NHS England

Clinical Commissioning Policy Proposition:

Rituximab for anti-NMDAR autoimmune encephalitis (all ages)

Reference: NHS England 1625

First published: TBC

Prepared by NHS England Specialised Services Clinical Reference Group for Paediatric Neurosciences

Published by NHS England, in electronic format only

Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About Acute Anti-NMDAR Autoimmune Encephalitis

Acute autoimmune encephalitis is a rare, debilitating neurological disorder with a significant burden to patients, families and society. It causes inflammation of the brain and in most cases it progresses rapidly into a severe syndrome including altered mental status, neurological and psychiatric symptoms or death. Acute anti N-methyl-D-aspartate brain cell-surface receptor (anti -NMDAR) autoimmune encephalitis (AE) is one of the commonest known types of autoimmune encephalitis, most often noted in children and young adults. It is characterised by abnormal behavioural and cognitive problems, seizures and movement disorders. If treatment does not work or the patient does not receive treatment, this may result in long term disabilities or death.

About current treatments

Second-line treatment is usually administered when the response to first-line therapy is inadequate or when the disease is known to be severe or relapsing. It typically includes immunomodulators such as; cyclophosphamide, azathioprine, mycophenolate mofetil or others. There are promising reports on use of rituximab for

this condition alone or alongside other immunomodulators. Patients are also treated with tumour resection as certain tumours may be associated with anti-NMDAR AE (e.g. ovarian teratoma).

About the new treatment

Rituximab is a monoclonal antibody inducing B-cell depletion that has been approved by the National Institute of Health and Care Excellence (NICE) in England and Wales for use in suppressing the body's immune response in some autoimmune disorders. It is currently not licensed to treat neurological inflammatory disease. Rituximab use is known to be associated with some adverse events.

What we have decided

NHS England has carefully reviewed the evidence to treat anti-NMDAR AE in children and adults with rituximab.

We have concluded that there is enough evidence to consider making the treatment available to a well-defined group of children and adults suffering from acute anti-NMDAR AE who have not or have inadequately responded to the first-line therapy by four weeks of treatment initiation OR within six weeks of first symptoms.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission rituximab for the treatment of acute anti- N-methyl-D-aspartate neuronal cell surface receptor autoimmune encephalitis (AE) when patients have not or have inadequately responded to first-line immunotherapies by four weeks of treatment initiation OR within six weeks of symptom/disease onset.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy

proposition.

A final decision as to whether rituximab treatment for patients with acute anti-NMDAR AE will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Acute AE is a debilitating neurological disorder that causes brain inflammation and develops as a rapidly progressive encephalopathy syndrome presenting with altered mental status and a range of neurological and psychiatric symptoms (Graus et al., 2016, Nosadini et al., 2015). The death rate is estimated to range from 2% to 5% but can approach 20% in patients who fail first line therapy and do not receive second-line immunotherapies (Dale et al., 2014, Titulaer et al., 2013).

One of the commonest known types of autoimmune encephalitis is associated with antibodies against NMDAR (anti-NMDAR). Anti-NMDAR AE is characterised by abnormal behavioural and cognitive dysfunctions, seizures, movement disorder, reduced consciousness, speech disorder, autonomic dysfunction, hypoventilation and memory deficit (Dalmau et. al, 2007; Dalmau et. al, 2008; Graus et al., 2016, Irani et. al 2010; Titulaer et al.,2013, Wright et al., 2015). The presence of tumour, most commonly ovarian teratoma in young women, is associated with anti-NMDAR AE especially in young adults (Florance et. al, 2009; Gong et. al, 2017;Graus et. al, 2016; Irani et al, 2010;Titulaer et al., 2013; Wright et. al, 2015).

