Record of the ad-hoc advice from the Rheumatology Subcommittee of PTAC
Meeting held on 31 August 2021, via Zoom

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.

This specific meeting was convened to seek rapid advice on potential alternatives for currently funded patients, following a supplier notification of a temporary supply disruption for tocilizumab. Members were offered the opportunity to provide advice via email or attend a video call with Pharmac staff. This record documents the advice and suggestions given by the Subcommittee members. No formal recommendations were sought by Pharmac or made by the Subcommittee.

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1. Attendance

Present

Marius Rademaker (Chair, PTAC member)
Priscilla Campbell-Stokes
Michael Corkill
Alan Fraser (PTAC member)
Andrew Harrison
Janet Hayward
Lisa Stamp (PTAC member)
Will Taylor

Apologies:
Keith Colvine
Elizabeth Dennett

2. The role of PTAC Subcommittees and records of meetings

2.1. 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.

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

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

2.4. 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'.

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

3. Tocilizumab supply disruption

3.1. The Subcommittee noted Pharmac staff had been informed that Roche's supply of tocilizumab to New Zealand would be temporarily affected in the coming months. The Subcommittee noted, based on current usage, Pharmac estimated a complete out of stock would occur in early October 2021. The Subcommittee noted Roche had indicated re-supply was expected in January 2022 and this would result in a three month out of stock (OOS).

3.2. The Subcommittee noted Pharmac staff were seeking advice on the following:

- funded alternatives available for patients currently receiving tocilizumab
- which patient groups or subgroups would not have a suitable funded alternative
- whether there were any suitable unfunded alternatives for patients currently receiving tocilizumab
- whether there were any clinical issues transitioning patients currently receiving tocilizumab
- which patient groups or subgroups, from those currently funded, would be the highest priority for ongoing tocilizumab treatment
- which groups Pharmac could engage with to support healthcare professionals and patients during the supply disruption.

3.3. The Subcommittee noted tocilizumab is listed on the Pharmaceutical Schedule, subject to funding restrictions, for the following indications:

- severe rheumatoid arthritis
- polyarticular and systemic juvenile idiopathic arthritis (JIA)
- adult-onset Still's disease
- idiopathic multicentric Castleman's disease
- cytokine release syndrome.

3.4. The Subcommittee noted approximately 400 patients were currently receiving Pharmac-funded tocilizumab via the Pharmaceutical Schedule. The Subcommittee noted a small number of patients (approximately 5) were receiving funded tocilizumab via the Named Patient Pharmaceutical Assessment (NPPA) pathway, primarily for large vessel vasculitis. The Subcommittee noted Pharmac had recently run a closed consultation on a proposal to widen access to tocilizumab for the treatment of Covid-19 and had approved a small number of NPPA applications for hospitalised patients with moderate to severe Covid-19.

3.5. The Subcommittee considered patients with some indications would be at high risk of life-threatening events without tocilizumab treatment. The Subcommittee also noted that tocilizumab was used for hospitalised COVID-19 patients who may also have a mortality risk without treatment. The Subcommittee considered stock should be preserved for those with the greatest health need for whom there is no funded alternative treatment.

3.5.1. The Subcommittee considered indications to prioritise for continued tocilizumab treatment would be systemic JIA and large vessel vasculitis. The Subcommittee considered priority also needed to be given to patients with adult-onset Still's disease or idiopathic multicentric Castleman's who had trialled funded alternatives or were at high risk if their treatment was changed. The Subcommittee considered minimising the risk of no treatment or the need to transition patients with polyarticular JIA would be beneficial, particularly paediatric patients.

3.6. The Subcommittee considered the cessation of treatment with no alternative funded options would be unacceptable to patients and clinicians for all indications. The Subcommittee considered reducing the dosing frequency of tocilizumab was unlikely to be a clinically suitable option for the funded indications and would also be unlikely to mitigate the OOS situation.

3.7. The Subcommittee noted that some of the alternatives suggested in the discussion did not have Medsafe approval for the proposed indications. The Subcommittee noted clinicians would be prescribing these treatments 'off-label' and that judgement was required based on the circumstances for each individual patient.

3.8. The Subcommittee considered it would be clinically suboptimal for patients who received benefit from a new (currently unfunded) treatment to change back to tocilizumab. Therefore the Subcommittee supported ongoing funding of any new treatments for patients currently receiving tocilizumab.

3.9. The Subcommittee considered clinicians would prioritise transitioning patients to manage this situation and avoid sudden treatment cessation. The Subcommittee considered the supply of alternative products was likely to be the rate-limiting step in transitioning patients. The Subcommittee considered patients would need to be transitioned by a specialist. This could be done over phone or zoom consultation if lockdown was extended, rather than an in-person consultation.

