**Rituximab in neurological disease: principles, evidence and practice**

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**Abstract**

**Rituximab is a widely used B-cell depleting monoclonal antibody. It is unlicensed in neurological disorders and treatment guidelines are lacking. However, as a rapidly acting, targeted therapy with growing evidence of efficacy and tolerability in several neuroinflammatory disorders, it is an attractive alternative to conventional immunomodulatory medications.**

**This practical review aims to explain the basic principles of B-cell depletion and therapeutic monoclonal antibodies. The evidence for rituximab in neurological diseases is presented, followed by the practical aspects of prescribing – dosing, monitoring, safety, treatment failure and use in special circumstances including co-existing viral hepatitis, pregnancy and lactation. An administration guide, checklist and patient information leaflet are provided, which can be adapted for local use. Finally, we review the safety data of rituximab and ocrelizumab (a newer and recently licensed B-cell depleting therapy for MS) and suggest monitoring and risk reduction strategies.**

**Introduction**

This article covers both the practical aspects of prescribing rituximab and some of the basic principles of B-cell depletion with monoclonal antibodies (mAbs). We briefly explain how rituximab compares to other B-cell depleting mAbs, which are relevant to neurologists. Those seeking a rapid overview of the indications and evidence for rituximab in specific disorders may wish to skip straight to table 1. Box 1 is a suggested administration guide; table 2 deals with adverse events and their management; and table 3 deals with specific prescribing circumstances, including pregnancy, breastfeeding and history of viral hepatitis. An example patient information sheet and an administration checklist are available as supplementary online material.

**B-cells – function and role in neurological disease**

B-cells secrete antibodies, present antigen and regulate the immune response by producing pro-inflammatory and anti-inflammatory cytokines. Only 2.5% of the total B-cell population is found within the peripheral circulation, made up predominantly of naïve mature B-cells and memory B-cells; the rest reside in bone marrow and lymphoid tissue.1 Antibodies may be of any immunoglobulin class (G, M, A, D or E) or subclass (e.g. IgG1-4), each of which have differing functions. Examples of disorders in which autoantibodies are almost certainly pathogenic include myasthenia gravis (MG) with acetylcholine receptor (AChR) antibodies (usually IgG1 or IgG3) or muscle-specific tyrosine kinase (MuSK) antibodies (IgG4), antibodies against the aquaporin-4 water channel in neuromyelitis optica spectrum disorders (NMOSD) (mainly IgG1) and antibodies to the N-methyl-D-aspartate receptor (NMDAR) (mainly IgG1) or leucine-rich glioma inactivated-1 (LGI1) (mainly IgG4) in autoimmune encephalitis. B-cells also play a crucial role in multiple sclerosis (MS) pathogenesis, evidenced by CSF oligoclonal IgG bands, meningeal-based ectopic B-cell follicles adjacent to areas of focal cortical demyelination2 and the efficacy of B-cell depleting therapies to treat MS.

**B-cell surface markers**

CD19 and CD20 are B-cell transmembrane proteins. They can be used as targets for drugs and as surface markers (in flow cytometry to quantify B-cell populations and assess treatment response). CD19 is expressed more widely throughout B-cell development than CD20 but both markers are absent on long-lived plasma cells (figure 1). In healthy adults CD19+ or CD20+ B-cells comprise 12-22% of the total circulating lymphocyte population (absolute reference range = 50-500 cells/mm3).

CD27 is expressed by memory B-cells and certain other immune cell types. The combination of CD19 and CD27 is specific to memory B-cells. This subset of long-lived B-cells, capable of rapid differentiation into high-affinity plasma cells following repeated antigen exposure, may be an important target in the treatment of autoimmune neurological disease.3 4

**B-cell depleting monoclonal antibodies**

Monoclonal antibodies (mAbs) are immunoglobulins produced by a single clone of plasma cells. They bind via their two identical Fab (fragment antigen binding) domains to a single epitope and activate the immune system via their Fc (fragment crystallisable) domain. Cells expressing that epitope are killed, therefore allowing highly targeted immunotherapy for a variety of neoplastic and autoimmune diseases. Available B-cell depleting mAbs have Fab domains targeted to CD20 or CD19, and so selectively deplete the circulating B-cell population, with the exception of mature antibody-secreting plasma cells. Those used in the treatment of neuroinflammatory diseases are shown in table 1.

Rituximab was the first anti-CD20 mAb to be approved in 1997 for the treatment of B-cell lymphomas. It has since been licensed to treat refractory rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Unlicensed use for neuroinflammatory disease is growing.

Rituximab is a first generation, chimeric mAb made by fusing a murine (rodent) Fab domain with a human Fc domain (‘chimeric’ is from the mythological *Chimera* – a monstrous fire-breathing hybrid creature, part lion and part goat). The Fc domain activates various immune mechanisms as shown in figure 2. 90% of circulating B-cells are killed within three days of infusion. Reduction of pathogenic antibody titres correlates with efficacy in some disorders. However, rituximab is likely to affect the whole spectrum of B-cell function, and secondary changes in T-cell function, such as induction of immunoregulatory T-cells, may be important in some neuroinflammatory disorders. Sparing of CD20negative long-lived plasma cells is hoped to preserve lasting humoral immunity.

In comparison to first generation mAbs, second generation mAbs have improved Fab domains, often humanized or fully human, which improves B-cell killing and tolerability (figure 3). Ocrelizumab (humanized) was recently approved to treat relapsing and progressive MS. Ofatumumab, a fully human mAb given by once monthly subcutaneous injection, is in clinical trials. Third generation mAbs have been further engineered to improve their Fc-mediated immune functions or half-life. Ublituximab (TG-1101), a rapidly infusible chimeric glycoengineered mAb, is also being trialled in MS currently.