Most types of AE have significant clinical overlap (Nosadini et al, 2015). Impairment in many of these conditions appears to be associated with the degree of active inflammation, and therefore the mainstay of treatment is immunosuppression. First-line immunotherapies generally consist of corticosteroids (intravenous and oral), intravenous immunoglobulin (IVIg) and/or plasma exchange (PLEX) (Nosadini et al., 2015). Second-line treatment is usually administered when the response to first-line therapy is inadequate or when the disease is known to be severe or relapsing. It typically includes cyclophosphamide, azathioprine, mycophenolate mofetil or others (Nosadini et al., 2015). Patients are also treated with tumour resection if one is present.

Current evidence suggests that the use of second-line immunotherapies for AE associated with antibodies to cell surface antigens is beneficial, more commonly associated with a better outcome and lower rates of relapses (Dale et al., 2014, Nosadini et al., 2015, Titulaer et al., 2013). Evidence also suggests that early commencement of immunotherapy favours a better neurological outcome and may prevent major disability (Dale et al., 2014; Nosardini et al., 2015; Titulaer et al., 2013).

Rituximab is a chimeric monoclonal antibody against CD20-positive B lymphocytes (B cells) inducing B-cell depletion (Dale et al., 2014, Lee et al., 2016) that has been approved by the National Institute of Health and Care Excellence (NICE) in England and Wales for use in suppressing autoimmune disorders. It is currently not licensed to treat neurological inflammatory disorders, leading to off-label use as a second-line immunotherapy in patients with severe or refractory diseases who fail the first-line treatment (Dale et al., 2014; Nosadini et al., 2015).

Rituximab is known to be associated with adverse events, particularly anaphylactic reactions, its interaction with live vaccines and infectious side effects (such as virus reactivations, bacteria in the blood (bacteraemia) and sepsis). Most evidence on the safety and efficacy of rituximab comes from studies in patients with lymphomas and rheumatoid arthritis. About 10% of patients with any autoimmune neurological disorders treated with rituximab experience hypotension and bronchospasm, usually at the first administration of the drug. Severe manifestations such as acute respiratory distress syndrome (ARDS), myocardial infarction, ventricular fibrillation and cardiogenic shock have been reported but these are uncommon (Kosmidis, 2010).These studies suggest close monitoring is mandatory in patients with poor general condition and pre-existing pulmonary and cardiac insufficiency (Waubant 2008). Caution is also required in patients that receive rituximab and other immunosuppressive therapies together to avoid progressive multifocal leukoencephalopathy (PML) mostly in patients with disorders characterised by proliferation of lymphoid tissue (lymphoproliferative disorders) (Carston et al.,2009).

There are few case reports of posterior reversible encephalopathy syndrome

(PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) in immunocompromised patients or patients receiving a combination of immunotherapy and/or chemotherapy. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The best available evidence related to children suggests that the rate of infectious complications in children treated with rituximab varies based on underlying diagnosis and was estimated to be 7.2% in children with autoimmune disorders (Kavcic et al., 2013).

4 Definitions

Autoimmune encephalitis (AE) is an acute inflammation of the brain resulting from body's own antibodies attacking brain tissue (e.g. neuronal cell-surface antigens such as extracellular epitopes of synaptic receptors) and impairing its function. It progresses rapidly into encephalopathy syndrome including altered mental status and a range of neurological and psychiatric symptoms.

NMDAR Receptor is a synaptic receptor composed of two glutamate-binding GluN2 (NR2) subunits and two glycine/D-serine-binding GluN1 (NR1) subunits. It is critically involved in normal neural network formation, synaptic plasticity, and higher brain functions such as learning and memory.

Relapse is defined as the new onset or worsening of symptoms occurring after at least 4 weeks of improvement or stabilisation.

Adverse event is any unwanted experience associated with the use of a medical product in a patient. It is usually classified using Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Ovarian Teratoma, also referred to as dermoid cyst of the ovary, is a tumour, usually benign and mature composed of tissues not normally present in the ovary, typically containing a diversity of tissues including hair, teeth, bone and thyroid.

