Record of the Neurological Subcommittee Meeting held on 7 February 2019

Contents

Present from the Subcommittee:
Mark Weatherall (Chair, PTAC Chair)
John Fink
Richard Hornabrook
Ian Hosford (PTAC member)
John Mottershead
Giles Newton-Howes (PTAC member)
Ian Rosemergy
Paul Timmings

Present from PHARMAC:
Adrienne Martin
Andrew Oliver
John Wyeth
Peter Murray
Dee Alexander
Hannah Hoang
Hayden Spencer

Summary of recommendations

2.3 The Subcommittee **recommended** that rituximab be funded as a first line agent for the treatment of a severe episode of NMOSD with a high priority.

2.4 The Subcommittee **recommended** that the requirement for a rise in CD counts be removed from the proposed Special Authority criteria, as at this time there was insufficient evidence to support what would constitute a significant rise to guide retreatment.

2.5 The Subcommittee **recommended** that rituximab be funded for NMOSD subject to Special Authority criteria. (as detailed in paragraph 2.5).

2.6 The Subcommittee **recommended** that access to tacrolimus should not be widened for the treatment of NMOSD.

1. Rituximab

Background

1.1 The Subcommittees considered a paper from PHARMAC staff regarding rituximab and tacrolimus for the treatment of Neuromyelitis Optica Spectrum Disorder

(NMOSD).

Recommendations

1.2 The Subcommittee **recommended** that rituximab be funded as a first line agent for the treatment of a severe episode of NMOSD with a high priority.

1.3 The Subcommittee **recommended** that the requirement for a rise in CD counts be removed from the proposed Special Authority criteria, as at this time there was insufficient evidence to support what would constitute a significant rise to guide retreatment.

1.4 The Subcommittee **recommended** that the Special Authority criteria for NMOSD be as follows (additions to existing recommended criteria in bold and deletions in strikethrough):

> **Initial – (Neuromyelitis Optica Spectrum Disorder)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
>
> 1. **The patient has experienced a severe episode or attack of NMOSD (rapidly progressing symptoms and clinical investigations supportive of a severe attack of NMOSD); or**
> 2. The patient has experienced a breakthrough attack of NMOSD; and
> 3. Both:
>
> 3.1 The patient is receiving treatment with mycophenolate; and
>
> 3.2 The patient is receiving treatment with corticosteroids.
>
> **Note:** Initial approval is for either 2 doses of 1,000 mg rituximab to be administered fortnightly, or for 4 doses of 375 mg/m^2 rituximab to be administered weekly for 4 weeks.
>
> **Renewal** – **(Neuromyelitis Optica Spectrum Disorder)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:
>
> All of the following:
> 1. The patient has responded to the ~~initial~~ **most recent** course of rituximab; and
> 2. The patient has not received rituximab in the previous 6 months.
> ~~3. The patient's CD19 or CD27 levels have risen significantly.~~

1.5 The Subcommittee **recommended** that access to tacrolimus should not be widened for the treatment of NMOSD.

Discussion

1.6 The Subcommittee noted that in November 2017, PTAC considered a clinician application for widening access to rituximab for the treatment of NMOSD, in patients who do not respond to azathioprine or mycophenolate.

1.7 The Subcommittee noted that PTAC made the following recommendations:

- that access to rituximab be widened to include treatment of patients with neuromyelitis optica spectrum disorder not responsive to oral agents, with a high priority; and

- the following restrictions for rituximab when used for the treatment of neuromyelitis optica spectrum disorder, in patients who do not respond to treatment with mycophenolate:

- **Initial – (Neuromyelitis Optica Spectrum Disorder)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

  1. The patient has experienced a breakthrough attack of NMOSD; and
  2. Both:

     2.1 The patient is receiving treatment with mycophenolate; and

     2.2 The patient is receiving treatment with corticosteroids.

  Note: Initial approval is for either 2 doses of 1,000 mg rituximab to be administered fortnightly, or for 4 doses of 375 mg/m^2 rituximab to be administered weekly for 4 weeks.

