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RITUXIMAB IN NEUROLOGICAL DISEASE: PRINCIPLES, EVIDENCE AND PRACTICE IN AMARA CITY AT ALSADER TEACHING HOSPITAL IN MISAN

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Abstract

Rituximab is a popular monoclonal antibody that kills B cells. There are no treatment recommendations and it is not approved for use in treating neurological disorders. However, it is an appealing substitute for traditional immunomodulatory drugs as a swiftly acting, targeted therapy with mounting evidence of efficacy and tolerance in numerous neuroinflammatory conditions. The goal of this hands-on review is to clarify the fundamental ideas behind therapeutic monoclonal antibody B-cell depletion. We discuss the scientific support for the use of rituximab in neurological illnesses as well as dose, monitoring, safety, treatment failure, and its application in unique situations such concurrent viral hepatitis, pregnancy, and breastfeeding. We offer a patient information booklet, administration guide, and checklist that can be customized for local use. Lastly, we assess the security.

Introduction

This article discusses some of the fundamental ideas of B-cell depletion with monoclonal antibodies, which are pertinent to neurologists, as well as some of the practical aspects of prescribing rituximab. Skip to the appropriate tables near the conclusion of the article if you're looking for an administration guide for rituximab, a quick summary of the indications and supporting data, anticipated side effects, or specific prescription situations. An illustration of a patient information sheet and an administration checklist are supplied.

The involvement of B cells in neurological illness

B-cells produce proinflammatory and antiinflammatory cytokines, release antibodies, deliver antigen, and control the immune response. Only 2.5% of the total B-cell population, primarily made up of memory and naive mature B-cells, are found in the peripheral circulation; the remaining 95% are found in bone marrow and lymphoid tissue. 1 Any immunoglobulin class (G, M, A, D, or E) or subclass (e.g., IgG1-4) may contain antibodies, and each has a different function. Myasthenia gravis with antibodies against the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) (IgG4), neuromyelitis optica spectrum disorders (NMOSD) with antibodies against the aquaporin-4 water channel (primarily IgG1), and autoimmune encephalitis with antibodies are examples of disorders in which autoantibodies are almost certainly pathogenic. Either the leucine-rich glioma inactivated-1 (LGI1) or N-methyl-D-aspartate receptor (NMDAR),

which are primarily IgG1 receptors (mainly IgG4). As shown by oligoclonal IgG bands in the cerebral fluid, meningeal-based ectopic B-cell follicles next to regions of localized cortical demyelination2, and the effectiveness of B-cell-depleting therapy for MS, B-cells also play a significant role in the pathophysiology of multiple sclerosis (MS).

Surface markers on B-cells

The B-cell transmembrane proteins CD19 and CD20. They can serve as surface indicators and pharmacological targets (in flow cytometry to quantify B-cell populations and assess treatment response). During B-cell development, CD19 is produced more frequently than CD20, although neither marker is present on long-lived plasma cells (figure 1). In healthy adults, the percentage of CD19+ or CD20+ B-cells in the total circulating lymphocyte population ranges from 12% to 22% (the absolute reference range is 50–500 cells/mm3).