Modified Rankin Scale (mRS) is a scale for measuring the degree of neurological disability or dependence in daily activities modified for use in paediatric disorders. The scale ranges from 0 to 6 (0 No symptoms at all; 1 No significant disability

despite symptoms: able to carry out all usual duties and activities; 2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3 Moderate disability: requiring some help, but able to walk without assistance; 4 Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 Severe disability: bedridden, incontinent, and requiring constant nursing care and attention; 6 Dead).

P (p-value) is the level of marginal significance within a statistical hypothesis test representing the probability of the occurrence of a given event. It helps determine the significance of the results.

Paraneoplastic refers to a syndrome or other systemic disturbance associated with but not directly related to a primary tumour or its metastases.

Progressive multifocal leukoencephalopathy (PML) is a rare condition caused by reactivation of a virus, occurring particularly when patients are very immunosuppressed, resulting in life threatening and often fatal brain inflammation

5 Aims and Objectives

This policy proposition considered NHS England's commissioning position for rituximab as second-line therapy for a well-defined cohort of patients with acute anti-NMDAR AE who have not or have inadequately responded to first-line immunotherapies.

The objectives are to:

- Provide an overview of the current evidence for use of rituximab in patients with acute anti-NMDAR autoimmune encephalitis to ensure evidence-based commissioning;
- Provide a rationale and propose criteria for commissioning of rituximab usage in paediatric and adult settings aiming at improving health and care outcomes.

6 Epidemiology and Needs Assessment

AE is a rare debilitating neurological disorder that represents a significant burden to patients, families and society (Graus et al., 2016). Anti-NMDAR AE is noted most often in young adults and children (Titulaer et al., 2013). The true incidence of AE is not known. Current evidence suggests that the incidence of anti-NMDAR encephalitis, the commonest type of AE accounting for approximately 27% of all Autoimmune Encephalitis cases (Hacohen et al., 2013).

0.85 per million children (aged under 18 years) per year (95% confidence interval 0.64 to 1.06) are estimated to have NMDAR AE (Wright et al., 2015). The paediatric presentation has been described as more 'neurological' than the more psychiatric presentation in adults (Titulaer et al., 2013). As such, it is estimated that there are approximately 11 children (range 8-13) diagnosed with acute anti-NMDAR encephalitis every year among 12.2 million children living in the UK.

It should be noted that these figures may underestimate the true incidence. Furthermore, some additional cases with anti-NMDAR AE emerge every year due to disease relapse occurring in 8% to 29% of patients (Zekeridou et al., 2015).

The majority of patients (approximately 80%) are young women with an estimated median age of onset of 21 years; however this ranges from 8 months to 85 years. (Dalmau et al., 2008; Dalmau et al., 2011)

In adults the proportion of paraneoplastic case varies (20.4 – 59.2%) but is higher than in paediatric cases (2.2 – 7.7%) (Dalmau et al., 2008; Nosardini et al., 2015 ;).

Approximately 44% of patients with anti NMDAR AE do not respond to first line therapy (Titulaer et al., 2013), thus are likely to need second-line therapy, although tumour removal may influence this response (39% with tumours fail first line therapy versus 48% without tumour).

Currently there are around 70 laboratory confirmed anti NMDAR AE cases annually based on the Oxford Autoimmune Neurology Group laboratory that process 60% of UK's requests.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of rituximab for the treatment of a well-defined cohort suffering from acute anti-NMDAR AE who have not or have inadequately responded to the first-line therapy by four weeks of treatment initiation OR within six symptomatic weeks.

Evidence summary

A total of 11 studies were considered in the evidence review which fit the selection criteria. These studies provide some evidence on the efficacy and safety of rituximab used as a second-line immunotherapy. Rituximab was used alone or in combination with other first and second line immunosuppressive therapies.

