Record of the Rheumatology Subcommittee of PTAC Meeting held on 14 May 2021

Rheumatology Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Rheumatology Subcommittee meeting; only the relevant portions of the meeting record relating to Rheumatology Subcommittee discussions about an application or PHARMAC staff proposal that contain a recommendation are generally published.

The Rheumatology Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at an upcoming meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present

Marius Rademaker (Chair, PTAC member)
Alan Fraser (PTAC member)
Andrew Harrison
Janet Hayward
Lisa Stamp (PTAC member)
Will Taylor

Apologies:
Elizabeth Dennett
Keith Colvine
Michael Corkill
Priscilla Campbell-Stokes

2. Summary of recommendations

2.1. The Subcommittee **recommended** the requirement for C-reactive protein (CRP) to be greater than 15 mg/L be removed from the Special Authority for adalimumab and etanercept for rheumatoid arthritis with a **high priority** within the context of rheumatology treatments, as follows (relevant criteria shown only):

~~2.7.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or~~

~~2.7.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.~~

2.2. The Subcommittee **recommended** that the required number of active joints for adalimumab and etanercept for rheumatoid arthritis be reduced from 20 to 15 with a

high priority within the context of rheumatology treatments, as follows (relevant criteria shown only):

2.6.1 Patient has persistent symptoms of poorly controlled and active disease in at least **15** ~~20~~ swollen~~, tender~~ joints; or

2.6.2 Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip

2.3. The Subcommittee **recommended** the requirement for patients to trial csDMARDs be amended in the Special Authority for adalimumab and etanercept with a **medium priority** within the context of rheumatology treatments, as follows (relevant criteria shown only):

2.3 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and

2.4 Any of the following:

2.4.1 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of oral or parenteral methotrexate in combination with sulfasalazine and hydroxychloroquine sulphate (at maximum tolerated doses); or

2.4.2 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of leflunomide alone or in combination with another agent; or

2.4.3 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of ciclosporin alone or in combination with another agent

2.4. The Subcommittee **recommended** the application for the inclusion of patient-reported outcomes (e.g. HAQ-DI) in the Special Authority for first-line biologics (adalimumab and etanercept) for rheumatoid arthritis be **declined**.

3. The role of PTAC Subcommittees and records of meetings

3.1. This meeting record of the Rheumatology Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

3.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

3.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.4. The Rheumatology Subcommittee is a Subcommittee of PTAC. The Rheumatology Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Rheumatology Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for rheumatology treatments that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for rheumatology treatments that differ from the Rheumatology Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Rheumatology Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for rheumatology treatments.

4. Adalimumab and etanercept for the treatment of rheumatoid arthritis Special Authority amendments

Application

4.1. The Subcommittee considered an application from AbbVie for amendments to the Special Authority for adalimumab (Humira) for the treatment of rheumatoid arthritis (RA).

4.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendations

4.3. The Subcommittee **recommended** the requirement for C-reactive protein (CRP) to be greater than 15 mg/L be removed from the Special Authority for adalimumab and etanercept for rheumatoid arthritis with a **high priority** within the context of rheumatology treatments, as follows (relevant criteria shown only):

~~2.7.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or~~

~~2.7.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.~~

4.4. The Subcommittee considered the following for this patient group when making this recommendation:

4.4.1. high health need of patients with RA who have a CRP < 15 mg/L

4.4.2. lack of effective funded alternatives for patients who have not achieved low disease activity with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)

4.4.3. high disease activity and its impact on quality of life

4.4.4. high health benefit that can be gained from biologic treatment

4.4.5. undesirable impacts of using prednisone for at least three months when it may not normally be indicated.

4.5. The Subcommittee **recommended** that the required number of active joints for adalimumab and etanercept for rheumatoid arthritis be reduced from 20 to 15 with a **high priority** within the context of rheumatology treatments, as follows (relevant criteria shown only):

2.6.1 Patient has persistent symptoms of poorly controlled and active disease in at least **15** ~~20~~ swollen~~, tender~~ joints; or

2.6.2 Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip

4.6. The Subcommittee considered the following for this patient group when making this recommendation:

4.6.1. high health need of patients with a swollen joint count of 15-19

4.6.2. lack of effective funded alternatives for who have not achieved low disease activity with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)

4.6.3. high disease activity and its impact on quality of life

4.6.4. high health benefit that can be gained from biologic treatment.

