Severe Asthma Stakeholder Meeting
Outcome Statement

Friday 14 December 2018

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC) and Drug-Utilisation Sub-Committee (DUSC), representatives of the Centre of Excellence in Severe Asthma, Asthma Australia, National Asthma Council Australia, GlaxoSmithKline Australia Pty Ltd, Novartis Pharmaceuticals Australia Pty Ltd, AstraZeneca Australia and the Department of Health were in attendance.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

The PBAC Chair outlined that the objective of the stakeholder meeting was to receive advice and clinical perspectives on the treatment of severe asthma within the context of effective use of biologic medicines. The PBAC Chair noted that the meeting provided the opportunity to address concerns raised by sponsors and clinicians in early 2018.

Background

There are currently three biologic medicines available for the treatment of severe asthma. Omalizumab was the first biologic medicine to be listed on the PBS for uncontrolled severe allergic asthma. PBS eligibility criteria were developed based predominantly on relevant omalizumab clinical trials presented to the PBAC and stakeholder consultation. The PBS restrictions for mepolizumab and benralizumab were developed for consistency with the omalizumab PBS listing.

For the purposes of continuing to receive PBS-subsidised treatment with biologics for severe asthma, an adequate response is defined as:

- A reduction in ACQ-5 (asthma control questionnaire) score of at least 0.5 from baseline; OR
- Maintenance oral CS dose reduced by at least 25% from baseline and no deterioration in ACQ-5 score from baseline.

The maximum duration of initial treatment is 32 weeks for mepolizumab and benralizumab, with response assessed at 26-30 weeks for mepolizumab and 20-24 weeks for benralizumab. The maximum duration of initial treatment is 28 weeks for omalizumab, with response assessed at 22-26 weeks.

The current PBS restrictions for biologics for severe asthma do not permit use of a biologic in combination, or within 6 months of treatment with another PBS-subsidised biologic. The six month treatment break was originally based on the omalizumab restriction, and related to re-trial of omalizumab in patients with inadequate response, and this requirement was subsequently also applied to switching between different biologics. The treatment interval applies regardless of the reason for switching, including if the switch is due to adverse events, partial or non-responsiveness, or patient/clinician choice.

The three biologic agents have different modes of action. Mepolizumab and benralizumab both target the interleukin-5 (IL-5) pathway (i.e. eosinophil-mediated inflammation). Benralizumab is an IL-5 receptor α antagonist, while mepolizumab targets the IL-5 ligand. On the other hand, omalizumab targets the immunoglobulin E pathway (allergic asthma).

An article published in the American College of Allergy, Asthma & Immunology journal in 2016[1], not limited to severe asthma, examined the frequency and overlap of atopic, eosinophilic, and TH2-high asthma phenotypes, the latter using a non-standard definition (IgE ≥100 IU/L and blood eosinophils ≥140/µl). The study included 269 children and 310 adults aged 6-64 years across the spectrum of asthma severity. At a higher eosinophil cut-off point, a greater proportion of eosinophilic asthma can be classified as atopic or TH2-high, but a lower proportion of atopic or TH2-high asthma can be classified as eosinophilic. Approximately 70% or more of children and adults with asthma were 1 of these 3 phenotypes.

The half-lives of the biologics used to treat severe asthma are as follows:

- Benralizumab = 15 days
- Mepolizumab = 16-22 days
- Omalizumab = 22 days (±8 days)

Therefore these medications would not be expected to be eliminated from the body until 75-110 days (2.5-4 months) after the last injection (based on clearance requiring 5 elimination half-lives).

The PBAC received two minor submissions at the March 2018 PBAC meeting requesting removal of the six month interval when switching between biologic therapies. At this time, the PBAC noted that support for the change was provided by two organisations: the Thoracic Society of Australia and New Zealand; and the Centre of Research Excellence in Severe Asthma, both proposing that the six month interval between switching be removed or replaced with a shorter (1-2 month) interval. The input noted potential risks associated with a 6 month treatment interval in patients with severe asthma including:

- Increased risk of asthma exacerbations.

[1] Tran et al. *Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma.* Ann Allergy Asthma Immunol 2016; 116(1):37-42.

- Increased requirements for oral corticosteroids, with corresponding increase in risk of adverse events.

The PBAC deferred making a decision about the request to remove the six month treatment break when switching between biologics, noting that further stakeholder consideration of the issue should take into account the inter-related issues associated with re-trialling, switching and cycling of biologics in asthma.