  Renewal – **(Neuromyelitis Optica Spectrum Disorder)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

  All of the following:
  1. The patient has responded to the initial course of rituximab; and
  2. The patient has not received rituximab in the previous 6 months; and
  3. The patient's CD19 or CD27 levels have risen significantly

- that rituximab for the first line treatment of patients with neuromyelitis optica spectrum disorder who present with an initial severe episode or relapse, be referred to the Neurological Subcommittee for review;

- that the Neurological Subcommittee review the evidence for use of first line tacrolimus for NMOSD;

- that further advice should be sought from the Neurological Subcommittee to quantify appropriate increases for the proposed renewal criteria which require a significant rise in either CD19 or CD27.

Rituximab for severe episodes of NMOSD

1.8 The Subcommittee considered a retrospective cohort study by Kim et al. (Multiple Sclerosis Journal 2017, 1-7, DOI:10.1177/1352458516687403) investigating predictors of response to first line therapy in NMOSD.

- The authors retrospectively evaluated 116 medical records who were treated with azathioprine or mycophenolate for at least 6 months. Poor response was defined as ≥2 relapses or ≥1 severe relapse. In addition, the

authors also investigated the outcomes of first line rituximab in patients that were predicted to have a poor response to azathioprine or mycophenolate treatment.

- A severe relapse was defined as an EDSS score of ≥6.0, or an increase of >0.5 points if the patient has a baseline EDSS score of ≥6.0. For optic neuritis cases, a severe relapse was defined as a new worsening of visual acuity ≤0.1 in patients with a baseline visual acuity >0.1 (VA decimal). If the baseline vision result was light perception, hand motion, or counting fingers, a severe relapse was defined as any decrease in visual acuity that was accompanied by MRI evidence of optic neuritis.

- The Subcommittee noted that 71 out of a total of 116 (61%) patients had experienced a severe attack before therapy, and of those with a severe attack 36 (51%) failed to respond to therapy. The Subcommittee noted that if a patient had no history of a prior severe attack then only 4 out of 45 patients (9%) failed to respond.

- The Subcommittee noted that 29 out of the 40 poor responders switched to rituximab and over a median follow up period of 57 months 3 (10%) of the 29 patients experienced a poor response to rituximab and in 1 (3%) patient EDSS worsened due to a relapse after rituximab treatments, whereas 26 (90%) of 29 patients showed a good response to rituximab.

- The Subcommittee considered that 41 out of the 56 patients who received rituximab first line had a history of a severe attack prior to treatment, and over a median period of 90 months of rituximab treatment 3 (7%) patients and 2 (5%) patients exhibited a poor response and worse EDSS scores, respectively.

- The Subcommittee considered that there was likely an element of selection bias present as severe patients tended to be offered rituximab as first line which could lead to an underestimate of poor response to azathioprine and mycophenolate.

1.9 The Subcommittee considered that the current treatments in NZ for a severe initial attack are IV methylprednisolone 1g per day for five days, followed by oral steroids with a tapering dose over two to eight weeks, or plasma exchange consisting of five to seven plasma exchanges on alternate days as an inpatient and IVIG if a patient did not respond to plasma exchange.

1.10 The Subcommittee noted the high health need of people with NMOSD; that attacks can have catastrophic effects on quality of life that that the disease is associated with a high mortality rate. The Subcommittee noted that any attack is potentially severe or fatal and may leave the patient with high residual disability post-relapse, and that more severe relapses or episodes of the disease are associated with worse outcomes

1.11 The Subcommittee considered, based on the Kim et al. (2017) publication, that for those patients who do not have a history of a severe episode or relapse, most respond to treatment with azathioprine or mycophenolate; and, that for this population rituximab remained an appropriate second line option for any patients

who subsequently do not respond.

1.12 The Subcommittee considered, based on the publication by Kim et al. (2017), and the health need of patients who experience a severe episode or attack, that rituximab would be the most appropriate first line treatment.

1.13 The Subcommittee considered the quality of the evidence to be weak but the effect size to be large.

1.14 The Subcommittee considered that a severe episode or attack was not necessarily always the initial attack and could present at any time. For this reason, and the evidence considered, the Subcommittee **recommended** that rituximab should be funded as a first line treatment for patients with NMOSD with a severe episode or attack with a high priority.

