WADEP – Drug Submission Review

Rituximab for NMDA Receptor Encephalitis

General Information

<table>
<thead>
<tr>
<th>Approved (generic) name</th>
<th>Rituximab</th>
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<tbody>
<tr>
<td>Proprietary (brand) name</td>
<td>Mabthera®</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Strength and proposed dosing</td>
<td>375mg/m² weekly for 4 weeks (average rounded to 700mg)</td>
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<tr>
<td>Sponsor or manufacturer</td>
<td>Roche Products Pty Ltd</td>
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<tr>
<td>Cost per dose</td>
<td>$2,846 ($11,384 per course)</td>
</tr>
<tr>
<td>TGA Approved for indication</td>
<td>Rituximab is not ARTG listed for anti-NMDA receptor encephalitis</td>
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Indication

Requested formulary listing:

Treatment of anti-NMDA receptor (NMDA-R) encephalitis not responding appropriately to 1st line treatment. Prescription and/or recommendation should be by a consultant neurologist. A treatment algorithm has been proposed by the applicant and is attached as Appendix A.

Target population in the submission

The submission is for rituximab to be used for inpatients.

Current WA hospital formulary approval:

All indications as per the PBS schedule:

- B-cell non-Hodgkin’s lymphoma
- Chronic lymphocytic leukaemia
- Rheumatoid arthritis

Royal Perth Hospital non-PBS indications:

- Treatment of humoral rejection in cardiac transplant patients, antibody-mediated rejection in lung, heart/lung and renal transplant patients
- Idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura
- Autoimmune haemolytic anaemia (AIHA)
- Severe haemophilia
- Waldenström’s macroglobulinaemia
- Burkitt’s lymphoma
- Interstitial lung disease in systemic sclerosis (SScl-ILd)
- Glomerulonephritis

Sir Charles Gairdner Hospital non-PBS indications:

- ITP, AIHA and refractory immune thrombocytopenia
**Disease description and drug mode of action**

Anti-NMDA encephalitis is an antibody associated neurological disease discovered in 2007. The disease develops in multiple stages from psychosis, memory deficits, seizures, language disintegration and unresponsiveness with catatonic features (1). Approximately 80% of patients are women with increasing findings in teenagers and children. The disease may be associated with ovarian teratoma however patients may not have an underlying or detectable tumour (2). Patients without tumours have been reported to have worse prognosis and increased relapse rates.

Patients may require intensive care support for weeks to months followed by extensive physical and psychiatric rehabilitation. Around 75% recover or have mild sequelae; the remaining 25% will remain severely disabled or die.

Immunopathogenesis of this disease is possibly linked to antibody immune-response of the B cell and plasma cells derived from B cell (3). Rituximab is an anti-CD20 monoclonal antibody which causes B cell lysis.

**Evaluation by other jurisdictions**

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<tr>
<th>Australian</th>
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<tbody>
<tr>
<td>Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>Rituximab has not been evaluated by PBAC for NMDA-R Encephalitis</td>
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<tr>
<td>South Australian Medicine Evaluation Panel (SAMEP)</td>
<td>SAMEP have not reviewed rituximab for NMDA-R Encephalitis</td>
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<tr>
<th>International</th>
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<tbody>
<tr>
<td>Canadian Agency for Drugs and Technologies in Health</td>
<td>CADTH have not reviewed rituximab for use in NMDA-R Encephalitis</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>NICE have not reviewed rituximab for use in NMDA-R Encephalitis</td>
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**Summary of current best-practice/alternative treatment**

Current management is focused on immunotherapy and detection and removal of a teratoma. First-line treatment of the disease is corticosteroids with intravenous immunoglobulin (IVIg) or plasma exchange ± tumour removal. Treatment is evolving with greater understanding of the disease. In the study by Titulaer 472 patients were treated with first-line immunotherapy of which 251 (53%) had symptom improvement within 4 weeks. During 24 month follow-up 241 of these patients reached mRS 0-2 (median=3 months), at 24 months follow-up 115 patients were seen with 111 (97%) patients had good outcome. Predictors of a good outcome include avoidance of ICU (lower severity in disease), and early immunotherapy and tumour removal in the first stage of NMDAR encephalitis.
Summary of clinical evidence

Due to the recent discovery in 2007 and relative rarity of the disease clinical studies are lacking. The effects of rituximab have not been studied in randomised control trials; case studies or observational studies provide the bulk of the evidence.

