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Practical considerations on the use of rituximab in autoimmune neurological disorders

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***Abstract*:** Rituximab (Mabthera, Rituxan) is a chimeric human/murine monoclonal antibody against CD-20 surface antigen expressed on B-cells. Rituximab, by causing B-cell depletion, appears to be effective in several autoimmune disorders; it has been approved for rheumatoid arthritis and is a promising new agent in the treatment of several autoimmune neurological disorders. A controlled study in patients with relapsing remitting multiple sclerosis has shown that rituximab significantly reduces the number of new MRI lesions and improves clinical outcome; it also showed some promise in a subset of patients with primary progressive MS. The drug is also effective in a number of patients with Devic's disease, myasthenia gravis, autoimmune neuropathies, and inflammatory myopathies. The apparent effectiveness of rituximab has moved B-cells into the center stage of clinical and laboratory investigation of autoimmune neurological disorders. We review the evidence-based effectiveness of rituximab in neurological disorders based on controlled trials and anecdotal reports, including our own experience, and address the immunobiology of B-cells in autoimmune central nervous system (CNS) and peripheral nervous system (PNS) disorders. In addition, we provide practical guidelines on how best to use this drug in clinical practice and highlight its potential toxicity.

***Keywords*:** rituximab, B-cells, autoimmune neurological disorders, practical guidelines, toxicity, immunotherapy, B cell depletion

Introduction

B-cell life circle and homeostasis

Bone marrow derived B-cells are traditionally divided into two subgroups, the B1 and B2 lines. B1 cells are long-lived, self renewing, and crucial in the defense against bacteria in peritoneal and pleural cavities. B1 cells are part of the 'innate' immune system and have the capacity to produce large quantities of polyreactive IgM antibodies. In contrast, B2 cells represent the adaptive immune system and differentiate in the bone marrow, independently of an antigen, into immature B-cells. They subsequently enter the antigen-dependent phase in the peripheral lymphoid tissues, but also into the brain, where they differentiate from mature but naïve cells into memory cells, plasmablasts and long-lived plasma cells. Specific CD (cluster of differentiation) markers, such as CD20, CD19, CD138, BAFF-R point to the transitional phases through which B-cells pass during maturation [Dalakas, 2008a; Browning, 2006; Dalakas, 2006]. To ensure self-tolerance, autoreactive B-cells are rejected in two major checkpoints. The first checkpoint is in the bone marrow through deletion, anergy and receptor editing; the second checkpoint is in the periphery, possibly with positive and negative selections [Yurasov, 2005]. Recent evidence suggests that migration of antibody-producing B-cells into the central nervous system is regulated by a network of inflammatory cytokines such as CXCL10, CCL2, CCL3 or homeostatic chemokines such us CXCL12, CXCL13, CCL19. During an autoimmune process in the central nervous system (CNS) and peripheral nervous system (PNS) these cytokines are unregulated, modulate B-cell trafficking and enhance B-cell survival. B-cell migration into the nervous tissue is also facilitated by the adhesion molecules VLA-4 and LFA-1, expressed on the B-cell surface, and their counter receptors VCAM1 and ICAM1, respectively, on endothelial cell wall [Dalakas, 2008a; Meinl *et al.* 2008; Meinl *et al.* 2006; Krumbholz *et al.* 2006; Alter *et al.* 2003].

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B-cell survival into the central nervous system is largely facilitated by two members of the tumor necrosis factor (TNF) superfamily, the proliferation inducing ligant (APRIL) and the B-cell activating factor (BAFF). These factors are secreted by monocytes, macrophages and dendritic cells but also by activated astrocytes within the inflamed tissue of the brains of patients with multiple sclerosis (MS), playing a role in clonal expansion and persistence of B-cells *in situ* in the targeted tissues [Meinl *et al.* 2008; Farina *et al.* 2007; Meinl *et al.* 2006; Thangarajh *et al.* 2006; Krumbholz *et al.* 2005; Thangarajh *et al.* 2005].

Ectopic B-cell follicles are present in the intermeningeal spaces of MS-affected brains and enter the cerebral sulci in up to 40% of patients with secondary progressive multiple sclerosis (SPMS) [Magliozzi *et al.* 2007]. These observations provide the rationale to explore the role of anti-B cell agents, such as rituximab, in the management of patients with MS, as discussed below.

