mepolizumab and reslizumab, but may also be eligible for treatment with dupilumab[20]. NICE recommends that dupilumab is stopped if the rate of severe asthma exacerbations has not been reduced by at least 50% after 12 months[18].

In Wales, all four biological medicines for Th2 asthma are included within the New Treatment Fund (NTF) and are on the formulary of every health board. The positive appraisal recommendation for omalizumab pre-dates the NTF, however it is also on the formulary of every health board. All of these medicines are available in Wales under commercial arrangements making the budget impact significantly lower than what would be indicated by list prices.

The *All Wales Adult Asthma Management and Prescribing Guideline* states that any patients receiving two or more courses of oral steroids in a 12-month period, despite adherence with optimised therapy, should be referred to secondary care specialists[4]. Patients considered eligible for these biological medicines should be assessed prior to the commencement of treatment to confirm that uncontrolled asthma is the cause of their ongoing symptoms, inhaler technique is correct, and they are adherent to their current treatments[21]. The relevant NICE technology appraisals should be consulted for the specific eligibility criteria, as well as the individual summaries of product characteristics for the specific prescribing information.

Severe asthma specialist teams can assess the suitability of patients for biological medicines, including making use of the All Wales Severe Asthma multidisciplinary team. Guidance advises that biological medicines should be prescribed under the supervision of a specialist severe asthma team. The initial doses are usually administered in a specialist centre where the appropriate resources are available[21]. Patients can then be transferred to homecare teams once stable, as the majority of these biological medicines are available for patient self-administration[22]. There is some emerging evidence that, in some patients, initiation can be made safely at home via homecare services[23]. However, given severe asthma patients are likely to require specialist input in other aspects of their care (for example, decreasing oral corticosteroid use), routine commencement at home would be unlikely for the

majority of patients. Therefore, having specialist staff such as respiratory nurse practitioners and pharmacists to support an increase in the use of the biological medicines for severe asthma is likely to be necessary in some organisations.

A retrospective study reported real world outcomes for the use of mepolizumab for patients across four health boards in Wales. In this cohort of 81 patients the use of the biological medicine was associated with a mean reduction in exacerbation frequency and corticosteroid dose of 74% and 56% respectively. These improvements were reported for the 84% of patients who were responsive to the medicine[24].

In order to maintain a complete medication record for medicines reconciliation it is important that the use of the biological medicine is clearly communicated to primary care. Biological medicines should be prescribed by brand name and this should be the name used in all medication records[25]. As the biological therapies are 'add-on options' it is essential that patients still receive their annual asthma reviews with their GP, specialist nurse or pharmacist, that their inhaler technique is regularly checked and they have an up-to-date and complete asthma plan[26]. Regular reviews within primary care can also help to identify the patients with uncontrolled asthma and support increasing access to these biological medicines for eligible patients.

As with any change in the patient's medication, the decision to start a biological medicine for severe asthma should be a shared decision made between the prescriber, the patient and, where appropriate, the patient's carer[27]. Some patients may not want to start a biological therapy, given that it is potentially a life-long treatment and it is administered via regular injections[2,8,9].

1.2 Recommendation

Severe uncontrolled asthma patients should be reviewed for suitability of biological medicine treatment where appropriate.

1.3 Exceptions

- All patients who are contraindicated to biological medicines for severe uncontrolled asthma as stated within the Summary of Product Characteristics.
- Patients in whom a shared decision has been made not to commence a biological medicine for severe uncontrolled asthma.

2.0 Resources

Supporting information for implementation of the recommendations

1. NICE Technology Appraisals
   - Omalizumab TA278
   - Reslizumab TA479
   - Mepolizumab TA671
   - Benralizumab TA565
   - Dupilumab TA751

2. Summaries of product characteristics
   - These are accessible here: Electronic medicines compendium (EMC) – medicines.org.uk

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