Anti-CD19 B-cell depleting therapies may offer better efficacy (and potentially higher risks) than anti-CD20 therapies due to the broader expression of CD19 throughout B-cell development, including the plasmablast phase (figure 1). Inebilizumab (MEDI-551) is in a phase 3 trial in NMOSD.5

**Biosimilars**

Most mAbs are costly. However, once the original drug patent expires, cheaper, copy versions – ‘biosimilars’ – become available. Competing companies do not have access to the original molecular clone, cell bank or exact manufacturing process, which may result in slight differences to these complex molecular structures. Therefore biosimilars are not truly ‘generic’. To gain a licence, biosimilars must be shown to be highly similar in structure, purity and biological activity to the original mAb; however, repetition of clinical trials for each indication is not required. Rituximab’s patent expired in 2016 and two biosimilars, Truxima and Rixathon, have been approved by the European Medicines Agency. Dosing and administration protocols are identical. British National Formulary prices are currently £1746 for MabThera 1g (the original form of rituximab), versus £1572 for Truxima or Rixathon.6 However, prices to NHS hospitals vary substantially according to regional contracts and discussion with the hospital pharmacy department is advised. Patients should be informed of the switch and monitored to ensure that tolerability and side effects remain unchanged.

**Indications and evidence for rituximab in neurology**

An understanding of the evidence for rituximab in neuroinflammatory disorders should inform off-license prescribing (see table 1 for a briefer summary).

*Multiple sclerosis (MS)*

With a choice of licensed disease-modifying therapies (DMTs) supported by phase III randomised controlled trials (RCTs), use of rituximab in the UK for MS is rare. However, there is evidence suggesting efficacy, and it may be an option in occasional cases (especially if licensed co-morbidities, such as active RA, facilitate funding). Phase I and II trials of rituximab in relapsing remitting MS (RRMS) met their primary endpoints.7-9 A large 96-week multicentre RCT in primary progressive MS failed to demonstrate a delay to confirmed disease progression, but subgroup analysis showed a benefit in younger patients, particularly with inflammatory lesions.10 Trials in MS then ceased, probably due to the impending expiration of rituximab’s patent and the emergence of newer B-cell depleting therapies from the same manufacturer. Sweden is the biggest off-license prescriber of rituximab for all forms of MS and has published class IV evidence of safety and efficacy in a large multicentre cohort (n=822).11 The dose used is 500-1000mg 6-12 monthly. A recent real-word retrospective comparative study demonstrated efficacy in RRMS comparable to natalizumab and fingolimod, and significantly better than injectable DMTs and dimethyl fumarate. Rituximab was superior to all drugs in terms of discontinuation rate.12 Although this is relatively low quality evidence, there is a clear indication that rituximab is an efficacious therapy for MS, which would be expected in light of the recent positive RCTs for newer B-cell therapies.

*Neuromyelitis optica spectrum disorders (NMOSD)*

No immunosuppressive therapy in NMOSD is yet validated by a high quality RCT, though three RCTs are ongoing. Rituximab use is supported by numerous, predominantly retrospective, case series amounting to over 400 patients and demonstrating consistent reductions in annualised relapse rate (ARR). A variety of dosing strategies are in use, which are discussed later in ‘dosing and monitoring’. A recent meta-analysis calculated a mean reduction in relapse rate of 79%.13 As such, rituximab currently has the best evidence of any immunotherapy used in NMOSD, but due to the relatively high cost, it remains second-line therapy for patients in the UK. It is available for patients who have relapsed despite adequate treatment with azathioprine or mycophenolate mofetil in combination with low-dose prednisolone.14 Funding can be obtained through The Specialised NHS England Service for NMO ([www.nmouk.nhs.uk](http://www.nmouk.nhs.uk)).

*Autoimmune encephalitis (AIE)*

As most AIE is monophasic, Rituximab’s role is usually as a second-line acute therapy (single course) to maximise neurological recovery, rather than as a long-term maintenance treatment (as with MS/NMOSD). The weekly 375mg/m2 dosing regime is most commonly used. Limited retrospective evidence supports its use when there has been an inadequate response to intravenous corticosteroids, plasma exchange and intravenous immunoglobulin (IVIg). No evidence compares the effects of individual immunotherapies in AIE, so it is not possible to ascribe therapeutic benefits solely to rituximab. However, its rapid onset of action, established efficacy in other antibody-mediated diseases and good safety profile with short-term use make it an attractive option. The major study supporting rituximab use in AIE is a retrospective comparison of outcomes in 161 patients. Functional improvement measured by modified Rankin Scale (mRS) occurred more frequently in the rituximab-treated group, regardless of antibody status (p=0.001).15

Additional evidence exists specifically for anti-NMDAR encephalitis, which is the most common subtype of AIE. A large prospective cohort study (n = 577) found that 78% of patients who failed first-line and received second-line immunotherapy (rituximab and/or cyclophosphamide) had a good outcome at 24 months, compared to 55% of patients who failed first-line and did not receive second-line therapy.16 A study of rituximab in paediatric neuroinflammatory disease included 44 patients with anti-NMDAR encephalitis. 97% of these patients had some benefit from second-line rituximab therapy, especially when given early.17 In light of these studies, a UK clinical commissioning policy, published in March 2018, agreed to routinely fund rituximab for adult and paediatric patients with anti-NMDAR encephalitis that have an inadequate response to first-line therapy (failure to improve by two or more points on the mRS scale by four weeks from first-line treatment initiation or by six weeks from symptom onset).18

Evidence for AIE with less common antibodies is limited to case reports and small case series, which are frequently confounded by co-administration of multiple immunotherapies. For example, there are two case series reporting outcomes after rituximab in seven patients with anti-LGI1 encephalitis. Three patients (43%) had good outcomes and one patient had a possible response.19 20 The emerging theme in AIE, irrespective of antibody status, is that early and aggressive immunotherapy is beneficial. It seems plausible that rituximab, or similar B-cell depleting therapies, will increasingly form part of immunotherapy algorithms.