1.15 The Subcommittee considered that the criteria used in Kim et al. (2017) to define a severe attack was probably too difficult to use in clinical practice due to the speed of onset of some attacks. The Subcommittee considered that Neurologists would be able to ascertain the difference between a severe and a non-severe attack and that a more pragmatic definition to use in Special Authority criteria could be 'rapidly progressing symptoms and clinical investigations supportive of a severe attack of NMOSD'.

1.16 The considered that the renewal criteria for rituximab for severe attacks or episodes of NMSOD (first line use) could be the same as that for rituximab for NMOSD not responsive to treatment with mycophenolate (second line use).

1.17 The Subcommittee considered that NMOSD was a relatively rare condition but that due to a growing awareness of the condition that it was becoming diagnosed more frequently. The Subcommittee considered, based on Bukhari et al. (J Neurol Neurosurg Psychiatry 2017;88:632-38), that the prevalence of NMOSD in NZ was around 32 patients per year and that these numbers could double over the next 5 years. The Subcommittee considered that around a third or these patients would experience a severe attack or episode.

Rituximab for NMOSD criteria

1.18 The Subcommittee considered the following publications with regards to the use of CD19 and CD27 levels as markers for retreatment with rituximab:

- Kim et al. Multiple Sclerosis Journal 2017, 1-7 DOI:10.1177/1352458516687403
- Kim et al. Arch Neurol 2011;68(11):1412-20
- Kim et al. JAMA Neurol 2013;70(9):1110-7
- Lebrun et al. Neurol Ther 2018;7:373-83
- Zhang et al. Acta Neurol Belg 2017; DOI 10.1007/s13760-017-0795-6

1.19 The Subcommittee considered that based on the evidence there was a lack of information on how to monitor CD counts and as to what constitutes a significant

rise with regards to the need for retreatment.

1.20 The Subcommittee **recommended** that this criterion should be removed altogether from the criteria, and that the requirements for a patient to have responded to treatment and not have received rituximab in the previous six months were sufficient to ensure that appropriate use was being targeted to those most likely to benefit.

Tacrolimus as a first line agent for NMOSD

1.21 The Subcommittee considered that tacrolimus was a calcineurin inhibitor and that its mechanism of action involved suppression of T-cell activation, T-cell dependent B-cell proliferation as well as various lymphokines.

1.22 The Subcommittee noted that tacrolimus is used as a standard part of renal transplant immunosuppression regimens.

1.23 The Subcommittee noted that tacrolimus is dosed orally by weight and then guided by blood concentration assays.

1.24 The Subcommittee noted that side effects of tacrolimus include neurotoxicity, renal and liver impairment, diabetes mellitus, infections, malignancy, hypertension and insomnia.

1.25 The Subcommittee considered that patients prescribed tacrolimus require regular monitoring for blood concentrations and possible side effects.

1.26 The Subcommittee considered the following publications:

- Chen et al. Sci Rep 2017;7:831
- Tanaka Mult Scler J 2015;21:669
- Kageyama et al J Neurol 2013;260:627-634
- Zheng et al. Intern Med 2014;53(20):2377-80
- Meyts et al. Eur J Paed Neurol 2011;15(3):265-7
- Mok et al. J Rheum 2008;35(1)172-4

1.27 The Subcommittee considered that the evidence to support a benefit of tacrolimus for the treatment of NMOSD consisted of small retrospective studies or case reports. The Subcommittee considered that there was no direct evidence to support a benefit over and above mycophenolate or azathioprine; but that based on the evidence it was likely to provide similar level of benefit to that of azathioprine.

1.28 The Subcommittee considered that Neurologists in New Zealand are not familiar with the use of tacrolimus as an immunosuppressant. The Subcommittee considered that if tacrolimus was funded for the treatment of NMOSD that Neurologists would not use it and would continue to use azathioprine or mycophenolate. Based on this, the Subcommittee **recommended** that tacrolimus

not be funded for treatment of NMOSD.

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Mark Weatherall, Chair Date