The retrospective observational multi-centre study of 144 children (Dale et al., 2014) provided the best available evidence for using rituximab in treatment of children with autoimmune and inflammatory CNS disorders. In the study, 87% of all patients and 97% of patients with anti-NMDAR encephalitis had some form of benefit from rituximab treatment used as second-line, especially when received early. 17% of patients had modified Rankin Scale (mRS) of 0-2 (considered to be a good neurological disability score) at rituximab initiation compared to 74% at outcome. The change in mRS 0-2 was greater in patients given rituximab early compared to those treated later. The study reported a total of three deaths (2%), of which two occurred due to infectious adverse event.

In addition, the large prospective cohort study of 577 all age patients (Titulaer et al., 2013) found that 78% of patients with anti-NMDAR encephalitis who failed first-line and received second-line immunotherapy (with rituximab and/or cyclophosphamide) had good outcome at 24 months, compared to 55% of patients who failed first-line and did not receive second-line therapy. Early treatment was associated with good outcome ($p<0.001$). Furthermore the use of immunotherapy ($p=0.038$) and use of second-line immunotherapy in patients without tumour ($p=0.007$) were associated with fewer relapses. Overall 30 of 501 patients died, including 6 of 177 children. At 24 months' follow-up, 10% mortality rate was estimated (24 deaths among 252

patients who were followed up at 24 months').

Rituximab used as second-line therapy was generally well tolerated with 2-3% of children reporting severe infusion and infectious adverse effects of grade 4 or more (Dale et al., 2014).

It should be noted that all studies (including the large cohorts) presented in the evidence review are low grade studies and have significant limitations that affect generalisability of results and their application in clinical practice. There are no studies that compare the effects of individual immunotherapies, thus it is not possible to ascribe therapeutic benefits solely to rituximab. Furthermore, it is unclear if patients with anti-NMDAR encephalitis are more likely to benefit, whether use of rituximab has any benefits over different second-line therapies such as cyclophosphamide, or at which stage of disease it should be used (acute, subacute or chronic).

Better quality evidence is needed to investigate the safety and efficacy of rituximab monotherapy in patients with autoimmune CNS disorders (and anti-NMDAR encephalitis in particular), to compare rituximab with other immunotherapies, to determine the most optimal dosage regimen and timing of rituximab therapy to yield maximum benefit, and to standardise diagnostics and safety monitoring.

8 Proposed Criteria for Commissioning

Employing Rituximab as a second line agent is a key immunotherapeutic strategy in the acute treatment of anti-NMDAR AE. Rituximab selectively targets B cells and provides sound biological basis for treatment of an antibody mediated disorder. Whilst other immunosuppression therapy is available for use as second line therapy in acute anti-NMDAR autoimmune encephalitis, their slow pace of response (e.g. mycophenolate) and side effects (e.g. cyclophosphamide) in children and adults limits their utility.

It is proposed to routinely commission rituximab for children and adults, including those with an identifiable tumour (e.g. ovarian teratoma) when all of the following

inclusion criteria have been met.

- Patients with a confirmed diagnosis of anti-NMDAR autoimmune encephalitis[1];
- Patients have had adequate first line immunotherapy e.g. intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIG), plasma exchange (PLEX) given either sequentially or in combination as detailed in the pathway figure on page 16
- Patients have failed or not responded adequately to first line immunotherapy, defined as deterioration of less than 2-point scale improvement in mRS and/or not attained a minimum score of 2 by four weeks of treatment initiation (usually within 6 weeks of symptom onset).
- For patients aged 18 years and younger, they must have been reviewed by a Consultant Paediatric Neurologist and managed within a tertiary paediatric neurology service.
- In patients aged over 18 years of age, the use of rituximab must be discussed with a regional adult neurologist with expertise in neuro-inflammation, but by agreement can be managed within a setting with experience of the use of rituximab.
- Patients aged 16-18 years of age can be treated in either the paediatric or adult pathway.

Rituximab should only be administered in an area where full resuscitation facilities and close monitoring are available; either in a day-case setting or in acute admissions wards depending on clinical requirements. A doctor should be present on the ward/unit while the infusion is commenced. The lowest acquisition cost of rituximab must be used.