B-cell functions in the immune network

B-cells are capable of internalizing antigens bound to B-cell receptors (BCR) and present them attached to MHC II molecules on their surface to the T-cell receptor (TCR) of CD4+ cells leading to clonal expansion of antigen specific T-cells [Drake *et al.* 2006; McLaughlin and Wucherpfennig, 2008; Vascotto *et al.* 2007]. B-cells are excellent antigen presenting cells (APCs) to CD4+ cells and this interaction leads to positive feedback and further accumulation of autoreactive B-cells [Chan *et al.* 1999]. Autoreactive B-cells contribute to the pathology of neurological disorders by the production of antibodies that cause tissue damage through complement activation or antibody-dependent-cell mediated cytotoxicity [Dalakas, 2008a]. Like T-cells, B-cells are very efficient in cytokine production but they are not homogenous regarding this function. The B-cells primed by Th-1 cells produce mainly INF-γ and IL-12, while B-cells primed by Th2 cells produce IL-2, IL-13 and IL-4 [Lund, 2008]. IL-10, recently recognized as a downregulatory cytokine, is produced almost exclusively by naïve B-cells, while proinflammatory cytokines such as lymphotoxin (LT) and TNF-alpha are largely secreted by memory B-cells [Duddy *et al.* 2007]. LT promotes B-cells to form ectopic organized lymphoid structures in sites of chronic inflammation, as noted within the intermeningeal spaces in a substantial proportion of patients with secondary progressive multiple sclerosis (SPMS) [Magliozzi *et al.* 2007; Browning, 2006; Rovaris *et al.* 2006]. B-cell composition in MS lesions increases later as the disease progresses [Lassmann *et al.* 2007; Pittock and Luccineti, 2007]. This suggests that a MHC Class I-CD8+ dominated process in early stages of the disease may be switched to MHC Class II-CD4+ predominance, at least in a subset of MS patients.

Experience with rituximab

Manipulating B-cells and immunoglobulin levels with rituximab

Rituximab is a human/murine chimeric monoclonal antibody initially approved for the treatment of non-Hodgkin B-cell lymphomas. The remarkable role of B-cells in autoimmunity has prompted studies investigating rituximab in suppressing autoimmune disorders. The first success came in rheumatoid arthritis where controlled studies have shown benefit. Since then, the drug has been explored in other autoimmune disorders including diseases of the CNS and PNS (Table 1) [Arkfeld, 2008; Linker *et al.* 2008; Waubant, 2008].

Rituximab binds CD20, a 33–35 kDa nonglycosylated protein expressed on the surface of B-cells. CD20 appears at the pre-B-cell stage in the bone marrow; it persists through B-cell life cycle and is lost during final maturation to plasma cells. The exact role of CD20 is largely unknown, but recent data indicate that it could play an important role in Ca2+ influx across membranes promoting activation of B-cells [Cartron *et al.*, 2004]. Because CD-20 is not present in the antibody-producing plasma cells the level of serum immunoglobulin is not expected to change after rituximab infusion. However, a reduction of rheumatoid factor in rheumatoid arthritis and in IgM-MAG antibodies in anti-MAG neuropathy has been noted [Dalakas, 2008a; Benedetti *et al.* 2007; Browning, 2006; Renaud *et al.* 2003] probably due to depletion of CD27+ memory B cells, the precursors of the short-lived plasma cells; as the CD27+ memory B cells slowly reappear, so do the IgM-producing short-live plasma cells [Dalakas *et al.* 2009]. Rituximab depletes B-cells from the circulation 1 month after administration; B-cells start to reappear in the periphery after 6–8 months [Dalakas, 2008b]. Recent data from MS patients suggest that rituximab is detectable in the cerebrospinal fluid (CSF) after i.v. administration for up to 24 weeks [Petereit and Rubbert-Roth, 2009], and can cause depletion not only of B cells in the periphery but also of the perivascular B cells in the brain parenchyma [Martin Mdel, 2009].

Table 1. Evidence-based effectiveness of rituximab in neurological disorders.