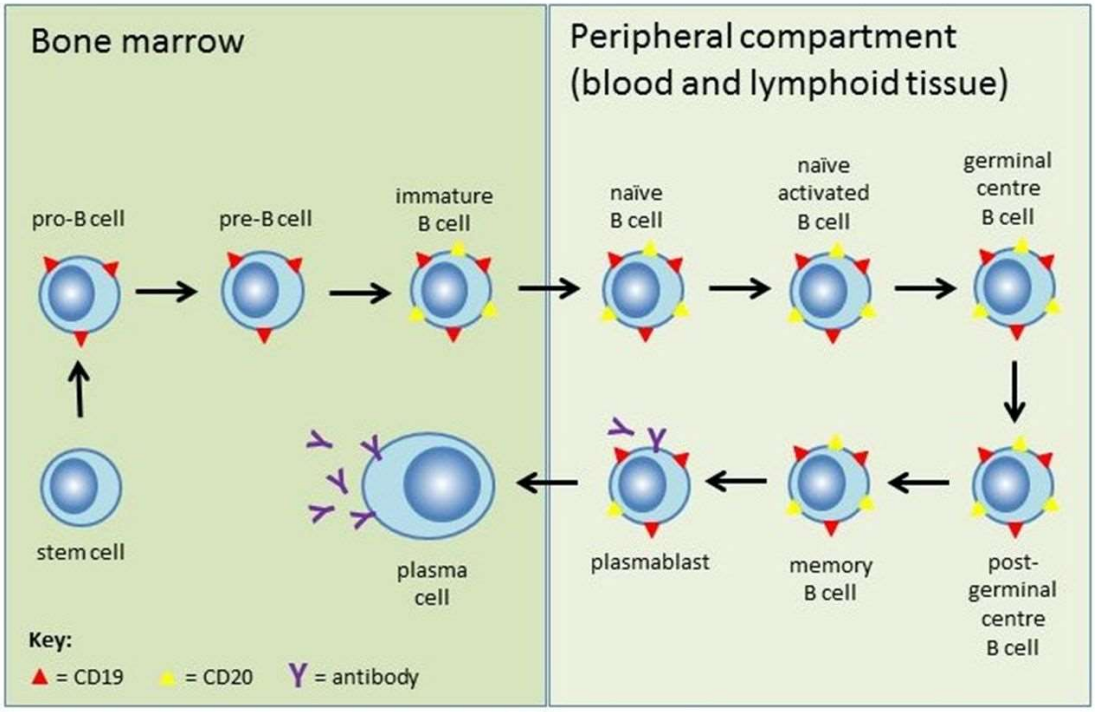

Figure 1

Stages of B-cell development and surface marker expression are shown in Figure 1. In the bone marrow, pluripotent haematopoietic stem cells grow into naive mature B cells. When they reach the spleen and lymph nodes, secondary lymphoid organs, they travel there where they are activated by antigens in the lymph fluid and develop into memory B-cells or plasmablasts. While plasmablasts develop into antibody-secreting plasma cells that live in the bone marrow or lymphoid tissue, memory B-cells either circulate in the blood or stay in germinal centers. At the plasmablast stage, CD20 (yellow triangles) disappears after first appearing at the stage of immature B-cells. The great majority of plasmablasts and virtually all plasma cells, which are responsible for producing most antibodies, do not express CD20. Wider expression of CD19 (red triangles) is seen from the pro-B-cell stage.

Memory B-cells and some other immune cell types express CD27. Memory B-cells only express

CD19 and CD27 in combination. This long-lived B-cell subgroup, which can quickly differentiate into high-affinity plasma cells after repeated antigen exposure, may be a key target in the therapy of autoimmune neurological diseases. 3 4

Monoclonal antibodies that eliminate B cells

Immunoglobulins called monoclonal antibodies are created by a single clone of hybridoma cells (antigen-specific plasma cells fused with myeloma cells). Their two identical fragment antigen binding (Fab) domains bind to a single epitope, and their fragment crystallisable (Fc) domain stimulates the immune system. A range of neoplastic and autoimmune illnesses can be treated with highly targeted immunotherapy because cells that express that epitope are eliminated. With the exception of mature plasma cells that secrete antibodies, available B-cell-depleting monoclonal antibodies with Fab domains that target CD20 or CD19 selectively eliminate the circulating B-cell population. Those used to treat neuroinflammatory disorders are depicted in figure 2.