Discussion and outcomes

Misalignment of current clinical guidelines and PBS listings for the biologic medicines prompted discussion for the first two items.

Initiation criteria

- Stakeholders considered that the current criteria quite reasonably reflect the trial populations; however, concerns surrounding long-term oral corticosteroid (OCS) use and the associated burden of illness were raised. It was noted that recent trials from the New England Journal of Medicine[2,3] indicate that an eosinophil count of ≥ 150 cells per µL for patients on long term OCS (versus the ≥ 300 cells per µL cut-off in the PBS restriction for initial access to biologics) is more appropriate, although for some patients, OCS will suppress eosinophils below this threshold without controlling asthma.
- Stakeholders noted there is a cumulative cost associated with managing ongoing adverse events caused by OCS, as well co-morbidities that worsen these effects. It was also noted that patients on maintenance OCS need to be destabilised in order to qualify for PBS-subsidised biologic medicines, which stakeholders did not consider to be best practice.
- Stakeholders noted that the criterion, FEV1 score ≤ 80% predicated normal in the previous 12 months, does not align with current international guidelines. It was noted that this score excludes younger patients (i.e. those in their 20s), who may have overall better lung function, but who still experience severe exacerbations.
- Stakeholders considered that reduction in severe exacerbations through use of a biologic would have the desirable effect of reducing the need for OCS use (with its attendant adverse effects) in such patients.
- Stakeholders noted that it is hard to confirm the diagnosis of asthma in a patient with severe asthma, particularly as these patients are already receiving high dose inhaled corticosteroid treatment, and many patients with long-standing or severe asthma will have developed persistent airflow limitation. They considered that adding in a multi-disciplinary team (MDT) as part of the diagnostic criteria would be appropriate, as an alternative to the

[2] Nair P, Wenzel S, Rabe KF et al. *Oral glucocorticoid-sparing effect of benralizumab in severe asthma.* N Engl J Med 2017; 376:2448-2458.

[3] Rabe KF, Nair P, Brusselle G et al. *Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma.* N Eng J Med 2018; 378:2475-2485.

current requirement to satisfy diagnostic criteria based on bronchodilator reversibility, airway hyper-responsiveness or peak flow variability. These investigations are primarily intended for confirming the diagnosis of asthma in patients at the onset of disease when they are not yet on any maintenance asthma treatment.

- Stakeholders noted the PBS forms to be complicated and not user friendly. The PBAC Chair considered that feedback would need to be passed onto the Department of Human Services (DHS) regarding any form changes.
- The PBAC Chair advised that the Committee would be open to amending the restriction criteria, e.g. a criterion for confirming diagnosis of asthma, and a separate criterion for confirmation of uncontrolled asthma. It was also requested that the omalizumab initiation criteria be updated to remove the word "RAST" and replace with the wording in the omalizumab paediatric listing, that is "Past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE".
- Stakeholders noted that a reduction in exacerbations with tiotropium is modest and considered it reasonable to trial in some patients, but not in those with high eosinophils.
- Stakeholders noted a decision tree for severe asthma published in November 2018 by the Global Institute for Asthma (GINA), which recommends checking for contributing factors to poor symptom control and exacerbations, such as incorrect inhaler technique, before moving patients onto specialists. It was also noted that the decision tree reflects management options, which may include the addition of tiotropium in some patients.

In summary, stakeholders agreed that the principle objectives are to control asthma and reduce OCS use, and that re-examining some of the PBS initiation criteria for biologic medicines would be beneficial, particularly examining blood eosinophil levels for patients on long-term maintenance OCS, FEV1% predicted, and to include confirmation of the diagnosis of asthma by a MDT and updated wording around the assessment of atopy.

Continuation criteria

- Stakeholders noted that the assessment and responses associated with the ACQ are quite subjective and considered that the PBS restriction is not reflective of the way in which ACQ scores were used in the data. Stakeholders advised that, if patients are responding to a biologic based on OCS reduction, the continuation criteria should reflect an ACQ score that is the same or within 0.5 from baseline (i.e. not worsening (increasing) by more than the minimal clinically important difference of 0.5).
- Stakeholders noted the asthma control test (ACT) to be an alternative measure of symptom control and considered that further investigation, would be appropriate.
- Stakeholders noted that, with respect to omalizumab use in children, there is evidence in the trials for a reduction in exacerbations as a basis for

continuing therapy. It was considered that this could be extended to adults and incorporated into the continuation criteria.