Exclusion criteria:

Patients will be excluded from further treatment if they have had a severe life threatening infusion reaction to previous rituximab treatment, and or are considered by their clinician to be at higher risk due to contraindications as noted below.

[1] A diagnosis of definite or highly probably anti-NMDAR encephalitis based on the Graus criteria. A definite diagnosis can be made with a positive CSF and/or serum (definite) for NMDAR antibody.

Contraindications:

As per the drug company information on contraindications (see Summary of Product Characteristics).

Cautions:

- Patients with a history of cardiovascular disease or renal impairment should be appropriately reviewed prior to dosing
- Rituximab should be used carefully in patients with history of severe infections, particularly tuberculosis and viral hepatitis (particularly hepatitis B). Patient should have undergone specialist assessment and be on active treatment and have stable risk of infection prior to onset of rituximab therapy.
- The safety of vaccination, especially with live vaccines following treatment with rituximab is not known. Live vaccines are currently contraindicated post rituximab whilst B cells are depleted, and/or patients are on additional immunosuppressive therapy.
- Some patients may present with mono-symptomatic psychiatric presentations; and must meet the diagnosis of definite or highly probably anti-NMDAR encephalitis based on the Graus criteria

Dosage of rituximab:

Paediatric patients: 375mg/m2 (capped at 500mg) x 4 doses at weekly intervals

Adults: 1g x 2 doses two weeks apart.

Response to the treatment must be monitored by modified Rankin Scale (mRS) score and improvement of neurological syndrome. Depletion of B cells can be monitored by CD19/20 levels in peripheral blood if clinically indicated (e.g. stopping criteria).

A top up dose of rituximab during acute treatment in a patient who has not responded to one rituximab treatment course (from 4 weeks following completion of first treatment course) can be considered (Child: 375mg/m2 x2 doses at weekly intervals; Adult: 1g) if the patient has a higher clearance of rituximab which is

confirmed by demonstrating failure to achieve B cell depletion.