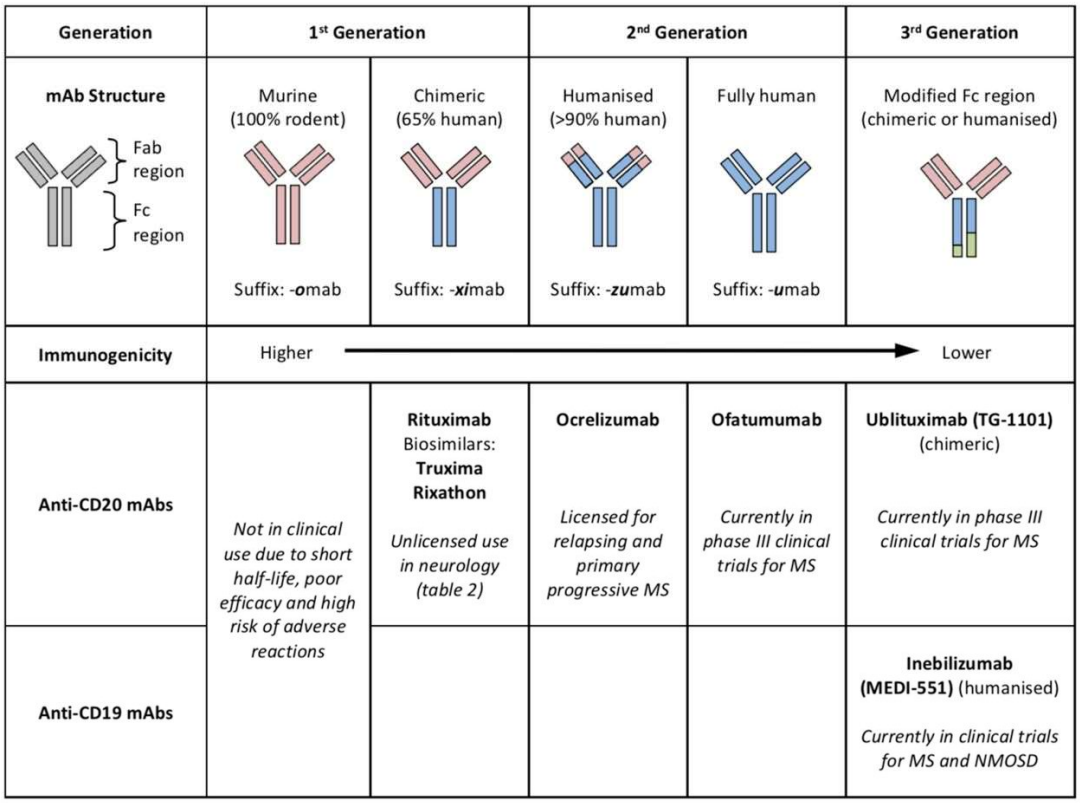

Figure 2: Neurology's use of B-cell-depleting monoclonal antibodies. Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), monoclonal antibody.

The first anti-CD20 monoclonal antibody to be licensed for the treatment of B-cell lymphomas was rituximab (1997). Since then, it has been approved for the treatment of ANCA-associated vasculitis and refractory rheumatoid arthritis. The use of illegal drugs for neuroinflammatory diseases is expanding. Rituximab is a first-generation chimeric monoclonal antibody created by

combining a human Fc domain with a murine (rodent) Fab domain (the term "chimeric" comes from the mythical creature known as the Chimera, a terrible fire-breathing hybrid comprised of parts lion and goat). Figure 3 illustrates how the Fc domain stimulates numerous immunological responses.

Within three days of the first rituximab injection, 90% of the circulating B-cells are destroyed. In several illnesses, effectiveness is correlated with a decrease in pathogenic antibody titers. The full spectrum of B-cell function is likely to be affected by rituximab, though, and secondary T-cell function modifications, like the activation of immunoregulatory T cells, may be significant in some neuroinflammatory illnesses. It is envisaged that sparing CD20-negative long-lived plasma cells will protect enduring humoral immunity.