3.10. The Subcommittee considered demand for many of the suggested alternatives may be increased internationally, due to the interest in potential usage for many of these pharmaceuticals in the treatment of Covid-19. The Subcommittee considered it was important that any alternative options considered by Pharmac had robust supply in order to minimise the risk that patients would need to be transitioned again.

3.11. The Subcommittee considered clear and broad communication to healthcare professionals and the sector would be key and that this should occur as soon as possible. The Subcommittee considered it would take planning and substantial work from specialists to transition patients as quickly as possible. The Subcommittee considered the following groups should be included within communications:

- the New Zealand Rheumatology Association
- Arthritis New Zealand
- the Royal New Zealand College of General Practitioners
- Primary Health Organisations
- Health Pathways
- rheumatology clinical nurse specialists
- pharmacists

- infusion services.

3.12. The Subcommittee considered that communication with hospital and community infusion services, as part of any transition, would be critical.

Rheumatoid arthritis

3.13. The Subcommittee noted approximately 300 patients were receiving tocilizumab for rheumatoid arthritis.

3.14. The Subcommittee considered adalimumab, etanercept, rituximab and infliximab were funded alternatives for patients who had not previously trialled these biologic therapies. The Subcommittee considered patients with no available biologic therapies could be prescribed high dose steroids to manage their disease. However the Subcommittee considered this was not clinically appropriate as a long-term option (as in this case) given the significant side effects associated with high dose steroid usage.

3.15. The Subcommittee considered the majority of patients would have no funded alternatives.

3.15.1. The Subcommittee considered most patients would have previously received two anti-TNFs and rituximab before progressing to tocilizumab.

3.15.2. Half to two-thirds of patients would have trialled all funded alternatives.

3.15.3. One-third to half of patients would have trialled and received inadequate benefit from two anti-TNFs and therefore would be unlikely to respond to a third. These patients would also not have a suitable funded alternative treatment.

3.16. The Subcommittee considered treatment cessation would likely result in disease flare and loss of disease control for patients.

3.17. The Subcommittee considered JAK inhibitors would be the most appropriate unfunded alternative. The Subcommittee noted two JAK inhibitors (tofacitinib and upadacitinib) are under assessment as part of Pharmac's funding assessment process. The Subcommittee noted both treatments were recommended for funding by PTAC with a medium priority. The Subcommittee had previously considered tofacitinib and recommended its listing with a medium priority in 2017.

3.18. The Subcommittee noted JAK inhibitors would provide patients with a new mechanism of action compared with currently funded treatments. The Subcommittee considered it would be appropriate to treat the majority of patients receiving tocilizumab with JAK inhibitors. The Subcommittee considered up to 25% of people may be intolerant or not receive adequate benefit from a JAK inhibitor.

3.19. The Subcommittee did not consider there would be significant clinical issues with transitioning patients to a JAK inhibitor. The Subcommittee considered transitioning patients would need to be started as soon as possible, particularly given the volume of patients who may need to transition in a short period of time. The Subcommittee considered it would be a significant challenge to transition patients back to tocilizumab, given the suitability of JAK inhibitors compared to tocilizumab (oral treatments compared with an infusion) and the efficacy of JAK inhibitors.

3.20. The Subcommittee noted the increased incidence of Herpes Zoster infection in patients receiving JAK inhibitors and considered it would be beneficial to provide patients with the recombinant Herpes Zoster vaccine prior to initiation on JAK inhibitor therapy. The Subcommittee noted the current situation was time-sensitive and the funded Herpes Zoster vaccine was a live attenuated vaccine, which would not be suitable for this patient group. The Subcommittee considered, while not ideal, patients could be initiated on JAK inhibitor therapy without first receiving a Herpes Zoster vaccination.

3.21. The Subcommittee considered many patients are likely taking tocilizumab as the last available funded biologic therapy and would respond better to a JAK inhibitor. The Subcommittee considered uptake of a JAK inhibitor would be rapid given the suitability of oral treatment and the reduction in burden on infusion services.

Polyarticular JIA

3.22. The Subcommittee noted approximately 19 patients were receiving tocilizumab for polyarticular JIA.

3.23. The Subcommittee considered secukinumab may be funded treatment option for patients with enthesitis-related arthritis or psoriatic polyarticular JIA and rituximab for other patients with polyarticular JIA (noting they are not currently funded for this indication).

3.24. The Subcommittee considered the majority of patients would have no funded alternatives. The Subcommittee considered secukinumab and rituximab would not be suitable for all polyarticular JIA patients and that the prescribers would need to determine the best treatment option for their patients.

3.25. The Subcommittee considered treatment cessation would result in disease flare and loss of disease control.

3.26. The Subcommittee considered tofacitinib may be a suitable unfunded alternative for patients with polyarticular JIA, noting the oral liquid has FDA approval for use in treatment of polyarticular JIA in patients over the age of two. The Subcommittee considered upadacitinib may be an unfunded alternative however noted upadacitinib for polyarticular JIA was only in phase I trials. The Subcommittee considered abatacept may be another unfunded alternative.