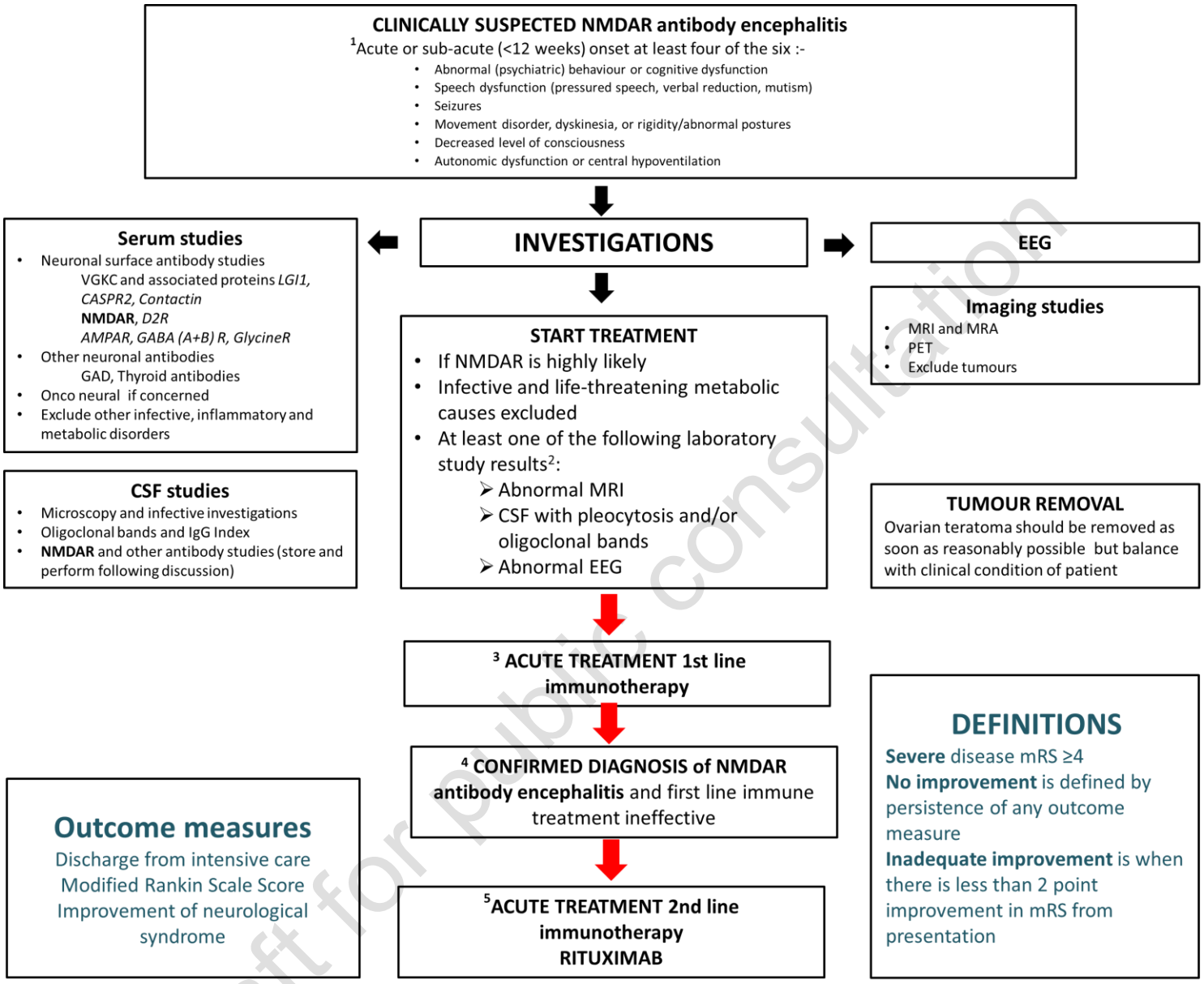
A subsequent treatment course of rituximab treatment, often termed **"re-dosing"** should only be considered in a patient that has relapsed[2] who has previously responded (improved ≥ 2 mRS) to the first course of rituximab treatment; and have undergone adequate 1st line treatment at relapse.

For patients with severe life threatening inflammation, rituximab may be used in combination with another second-line immunotherapy, usually cyclophosphamide, to provide urgent (faster speed of action) and broader (targeting more components of the immune system) treatment to reduce brain inflammation.

[2] Any recurrence of symptoms fulfilling the Graus clinical criteria following prior symptom remission

9 Proposed Patient Pathway

Figure 1



1. Proposal is based on Graus et al., 2016 ***Lancet Neurol.*** 15(4):391-404; supported by the largest cohort of 577 patients, where only 1% of patients had monosymptomatic disease during the first month of illnesss (Titulaer et al., 2013 Lancet Neurol12:157-65)
2. As CSF and MRI more likely to be normal in children; care need to be given using this criteria; and that some of the results may not be available at time of initiating treatment.
3. First line treatment involves oral or IV corticosteroids which may be supplemented with IVIG/PLEX depending on clinical policies and patient circumstances
4. Diagnosis is confirmed (**DEFINITE)** on identification of NMDAR antibodies in serum and/or CSF. In patients who have predominantly monophasic presentation or do not have the full clinical picture as proposed by Graus et al., 2016, CSF NMDAR positivity is required to confirm diagnosis (**highly PROBABLE).** Patients may be advised of support from the Encephalitis Society www.encephalitis.uk
5. Patients with **DEFINITE** and in some circumstance **highly PROBABLE** disease who continue to deteriorate, do not improve of have inadequate improvement needs to be considered for Rituximab.

10 Proposed Governance Arrangements

Rituximab will be available for paediatric cases following agreement by a Paediatric Neurology Consultant and treated in a tertiary paediatric neurology unit. The adult cases should be treated after discussion and approval by a regional adult neurologist with expertise in neuro-inflammation but by agreement can be managed within a setting with experience of the use of rituximab. Patients aged 16 – 18 may be treated either in the paediatric or adult pathway.