RRMS	**Controlled studies** In a 48 week double–blind study 104 patients enrolled. 69 received 1 g of rituximab and 35 received placebo. The number of patients with relapses was reduced by 58% at week 48 compared with placebo. Patients were not followed by EDSS [Hauser *et al.* 2008].
	Uncontrolled studies Rituximab was safe as add-on therapy and EDSS remained stable in most of 16 patients treated [Cross *et al.* 2006]. Rituximab was safe for 26 patients. 80.8% were free of relapses and had fewer Gd-enhancing lesions over 72 weeks [Bar-Or *et al.* 2008].
PPMS	**Controlled studies** In a placebo controlled phase II/III trial (OLYMPUS), 439 patients were randomized to receive rituximab or placebo (2 : 1). Rituximab slowed disease progression in patients below 51 years with active Gd-enhancing lesions on MRI scans [Hawker *et al.* 2009].
NMO	**Uncontrolled studies** In a multicenter retrospective analysis of 25 patients who received 2 g of rituximab in one month, 36% showed EDSS stability and 44% improved in EDSS score [Jacob *et al.* 2008]. 8 patients resistant to immunotherapies received rituximab for 1 month. None of them had a relapse for 1 year and they also improved by 2 points in EDSS score [Cree *et al.* 2005].
MMN	**Uncontrolled studies** 9 anti-GM1 positive MMN patients received rituximab for 1 month and compared with untreated controls. One year after the initial treatment muscle power improved by at least 12% in 86% of the treated group [Pestronk *et al.* 2003].
	4 patients with MMN, all improved after receiving rituximab by 16% or more in quantitative muscle tests [Levine and Pestronk, 1999]. In 2 IVIg dependent MMN patients, rituximab reduced the total dose of IVIg that was required to maintain clinical stability in 1 patient by 43% [Gorson et al. 2007].
MAG	**Controlled studies** In a double-blind, placebo-controlled study 13 patients received four weekly infusions of 375 mg/m^2 rituximab and compared with 13 who received placebo. Clinical improvement was noticed in 7 of 13 (53.8%) rituximab-treated patients [Dalakas *et al.* 2009].
	Uncontrolled studies 9 patients with anti-MAG neuropathy received rituximab for 1 month and 6 showed clinical improvement. 2 patients remained stable and 1 worsened during 12 months [Renaud *et al.* 2003]. 8 patients with anti-MAG neuropathy received 750mg/m^2 every week for 1 month, instead of the standard 375mg/m^2. 4 patients improved, 3 were stable, 1 worsened [Renaud *et al.* 2006]. 3 patients with anti-MAG polyneuropathy received rituximab for 1 month. 8 patients (62%) improved clinically due to reduction in sensory ataxia and increase in muscle strength, 2 patients (15%) were stable and 3 patients (23%) worsened [Benedetti *et al* 2007].
CIDP	**Uncontrolled studies** Rituximab failed to reduce the total amount of IVIg needed to maintain remission in two patients with IVIg-dependent CIDP [Gorson et al. 2007].
MG	**Uncontrolled studies** 6 patients with severe MG responded to rituximab given at 375mg/m^2 every week for 1 month without side effects; in one the improvement was sustained for 22 months [Illa *et al.* 2008].
OPS	**Semi-controlled studies** 16 children with OMS received rituximab (345mg/m^2 every week for 1 month) and compared with 16 children not having OMS. 81% of OMS patients had better motor performance after rituximab therapy [Pranzatelli *et al.* 2006].
DM	**Controlled studies** Under way, sponsored by the NIH.
	Uncontrolled studies In an open-label study 8 patients received 2 g of rituximab in 2 doses 2 weeks apart. 3 patients (38%) had partial remission [Chung *et al.* 2007].
PM	**Controlled studies** Under way, sponsored by the NIH.
	Uncontrolled studies In an open-label study 4 patients with PM responded to rituximab with significant improvement in muscle power [Mok *et al.* 2007].

*RRMS, Relapsing–remitting multiple sclerosis; PPMS, Primary progressive multiple sclerosis; NMO, Neuromyelitis optica; MMN, Multifocal motor neuropathy; MAG, Myelin-associated glycoprotein; CIDP, Chronic inflammatory demyelinating polyneuropathy; MG, Myasthenia gravis; OPS, Opsoclonus-myoclonus syndrome; DM, Dermatomyostis; PM, Polymyositis; EDSS, Expanded disability status scale; NIH, National Institutes of Health.

Rituximab causes B-cell lysis by three main mechanisms, namely complement activation and membranolytic attack complex formation, antibody-dependent cellular cytotoxicity on CD20 B-cells, and apoptosis [Cartron *et al.* 2004; Cardarelli *et al.* 2002]. The lysis via complement activation appears to be the fastest acting mechanism based on the occurrence of symptoms related to 'cytokine release syndrome' noted rarely in some patients immediately after the first infusion [Gürcan *et al.* 2009; Cartron *et al.* 2004; Di Gaetano *et al.* 2003]. Although less efficiently, rituximab opsonization on B-cells activates Antibody-dependent cellular cytotoxicity (ADCC) through recruitment of natural killer (NK) cells and macrophages which express Fcγ receptors (FcγRs) [Lefebvre *et al.* 2006; Cartron *et al.* 2004; Di Gaetano *et al.* 2003]. Rituximab is also capable of inducing apoptosis by forcing CD20 into lipid-raft environments, resulting in altered calcium flux into B-cells [Dalakas, 2008a; Browning, 2006].