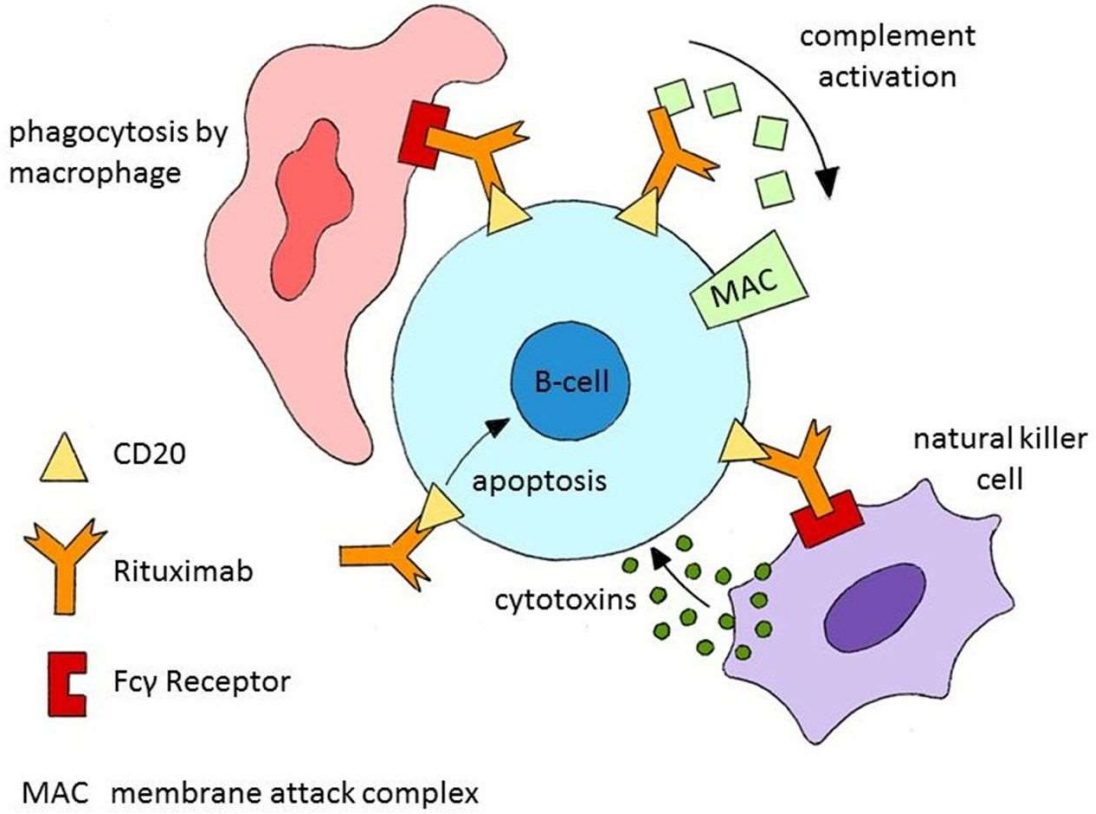

Figure 3: Rituximab eliminates CD20+ B-cells by three separate pathways: (1) complement-dependent cytotoxicity; (2) antibody-dependent cellular cytotoxicity mediated by Fc receptors on the surface of natural killer cells, granulocytes, and macrophages; (3) activation of apoptosis.

Second-generation monoclonal antibodies feature enhanced Fab domains, which are frequently humanized or totally human and improve B-cell killing and tolerability, in comparison to first-generation monoclonal antibodies (figure 2). Recently, ocrelizumab (humanized) was authorized for the treatment of relapsing and progressive MS. Clinical trials are being conducted with ofatumumab, a completely human monoclonal antibody administered by monthly subcutaneous injection. The Fc-mediated immunological functions or half-life of third-generation monoclonal antibodies have been considerably enhanced. Currently being tested in MS is ubituximab (TG-1101), a fast infusible chimeric glycoengineered monoclonal antibody. Because CD19 is expressed

more widely throughout B-cell development, including the plasmablast phase, anti-CD19 B-cell-depleting treatments could be more effective (and possibly carry higher hazards) than anti-CD20 treatments (figure 1). A phase 3 trial of inebilizumab (MEDI-551) is being conducted in NMOSD.

Biosimilars

Monoclonal antibodies are typically expensive. However, once the patent on the original medication expires, less expensive copies, or "biosimilars," become accessible. Competing businesses are unable to access the original molecular clone, cell bank, or precise manufacturing procedure, which could cause these intricate molecular structures to change somewhat. Because of this, biosimilars are not really "generic." Biosimilars must be proved to be highly similar to the original monoclonal antibody in terms of structure, purity, and biological activity in order to obtain a license; however, it is not required to perform clinical trials for every indication. The European Medicines Agency (EMA) has approved two biosimilars, Truxima and Rixathon, since the patent for Rituximab expired in 2016. The administration and dosing procedures are the same. Currently, MabThera 1 g (the original version) costs £1746 according to the British National Formulary.

Rituximab indications and supporting data in neurology

Off-license prescribing should be guided by knowledge of the evidence for rituximab in neuroinflammatory diseases (see table 1 for a succinct summary).