*Primary angiitis of the CNS (PACNS)*

High-dose corticosteroids with or without cyclophosphamide form the mainstay of treatment for this rare condition.21 Favourable outcomes with rituximab are reported in two small case series, in which 2/2 and 6/7 patients appeared to respond.22 23 There are additional case reports describing its use.24

*ANCA-associated vasculitis (AAV)*

AAV will occasionally present to the neurologist, for example with mononeuritis multiplex, but is likely to be co-managed with other vasculitis experts. Rituximab is licensed and recommended by recent European Guidelines for organ- or life-threatening disease.25 This follows two RCTs, in which rituximab (375mg/m2 weekly for four doses) was non-inferior to cyclophosphamide for remission induction.26 27 It may be more effective than cyclophosphamide for relapsing disease.27 NHS England will fund rituximab where cyclophosphamide has failed or is contra-indicated (e.g. patients who wish to preserve their reproductive potential).28

*Stiff person syndrome (SPS)*

Although some previous case reports suggested a possible benefit of rituximab for SPS,29-31 a single small double-blind RCT (n = 24) did not identify significant changes in any outcome measures six months post-rituximab.32

*Immune-mediated peripheral neuropathies*

A UK clinical commissioning policy, published in December 2017, reviewed the evidence for rituximab to treat chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), non-systemic vasculitic neuropathy (NSVN) and IgM paraprotein-associated demyelinating neuropathy with antibodies to myelin-associated glycoprotein (anti-MAG neuropathy). It concluded that there is insufficient evidence to make rituximab routinely available for these disorders.33 However, there may be circumstances, in which rituximab could be beneficial, as discussed below. Most studies have used 375mg/m2 weekly for four weeks.

Rituximab has been used in CIDP following inadequate response to conventional therapy (corticosteroids, IVIg and plasma exchange). A Cochrane review (2013) identified 17 published CIDP cases treated with rituximab, of which 12 (71%) improved after treatment.34 The largest series has ten patients, of whom six (60%) improved.35 In a multicentre retrospective analysis, 18/110 (16.4%) refractory CIDP cases received rituximab. The response rate (improvement in mRS by at least one point) was 33% – comparable to Azathioprine or Cyclophosphamide.36 Recently, marked improvement following rituximab in CIDP patients with IgG4 antibodies against paranodal proteins (anti-neurofascin155/CNTN1) has been reported. These cases account for less than 10% of all CIDP patients but they are often relatively resistant to IVIg and corticosteroids, highlighting the importance of serological testing and suggesting a potential role for rituximab in a subset of CIDP patients that needs further exploration.37 38

Data for rituximab in multifocal motor neuropathy is limited to small case series and is conflicting. IVIg is the mainstay of therapy. When rituximab was used as monotherapy in seven patients in two separate observational studies, all showed some improvement in muscle power.39 40 When given as an adjunct to IVIg in a small open-label trial (n=6), there was no significant change motor function or IVIg dose required.41 In two further cases, one patient reduced and one increased their IVIg requirement.42

NSVN is a peripheral nerve vasculitis in the absence of clinical or laboratory evidence of systemic vasculitis. The Peripheral Nerve Society Guideline (2010) lists rituximab as an unproven treatment option, favouring high-dose corticosteroids and escalation to cyclophosphamide if needed.43 Rituximab could possibly be considered on an individual funding basis in refractory NSVN patients, on the basis of its efficacy in AAV.44

Two placebo-controlled trials of rituximab for anti-MAG neuropathy showed marginal benefits. In the first study, 4/13 (31%) rituximab-treated patients improved by one or more Inflammatory Neuropathy Course and Treatment (INCAT) score compared with 0/13 placebo-treated patients (p=0.036).45 In the second study (n=54), there was no significant difference in the absolute INCAT sensory score between the groups (negative primary outcome), but the number of patients with improvement in INCAT disability score was higher in the rituximab-treated group (p=0.027).46 Several prospective observational studies report improvements in roughly half to two thirds of patients.47-50

*Myasthenia gravis (MG)*

International Consensus Guidelines (2016) advise that “rituximab should be considered as an early therapeutic option in patients with MuSK-MG who have an unsatisfactory response to initial immunotherapy”.51 A formal consensus could not be reached for AChR-MG. Several, predominantly retrospective, observational studies and two systematic reviews have investigated rituximab as an acute therapy (usually a single course with variable dosing) for refractory MG (persistent weakness or need for high dose corticosteroids despite conventional immunosuppression).

Despite many case series being shared between the systematic reviews, the reported response rates in AChR-MG are discordant, with 30-80% of patients achieving a Myasthenia Gravis Foundation of America post-intervention status (MGFA-PIS) of ‘minimal manifestations or better’ following rituximab. 52 53 This may be explained by variability in patient selection, inclusion of many ‘burnt out’, unresponsive cases and inclusion of cases where MGFA-PIS was not used as an outcome measure in the original report. Response did not correlate well with AChR antibody titres.53 Two ongoing RCTs may help to better define rituximab’s role in AChR-MG in the near future.

In comparison, response rates in MuSK-MG were high (72-89%) in both reviews.52 53 A further blinded prospective review found 67% of rituximab-treated patients obtained MGFA-PIS of ‘minimal manifestations or better’ versus 26% of controls.54 The benefit of rituximab in MuSK-MG appears to be more prolonged and correlates better with antibody titres.53 55 MuSK antibodies are of the IgG4 subtype whereas AChR antibodies are of the IgG1/3 subtype. The superior efficacy of rituximab may therefore be explained by selective depletion of short-lived IgG4-producing B-cells.55