Clinical trials with rituximab in neurology

Relapsing–remitting multiple sclerosis

A phase II unblinded clinical study of 16 relapsing–remitting multiple sclerosis (RRMS) patients was initially conducted to evaluate the safety of rituximab as add-on therapy in MS patients already receiving one of the FDA-approved disease modifying drugs (beta-interferon 1a, beta-interferon-1b or glatiramer acetate). Rituximab was administered at 375 mg/m^2 every week for 1 month. In this limited study, the EDSS of most patients remained stable. Twenty-four weeks after rituximab infusions, a reduction in the CSF B-cells (by 90%) and the CSF T-cells (by more than 50%) was noted [Cross *et al.* 2006]. Clinical benefit from rituximab administration has also been reported in two patients with isolated monophasic myelitis, who presented with variable impairment of motor, sensory, bowel/bladder functions [Pawate and Sriram 2009]. Patients with fulminant RRMS unresponsive to immunosuppression who had a clear clinical benefit after rituximab therapy have been reported in the past. [Leussink *et al.* 2008; Chan *et al.* 2007; Stüve *et al.* 2005].

Long term rituximab therapy, for up to 48 months, was safe and effective in two patients with active RRMS unresponsive to immunosuppression [Stüve *et al.* 2009]. A phase I, open-label, multicenter study of 26 patients with RRMS was conducted over a 72 week period with 1 g of rituximab administered on days 1 and 15 and a repeat course on weeks 24 and 26. The primary endpoint was safety of rituximab through week 72. Secondary endpoints were the number of patients who had a relapse, the number of relapses per patient during the study and a reduction in CD19 lymphocyte counts. Over the 72 week time period, 21 (80.8%) patients remained relapse-free; four patients had one relapse and one patient reported two relapses. The mean number of Gd-enhancing lesions was decreased at week 72. B-cell counts were near zero by week 2 [Bar-Or *et al.* 2008]. Detailed clinical evaluation of the patients with Expanded Disability Status Scale (EDSS) scores was not, however, included.

The largest and only double-blind, placebo-controlled phase II trial was conducted in 104 patients with RRMS over a 48 week period; 69 patients received 1 g of rituximab and 35 patients received placebo on days 1 and 15. The primary outcome was the number of gadolinium (Gd) enhancing lesions on MRI of the brain. Clinical efficacy, a secondary outcome, was based on the rate of relapses. Patients were not followed clinically with EDSS scores. The patients who received rituximab, compared with those who received placebo, had significantly fewer Gd-enhancing lesions on brain MRIs over the 48 week period; the number of lesions was also reduced by 91%. Further, the number of patients with relapses was reduced at week 48 in the rituximab group compared to the placebo group by 58% (20, 3% *versus* 40%, $p = 0.04$) [Hauser *et al.* 2008].

Primary progressive MS

Rituximab was tried in five patients with primary progressive MS (PPMS) at a dose of 375 mg/m^2 every week for 1 month. CD19+ B-cells were depleted in the peripheral blood within 1 to 2 months after rituximab therapy in four patients, but only one patient demonstrated a significant reduction in CD19+ CSF B-cell count. The drug was ineffective. Whether this was due to inability of the drug to reach the CSF compartment in high enough concentrations (if the blood–brain barrier is not compromised) or it was due to the low percentage of naïve B-cells expressing the CD-20 molecule in the CSF, remains unclear [Monson *et al.* 2005].

A randomized, placebo-controlled double-blind clinical trial (OLYMPUS) was conducted to evaluate the safety and efficacy of rituximab in PPMS using time to confirmed disease progression (CDP) as a primary endpoint. In this study (using 2 : 1 randomization) 439 PPMS patients received 1 g rituximab or placebo every 24 weeks through 96 weeks. There was no statistically significant differences in time to CDP between rituximab and placebo, although a subgroup analysis showed that time to CDP was longer in the rituximab cohort who were below the age of 51 and with Gd-enhancing lesions on MRI. Serious infections occurred in 4.5% of rituximab patients and in less than 1% of the placebo group [Hawker *et al.* 2009].

We have treated eight patients with PPMS or SPMS with rituximab over the last 2 years. In four patients, we noticed mild improvement in muscle power and ataxia. Two of the patients who benefited from the drug relapsed at 6 to 8 months and they received another course of 2 g of rituximab (1 g in two doses 2 weeks apart). Two wheelchair-bound patients reported better bladder function which was clinically significant for

their quality of life. Two patients had no benefit and one patient reported worsening in spasticity after the second infusion.

Neuromyelitis optica

Neuromyelitis optica (Devic's disease) is a severe inflammatory disease of the CNS which predominantly affects optic nerves and spinal cord. An NMO-IgG specific antibody against aquaporin-4 (AQP4), the main water channel in the CNS, appears to be highly specific for the disease and may play a role in its pathogenesis. Recently it has been shown that human anti-AQP-4 antibodies are capable of augmenting the disease and inducing NMO-like lesions in animals with autoimmune encephalomyelitis (EAE) [Bradl *et al.* 2009]. There is no standard therapy for the disease which is characterized by frequent relapses. In one study, treatment of Devic's disease with rituximab resulted in reduction of AQP4 titers in the patient's serum and the rate of clinical relapses [Jarius *et al.* 2008].