4.7. The Subcommittee **recommended** the requirement for patients to trial csDMARDs be amended in the Special Authority for adalimumab and etanercept with a **medium priority** within the context of rheumatology treatments, as follows (relevant criteria shown only):

2.3 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and

2.4 Any of the following:

2.4.1 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of oral or parenteral methotrexate in combination with sulfasalazine and hydroxychloroquine sulphate (at maximum tolerated doses); or

2.4.2 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of leflunomide alone or in combination with another agent; or

2.4.3 Patient has tried and not responded to a minimum of three months, at the maximum tolerated doses, of ciclosporin alone or in combination with another agent

4.8. The Subcommittee considered the following for this patient group when making this recommendation:

4.8.1. the unmet health need of patients who would not respond to a third csDMARD

4.8.2. the high health benefit from biologic treatment

4.8.3. the costs to the sector of irreversible joint damage as a potential result of delaying biologic treatment.

4.9. The Subcommittee **recommended** the application for the inclusion of patient-reported outcomes (e.g. HAQ-DI) in the Special Authority for first-line biologics (adalimumab and etanercept) for rheumatoid arthritis be **declined**.

4.10. The Subcommittee considered the lack of unmet health need, high administrative burden on patients and healthcare professionals and potential access inequities when making this recommendation.

Discussion

Background

4.11. The Subcommittee noted an application from AbbVie for the widening of access for adalimumab for patients with RA as follows:

4.11.1. Amendment of C-reactive protein (CRP) levels from ≥ 15 mg/L to abnormally elevated

4.11.2. Removal of the term 'severe, active and erosive'

4.11.3. Reduction in the number of prior conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) trialled from three to two

4.11.4. Reduction in the number of active joint counts from 20 to 15

4.11.5. Inclusion of patient-reported outcomes (HAQ-DI) in the renewal criteria.

4.12. The Subcommittee noted PHARMAC staff were not seeking advice on the removal of the term 'severe, active and erosive' (as PHARMAC staff were progressing this from previous advice received) and that the Subcommittee had previously recommended the amendment of CRP levels to 'abnormally elevated'.

4.13. The Subcommittee noted there are approximately 525 people a year in New Zealand who initiate a first-line biologic DMARD (bDMARD) for RA. Based on an approximate incidence rate of 40 per 100,000 (ie an incidence 2,000 people per year in NZ), this was about 26%.

4.14. The Subcommittee considered the current Special Authority criteria are strict and restrict funding to individuals with a high disease activity. The Subcommittee considered there are people who would likely gain significant benefit from biologic treatment who are currently unable to access funded biologics for RA.

4.15. The Subcommittee noted PTAC considered the following four key pivotal trials when considered adalimumab for RA in 2004:

4.15.1. The ARMADA trial (Weinblatt et al., Arthritis Rheum. 2003 Jan;48(1):35-45); a randomized, double-blind, placebo-controlled trial which compared adalimumab in combination with methotrexate to methotrexate alone over 24 weeks (n=271).

4.15.2. The STAR trial (Furst et al., J Rheumatol. 2003 Dec;30(12):2563-71); a double-blind, placebo-controlled trial which focussed on safety aspects of 40 mg adalimumab vs placebo every other week, over 24 weeks, and was done in combination with other DMARDS (n=636).

4.15.3. Keystone et al (Arthritis Rheum. 2004 May;50(5):1400-11); a randomized, placebo-controlled, 52-week trial which assessed radiographic endpoints over 52 weeks (n=619).

4.15.4. van de Putte et al (Ann Rheum Dis. 2004 May;63(5):508-16); a double blind, placebo-controlled phase III trial of adalimumab over 6 months (n=544).

4.16. The Subcommittee considered that PTAC, when considering the original listing of adalimumab for RA, based the recommended Special Authority criteria on the distribution of participant characteristics in the pivotal RCTs, rather than the inclusion criteria for the trials. The Subcommittee considered this assumes that trial participants with above average disease activity markers respond better to treatment than those with below average disease activity markers and that patients with lower CRP and/or joint counts would have lower health needs. This was not considered a valid assumption.

C-reactive protein

4.17. The Subcommittee considered the current CRP criteria (≥ 15 mg/L) prevents some patients from accessing biologic treatment in a timely manner, and highlighted that some clinicians were using the prednisone criterion as a workaround for those patients with a CRP < 15 mg/L. The Subcommittee considered the Special Authority was increasing the use of inappropriate prednisone prescribing.