**Table 1: Indications for rituximab in neurology**

|  |  |  |  |
| --- | --- | --- | --- |
| **Disorder** | **Indication** | **Summary of best evidence** | **UK usage and funding** |
| Relapsing remitting multiple sclerosis | Maintenance therapy for relapse prevention | Positive phase I and II trials and large real-world retrospective studies in Sweden suggesting good efficacy, safety and tolerability.7-12  | Rarely used in UK as there are several licensed DMTs. No established funding pathway. |
| Neuromyelitis optica spectrum disorders | Maintenance therapy for relapse prevention | Predominantly retrospective case series (of more than 400 patients in total), which consistently show a marked benefit.13 | Second-line therapy for patients that relapse despite adequate treatment with azathioprine or mycophenolate mofetil in combination with low dose prednisolone.14 Funded through the UK NMO Service ([www.nmouk.nhs.uk](http://www.nmouk.nhs.uk)).  |
| Autoimmune encephalitis (other than anti-NMDAR) | Acute therapy | One large retrospective study and several case reports suggest a benefit but there are no comparative studies of individual immunotherapies.15 | Consider if there is inadequate response to first line therapy. Funding is via IPFR to NHSE or through local Trust resources. |
| Anti-NMDAR encephalitis | Acute therapy | Three retrospective studies suggest a benefit but there are no comparative studies of individual immunotherapies.15-17 | Commissioned by NHSE as second-line therapy if there is inadequate response to corticosteroids, plasma exchange and IVIg by four weeks from first-line treatment initiation or by six weeks from symptom onset.18  |
| Primary angiitis of the CNS | Acute therapy  | Small case series (approximately ten patients in total).22-24 | Consider if there is inadequate response to corticosteroids and cyclophosphamide. Funding is via IPFR to NHSE or through local Trust resources. |
| ANCA-associated vasculitis | Remission induction and relapsing disease | Two RCTs have demonstrated non-inferiority to cyclophosphamide for remission induction.26 27 | Licensed and recommended by NICE in combination with corticosteroids as an option for inducing remission of severe disease, when cyclophosphamide has failed, is contra-indicated or the patient has not completed their family.28  |
| Stiff person syndrome | Treatment of refractory disease | Case reports suggested a possible benefit but a single small RCT was negative.29-32 | May consider if there is inadequate response to first line therapy. Funding is via IPFR to NHSE or through local Trust resources. |
| Immune-mediated peripheral neuropathies | Treatment of refractory disease | Mostly small retrospective series in which benefits are modest.34-50 An uncommon subset of CIDP patients with antibodies to paranodal proteins may benefit more so (case reports).37 38 Two small RCTs in anti-MAG neuropathy showed marginal benefits.45 46  | NHSE will not routinely commission rituximab for refractory CIDP, MMN, NSVN or anti-MAG neuropathy.33 May consider in exceptional circumstances, particularly in IgG4-mediated disease. Funding is via IPFR to NHSE or through local Trust resources.  |
| Myasthenia gravis | Treatment of refractory disease | Mostly small retrospective case series. Evidence of benefit is much clearer in MuSK-MG than AChR-MG. Clinical trials in AChR-MG are ongoing.  | Consider if there is inadequate response to first line therapy, particularly in MuSK-MG. Funding is via IPFR to NHSE or through local Trust resources. |

**Abbreviations:** DMTs = disease modifying therapies, IPFR = individual patient funding request, NHSE =National Health Service England, NICE = National Institute for Health and Care Excellence, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy, NSVN = non-systemic vasculitic neuropathy.

**Dosing and monitoring of rituximab**

Rituximab is given by intravenous infusion over 3-6 hours. There is no validated dosing strategy for neuroinflammatory disease and there is great heterogeneity in the literature. Box 1 is a suggested administration guide. The two most common dosing regimens are, either 375mg/m2 body surface area given once weekly for four weeks (adopted from haemato-oncology), or two infusions of 500-1000mg given a fortnight apart (adopted from clinical trials in rheumatoid arthritis). Following two 1000mg infusions, the mean half-life of rituximab is 20.8 days (range 8.58 to 35.9 days).56

In RA there is no significant difference in the clinical responses after high dose (2 x 1000mg) and lower dose (2 x 500mg) rituximab regimes.57 The clinical response correlates with the degree of B-cell depletion, not the rituximab dose used.58 The same is likely to be true in neuroinflammatory disease. Doses as low as 100mg weekly for 3-4 weeks have been used successfully in small series of patients with MS, NMOSD and anti-NMDAR encephalitis.59-62

Near complete B-cell depletion occurs within a fortnight of infusion and usually persists for 6-12 months. Therefore, where maintenance treatment is planned, repeated courses have commonly been administered at regular 6-monthly intervals. However, patients vary significantly in both the initial rituximab dose required to achieve B-cell depletion and the time to B-cell repopulation. In a study of NMOSD patients, 17% repopulated their B-cells before six months.63 Prolonged B-cell depletion lasting over three years following a single dose of rituximab is also reported.64 This makes a case for monitoring and retreating according to B-cell repopulation, which will identify ‘early repopulators’ at risk of disease relapse, and limit over-treatment of patients with sustained B-cell depletion, thereby preventing complications and reducing cost.

Although rituximab is an anti-CD20 antibody, quantification CD19+ cells using flow cytometry is the preferred method for monitoring B-cell depletion and repopulation. This is because rituximab still present in serum could block binding of fluorophore-labelled anti-CD20 antibodies used in flow cytometry, thereby interfering with the detection of B-cells.

Amongst the several relapsing illness that may benefit from rituximab, relapses from NMOSD pose the highest risk of permanent disability. However the critical threshold of B-cells in the measurable peripheral circulation that is associated with NMOSD relapse is undetermined and is likely to vary with the disease and individual. Neurologists have retreated when the CD19+ B-cell count becomes detectable65 or greater than 0.1% of total circulating lymphocyte count.66 Some measure the much smaller memory B-cell (CD19+/CD27+) population (see box 1 – option 2).4 67 Switching from 6-monthly infusions to memory B-cell-monitored treatment reduces cumulative rituximab dose without apparent loss of efficacy.68 However, standardisation of flow cytometry techniques and inaccuracy when quantifying very small cell populations can pose problems.69 In the UK NMO Service we use monthly CD19+ B-cell monitoring and have found 1% (an arbitrary value based on clinician experience) to be an acceptable cut-off for retreatment for the majority of patients.70 In those who relapse with a detectable B-cell count below 1%, retreatment aiming for complete suppression is suggested before considering treatment failure and switching immunotherapy.