In a recent multicenter, retrospective analysis, 25 patients with Devic's disease, who were unresponsive to other treatments, showed significant improvement with rituximab therapy. Patients were followed for 19 months after receiving the standard regimen of 2 g in 1 month. The median EDSS score at the start of the treatment with rituximab ($n = 25$) was 7 (range 3–9, 5) and at the last follow up was 5 (range 3–10). The EDSS score remained stable in nine patients and improved in 11. In five patients EDSS worsened. The annualized post-treatment relapse rate was lower than the pretreatment rate [0 (range, 0–3, 2] *versus* 1, 7 (range, 0, 5–5) relapses, $p < 0.001$] [Jacob *et al.* 2008]. This study although retrospective and uncontrolled showed that up to 80% of patients with Devic's disease may benefit from rituximab. Concerns about short-term and long-term safety should, however, be considered especially when patients have received other drugs. Two patients in the Jacob study died: one 9 months after the first infusion from *C. difficile* colitis and the other 6 months after the last dose from suspected sepsis following urinary tract infection. Whether rituximab was related to these deaths is unclear because both cases had severe relapses with lesions in the brainstem and hypothalamus and were treated with mitoxandrone before rituximab infusions.

In another study, eight patients with NMO resistant to immunomodulating therapies received rituximab at the standard regimen of 375 mg/m^2 every week for 1 month. Six of these patients remained relapse-free in the 12 month follow up period; five patients were re-treated with rituximab when their CD19+ became detectable in the periphery. The pretreatment median EDSS score was 7, 5 and the post treatment 5, 5 ($p = 0.013$) [Cree *et al.* 2005].

We have treated four patients with Devic's disease, unresponsive to other agents. One with very advanced disease noted clinically insignificant changes after two courses of therapy. Another with frequent relapses almost normalized and remains free of relapses up to 8 months; one other noted improvement in muscle strength and ataxia. A fourth patient with negative NMO-IgG but extensive myelitis unresponsive to cyclophosphamide and steroids, noted significant improvement in muscle strength after 2 months. She relapsed 8 months later but she improved again after re-treatment.

Peripheral neuropathies

Multifocal motor neuropathy. Multifocal motor neuropathy (MMN) is a purely motor neuropathy with multifocal conduction blocks, and slowly progressive proximal and distal weakness in the distribution of individual nerves. Up to 50% of patients have high titers of anti-GM1 autoantibodies in the serum. The majority of MMN patients respond to IVIg therapy but require frequent infusions to maintain stability. Some patients however respond less well and continue to have significant disability [Steck *et al.* 2008].

In two uncontrolled pilot studies of six MMN patients, rituximab was effective in improving muscle function in four patients lowering also the titers of IgM anti-GM1 antibodies [Gorson *et al.* 2007; Levine and Pestronk, 1999]. Two patients, who were IVIg dependent, needed a lower total IVIg dose to maintain stability after rituximab [Gorson *et al.* 2007; Rüegg *et al.* 2004].

In another study, a heterogeneous group of 21 patients with autoimmune related neuropathies was treated with rituximab and was compared with 13 untreated controls. Among them, nine had MMN with high serum IgM anti-GM1 antibodies (11 patients had evidence of motor conduction block in at least one nerve on electrodiagnostic testing). All patients in the treatment group received 375 mg/m^2 of rituximab every

week for 1 month. One year after the initial treatment, muscle power improved by at least 12% in 86% of the treated group; a reduction of IgM level and the anti-GM1 autoantibodies was observed [Pestronk *et al.* 2003].

We have treated three patients with MMN, two without improvement and one with significant response requiring less IVIg administration.

Anti-myelin associated glycoprotein neuropathy. Patients with anti-myelin associated glycoprotein (anti-MAG) neuropathy have a chronic sensorimotor demyelinating polyneuropathy with prominent gait ataxia. The disease is unresponsive to plasmapheresis, steroids and IVIg.

In a prospective open-label phase II clinical study, nine patients with anti-MAG polyneuropathy received 375 mg/m^2 of rituximab every week for 1 month. Six patients improved on the NDS (Neurologic Disability Score); two remained stable and one worsened during the 12 months observational period [Renaud *et al.* 2003]. Seven patients had better motor nerve conduction velocity of at least 10% in one ulnar nerve; however, two patients worsened. At 1 month, B-cells became undetectable until month 9. Anti-MAG antibody titers were reduced by at least 52% in eight of nine patients [Renaud *et al.* 2003]. The same authors treated another series of eight patients with anti-MAG neuropathy using double dose of rituximab at 750mg/m^2 every week for one month, instead of the standard 375 mg/m^2. These patients had either a monoclonal gammopathy of unknown significance (MGUS) or a low grade non-Hodgkin B-cell lymphoma and all of them had received 375 mg/m^2 of rituximab between 17 and 27 months before receiving the high dose. The double dose led two out of the eight patients to further clinical improvement, while in two others led to the first clinical response along with improvement in nerve conduction velocities and a reduction of anti-MAG antibody titers; three other patients remained stable and one worsened [Renaud *et al.* 2006]. Among them, an 80-year-old patient, who tolerated the drug well with no immediate side effects, died suddenly after 7 months [Renaud *et al.* 2006]. Of interest, in two patients with anti-MAG polyneuropathy rituximab worsened their condition [Broglio and Lauria, 2005].