3.27. The Subcommittee considered there were less clinical issues and risks transitioning patients with polyarticular JIA to an alternative treatment than patients with systemic JIA.

3.28. The Subcommittee considered rituximab and abatacept may require steroid bridging while the biologics reached efficacy and considered this was suboptimal.

3.29. The Subcommittee considered high dose steroids would be required for patients who did not respond to an alternative treatment and lost disease control. The Subcommittee considered this an important risk to consider, given the substantial impact steroids can have on growing and developing children and pubertal adolescents.

3.30. The Subcommittee considered patients could be transitioned from any age but that adult patients with polyarticular JIA would likely be easier to transition than paediatric patients, if unfunded alternatives were made available.

Systemic JIA

3.31. The Subcommittee noted approximately 23 patients were receiving tocilizumab for systemic JIA.

3.32. The Subcommittee noted there were no funded alternatives for patients with systemic JIA.

3.33. The Subcommittee considered there was a substantial mortality risk associated with treatment cessation.

3.34. The Subcommittee considered anakinra (an anti-IL-1) may be a suitable unfunded alternative for some patients where clinically appropriate. The Subcommittee considered anakinra may not be effective in patients with more arthritis features.

3.35. The Subcommittee considered JAK inhibitors could be considered for some patients with systemic JIA but there was very little evidence for the use of JAK inhibitors in this indication.

3.36. The Subcommittee considered the risk of hypersensitivity reactions in this patient group and that these were difficult to predict, resulting in significant clinical risks if transitioning patients between treatments.

3.37. The Subcommittee considered older patients may be able to transition to anakinra although considered the daily subcutaneous injections would pose a challenge for paediatric patients.

3.38. The Subcommittee considered adult systemic JIA patients may be easier to transition than paediatric patients if unfunded alternatives were made available.

3.39. The Subcommittee considered that, for this patient group, anti-IL-6 therapies would be preferable to anti-IL-1 therapies.

Adult-onset Still's disease

3.40. The Subcommittee noted approximately 18 patients were receiving tocilizumab for adult-onset Still's disease.

3.41. The Subcommittee considered adalimumab and etanercept were funded alternatives for patients who had not previously trialled these biologic therapies.

3.42. The Subcommittee considered the majority of patients would have no funded alternatives.

3.43. The Subcommittee considered there was a substantial mortality risk associated with treatment cessation.

3.44. The Subcommittee considered if there was no suitable alternative treatment available for this patient group, siltuximab or anakinra would be considered a 'last resort' treatment.

3.45. The Subcommittee considered there were significant clinical risks with transitioning patients between treatments.

3.46. The Subcommittee noted adult-onset Still's disease is an IL-1 and IL-6 responsive condition.

Idiopathic multicentric Castleman's disease

3.47. The Subcommittee noted approximately 18 patients were receiving tocilizumab for idiopathic multicentric Castleman's disease.

3.48. The Subcommittee considered siltuximab was a suitable funded alternative for patients who had not previously trialled it.

3.49. The Subcommittee considered patients who have previously trialled siltuximab would have no funded alternatives.

3.50. The Subcommittee considered there was a substantial mortality risk associated with treatment cessation.

3.51. The Subcommittee considered if there was no treatment available for this patient group, sarilumab would be considered a 'last resort' treatment option.

3.52. The Subcommittee did not raise any clinical issues with transitioning patients to suitable alternative treatments. The Subcommittee noted that idiopathic multicentric Castleman's disease is managed by rheumatologists and haematologists and noted Pharmac staff were also seeking advice from haematologists on this patient group.

3.53. The Subcommittee noted Polynesian Castleman's disease is uniquely IL-6 responsive.

Large vessel vasculitis

3.54. The Subcommittee noted approximately 4 patients were receiving tocilizumab for large vessel vasculitis (either giant cell arteritis or Takayasu arteritis) via the NPPA pathway.

3.55. The Subcommittee considered there were no funded alternatives available for these patients. The Subcommittee considered tocilizumab is usually funded due to corticosteroid toxicity and therefore steroids could not be used to manage these patients.

3.56. The Subcommittee considered there was a substantial mortality risk associated with treatment cessation.

3.57. The Subcommittee did not identify any unfunded alternatives for this patient group.

3.58. The Subcommittee considered there was significant clinical risk in transitioning these patients to an alternative treatment.

Cytokine release syndrome

3.59. The Subcommittee noted tocilizumab is also listed on the Pharmaceutical Schedule for cytokine release syndrome. Cytokine release syndrome was not discussed in detail given the minimal impact on usage this indication has. Cytokine release syndrome has very low patient numbers (approximately 1-2 patients per year) and treatment is a one-off dose.

3.60. The Subcommittee was not aware of any funded or unfunded alternatives for this patient group.