The Australasian College of Dermatologists' submission to the PBS Post-Market Review of biologics for severe chronic plaque psoriasis

This document is submitted as a supplement to the Australasian College of Dermatologists' commentary on the draft Terms of Reference of this review, submitted in September 2016. The College has considered the final Terms of Reference and would like to provide additional comment on the use of biologics for severe chronic plaque psoriasis which may be used to further inform the post-market review.

The College and its representative makes itself available to the post-market review should any elaboration of these points or further discussion be required.

1. Terms of Reference

We are pleased to see that the name of the review has been altered from 'DMARDs' to 'biologics' for severe chronic plaque psoriasis.

2. Eligibility and PBS restrictions

The current PBS restrictions for the use of biologics in this indication limit access to those patients with a psoriasis area and severity index (PASI) score of >15 whilst on treatment or at no longer than one month following cessation of treatment. The patient must have failed to have achieved an adequate response to at least 3 of the 4 following treatments: phototherapy, methotrexate, cyclosporine or acitretin. Failure is defined as: not achieving a PASI score of ≤15 after a minimum of 6 weeks of therapy at a prescribed dose; contraindication according to the TGA product information for that agent; or intolerance/toxicity as defined on the PBS website. In addition, if patients have significant involvement of the palm, sole or face, and have demonstrated a lack of response to the same therapies as for whole body psoriasis, they may qualify for biologic therapy on the PBS.

The College would like to highlight the following considerations regarding PBS restrictions:

- Whilst significant involvement of the face, palms and soles may impact severely on patients' quality of life, the current PBS criteria do not have the scope to allow patients with significant involvement of the dorsal hands and/or feet, scalp, genital and/or nail involvement to qualify for biologic treatment. In 2011, the European-based Progressive Psoriasis Initiative recommended that significant involvement of palms, soles, face, scalp, genital, exposed sites and nails should be classified as moderate-to-severe disease and therefore eligible for systemic therapy including biological agents.[1]

- The current restriction of a PASI score of >15 is higher than the qualification criteria for the majority of the Phase 3/pivotal trials for biologic agents in psoriasis. As a baseline requirement, most trials have a PASI score of >12 after a washout period from prior systematic therapies of at least 1 month.

- Most Western nations that have a restriction on access to biologics including Germany, the United Kingdom and Canada have a baseline body surface area (BSA) of 10% or PASI requirement of 10, some with a dermatology Live Quality Index (DLQI) score of at least 10. While the Pharmaceutical Benefits Advisory Committee consider the PBS listing of agents based on cost per

quality adjusted life year (QALY), the impact of disease on quality of life indicators (such as the DLQI) or other patient reported outcome measures are not considered as components for qualification or continuation for biologics on the PBS.

3. Failure of non-biologic treatments

To qualify for a biologic on the PBS, patients with psoriasis must have failed 3 out of 4 of the therapies listed above. This criterion has been interpreted differently in some cases, for example the pharmacist advisers of the Complex Drug Program in Hobart interpret this to mean that if a patient has a contraindication to one therapy, they must have been exposed to the remaining 3 treatments (or also have a contraindication) in order to qualify. In contrast, our understanding is that if a patient was contraindicated to one treatment they would require exposure to a further 2, not the remaining 3. An additional confounding factor has been the recent introduction of the '10 year rule', which sees any patient that has failed to respond to a therapy or has had a toxicity to a therapy more than 10 years prior to application must be re-exposed to that agent. Thus, there are certain ambiguities around treatment failure and PBS eligibility which would benefit from clarification. Of note, the Australian consensus treatment goals for moderate-to-severe psoriasis, in addition to defining moderate-to-severe psoriasis as PASI >10 and/or DLQI > 10, also recommended that patients should be required to fail no more than 2 of 4 therapies.[2]

With regards to cyclosporine and toxicity, the current recommendation in the product information suggests that if there is 30% rise in creatinine concentration, the dose should be reduced; if creatinine levels do not reduce within a month, cyclosporine should be ceased. Currently the toxicity criteria require creatinine levels to reach 1.5 times the upper limit of normal, regardless of baseline level. In addition, the product information states that if hypertension develops during cyclosporine treatment and cannot be controlled with appropriate therapy, this agent should be discontinued. Current international consensus is that for dermatological indications, cyclosporine should not be given for more than 2 years cumulatively over a lifetime. We would like to see a revision of the toxicity criteria for cyclosporine particularly with regards to renal function, blood pressure and duration of therapy.