An uncontrolled open-label trial in 13 patients with anti-MAG polyneuropathy treated with 375 mg/m^2 weekly for 1 month displayed increased strength and reduced the sensory ataxia resulting in improved ambulation and daily activities in eight out of the 13 (62%) patients; two other patients (15%) remained stable and three patients (23%) worsened. Three patients improved electrophysiologically by over 10% in peroneal nerve MCV, two patients worsened and three patients remained stable. Median serum IgM levels decreased by 39% ($p < 0.05$) after 12 months and anti-MAG antibody titers were reduced by 68% after 1 month [Benedetti *et al.* 2007]. Ten patients from this study who initially responded well to rituximab therapy were prospectively followed without treatment for another 36 months. A sustained clinical benefit after a single rituximab course was noted, lasting up to 24 months in 80% of them and up to 36 months in 60% [Benedetti *et al.* 2008a, b].

The first and largest double-blind, placebo-controlled study in MAG neuropathy using rituximab was conducted by Dalakas *et al*. Twenty-six patients were randomized to four weekly infusions of 375 mg/m^2 rituximab or placebo. Sample size was calculated to detect changes in Inflammatory Neuropathy Course and Treatment (INCAT) leg disability scores of greater than or equal to one at month 8. IgM levels, anti-MAG titers, B cells, antigen-presenting cells, and immunoregulatory T cells were monitored every 2 months. Thirteen MAG patients were randomized to rituximab and 13 to placebo. Randomization was balanced for age, electrophysiology, disease duration, disability scores, and baseline B cells. After 8 months, by intention to treat, four out of 13 rituximab-treated patients had an improved INCAT leg score greater than or equal to one compared with none of 13 patients taking placebo ($p = 0.096$). Excluding one rituximab-randomized patient who had normal INCAT score at entry, and thus could not improve, the results were significant ($p = 0.042$). The time to walk 10 m was significantly reduced in the rituximab group by intention to treat. Clinically, walking in seven out of 13 rituximab-treated patients improved. At month 8, IgM was reduced by 34% and anti-MAG titers by 50%. The most improved patients were those with high anti-MAG titers and most severe sensory deficits at baseline. The number of Foxp3-positive immunoregulatory T cells significantly increased 8 months after rituximab. It was concluded that the benefit of rituximab may be exerted by

reducing the putative pathogenic antibodies or by inducing immunoregulatory T cells [Dalakas *et al.* 2009].

Subacute ataxic neuropathy (ganglionopathy) without paraproteinemia. This neuropathy is identical to the paraproteinemic one with anti-MAG or other glycolipid antibodies, and to the ataxic neuropathy seen in Sjögren's syndrome or as a paraneoplastic manifestation. If all known causes, including degenerative, are excluded, we have called this neuropathy chronic idiopathic ataxic neuropathy [Dalakas, 1986]. The neuropathy (probably a ganglionopathy) is notoriously unresponsive to therapies but is suspected that a subset of them have an autoimmune basis and may respond to immunotherapy if treated early. We have treated six patients with ataxic neuropathy; four of them noted significant improvement in their ataxia and one was cured. The results, although uncontrolled, are important because this form of sensory ataxic neuropathy is notoriously resistant to therapies.

Chronic inflammatory demyelinating polyneuropathy. Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common acquired autoimmune demyelinating neuropathy. Patients respond to steroids, plasmapheresis and IVIg but require frequent infusions of IVIg (at least once or twice per 6 weeks) or a high-dose steroid regimen to maintain the response. A number of patients, up to 40% in one series [Nobile-Orazio, 2005], do not respond well to these therapies and remain with significant disability. There is a need for an effective immunosuppressant in CIDP, either as add-on therapy for the poor responders or as a steroid or IVIg-sparing agent. Because immunosuppressants have not been effective in CIDP, rituximab is a reasonable drug to try. The experience with rituximab up to now, although limited to case reports, appears encouraging [Bennedetti, 2008; Münch *et al.* 2007; Gono *et al.* 2006; Briani *et al.* 2004]. Rituximab failed to reduce the total amount of IVIg needed to maintain remission in two patients with IVIg-dependent CIDP [Gorson *et al.* 2007].