**Box 1: Rituximab administration guide***Italicised points reflect our personal practice rather than established recommendations.*

**Prior to first infusion:**
Exclude contra-indications: Hypersensitivity to rituximab / murine proteins
 Active, severe infection (e.g. TB, sepsis, opportunistic infections)
 Severe immunocompromised state \*
 Severe heart failure or uncontrolled cardiac disease

Discuss risks and benefits, obtain consent (see example patient information sheet in supplementary online material)

Baseline investigations in all patients both emergency and elective:
- Full blood count, liver function tests and immunoglobulin levels \*\*
- HBV serology (HBVsAg + HBVcAb)– if positive, seek expert opinion and start prophylaxis before rituximab treatment
*- HCV and HIV serology*

In elective non-emergency use, and particularly when maintenance therapy is planned:

- Discuss contraception
- *Test for latent TB in high-risk groups (QuantiFERON-TB Gold or tuberculin skin testing, followed by chest radiograph if indicated).
- VZV serology if there is no history of primary infection.*

- Take immunisation history and give necessary non-live vaccines > 4weeks (and live vaccines >8 weeks) prior to first infusion.
*- In uncertain cases, titres could be obtained for important vaccines.*

*- We recommend Pneumococcal vaccine, preferably pre-treatment, for all patients if possible.*

\* CD3, CD4, CD8, CD19 and CD20 cell counts can be assessed and discussed with immunology when concerned.

\*\* Subnormal immunoglobulin levels do not preclude treatment

**On the day of infusion:**
Clinical assessment to exclude active infection
*Pregnancy test if appropriate
If possible, withhold antihypertensive medications that morning*

**Administration:**1000mg on day 1 and day 15 (**or** 375mg/m2 body surface area weekly for 4 weeks)
Give IV Methylprednisolone 100mg prior to infusion *(may consider omitting if already taking high-dose glucocorticoids)*

**If re-treatment is planned (usually for relapsing disease):**

**Option 1\***Monitor B-cell count (CD19+ cells) monthly. Retreat with single 1g infusion when it rises above 1%.

**Option 2\*\***Monitor memory B-cell population (CD19+/CD27+ cells) 6-weekly in first year, 8-weekly in second year, 10-weekly thereafter.
Retreat when it rises above 0.05% in the first 2 years and 0.1% thereafter.

**Option 3 (if B-cell monitoring is not possible or practical):**Repeat infusions at 6 months with further 1-2g.

\*UK NMO Service practice (adapted from 63). For repeated treatment cycles, we have found that giving a single 1g infusion is sufficient to maintain B-cell depletion and clinical outcomes in the majority of cases.

\*\* Regime developed for NMOSD maintenance therapy 4 67 – requires monitoring a very small subset of B-cell population. Discuss with local laboratory regarding feasibility and cost.

**Prior to subsequent infusions:**
Clinical assessment to exclude active infection  *Pregnancy test if appropriate*

*We perform baseline full blood count. We check immunoglobulin levels if there is history of recurrent infection, or in high risk patients for secondary antibody deficiency (including low baseline IgG, previous immunosuppression, combination therapy).
Retest as above if risk of exposure to viral hepatitis or TB*

**Abbreviations:** HBV = hepatitis B virus, HBVsAg = hepatitis B virus surface antigen, HBVcAb = hepatitis B virus core antibody, HCV = hepatitis C virus.

**Treatment failure**

Where treatment failure is suspected, we advise excluding alternative possibilities, such as intercurrent infection, and ensuring that B-cell depletion is adequate by checking a peripheral blood CD19+ B-cell count. Possible reasons for treatment failure include:

*Lack of efficacy of B-cell depletion*

In a large NMOSD cohort (n=100), nine patients (9%) experienced relapses despite CD19+/CD27+ memory B-cell depletion within target range.71 NMOSD relapses occurring on rituximab are generally milder than those occurring off treatment. Non-circulating B-cells (i.e. the majority of the total body B-cell population) and long-lived plasma cells are not thought to be depleted by rituximab and may have a role in breakthrough disease.

*Early relapses / delayed therapeutic onset*

Early NMOSD relapses have been reported following rituximab induction therapy.4 72 73 This may be due to incomplete B-cell depletion, or release of systemic B-cell activating factor (BAFF) induced by B-cell depletion, may promote autoantibody production by plasma cells, leading to transient rise in antibody titre and early relapses.74

*Incomplete B-cell depletion / early repopulators*

Genetic factors may explain why some patients do not maintain adequate B-cell depletion. These include polymorphisms in the BAFF gene or in the Fc gamma receptor 3A gene expressed by the effector cells that mediate B-cell killing.71 75 Another hypothetical reason might be the development of anti-drug antibodies.

*Anti-drug antibodies (ADA)*

The efficacy of some mAbs is reduced by ADAs, (e.g. anti-tumour necrosis factor agents). Fab fragment binding could have a neutralising effect and Fc fragment binding may increase drug clearance. However, the role of ADA in rituximab treatment failure is uncertain. ADA were identified in a third of MS patients treated with rituximab.76 They may have a greater effect in patients on low dose rituximab (100mg infusions) but higher, standard doses probably overcome the effects of ADAs.76 77 Outside of trials, ADA detection can be technically difficult, poorly standardised and is hard to obtain for routine use.

**Combination with other immunosuppressive medications**

Due to the risk of early relapse after rituximab initiation, we continue moderate-dose Prednisolone (usually 10-20mg daily) for 4-12 weeks. Thereafter, the decision to continue corticosteroids depends on the condition being treated and individual patient factors.