Any provider organisation treating patients with this intervention will be required to assure that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

11 Proposed Mechanism for Funding

From April 2013 the NHS England has been responsible for commissioning specialised services in line with published policy on behalf of the population of England.

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

12 Proposed Audit Requirements

All patients who receive rituximab for the treatment of AE must be entered onto an electronic patient registration system.

Rituximab treatment will be available through tertiary paediatric/adult neurology units that agree to audit and publish their results. This should include rates of adverse events related to the use of rituximab.

13 Documents That Have Informed This Policy Proposition

See Section 15 for references.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Armangue T, Moris G, Cantarín-Extremera V, Conde CE, Rostasy K, Erro ME, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015; 85: 1736–1743.

Brenton, J. N., Kim, J. & Schwartz, R. H. 2016. Approach to the management of pediatric-onset anti-n-methyl-d-aspartate (anti-nmda) receptor encephalitis: a case series. *J Child Neurol,* 31, 1150-5.

Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, Laubach J, Bawn SD, Gordon LI, Winter JN, Furman RR, Vose JM, Zelenetz AD, Mamtani R, Raisch DW, Dorshimer GW, Rosen ST, Muro K, Gottardi-Littell NR, Talley RL, Sartor O, Green D, Major EO, Bennett CL Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009 May 14; 113(20):4834-40.

Dale, R. C., Brilot, F., Duffy, l. V., Twilt, M., Waldman, A. T., Narula, S., Muscal, E., Deiva, K., Andersen, E., Eyre, M. R., Eleftheriou, D., Brogan, P. A., Kneen, R., Alper, G., Anlar, B., Wassmer, E., Heineman, K., Hemingway, C., Riney, C. J., Kornberg, A., Tardieu, M., Stocco, A., Banwell, B., Gorman, M. P., Benseler, S. M. & Lim, M. 2014. Utility and safety of rituximab in pediatric autoimmune and inflammatory cns disease. *Neurology,* 83, 142-150.

Josep Dalmau, Amy J Gleichman,* Ethan G Hughes,* Jeffrey E Rossi, Xiaoyu Peng, Meizan Lai, Scott K Dessain, Myrna R Rosenfeld, Rita Balice-Gordon, and David R Lynch 2008 Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies Lancet Neurol. Dec; 7(12): 1091–1098.

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M. R. & Balice-Gordon, R. 2011. Clinical experience and laboratory investigations in patients with anti-nmdar encephalitis. *The Lancet Neurology,* 10**,** 63-74.

Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7: 1091–1098.

Dalmau J, Tüzün E, Wu H-Y, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-

N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007; 61: 25–36.

Finke C, Prüss H, Heine J, Reuter S, Kopp UA, Wegner F, et al. Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies. JAMA Neurol 2017; 74: 50–59.

Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009; 66: 11–18.

Graus, f., Titulaer, M. J., Balu, R., Benseler, S., Bien, C. G., Cellucci, T., Cortese, I., Dale, R. C., Gelfand, J. M., Geschwind, M., Glaser, C. A., Honnorat, J., Höftberger, R., Iizuka, T., Irani, S. R., Lancaster, E., Leypoldt, F., Prüss, H., Rae-Grant, A., Reindl, M., Rosenfeld, M. R., Rostásy, K., Saiz, A., Venkatesan, A., Vincent, A., Wandinger, K.-P., Waters, P. & Dalmau, J. 2016. A clinical approach to diagnosis of autoimmune encephalitis. *The Lancet Neurology,* 15**,** 391-404. Gabilondo I, Saiz A, Galan L, Gonzalez V, Jadraque R, Sabater L, et al. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011; 77: 996–999.

Gong S, Zhou M, Shi G, Guo J, Chen N, Yang R, et al. Absence of NMDA receptor antibodies in patients with ovarian teratoma without encephalitis. Neurol Neuroimmunol Neuroinflamm 2017; 4: e344–2.