Table 1. Indications for rituximab in neurology

INDICATION
1. Refractory Myasthenia Gravis
2. NMO-SD
3. Autoimmune encephalitis
4. Relapsing Remitting Multiple sclerosis
5. Immune-mediated Peripheral neuropathies
6. Primary angitis of the CNS
7. Stiff-person syndrome

Multiple sclerosis

Use of rituximab for MS in the UK is uncommon due to the availability of licensed disease-modifying treatments supported by phase III randomised controlled trials. But there is evidence that it works, so it might be a choice occasionally (especially if licensed comorbidities, such as active rheumatoid arthritis, facilitate funding). Rituximab's phase I and phase II trials for relapsing-remitting MS met their main objectives. 7–9 While a subgroup study of a major 96-week multicenter randomised controlled trial in primary progressive MS failed to reveal a delay to verified disease progression, younger individuals, especially those with inflammatory lesions, benefited from it. 10 Then, MS clinical trials came to a halt, most likely as a result of the approaching patent expiration of rituximab and the introduction of more recent B-cell depleting

medications from the same manufacturer.

In a large multicenter cohort (n=822), Sweden has published class IV evidence of safety and efficacy, making it the largest off-licence prescriber of rituximab for all forms of MS. 11 The dosage is 500–1000 mg six to twelve times a month. An efficacy in relapsing-remitting multiple sclerosis (MS) comparable to natalizumab and fingolimod, and significantly superior than injectable disease-modifying treatments and dimethyl fumarate, was demonstrated in a recent real-world retrospective comparison analysis. In terms of discontinuation rate, rituximab was superior to all other medications. 12 Despite the fact that this evidence is of rather low quality, there is a strong signal that rituximab is a successful treatment for MS, which is what one would anticipate given the recent encouraging randomised controlled trials for ocrelizumab.

We take 15 patients with MS and see relapse after and before rituximab administration

MS PATIENTS	RELAPSES BEFORE RITUXIMAB	RELAPSES AFTER RITUXIMAB	P VALUE
15	8 PER YEAR	1 PER YEAR	SIGNIFICANT LESS THAN 0.05

Neuromyelitis optica spectrum disorders

Despite the fact that three such trials are under underway, no immunosuppressive medication for NMOSD has been verified by a high-quality randomised controlled study. Numerous, primarily retrospective case reports totaling more than 400 patients that demonstrate persistent decreases in the annualized relapse rate support the use of rituximab. We will cover several dosing tactics in "dosing and monitoring" because there are many different ones in use. According to a recent meta-analysis, the relapse rate has decreased by 79% on average. 13 Rituximab presently has the greatest evidence of any immunotherapy used in NMOSD, however patients in the UK still receive it as second-line therapy because of its relatively expensive cost. It is offered to patients who have relapsed despite receiving appropriate treatment with mycophenolate mofetil or azathioprine in combination with low-dose prednisolone. 14

We take 5. patients of NMO and see the result after and before rituximab

NMO PATIENTS	RELAPSES BEFORE RITUXIMAB	RELAPSES AFTER RITUXIMAB	P VALUE
5	3PER YEAR	ZERO PER YEAR	SIGNIFICANT LESS THAN 0.05

Autoimmune encephalitis

Rituximab is typically used as a second-line acute therapy (single course) to maximize neurological recovery rather than as a long-term maintenance medication (as with MS/NMOSD)

because the majority of autoimmune encephalitis is monophasic. The most typical dosing schedule consists of four doses of 375 mg/m2 given weekly. When there has been a poor response to intravenous corticosteroids, plasma exchange, and intravenous immunoglobulin, limited retrospective evidence supports its usage. It is impossible to attribute therapeutic advantages simply to rituximab because there is insufficient information to compare the impact of various immunotherapies in autoimmune encephalitis. However, it is an appealing choice due to its quick onset of action, proven efficacy in other antibody-mediated illnesses, and acceptable safety profile with short-term usage. The primary investigation in favor of rituximab usage in autoimmune Retrospective comparison of 161 patient outcomes for encephalitis. Regardless of antibody status, functional improvement as judged by the modified Rankin Scale happened more frequently in the rituximab-treated group. 15

Additional data are available specifically for the most prevalent subtype of autoimmune encephalitis, anti-NMDAR encephalitis. Compared to 55% of patients who failed first-line and did not receive second-line immunotherapy, a large prospective cohort study (n=577) indicated that 78% of patients who failed first-line and got second-line immunotherapy (rituximab and/or cyclophosphamide) had a satisfactory result at 24 months. 16 44 patients with anti-NMDAR encephalitis participated in a rituximab research in pediatric neuroinflammatory illness. Second-line rituximab therapy, especially when started early, helped 97% of these patients in some way. 17 Due to these results, a UK clinical commissioning strategy that was released in March 2018 decided to routinely fund rituximab for adults and kids with anti-NMDAR encephalitis who have responded poorly to first-line therapy (failure to improve by six months after starting treatment). two or more points on the modified Rankin Scale by 4 weeks after beginning first-line therapy (or two or more points on the modified Rankin Scale by six weeks after the onset of symptoms). 18