We have treated three patients with CIDP unresponsive to standard regimens. Two of them have objectively improved and maintain their response with repeated infusions. One had a dramatic response; she was on crutches before treatment but normalized a few months later.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder characterized clinically by weakness and fatigability of skeletal muscles. In about 80% of patients there are circulating antibodies against muscle nicotinic acetylcholine receptor AchR (anti-AchR) and in up to 10% IgG antibodies against the muscle-specific receptor tyrosine kinase (MuSK) [Hoch *et al.* 2001]. Steroids, plasmapheresis, IVIg, immunosuppressants such as mycophenolate and thymectomy, are the mainstays of treatment. There is, however, a need for better therapies in difficult cases. Rituximab has been tried in some patients with MG whose disease was difficult to manage with the conventional therapies.

Six patients with severe MG, three AChR-positive and three MuSk-positive, who did not respond to various treatments, responded to rituximab given at 375 mg/m^2 every week for 1 month without side effects; in one of them the improvement was sustained for 22 months [Illa *et al.* 2008]. MuSK-Ab titers decreased significantly by 84.9% and AchR-Ab by 42.6%. Two other patients with aggressive MG and high titers of anti-MuSK antibodies responded also remarkably well to rituximab [Evoli *et al.* 2008; Hain *et al.* 2006] 2 months after infusion with reduction in the serum MuSK-Ab titers. Other reports also suggest that patients with AchR-Ab positive MG, including a 9-year-old child, have also responded [Chan *et al.* 2007; Takagi *et al.* 2005; Gajra *et al.* 2004; Wylam *et al.* 2003; Zaja *et al.* 2000]. However, a controlled study has not yet been performed.

We have treated two patients, one with ocular myasthenia who did not improve and a youngster with no apparent benefit up to 2 months later.

Opsoclonus–myoclonus syndrome

Opsoclonus–myoclonus syndrome (OMS) is a paraneoplastic syndrome that occurs in 2–3% of patients with neuroblastoma. In other cases it is considered autoimmune-mediated without an apparent tumor. B-cells are clonally expanded in the CSF of OMS patients [Pranzatelli *et al.* 2004].

The neurologic symptoms can respond to ACTH, corticosteroids, IVIg or plasmapheresis [Bell *et al.* 2008; Burke and Cohn, 2008] but some patients do not adequately respond to these therapies.

Sixteen children with OMS received rituximab (345mg/m^2 every week for 1 month) as add-on

therapy to ACTH, IVIg, or both, and were re-examined 6 months later. In this open-label study, the outcome measures were clinical (motor function measured with the OMS evaluation scales, behavior and sleep patterns) and immunologic (CSF CD19+ cells and Ig levels). Controls were 16, age and sex-matched children without OMS but with other neurological disorders for which they had undergone a lumbar puncture and had normal CSF. After rituximab therapy, 81% of OMS patients had better motor performance (measured with the OMS evaluation scale) and improved behavioral disturbances such as rage and sleep disturbance. The ACTH dose was reduced by 51% in nine out of 11 children who did not relapse. The percentage of CSF CD19+ and CD20+ was lowered in all children and was undetectable in six. Serum IgM fell by 69% below reference range. IgG and IgA titers showed no statistically significant changes [Pranzatelli *et al.* 2006]. Other case reports also confirm the benefit of rituximab in OMS children including a 3½-year-old patient with ganglioneuroblastoma [Bell *et al.* 2008; Burke and Cohn, 2008; Corapcioglou *et al.* 2008; Pranzatelli *et al.* 2005].

Inflammatory myopathies

This group of disorders includes dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). DM is caused by activation and deposition of complement on endomysial capillaries and subsequently lysis and muscle ischemia. In PM and IBM clonally expanded CD8-positive cytotoxic T-cells invade muscle fibers that express MHC class I antigens, which leads to fiber necrosis via the perforin pathway. Dermatomyositis responds better than polymyositis to immunotherapy while IBM is more difficult to treat. Therapeutic agents with variable efficacy include prednisolone, mycophenolate mofetil, methotrexate, cyclosporine and IVIg [Dalakas and Hohlfeld, 2003].

Small pilot trials and isolated case reports suggest that rituximab may be an alternative therapy for PM and DM patients refractory or intolerant to these agents.

Overall, an open-label studies, up to 86% of DM patients reported had partial or definite response [Touma *et al.* 2008; Chung *et al.* 2007; Cooper *et al.* 2007; Dinh *et al.* 2007; Levine, 2005]. An open-label study of four patients with PM refractory to corticosteroids and other immunosuppressants also responded to rituximab at week 28 with significant improvement in muscle power and reduction in CK levels; two patients returned to full muscle power [Mok *et al.* 2007]. In other case reports four patients with PM and DM have also responded and managed to taper off corticosteroids and immunosuppressants 4 months later [Noss *et al.* 2006; Lambotte *et al.* 2005]. A controlled trial in PM and DM, sponsored by the NIH is under way.