Granerod J, Ambrose HE, Davies N. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010; 10: 835–844.

Hacohen, Y., Wright, S., Waters, P., Agrawal, S., Carr, l., Cross, H., De sousa, C., Devile, C., Fallon, P., Gupta, R., Hedderly, T., Hughes, E., Kerr, T., Lascelles, k., lin, j. P., philip, s., pohl, k., Prabahkar, P., Smith, M., Williams, R., Clarke, A., Hemingway, C., Wassmer, E., Vincent, A. & Lim, M. J. 2013. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry,* 84**,** 748-55.

Irani S, Bera K, Waters P, Zuliani L, Maxwell S, Zandi M, Friese M, Kullman D, Beeson D, Lang B, Bien C and Vincent A. 2010. N-Methyl-D-aspartate antibody enchephalitis: temporalprogression of clicnical paraclinical observations in predominantly non-

praneoplastic dsiorder of both sexes *Brain133;1655-1667* Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010; 133: 1655–1667.

Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schneider SA, Pettingill P, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 2013; 136: 3151–3162.

Helen Barry, Susan Byrne, Elizabeth Barrett, Kieran C. Murphy,and David R. Cotter List, 2015, Anti-*N*-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment *BJPsych Bull* v.39(1); 2015 Feb

Kavcic, M., Fisher, B. T., Seif, A. E., Li, Y., Huang, Y.-S., Walker, D. & Aplenc, R. 2013. Leveraging administrative data to monitor rituximab use in 2875 patients at 42 freestanding children's hospitals across the united states. *J Pediatr,* 162**,** 1252-8.

Kosmidis,M., Practical considerations on the use of rituximab in autoimmune neurological disorders. 2010.Ther Adv Neurol Disord. Mar; 3(2): 93–105

Lee, W.-J., Lee, S.-T., Byun, J.-I., Sunwoo, J.-S., Kim, T.-J., Lim, J.-a., moon, j., lee, h. S., shin, y.-w., lee, k.-j., kim, s., jung, k.-h., jung, k.-y., chu, k. & lee, s. K. 2016. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. *Neurology,* 86**,** 1683-1691.

Nosadini, M., Mohammad, S. S., Ramanathan, S., Brilot, F. & Dale, R. C. 2015. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother,* 15**,** 1391-419.

Summary of Product Characteristics. Accessed April 2017: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

Shin Y-W, Lee S-T, Shin J-W, Moon J, Lim J-A, Byun J-I, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J. Neuroimmunol. 2013; 265: 75–81.

Titulaer, M. J., Mccracken, l., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., Honig, l. S., Benseler, S. M., Kawachi, I., Martinez-Hernandez, E., Aguilar, E., Gresa-Arribas, N., Ryan-Florance, N., Torrents, A., Saiz, A., Rosenfeld, M. R., Balice-Gordon, R., Graus, F. & Dalmau, J. 2013. Treatment and prognostic factors for long-term outcome in patients with anti-nmda receptor encephalitis: an observational cohort study. *The Lancet Neurology,* 12**,** 157-165.

Waubant E Review Spotlight on anti-CD20.Int MS J. 2008 Mar; 15(1):19-25.

Wright, S., Hacohen, Y., Jacobson, l., Agrawal, S., Gupta, R., Philip, S., Smith, M., Lim, M., Wassmer, E. & Vincent, A. 2015. N-methyl-d-aspartate receptor antibody-mediated neurological disease: results of a uk-based surveillance study in children. *Arch Dis Child,* 100**,** 521-6.

Zekeridou, A., Karantoni, E., Viaccoz, A., Ducray, F., Gitiaux, C., Villega, F., Deiva, K., Rogemond, V., Mathias, E., Picard, G., Tardieu, M., Antoine, J. C., Delattre, J. Y. & Honnorat, J. 2015. Treatment and outcome of children and adolescents with n-methyl-d-aspartate receptor encephalitis. *J Neurol,* 262**,** 1859-66.