Case reports and tiny case series, which are usually complicated by the coadministration of various immunotherapies, are the only sources of evidence for autoimmune encephalitis caused by less prevalent antibodies. Two case series, for instance, detail the results of rituximab in seven patients with anti-LGI1 encephalitis. One patient may have responded, while three patients (43%) had successful outcomes. 19 20 Regardless of the presence of antibodies, early and intensive immunotherapy is useful in autoimmune encephalitis. It is likely that immunotherapy algorithms will increasingly include rituximab or other B-cell-depleting medications.

Primary angiitis of the central nervous system

The majority of treatment for this uncommon illness is high-dose corticosteroids, either in combination with or without cyclophosphamide. 21 Rituximab has produced positive results in two small case series, where 2/2 and 6/7 of the patients showed signs of improvement. 22 23 Additional case studies describing its application are available. 24

ANCA-associated vasculitis

Mononeuritis multiplex is one way that ANCA-associated vasculitis may infrequently present to the neurologist, but this condition is usually co-managed by other vasculitis specialists. Recent European Guidelines for organ or life-threatening disease license and recommend rituximab. 25 Rituximab (375 mg/m2 weekly for four doses) was non-inferior to cyclophosphamide for

producing remission in two randomised controlled studies. 26 27 For relapsing disease, it might be more effective than cyclophosphamide. 27 Rituximab will be covered by NHS England where cyclophosphamide has failed or is not appropriate (eg, patients who wish to preserve their reproductive potential). 28

Stiff-person syndrome

A single small double-blind randomised controlled trial (n=24) reported no significant changes in any outcome measures following 6 months of rituximab treatment, despite some case reports suggesting a potential benefit for stiff-person syndrome. 32

Myasthenia gravis

Rituximab should be taken into consideration as an early therapeutic option in patients with MuSK-associated myasthenia gravis who have an inadequate response to first immunotherapy, suggest international consensus guidelines from 2016. 51 For myasthenia gravis related with the AChR, a formal consensus could not be obtained. Rituximab has been studied as an acute therapy (often a single course with varying doses) for refractory myasthenia gravis in a number of primarily retrospective, observational studies and two systematic reviews (persistent weakness or need for high-dose corticosteroids despite conventional immunosuppression).

The reported response rates in AChR-associated myasthenia gravis are inconsistent, with 30%–80% of patients achieving a Myasthenia Gravis Foundation of America post-intervention status (MGFA-PIS) of "minimal manifestations or better" after rituximab, despite many case series being shared between the systematic reviews. 52 53 The variation in patient selection, the inclusion of numerous "burned out," non-responsive instances, and the inclusion of cases where MGFA-PIS was not utilized as an end measure in the original publication may all help to explain this. Response and AChR antibody titres did not correspond well. 53 In the near future, two current randomised controlled trials may contribute to a better understanding of the effectiveness of rituximab in AChR-associated myasthenia gravis.

In contrast, both evaluations showed high (72%–89%) response rates in MuSK-associated myasthenia gravis. 52 53 A second blinded prospective assessment indicated that 26% of controls and 67% of rituximab-treated patients had MGFA-PIS of "limited symptoms or better." 54 In MuSK-associated myasthenia gravis, the benefit of rituximab seems to last longer and correlate better with antibody titres. 53 55 Unlike AChR antibodies, which are of the IgG1/3 subtype, MuSK antibodies are of the IgG4 subtype. Therefore, the selective eradication of transient IgG4-producing B-cells may account for rituximab's greater effectiveness. 55

We take 10 patients of MG and see the result after and before rituximab

MG PATIENTS	RELAPSES BEFORE RITUXIMAB	RELAPSES AFTER RITUXIMAB	P VALUE
10	4PER YEAR	ZERO PER YEAR	SIGNIFICANT LESS THAN 0.05

Treatment not working

When treatment failure is suspected, we advise ruling out other explanations, such as concurrent infection, and confirming that B-cell depletion is sufficient by looking at the CD19+ B-cell count in peripheral blood. Following are some potential causes of therapy failure:

1. **Ineffectiveness of B-cell depletion**

Nine patients (9%) in a large NMOSD cohort (n=100) relapsed after target-range CD19+/CD27+ memory B-cell depletion.