Combination with other immunosuppressive medications can be considered in some circumstances but must be balanced against the risk of immunocompromise. We generally reserve combination therapy for refractory disease. In the treatment of RA, rituximab is often combined with methotrexate or leflonumide but there is a paucity of evidence to guide practice in neuroinflammatory disease.

**Risks and adverse events**

The efficacy of rituximab and current safety data appear to support its use, and the longer term safety profile will become clearer with increasing use of B-cell depleting therapies like ocrelizumab. Tables 2 and 3 summarise the approach to adverse events and special prescribing circumstances. *Italicised* points denote personal practice, rather than established recommendations.

Rituximab’s relatively favourable safety profile is likely due to preservation of antibody production by CD20negative long-lived plasma cells. However, it remains uncertain whether long-term humoral immunity results entirely from these self-sustaining cells or whether replenishment of plasma cells by memory B-cells is required. Several studies have reported secondary antibody deficiency complicating rituximab therapy – a risk that appears to increase with repeated courses and lower pre-treatment levels of immunoglobulins.67 78-80 Not all patients with hypogammaglobulinaemia develop infections, but we recently reported a series of serious sino-pulmonary infections associated with hypogammaglobulinaemia occurring in NMOSD patients on long term rituximab.81 All patients had prior exposure to immunosuppressant medications. This has led to changes in our practice, with greater focus on pre-treatment vaccinations, B-cell monitoring to limit cumulative rituximab dose and targeted use of immunoglobulin replacement therapy (IVIg) to mitigate infection risk in selected patients (see box 1, table 2 and box 2). Monthly IVIg appears effective in preventing sino-pulmonary infections but carries a burden in terms of cost and patient experience.

**Table 2: Rituximab treatment risks and management**

Unless a separate reference is given, information is adapted from Mabthera SmPC, experience from RA.56 *Italicised points reflect personal practice rather than established recommendations.*

|  |  |  |
| --- | --- | --- |
| **Risk** | **Description** | **Recommended management** |
| **Infusion reactions** | The highest risk is with the first infusion (~30%). Most reactions are mild (headache, pruritis, throat irritation, flushing, rash, urticaria, pyrexia, hypo-/hypertension).Severe or life-threatening anaphylactoid infusion reactions leading to drug discontinuation are uncommon (<1/100 cases). Pre-treatment with corticosteroids reduces the frequency and severity of reactions.  | *If possible, withhold antihypertensive medications on the morning of the infusion.*Adhere to manufacturers’ advice regarding infusion rates. Unless contra-indicated, administer IV methylprednisolone 100mg prior to the infusion.Manage mild reactions with interruption or slowing of infusion, paracetamol and antihistamine. Restart infusion at a reduced rate once symptoms resolve. Manage severe reactions as per the Advanced Life Support algorithm. Have necessary equipment and medications available.  |
| **Mucocutaneous reactions** | Severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have very rarely been reported following rituximab infusion, some with fatal outcome (<1/10,000 cases).  | Do not re-treat with rituximab if patients develop a severe skin reaction. |
| **Adverse cardiac events** | Rituximab is not directly cardiotoxic but angina pectoris, arrhythmias and heart failure have been rarely reported (<1/1,000 cases). | Consider alternative treatment options in patients with severe uncontrolled cardiac disease. Manufacturers recommend ‘close monitoring’ of those with known cardiac disease.  |
| **Infections** | Most infections are mild to moderate, consisting of upper respiratory tract and urinary tract infections (very common, >1/10 cases). Bronchitis, sinusitis and gastroenteritis occur in 1/100-1/10 cases. Serious opportunistic infections are rare, including reactivation of hepatitis B. Hypogammaglobulinaemia and neutropenia may contribute to infection risk in some cases (see below). | Do not give rituximab to patients with active infection. Ask and counsel patients regarding infection or risk of infection.*We recommend annual influenza vaccine and 5-yearly pneumococcal vaccine throughout treatment.*See notes in table 3 regarding specific infectious risks: Hepatitis B, C and tuberculosis. |
| **Secondary antibody deficiency** | Decreased IgM levels are very common; decreased IgG levels are common. Hypogammaglobulinaemia seems to be time and dose-dependent.78 79 Prior exposure to immunosuppressant drugs may be an additional risk factor. 81 82 Patients with low IgG are at risk of infection, particularly recurrent bacterial sino-pulmonary infections, but risk does not correlate directly with IgG level.78 81 Patients with low baseline IgG levels are at particular risk of infection.80 | *Check baseline total serum immunoglobulin levels prior to starting rituximab. Be aware of higher infection risk in patients with low IgG and consider alternative options.**Recheck serum Ig in the context of severe or recurrent infections. See box 2 for approach to symptomatic secondary antibody deficiency.**Consider checking IgG levels in patients with a prior history of immunosuppressive medication use prior to re-treatment with rituximab.* |
| **Neutropenia** | May occur after first or subsequent infusions. The highest risk is 3-6 months post-infusion. Prevalence of 1.3-2.3% when rituximab is given for autoimmune indications;83 reported in MS and NMOSD.84-86 The severity and duration of neutropenia is unpredictable. Many cases are asymptomatic and self-limiting but grade IV neutropenia (<0.5/109/L) with severe infection is rarely reported.  | Check full blood count prior to administering rituximab and upon symptoms or signs of infection. *Observe cases of asymptomatic mild neutropenia. G-CSF has been used to hasten recovery in grade IV neutropenia or sepsis.86*Though it may recur, neutropenia is not a contraindication to ongoing rituximab therapy - several case series support ongoing use in autoimmune disease.83 85-87 |
|  **PML** | Rituximab may increase risk of PML in individuals already at risk due to pre-existing conditions or immunosuppression.Risk is estimated at 1 in 30,000 cases exposed to rituximab.88 No cases have yet been described when rituximab is used alone to treat neuroinflammatory disease. | Discuss PML risk during consent process.JCV antibody titres do not have an established role in rituximab use.*MRI if suggestive clinical features develop.* |
|  **PRES** | Described following rituximab administration in NMOSD and non-neurological indications. Prevalence of 0.5% in a large cohort of NMOSD patients.13 | *MRI if suggestive clinical features develop.* |
| **Malignancy** | No increased risk identified. |  |

**Abbreviations:** G-CSF = granulocyte colony stimulating factor, PML = progressive multifocal leukoencephalopathy, JCV = John Cunningham virus, PRES = posterior reversible encephalopathy syndrome.