4.18. The Subcommittee noted the 2019 EULAR guidelines (Smolen et al., Ann Rheum Dis. 2020 Jun;79(6):685-699) recommend 5 mg prednisone for everyone upon initiating treatment for RA. However, the Subcommittee considered this acted as a 'bridge to remission' rather than offering a long-term treatment option, given the clinical preference to minimise long-term steroid usage.

4.19. The Subcommittee noted the four pivotal trials had either no CRP eligibility criteria (ARMADA, STAR), > 10 mg/L (Keystone et al) or > 20 mg/L (van Putte et al) and that the mean CRP ranged from 15 to 52 in the study populations.

4.20. The Subcommittee noted the 2C-DAS28-CRP is a newer measure of disease activity in RA, and considered it better correlates to inflammation and joint erosion. The Subcommittee considered the 2C-DAS28-CRP was relatively easy to navigate, as it comprised only two main components (CRP and Disease Activity Score), however members were uncertain of its current use among clinicians.

4.21. The Subcommittee noted that, according to the 2C-DAS28-CRP measure, swollen joint count is the main determinant of the gross level of disease activity. The Subcommittee noted that very high disease activity was not possible without a swollen joint count of > 15 and that a high CRP can be present in low disease activity when the swollen joint count is low (less than 6). The Subcommittee considered that some individuals would never have an elevated CRP level, even with high or very high disease activity.

4.22. The Subcommittee considered the health need of patients with RA and a CRP of < 15 mg/L was comparable to the health need of those currently accessing funded adalimumab for RA. The Subcommittee considered that patients with high disease activity would likely benefit from biologic therapy, irrespective of their CRP, and that it was important to minimise the use of long-term steroids.

4.23. The Subcommittee considered the number of additional patients who would access treatment if the CRP criterion was removed would likely be small, as many patients with a CRP < 15 mg/L are likely to be taking prednisone in order to access funded biologic treatment. The Subcommittee considered the level of disease activity was still required to be very high given the required joint count.

Joint count

4.24. The Subcommittee considered the term 'active joints' was not used in practice and that there was inconsistency between interpretation of the current Special Authority wording 'tender, swollen joints'. The Subcommittee considered swollen joints was a more clinically appropriate wording for the Special Authority criteria. The Subcommittee noted 2C-DAS28-CRP would require patients to have their CRP measured. Therefore the Subcommittee considered evaluating swollen joint count rather than 2C-DAS28-CRP score was preferable in ensuring consistent access for patients, as measuring CRP may be a barrier to access for those in rural areas or from lower socio-economic households.

4.25. The Subcommittee considered ≥ 15 swollen joints to define high disease activity, in the context of RA. The Subcommittee considered that these patients had comparable health need to those with ≥ 20 swollen joints.

4.26. The Subcommittee considered first-line biologics (adalimumab and etanercept) were likely to provide as much health benefit to people with RA and a joint count of 15-19 as those with a joint count of ≥ 20.

4.27. The Subcommittee considered if the joint count was reduced to ≥ 15, the criterion regarding four large joints should remain unchanged. The Subcommittee noted the estimate by PHARMAC staff that patient numbers would increase by 15% if the number of swollen joints dropped from 20 to 15, and considered this was a reasonable estimate. The Subcommittee considered that high disease activity in the large joints was associated with greater risk of joint replacements, which would come at a significant cost to the health system.

4.28. The Subcommittee considered reducing the joint count would more effectively target those with the highest health need than reducing the prior treatment requirements to two conventional synthetic DMARDs (csDMARDs).

Prior treatments

4.29. The Subcommittee noted the 2016 EULAR (Smolen et al., Ann Rheum Dis. 2017 Jun;76(6):960-977) and 2015 ACR (Singh et al., Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25) RA treatment guidelines recommended a bDMARD after an inadequate response to two csDMARDs. The Subcommittee considered the evidence supporting this change was of weak quality.

4.30. The 2019 EULAR RA treatment guidelines (Smolen et al., Ann Rheum Dis. 2020 Jun;79(6):685-699) recommended a bDMARD is initiated after inadequate response to one csDMARD in the presence of poor diagnostic factors (eg early erosions, high disease activity). The Subcommittee considered it would be beneficial to discuss whether a specific subgroup of patients with RA should be eligible for earlier funded biologic treatment at a future meeting (ie those patients with erosions within the first two years of symptom onset).