- Stakeholders noted that it is difficult to assess whether exacerbations have been reduced over as short a period as 6 months. The GINA severe asthma Pocket Guide suggests a minimum of 4 months' treatment with biologics, with an extension to 6-12 months if the response is unclear after this time. It was also noted that some patients may contract a viral infection that increases their number of exacerbations and considered that these patients should not be ruled out from continuing treatment. Stakeholders discussed an extension from 6 months to 12 months to reduce paperwork, or to consider a telephone authority for the review. Stakeholders considered that if patients are going to respond, it will occur by the 6 month mark (which was the minimum timeframe for review from the data).
- There was also discussion around making the assessment timeframes consistent across all biologics, to avoid confusion and missing assessment windows.

In summary, the PBAC Chair noted the main issues surrounding this item were the method for assessing response, and whether to review patients at 6 or 12 months. Stakeholders advised that a 6 month assessment (for initiation) and a subsequent review in another 12 months might be appropriate, but that a criterion for partial responders may also need to be considered, or consideration of response by a MDT.

Re-trialling, switching and cycling of biologics

- Stakeholders expressed their concerns over the 6 month treatment break, noting that it significantly exposes patients to risks (i.e. increased exacerbations and OCS use). With respect to patients who do not respond to their first biologic, stakeholders questioned the logic of them having to wait the full 6 months before being able to trial a second biologic, potentially forcing them to reinitiate OCS. It was also noted that, if ceasing due to adverse events, it would be appropriate for patients to wait until the event has resolved, but that this would be very unlikely to take as long as 6 months.
- With respect to switching between biologics, stakeholders noted that the safety profile in patients moving from omalizumab to mepolizumab at the time of their next dose has been demonstrated. Furthermore, there was discussion around the data having shown a differential response for patients going from mepolizumab to benralizumab, but it was noted by GSK, the sponsor of mepolizumab, that it was unaware of any data to support this assertion.
- Stakeholders considered that clarity around reasons for switching is required; reasons such as adverse events, different dosing regimens, as well as efficacy with respect to no or partial response were considered reasonable.
- The appropriateness of reinitiating a previously trialled biologic, if for a reason other than lack of response, was also discussed.
- Stakeholders noted that a switch could occur when the next injection is scheduled, or a standard 4 weeks from the time of the last dose, both of

which allow time to send in the required paperwork. Stakeholders considered that, if a patient starts a second biologic due to failure of the first, new baseline results may be appropriate (although some may not meet the eosinophils and IgE requirement again). However, if a patient needs to be switched because of an adverse event, they should not have to re-establish baseline values.

- With respect to re-trialling a biologic, stakeholders noted that environmental factors have a significant impact on a patient's response, particularly in those with allergic asthma (the phenotype of which can change over time). Stakeholders considered the ability to re-try an agent to be useful here, but that there should be a reasonable break. It was also considered that the 6 month break is appropriate if the patient does not respond to a biologic and wishes to re-trial the same biologic.
- With respect to cycling between the biologics, stakeholders suggested no lifetime limit should apply, advising that it would be appropriate to leave this up to clinicians' discretion, or alternatively for patients trialling and failing all available biologics, a 12 month treatment break could be reasonable.

Other matters

- Stakeholders noted that the online PBS submissions have made a positive difference, but that the form currently says "severe allergic asthma", and considered that it be changed to "severe asthma", i.e. that a single form could be used for all of the biologics, as is the case in rheumatoid arthritis.
- Stakeholders also suggested that the form be simplified in terms of the drug name, class name and relevant criteria.

Summary and next steps

The PBAC Chair thanked participants for their time in attending the Stakeholder meeting and considered the advice provided on the direction of clinical practices for the treatment of severe asthma, with particular emphasis on access to biologic medicines, to be valuable.

Stakeholders highlighted the importance of the following key issues:

- Reducing exacerbations and OCS use in the severe asthma population
- Having a suitable method to assess patients' response and/or symptom control
- Re-examining certain aspects of the PBS restriction for biologic medicines to ensure that those most at risk are not excluded.

The PBAC Chair stated the outcomes of the meeting would be used to inform future PBAC considerations on this issue. The PBAC Chair indicated a willingness of the PBAC to work with the Department and sponsors with a view to amending certain aspects of the PBS criteria for biologic medicines.