The largest study in this condition is by Titulaer et al. (2013), this study was a multicentre observational study of 577 patients from 2007 – 2012. All patients had been tested positive for NMDAR antibodies and assessment of neurological status was done with a modified Rankin scale (mRS); good outcome was defined as mRS 0-2 (4).

Of 501 patients with >4 months follow-up, 92% were treated with first-line immunotherapy (steroids, IVIg and plasmapheresis) where 221 (47%) patients did not improve. Of these 221 patients, 125 (57%) were given second-line immunotherapy of rituximab and cyclophosphamide (27% in total). During the first 24 months 84/125 (67.2%) second-line treated patients had reached mRS 0-2 compared to 49/96 (51%) untreated patients. At 24 month follow-up 43/55 (78%) second-line treated patients compared to 32/58 (55%) had mRS 0-2 (multivariable analysis: OR 2.69, CI 1.24-5.8, p=0.012). Second-line immunotherapy significantly reduced relapse rates in patients with tumours (p=0.0007) and when patients were treated at relapse, second-line immunotherapy significantly reduced subsequent relapse (p=0.024).

In 2008 a case report by Ishiura et al. reported that a 41 year old women was given 6 doses of rituximab starting on day 93 (5). The patient recovered with CD20+ B lymphocytes decreasing from 8% - 0% after the first administration and near recovery and discharge on day 160. Ikeguchi et al. (2012) published a case report of a women who was treated for NMDAR encephalitis initially with methylprednisolone, IVIg and plasma exchange (3). Her condition did not improved with first-line immunotherapy and was subsequently given rituximab (day 100) for four weeks and started on azathioprine on day 160.

Dale et al. in 2014 studied the utility and safety of rituximab infusion in 39 paediatric NMDAR encephalitis along with other autoimmune and inflammatory CNS disease (6). The median duration of disease at rituximab administration was 0.1 years (0.005-5.1). Patients were found as having definite benefit (16/39), probable benefit (16/39), possible benefit (6/39), 1 patient with no benefit and no patients with worsening. The median Rankin score was 5 before administration, 4 at administration and 1 at outcome (79.5% had mRS 0-2 at outcome).

Literature review

Mann, Grebenciucova and Lukas conducted a literature review of published articles between 2007 – 2014 (7). They found that rituximab 375mg/m² weekly for 4 weeks plus cyclophosphamide 750mg/m² monthly until signs of improvement was recommended for patients who do not improve with first-line treatment after 10 days. Patients without tumours have higher relapse rates and therefore should be given immunosuppression (azathioprine or mycophenolate) for a minimum of 1 year.
Cost and cost-effectiveness

- No cost-effectiveness analyses or health technology assessment (HTA) on rituximab anti-NMDAR encephalitis was found
- Due to the severity and breadth of symptoms related to the disease (i.e. extensive ICU, psychiatric, surgical and cardiac involvement) the overall cost of treatment is expected to be high
- As there are few other recommended second-line treatment options other than rituximab the cost should be compared to supportive care for those that fail first-line immunotherapy – to separate care that would otherwise be given in addition to rituximab is difficult
- The submission’s expected patient numbers for WA of 1-2 per year seems appropriate. IPAs in WA hospitals have been infrequent:
  - 2 patients in 2013
  - 0 patients in 2014
  - 1 patient in 2015 to date

References

1. Up-to-Date. Paraneoplastic and autoimmune

Summary of WADEP discussion and review

Reviewer A (guest reviewer)

WADEP Meeting 9 April 2015

WADEP Final Recommendations

| WADEP Receipt of Drug Submission Form | 17 March 2015 |
| Date of WADEP meeting – Recommendation | TBC |
| Date of WATAG resolution – Final Recommendation | TBC |
| Date of SHEF-ORC resolution | TBC |
Appendix A. Proposed treatment algorithm for rituximab in anti-NMDA receptor encephalitis (2)