4.31. The Subcommittee noted the four pivotal adalimumab in RA trials considered by PTAC required either an inadequate response to at least one csDMARD or no requirement for previous treatment failure. The Subcommittee considered the evidence did not provide a clear conclusion on the effect of two versus three csDMARDs on biologic efficacy.

4.32. The Subcommittee considered the treat-to target-strategy in RA is agnostic on which pharmaceutical agent to use; the achievement of low disease activity is more important than the agent used to accomplish it. The Subcommittee considered that, while the likelihood of achieving the treatment target was lower with a third csDMARD than biologic treatment, that there was still a reasonable probability that a third csDMARD would achieve low disease activity. The Subcommittee considered it was likely at least 20% of patients would achieve low disease activity long-term on a third csDMARD and not require biologic treatment.

4.33. The Subcommittee considered there were differences in treatment approaches between clinicians in the combination and order of agents used when treating RA. Some members considered that leflunomide is associated with a number of tolerability issues and, if the requirement to trial three csDMARDs was reduced to

two, that triple therapy (ie oral or parenteral methotrexate in combination with sulfasalazine and hydroxychloroquine sulphate) should remain a requirement (if tolerated). The Subcommittee considered it important to leave agent flexibility for clinicians in order to support patients in achieving the best outcomes.

4.34. The Subcommittee suggested PHARMAC staff intended to remove the reference to intramuscular gold from the Special Authority, following its delisting from the Pharmaceutical Schedule.

4.35. The Subcommittee considered that if 20% of patients would otherwise achieve low disease activity on a third csDMARD, reducing the requirement to trial three csDMARDs down to two would result in a maximum of 120 additional patients per year on first line biologic treatment. The Subcommittee considered that because some patients are taking biologic monotherapy and therefore have different prior csDMARD requirements, the actual number of new patients may be lower than this. The Subcommittee considered that if changes to joint counts, CRP and prior csDMARDs were all implemented, this may be associated with a substantial increase in the number of patients initiating biologic treatment.

Patient-reported outcomes

4.36. The Subcommittee noted the applicant's rationale for inclusion of patient-reported outcomes in the Special Authority criteria was to align with EULAR and ACR guidelines. The application noted the Health Assessment Questionnaire-Disability Index (HAQ-DI) has extensive validation and widespread use.

4.37. The Subcommittee considered it was clear from RCTs that HAQ-DI scores do improve in response to TNF inhibitor treatment, however noted an average change of 0.22 (which is often considered a 'meaningful reduction') was also observed in placebo groups. The Subcommittee considered it was unclear as to the extent to which a functional change (ie reduction in HAQ-DI) would not be captured in improvement in disease activity. The Subcommittee considered it would be unusual that disease activity would remain high but that the patient experiences significant functional improvements. The Subcommittee considered it was not immediately clear what the driver would be for patients to see an improvement in HAQ-DI without a reduction in swollen joint count, and that this could reflect changes in health-related quality of life independent of biologic treatment. However, the Subcommittee considered the time for inflammation to significantly reduce is variable across patients, and that functional improvements may be seen before inflammation significantly reduced.

4.38. The Subcommittee considered concomitant disease, among other factors, would influence function and influence the reported HAQ-DI changes.

4.39. The Subcommittee noted the HAQ-DI questionnaire includes questions on twenty areas, and considered this would be a considerable administrative burden to both clinicians and patients. The Subcommittee considered the largest impact would be on primary care, as patients with stable disease are primarily managed by their GP. The Subcommittee considered the questionnaire burden may act as an access barrier for some patients.

5. Other Business

5.1. The Subcommittee considered the following items for discussion at a future meeting:

5.1.1. JAK inhibitors (noting PHARMAC has received funding applications for both tofacitinib and upadacitinib and the Rheumatology Subcommittee has not reviewed upadacitinib)

5.1.2. Funded treatment options for RA and current funding restrictions

5.1.3. Adalimumab funding restrictions for all rheumatological indications (including the funding of adalimumab for a specific subgroup of patients with RA as noted above, in 4.30).

5.1.4. The use of tocilizumab for giant cell arteritis

5.1.5. C5 inhibitors for vasculitis and SLE

5.1.6. IL23 p19 inhibitors for psoriatic arthritis and ankylosing spondylitis.