**Table 3: Other considerations and special circumstances when prescribing rituximab**

*Italicised points reflect personal practice rather than established recommendations.*

|  |  |  |
| --- | --- | --- |
| **Circumstance** | **Known risks** | **Recommended management** |
| **Pregnancy** | The safety of B-cell depleting biologic therapies is not fully known. In 153 exposed pregnancies, rates of miscarriage and congenital malformation were similar to expected rates in the general population.89Placental transfer of immunoglobulins (including rituximab) occurs from the second trimester onwards. Exposure during organogenesis is therefore likely to be very limited. Exposure in later pregnancy has resulted in neonatal B-cell depletion, which recovered in 3-6months.89 | Effective contraception (in both sexes) is advised by manufacturers during and for 12 months after treatment.6 56 Avoid in pregnancy unless potential benefit to the mother outweighs risk of B-cell depletion in the foetus 6 56 (see text section ‘risks and adverse effects’ for further discussion).Live vaccines should not be given to exposed babies for the first six months of life. *We counsel women prior to initiation on rituximab and perform a pregnancy test before each infusion.* |
| **Breastfeeding** | There are no studies formally assessing safety of rituximab during lactation. As a large molecule, it is unlikely to transfer to breastmilk in any significant amounts. The exception to this is the first 3 days post-partum when gaps between breast alveolar cells are larger and transfer of immunoglobulins is possible. Rituximab exhibits poor gastrointestinal absorption and is likely be destroyed in the baby’s gut.90 | Despite apparent low risks there is still insufficient evidence to guarantee safety. Manufacturer advise that women avoid breastfeeding during and for 12 months after treatment.6 56 *We counsel mothers and support their decision if they choose to breast feed.* |
| **Existing cardiac disease** | Severe cardiac disease is a contraindication to rituximab when used for RA or AAV (but not lymphoma) due to a higher risk of myocardial infarction, arrhythmia or decompensating severe heart failure.  | Consider alternative treatment options in patients with severe uncontrolled cardiac disease. |
| **Previous hepatitis B virus (HBV) infection** | **Risk of HBV reactivation post-rituximab is well described and includes fatal cases of fulminant hepatitis**.91 Reactivation can occur in both HBVsAg-positive and HBVsAg-negative HBVcAb-positive individuals (“reverse seroconversion”).91 | **Do not give rituximab to patients with active HBV hepatitis. Test HBVsAg, HBVcAb and liver function tests in all patients prior to starting rituximab**.91Refer those with positive serology to a specialist for prophylactic antiviral therapy, which must be continued for the duration of therapy. Monitor these patients with serial HBV DNA titres, liver function tests and HBVsAg (if HBVsAg-negative at baseline).92 |
| **Previous hepatitis C virus (HCV) infection** | Information is conflicting but reactivation of HCV seems to be much less common than HBV. Increases in HCV RNA load and hepatic flares are reported, but many cases are confounded by additional immunosuppressive / hepatotoxic medications.93 94 | *We recommend screening for HCV antibody prior to starting treatment. Positivity is not a contra-indication to Rituximab but we suggest such patients should be jointly managed with hepatology and monitored for HCV activity (HCV RNA titres and liver function tests).* |
| **Previous / latent tuberculosis (TB)** | Risk of TB reactivation after rituximab appears negligible,95 though co-administration with glucocorticoids may contribute additional risk. | Do not give rituximab in cases of active TB.*Although routine TB screening may be unnecessary,96 we screen for latent TB with QuantiFERON-TB Gold or tuberculin skin testing in high risk patients (e.g. from endemic regions).*  |
| **Vaccinations** | There is a theoretical risk that live vaccines (e.g. yellow fever, varicella zoster) may cause infection.Other standard inactivated vaccines are safe but they may be less effective after receiving rituximab.97 98 | Where possible give all routine vaccinations at least 4 weeks prior to initiating rituximab (and at least 8 weeks prior for live vaccines).56 96 Do not give live vaccines to patients treated with rituximab. *We recommend annual influenza vaccine and 5-yearly pneumococcal vaccine throughout treatment.* |

**Abbreviations:** RA = rheumatoid arthritis, AAV = ANCA-associated vasculitis, HBVsAg = hepatitis B virus surface antigen, HBVcAb = hepatitis B virus core antibody

**Box 2: Approach to managing symptomatic secondary antibody deficiency**

**This advice is appropriate for patients satisfying all three of the following criteria:**

1. Maintenance rituximab therapy
2. Serious or recurrent (particularly respiratory) infections
3. Total serum IgG < 6.0g/L

**Suggested management to mitigate infection risk *(we advise liaising with local immunology service)*:**

1. Check disease-specific circulating antibody titres against *Haemophilus influenzae* (Hib), *Clostridium tetani*
and Pneumococcal capsular polysaccharide.
2. If titres are below protective cut-off levels (Hib > 1mcg/ml, tetanus >0.1IU/ml, pneumococcus >50mg/L),99
vaccinate patient and retest titres after 6 weeks.
3. If titres remain below protective cut-off levels, then a therapeutic trial of replacement IV immunoglobulin (IVIg)
is warranted.100 \*
- Dosage should be initiated at 0.4-0.6g/kg/month
- Aim to replenish within normal range (6-16g/L)
4. Assess clinical response to replacement IVIg after 6 months (burden of infections\*\*) and consider the need for
long-term treatment.