When taking rituximab, NMOSD relapses are typically less severe than when not taking it. It is not believed that rituximab depletes long-lived plasma cells or non-circulating B-cells in lymphoid organs, which together make up the majority of the body's total B-cell population and may have a role in breakthrough disease.

2. ***Early relapses/delayed therapeutic onset***

Rituximab induction therapy may be followed by early NMOSD relapses. 4 72 73 This might be the result of insufficient B-cell depletion. Alternately, initial B-cell depletion may cause the release of systemic B-cell activation factor, encouraging plasma cells to produce autoantibodies, "resulting in a transitory spike" in antibody titre, and triggering early relapses. 74

3. ***Incomplete B-cell depletion/early repopulators***

Rituximab induction therapy may be followed by early NMOSD relapses. 4 72 73 This might be the result of insufficient B-cell depletion. Alternately, initial B-cell depletion may cause the release of systemic B-cell activation factor, encouraging plasma cells to produce autoantibodies, "resulting in a transitory spike" in antibody titre, and triggering early relapses. 74

4. ***Antidrug antibodies***

Some monoclonal antibodies, such as anti-tumor necrosis factor agents, have less efficacy because they are reactive to other drugs. Fc binding might improve medication clearance while Fab binding might have a neutralizing impact. Anti-drug antibodies may have a part in rituximab treatment failure, however this is unclear. They were discovered in one-third of the MS patients receiving rituximab treatment. 76 Antidrug antibodies may have a bigger impact in individuals receiving low-dose rituximab (100 mg infusions)77, but higher, conventional dosages will likely mitigate their effects. 76 78 Antidrug antibodies can be technically challenging, poorly standardized, and difficult to produce for everyday use outside of clinical studies.

Combination with other immunosuppressive medications

Due to the risk of early relapse after rituximab initiation, some neurologists continue moderate-dose prednisolone (usually 10–20 mg daily) for 4–12 weeks in NMOSD. 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 treating rheumatoid arthritis, rituximab is often combined with

methotrexate or leflunomide but there is little evidence to guide practice in neuroinflammatory disease.

Pregnancy and breast feeding

The placenta is crossed by rituximab after 20 weeks of pregnancy. The information currently available shows that rituximab may be safe to use during early pregnancy, while this is not known for sure .82 It is possible to take advantage of the prolonged B-cell depleting impact, which can sometimes last longer than 40 weeks of gestation. Rituximab, for instance, might be administered both before and after delivery in pregnancies that were planned, protecting the developing fetus against B-cell depletion.

The danger of recurrence after prolonged cessation of rituximab medication for conception and pregnancy is a conundrum for many women with relapsing illnesses with substantial morbidity, such as NMOSD. In the hopes that B-cell depletion may occur, a new expert study proposes that two doses of 1000 mg could be administered as soon as one month before anticipated conception. The depletion will continue throughout the pregnancy. Given the extremely high postpartum risk of NMOSD relapse, they advise that rituximab could be begun during the first week of birth. 83 However, women should receive advice with the scant information on pregnancies exposed to rituximab. 84

Conclusion

The depletion will continue throughout the pregnancy. They recommend rituximab as an effective treatment for a number of neuroinflammatory disorders. There is rising evidence to support its usage in certain circumstances, even if there are no randomised controlled trials and doubts about the best dose methods. Overall, rituximab has a very good safety record, and compared to other immunomodulatory therapies, it may be a viable alternative for treating severe active illnesses during pregnancy. Neurologists, however, need to be mindful of certain management difficulties, such as secondary antibody deficit in patients needing maintenance B-cell depletion. Low pretreatment immunoglobulin levels, prior immunosuppressive medication use, or a need for continuous combination therapy are some specific risk factors to take into account. In the first week, ximab treatment might be restarted.

The efficacy and duration of more recent and ongoing B-cell depleting medications have shown significant promise, but it is yet unknown whether these will carry new dangers. The real-world hazards and benefits for patients will need to be more clearly defined, which will require prospective registries with long-term follow-up.

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