It is also suggested that for female premenopausal patients, the requirement to have to fail 3 out of 4 systemic treatments be removed, so that treatment with acitretin is not considered due to its teratogenic potential and their unnecessary exposure to cyclosporine be avoided. The known toxicity and limitations of cyclosporine for long term therapy are well understood and documented, and the requirement to trial all three remaining agents for premenopausal women disproportionately place them at risk of potentially harmful adverse effects.

4. Other indicators of treatment response

For patients with psoriasis to continue biologic therapy, they currently require a reduction in PASI score of at least 75%. No consideration is given to improvement in any direct measures of quality of life. The Australian treatment goals project suggested that if there is a 50% reduction in PASI score and the DLQI score is ≤ 5, therapy should be continued. We would like the Post-Market Review Committee to consider including a quality of life measure such as DLQI into the assessment of response to therapy. Of note, the recent National Psoriasis Foundation Medical Board review of treatment targets for psoriasis suggested a target BSA involvement of less than 3% or >75% reduction in BSA as a means of assessing response to therapy.[3]

5. Duration of ineligibility after failure of biologics

Currently the PBS restrictions state that any patient failing 3 biologic therapies is ineligible for a biologic for a minimum of 5 years. This seems unreasonable as there are now 6 biologic agents available; furthermore, the more recently approved agents have higher response rates than those initially approved. There are some patients who have previously failed the least efficacious agents, efalizumab (which is no longer available) and etanercept, which were the only agents available when biologics were first approved for psoriasis. This includes some patients who have had 2 courses of efalizumab, who should they fail their second biologic (but equates to third course of biologic treatment) will find themselves ineligible for 5 years.

6. Combination therapy

Continuation rates of biologic treatment for psoriasis in Australia exceed rates reported in clinical trials for each of the biologics. It needs to be taken into consideration that for the trials, the investigational product was used as monotherapy. In real-world application, patients may be treated with their biologic agent plus topical agents, phototherapy, and/or methotrexate. Preliminary examination of data from the Australasian Psoriasis Registry suggests that at least 15% of patients on biologics are on systemic and/or phototherapy in addition to their biologic, as well as the majority of patients using topical agents. There are a small number of patients on combination with acitretin (for indications other than psoriasis) and cyclosporine (again for indications other than psoriasis, such as concomitant atopic dermatitis).

There are a number of patients with a combination of symptoms and signs of both psoriasis and psoriatic arthritis who would qualify and benefit from biologics but do not have access. Currently, a patient is managed for each condition by different relevant specialists and in certain cases the workup for a patient to gain access to biologics for psoriasis is hindered by their concomitant psoriatic arthritis treatment. For example, a patient may be prescribed methotrexate for psoriatic arthritis by their rheumatologist, however if this treatment is not effective at treating their psoriasis, it would need to be ceased in order to trial cyclosporine. Thus modification of eligibility criteria to address the patient with both psoriasis and psoriatic arthritis should be considered.

7. Administrative concerns

Currently submission for initiation or continuation of biologic agents on the PBS requires hard copy submission to Hobart, relying on Australia Post. This creates unnecessary delays. We encourage consideration of an electronic means of submission. The technology is available whereby this could be done whilst maintaining security and patient privacy.

There seems to be a lack of reciprocal communication to prescribers from Hobart including receipt of application, receipt of prescriptions, processing of prescriptions and recommended review dates. This information was available initially but seems to have progressively fallen by the wayside.

8. Compatibility with clinical trial eligibility criteria

Australia is now an attractive site for Phase 3 studies of new agents in dermatology, including for the indication of chronic plaque psoriasis. Sponsors recognise the quality of the data coming from Australia. There is significant expertise at a number of sites around the country. The usual entry criteria for the trials

include a PASI score of ≥12 and patients may be systemic therapy naïve upon entry into the trials. Unfortunately there does not seem to be a mechanism to transition patients that qualify for the trials to access the PBS subsidised drug. For patients who achieve PASI 75 on the trials, many of which continue for 3 to 5 years, it appears unjustifiable to make the patients cease the drug, have their disease worsen and then make them take 3 therapies in order to qualify, given their demonstrated response to treatment. As the numbers are relatively limited it would be worth consideration of 'grandfathering' these patients.

References

1. Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011 Jan;303(1):1-10.

2. Baker C, Mack A, Cooper A et al. Treatment goals for moderate to severe psoriasis: an Australian consensus. Australas J Dermatol. 2013 May;54(2):148-54.

3. Armstrong AW, Siegel MP, Bagel J et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis.J Am Acad Dermatol. 2017 Feb;76(2):290-298.