*\*Demonstration of functional immune deficiency – i.e. failure to mount an adequate response to test vaccination – is a requirement for initiating IVIg replacement therapy.100*

*\*\*Please note that replacement IVIg therapy is unlikely to reduce the frequency of urinary tract infections.*

**Pregnancy and breastfeeding**

Rituximab crosses the placenta after 20 weeks gestation. Although not known for certain, the existing evidence suggests that rituximab is possibly safe for use during early pregnancy (see table 3).89 The prolonged B-cell depleting effect (often greater than the 40 weeks of gestation) can be used advantageously. For example in planned pregnancies, rituximab could be administered prior to conception and after delivery, sparing the gestating foetus from B-cell depletion.

In relapsing conditions with high morbidity, such as NMOSD, the risk of relapse during protracted interruption of rituximab therapy for conception and pregnancy is a dilemma for many women. A recent expert review suggests that two doses of 1000mg could be administered as close as one month prior to planned conception in the hope that B-cell depletion will persist for the duration of pregnancy. They advise that rituximab could be resumed in the first week after delivery given the very high post-partum risk of NMOSD relapse.101 However, women should be counselled regards the limited data on rituximab-exposed pregnancies.102

**Ocrelizumab**

While this is review is primarily intended to cover rituximab, it may be remiss not to discuss ocrelizumab, as this is the first anti-CD20 therapy to gain a licence (FDA, EMA) for a neurological indication (MS). Ocrelizumab has been in development for more than a decade but its progress in rheumatoid arthritis was halted in 2010 after data from multiple phase III trials suggested an excess of serious infections and a poor benefit-risk profile when combined with methotrexate. However, trials in MS continued and it was licensed in The United States in March 2017 and in Europe in January 2018. The European license is for treatment of active relapsing MS and early primary progressive MS with imaging features of inflammatory activity. Recent phase III RCTs demonstrated that ocrelizumab reduced annualised relapse rates versus interferon beta-1a in relapsing MS (OPERA I and II), and reduced 12-week confirmed disability progression versus placebo in primary progressive MS (ORATORIO). 103 104 The trials used a fixed dosing schedule over two years of follow-up. The safety profile appeared favourable. Infusion reactions were frequent but rarely problematic. Upper respiratory tract infections were more common after ocrelizumab but there was no excess of serious or opportunistic infections. Ocrelizumab was associated with low total serum IgM in 16% of patients, but no increased infection risk was observed in these patients. There was no reduction in total serum IgG or disease-specific antibody titres over the 2-year follow-up period. An increased risk of malignancies (including breast cancer) was observed in the ocrelizumab trial arms but the incidence was within the background rate expected for an MS population. 103 104

Ocrelizumab has been licensed as a fixed 6-monthly dosing regimen with no specific immune function monitoring, despite the fact that considerable inter-individual variation is observed in time-to-repopulation of B-cells following ocrelizumab.105 The experience of ocrelizumab in clinical trials may seem inconsistent with our and others real-world experience of rituximab, in which we have observed the coexistence of secondary antibody deficiency and increased rate of infections in NMOSD patients on maintenance therapy.78-81 We postulate that this may relate to a degree of baseline immune dysfunction caused by prior immunosuppressive medication and a longer treatment duration than is recorded in the pivotal ocrelizumab studies. This echoes experience in vasculitis, where previous immunosuppressive therapy (particularly cyclophosphamide) has been identified as a risk factor for greater decline in immunoglobulin levels and more prolonged B-cell depletion post-rituximab.25 82 In contrast, the vast majority of patients recruited to OPERA I and II were treatment-naïve or had used non-immunosuppressive DMTs. Safety information on ocrelizumab from post-marketing surveillance will be useful to further inform risk and to guide whether flexible dosing may become preferable in certain situations. Sequential treatment effects following high efficacy DMTs are also yet to be explored.

**Conclusion**

Rituximab is a valuable treatment option for a variety of neuroinflammatory conditions. While RCTs are lacking and questions remain about optimal dosing strategies, there is a growing body of evidence to support its use in specific situations. Overall, rituximab has an excellent safety profile, and relative to other immunomodulatory treatments, it may be an option for the management of severe active diseases in pregnancy. However, neurologists need to be aware of specific management issues, including secondary antibody deficiency in patients requiring maintenance B-cell depletion. Specific risk factors to consider include low pre-treatment immunoglobulin levels, prior use of immunosuppressive drugs or a requirement for ongoing combination therapy.

Newer and more costly B-cell depleting therapies show additional promise in recent and ongoing trials but it remains to be seen if more effective and prolonged B-cell depletion will pose additional risks. Prospective registries with extended follow up will be important in better defining the real-life risks and benefits for patients.

**Legends**

**Figure 1: Stages of B-cell development and expression of B-cell surface markers**

Pluripotent haematopoietic stem cells develop into naïve mature B-cells in the bone marrow. They then migrate to secondary lymphoid organs (spleen and lymph nodes), where they are activated by antigens in circulating lymph and mature into memory B-cells or plasmablasts. Memory B-cells either circulate in the bloodstream or remain in germinal centres, while plasmablasts mature to antibody-secreting plasma cells that reside in the bone marrow or lymphoid tissue. CD20 (yellow triangles) appears at the immature B-cell stage and is lost at the plasmablast stage. Most plasmablasts and nearly all plasma cells (which produce the vast majority of antibodies) do not express CD20. CD19 (red triangles) has wider expression from the pro-B-cell stage through to plasmablasts and a proportion of plasma cells, but not terminally differentiated plasma cells.

**Figure 2: Rituximab depletes CD20+ B-cells via three different mechanisms**

(1) Antibody-dependent cellular cytotoxicity mediated by Fcγ receptors on the surface of natural killer cells, granulocytes and macrophages; (2) complement-dependent cytotoxicity due to C1q binding; (3) induction of apoptosis.

**Figure 3: B-cell depleting monoclonal antibodies in neurology**

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