CPAG Summary Report for Clinical Panel – Rituximab for NMDAR Paediatric Autoimmune encephalitis

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Benefit determined [C]	Measures of mobility were included within a conglomerate of characteristic symptoms (e.g. abnormal behaviour, dyskinesia, movement disorders or seizures). A study (Dale et al. 2014) of 144 children with CNS autoimmune and inflammatory disorders, the anti-NMDAR autoimmune encephalitis cohort who was treated with rituximab as second-line therapy with a median follow-up of 1.3 years, 32/39 (82%) patients had ongoing disability (incl. two deaths) after the last follow up. Whilst 7/39 (18%) recovered fully. This was an uncontrolled retrospective observational study with multiple confounders present, thus ascribing therapeutic benefits to rituximab is inaccurate.
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Benefit determined [C]	Modified Rankin Scale (mRS) describes neurological disability where the scale of 0-2 is good outcomes, 3 is Moderate disability;

			requiring some help, but able to walk without assistance, 4 is Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, 5 is Severe disability; bedridden, incontinent and requiring constant nursing care and attention and 6 is death. A study of 577 patients (211 children and 366 adults) with anti-NMDAR encephalitis (Titulaer et al. 2013) treated with different immunotherapies. Of those (101/221) 45.7% of patients who failed first line immunotherapy received rituximab (alone or in combination with cyclophosphamide). Overall 394/501 patients had good outcome with mRS of 0-2 at four months follow up. At 24 month follow-up, 81% (203/252) had good outcome. Predictors of good outcome were early treatment and no admission to ICU. At 24 months, 78% (84/125) of patients who failed first-line and received second-line therapy had a good outcome, compared to 55% (49/96) of patients who failed first-line and did not receive second-line therapy. This was an uncontrolled prospective observational study, with a large sample size but significant loss to follow up; therefore, the results must be used with caution. The effect of individual treatments could not be compared; hence sole rituximab treatment effect is unclear.
10.	Safety	Adverse events identified [C]	A study (Dale et al. 2014) reported on safety outcomes as infusion related adverse events, B cell depletion and deaths. It included 144 children with autoimmune and inflammatory CNS disorders treated with rituximab as second-line therapy; of those 39 had anti-NMDAR encephalitis. <u>Infusion related Adverse Events</u>

			Infusion related adverse events *(AE)* is defined as any unwanted hypersensitivity or allergic reactions that occurred during rituximab infusion and infectious complications attributed to rituximab usage. 18/144 (12.5%) had recorded infusion *AE*s. Of those, • 3 patients had a grade 4 reaction (anaphylaxis) that was resolved without complication with standard therapy. • One patient with infusion-related fever had a transient exacerbation of seizures. • One patient was unable to tolerate rituximab due to worsening hypersensitivity. There was no difference in infusion *AE*s between those on antihistamine prophylaxis and those without it, and no increased risk in younger children (≤5 years). <u>Infections</u> 11/144 (7.6%) had recorded infection related complications. Of those, • 2 patients had a grade 5 *AE* (death; both were anti-NMDAR patients) • 2 children a grade 4 *AE* (life-threating or disabling); and 7 children a grade 3 *AE* (hospitalisation or IV antibiotics). Grade 4 &5 infectious *AE*s occurred in a median of 30 days (range 3-38) after rituximab initiation. There was no difference in infectious *AE*s between those on antibiotic prophylaxis and those without it, and no increased risk in younger children (≤5 years). <u>B cell depletion</u> B cell depletion reduced response to vaccines and new antigens thus may be linked to increased risk of opportunistic infections and

			malignancy but the likelihood of such reposes is disputed and is dependable on length of treatment. B cell depletion was recorded in 124/144 patients. 119/124 (96%) had B-cell depletion after rituximab (the actual values were not recorded), which was present >12 months in 12 children. 27/124 had documented hypogammaglobulinemia. There was no difference between younger and older children, except an increased rate of hypogammaglobulinemia in children ≤5 years. <u>Deaths</u> 3/144 (2%) patients died (of whom 2/39 anti-NMDAR patients died of Adverse Events (AE) and one patient with GAD Ab- receptor encephalitis died of refractory status epilepticus). The study which reported the above outcomes was an uncontrolled retrospective observational study with multiple confounders present, thus results should be used with caution.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1	Paediatric Cerebral Performance Category (PCPC) scale	Grade C	The PCPC scale is not as precise an objective measures as functional status scale but it is used significantly in PICU settings where PCPC of 1-full recovery or 2 - substantial recovery. A study (Armangue et al. 2013) which included 20 children with anti-NMDAR encephalitis treated with different immunotherapies. 7/20 (35%) children received rituximab (alone or in combination). Median follow up period was 17.5 months (range 4-149). At last follow-up, 17/20 patients (85%) had substantial recovery. Of those; 12 fully recovered (8-12 months after symptom onset in 8 cases, and 3-5 months in 4 cases).

			The study was a retrospective observational study; with a very small sample size thus its findings are not generalizable. Patients received different treatments and only a few patients were treated with rituximab, thus ascribing therapeutic benefits directly to rituximab is not possible.
2	Initial improvement / Response to treatment with rituximab	Grade C	Initial improvement was defined as time to first signs of improvement using mRS as a measure for outcomes. In a study (Zekeridou et al. 2015) which included 36 children with anti-NMDAR encephalitis treated with different immunotherapies, 26/36 (72%) received rituximab (alone or in combination). Median time between first and second-line therapy was 26 days (range 7-198). In the 26 cases treated with rituximab, median duration between first rituximab administration and first sign of improvement was 24 days (range 5-150). This was a retrospective observational study, with a small sample size, not generalizable. Patients received different treatments, and despite more frequent and earlier use of second-line immunotherapy, especially rituximab, ascribing therapeutic benefits directly to rituximab is not possible.
3	Relapse	Grade C	Relapse is defined as the new onset or worsening of symptoms occurring after at least 2 months of improvement or stabilisation. A study (Titulaer et al. 2013) that included 577 patients (211 children and 366 adults) with anti-NMDAR encephalitis treated with different immunotherapies. Of those, 501 patients (177 children) were followed-up for at least 4 months and had their treatment effects and outcomes assessed. 101/501 (20%) patients received rituximab (alone or in combination with cyclophosphamide). During the 24 month follow-up, 45 patients had clinical relapse (representing a 12% risk within 2 years), of whom 15 (33%) had multiple relapses. Compared

			with the initial episode, 46/69 (67%) relapses were less severe, 24 (35%) mono-symptomatic, 16 (23%) similar and 7 (10%) worse. The use of immunotherapy in the initial episode, use of second-line therapy and teratoma identified at presentation were associated with a lower frequency of relapses. The study was an uncontrolled though prospective observational study, with a large sample size but significant loss to follow up. The effect of individual treatments could not be compared; hence sole rituximab treatment effect is unclear.