Single case reports

Two patients with Sjögren's syndrome associated neuropathy and another patient with stiff person syndrome (SPS) responded very well to rituximab [Gorson *et al.* 2007; Seve *et al.* 2007; Baker *et al.* 2005]. Experience is, however, too limited to make any conclusions about drug effectiveness.

Dosing, tolerance and safety

Rituximab was initially administered in B-cell lymphomas at a dose of 375 mg/m^2 weekly for 4 weeks. We now use a more fixed regimen at a dose of 2 g (two infusions of 1 g, 2 weeks apart) based on safety and efficacy data in lymphomas and rheumatoid arthritis [Waubant, 2008].

We initiate the infusions of the drug at a rate of 60 mg/h and in the absence of infusion-related reactions we increase the infusion rate by 60 mg/h increments every 30 minutes, to a maximum of 240 mg/h.

The average half life of the drug after completion of an infusion is 21 days. The infusions can be repeated after 6–12 months if the patient relapses [Dalakas, 2008a].

Rituximab is very well tolerated although mild-to-moderate infusion-related reactions can be observed. It is recommended to stop all antihypertensive agents at the day of infusion since rituximab can cause hypotension. Patients who experience symptomatic hypotension during the infusion respond well to an interruption of infusion for 30 to 60 minutes and restarting at a lower initial rate of not more than one-half of the previous rate. Other relatively common infusion-related reactions are flu-like symptoms such as fever, rigors and headache. Anaphylactic or skin reactions can occur rarely but respond well to intravenous methylprednisolone and interruption of infusion. Premedication with antihistamine is advisable to prevent such reactions.

More serious side effects such as the 'cytokine release syndrome' are not common. About 10% of patients treated with rituximab experience hypotension and bronchospasm, usually at the first administration of the drug. Although more severe manifestations such as acute respiratory distress syndrome (ARDS), myocardial infarction, ventricular fibrillation and cardiogenic shock have been reported, we have not seen such reactions in more than 100 cases with neurological disorders that we have infused. These symptoms might be the result of marked cytokine release a few hours after the first infusion [Kimby, 2005]. In general, most of the infusion-related reactions tend to dissipate after the first infusion. Close monitoring is mandatory in patients with poor general condition and pre-existing pulmonary and cardiac insufficiency.

The most common infusion-related reactions noted in our patients were transient hypotension and mild to moderate allergic reactions that responded very well to methylprednisolone. One patient had a pulmonary edema during rituximab infusion, due to undiagnosed heart failure, but responded well to diuretics.

Rituximab has an excellent safety profile but infections from common bacteria or viral agents can occur. Cases of progressive multifocal leucoencephalopathy (PML) have been reported in patients who suffered from B-cell malignancies and received rituximab plus chemotherapy (R-CHOP, fludarabine) [Bonavita *et al.* 2008; Yokoyama *et al.* 2008]. In summary, a literature review from 1997 to 2008 revealed 57 cases of PML after treatment with rituximab and other agents, mostly in patients with lymphoproliferative disorders [Carson *et al.* 2009].

Recently the FDA notified healthcare professionals about the first case of PML in a patient with rheumatoid arthritis treated with rituximab who had not previously received treatment with a TNF antagonist [FDA, 2009].

Vigilance is therefore recommended for the possible development of such incidents, especially after long-term therapy and in patients who receive other concomitant immunosuppressive therapies.

Regulatory and licensing concerns

The success of rituximab, highlighted in this article, may be offset by regulatory and patent issues. In all countries, rituximab remains 'off-label' and may remain in this status for quite some time, unless results from the ongoing trials confirm its efficacy and it gains FDA approval. The enthusiasm we see in practice, based on the aforementioned results, is often hampered by the difficulty in persuading the regulatory authorities, especially in certain countries, to approve rituximab for a given disease. Patent rights may also add to the complexity in the years to come. Whether the humanized version, ocrelizumab, will provide a solution remains to be determined.

Conclusion

Rituximab is emerging as a novel therapeutic option in several autoimmune neurological disorders. The randomized clinical trials already conducted do not only show clear benefits in RRMS and in anti-MAG neuropathy patients but they also help us understand the ongoing immune deregulation and the role of B-cells in these disorders. From uncontrolled but large series, it appears that rituximab may be helpful in some patients with NMO-IgG, SPMS or PPMS, and for some autoimmune or ataxic neuropathies, autoimmune myopathies and neuromuscular junction disorders. In a much broader view, rituximab points to a new, more targeted and effective immunotherapy for the treatment of various chronic autoimmune neurological diseases and additional controlled trials are called for.

Conflict of interest statement

The authors have declared that there is no conflict of interest.

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