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An update on the evidence for the efficacy and safety of rituximab in the management of neuromyelitis optica

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***Abstract*:** Neuromyelitis optica spectrum disorders (NMOSDs) is a new concept which includes classical neuromyelitis optica (NMO) and partial forms of NMO such as recurrent optic neuritis with positive aquaporin-4 antibodies (AQP4) or brainstem symptoms (intractable hiccups or vomiting). This disease is clearly distinguished from multiple sclerosis (MS) and the therapeutic approach is clearly different. Rituximab is actually considered to be one of the most efficient treatments of NMOSD, even if class I studies are clearly lacking. In the present review, we describe the state of the art about rituximab treatment in NMOSD, including adults and children, plus its efficacy and tolerance and we also underline the questions that should be addressed in the near future.

Keywords: Rituximab, CD20, B lymphocyte, neuromyelitis optica, monoclonal antibody

Introduction

Neuromyelitis optica (NMO) is a rare inflammatory and demyelinating disease of the central nervous system. The therapeutic strategy to prevent relapses is based on the use of immunosuppressants (ISs). When NMO is particularly severe or when patients do not respond to a first line therapy, a new IS infused intravenously is usually prescribed. In these patients, data suggest an effect of cyclophosphamide, mitoxantrone and rituximab (RTX), each used at a dosage similar to that used in multiple sclerosis (MS) [Collongues *et al.* 2011]. To date, there is an increasing amount of evidence for a strong effect of RTX in NMO leading to a growing number of publications in recent years. We propose to review the data on the efficacy and tolerability of RTX in NMO.

Pharmacology of rituximab

RTX is a chimeric monoclonal antibody (mAb) against human B-lymphocyte antigen, CD20, initially approved for the treatment of non-Hodgkin B-cell lymphomas. CD20 is expressed at the membrane of the B lymphocyte from the stage of pre-B cells to mature B lymphocytes. In an exceptional manner, CD20 is also expressed in less than 5% of T lymphocytes [Hultin *et al.* 1993]. This cluster is not present on stem cells and plasmocytes that permit maintenance of a constant level of immunoglobulin, and therefore confers a relative protection against opportunistic infection.

RTX consists of a variable light chain of murine anti-CD20 and a constant heavy chain (Fc) of human IgG-1 associated with a light chain Kappa. Its major mechanism of action results in a destruction of B cells via CD20 linkage, caused by phagocytosis by macrophage and neutrophils, complement-dependent cytotoxicity (CDD) or antibody-dependent cellular cytotoxicity (ADCC) involving natural killer (NK) cells. These mechanisms depend on the Fc portion of the antibody binding to the Fc gamma receptors (FcγRs) on immune cells. Other mechanisms are aggregation of targeted cells or direct cell death through CD20 signaling [Golay *et al.* 2013].

Studies on pharmacokinetics (PK) show that RTX infused intravenously has a terminal half-life of about 120 hours and can persist in the body for up to 6–9 months after treatment stops [Boye *et al.* 2003]. A weak diffusion in the CNS has been observed because RTX may not traverse the blood–brain barrier. After intravenous (IV) administration, maximal RTX levels in cerebrospinal

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fluid (CSF) are generally less than 1% of serum levels [Harjunpaa *et al.* 2001; Lampson, 2011]. RTX depletes B cells from the circulation 1 month after administration. Depth of B-cell depletion is variable among patients but restoration of the B-cell repertoire generally takes 9–12 months from the last perfusion of RTX [Dass *et al.* 2008]. In the setting of a disrupted blood–brain barrier, depletion occurs not only in the periphery but also in the perivascular area in the brain parenchyma [Batchelor *et al.* 2011].

Efficacy of rituximab in adults with neuromyelitis optica

Open-labeled studies

To date, no randomized controlled trials have been performed to explore the effect of RTX in NMO. Available studies are open labeled and have provided consistent data in favor of a positive effect of RTX in NMO [Cree *et al.* 2005; Jacob *et al.* 2008; Bedi *et al.* 2011; Kim *et al.* 2011, 2013a, 2015; Pellkofer *et al.* 2011; Lindsey *et al.* 2012; Ip *et al.* 2013; Yang *et al.* 2013; Collongues *et al.* 2015; Radaelli *et al.* 2015; Zephir *et al.* 2015]. The main results of studies, all including at least five NMO patients, are summarized in Table 1. Except for two of the studies [Cree *et al.* 2005; Jacob *et al.* 2008], all patients meet the 2006 NMO criteria [Wingerchuk *et al.* 2006]. The studies show a strong reduction in the annualized relapse rate (ARR) in a wide range of follow up, from 12 to 60 months. In four studies, the mean ARR was null, and patients were free from relapse in a mean 60% of cases. Disability, evaluated by the Expanded Disability Status Scale (EDSS), was improved in most of the studies, except for two. In the study by Lindsey and colleagues, two patients experienced a major impairment from EDSS, from 3.5 to 8.3 and 0 to 8.0, respectively, that raises the question of the time period between relapse and EDSS evaluation, because these data are not provided in the study. [Lindsey *et al.* 2012]. For example, in the study by Bedi and colleagues, EDSS data were used only when the assessments were made at least 1 month before, or after, an exacerbation [Bedi *et al.* 2011]. Therefore, these data do not support classifying the disability as residual. In the study by Pellkofer and colleagues, one patient died due to cardiovascular failure that could impact the overall results in this cohort of 10 patients [Pellkofer *et al.* 2011].

In addition, timing of relapse after RTX treatment needs to be considered, as for Lindsey and colleagues, three patients had relapse within the first month after RTX [Lindsey et al. 2012], and for Pellkofer and colleagues, one patient died during the first month after RTX induction [Pellkofer *et al.* 2011].

Another caveat is that most of these studies have included patients who received interferon (IFN) before RTX that could artificially worsen the course of NMO before RTX and therefore inflate the efficacy of RTX. The absence of precision concerning the time between relapse and EDSS pre-RTX could also drive the same conclusion.

Rituximab in the area of predictive factors of disability

A retrospective study has defined the effect of IS treatment in NMO and NMOSD, that is, longitudinally extensive transverse myelitis or optic neuritis with AQP4 antibodies, on ARR [Mealy *et al.* 2014]. Modalities of prescription were made with respect of at least 6 months of treatment for azathioprine (AZA; $n = 32$) or mycophenolate mofetil (MMF; $n = 28$), and 1 month for RTX ($n = 30$). After a mean follow up of 2 years, RTX reduced the ARR of 88.2% and a complete remission was observed in 66%. The MMF reduced the ARR of 87.4% and AZA of 72.1%. The comparative analysis of the efficacy related to RTX; MMF and AZA show a similar efficacy to MMF and RTX but a lower efficacy of AZA alone. It was noted that refractory patients could be responders to RTX, despite a nonresponse of MMF or AZA prescribed as a first-line therapy.

Another study has found that the time to next attack in 58 patients with NMO or NMOSD was independently increased by 1.31 times (95% confidence interval (CI) 1.02–1.67, $p = 0.035$) with each additional cumulative attack experienced, by 5.34 times (95% CI 1.57–18.13, $p = 0.007$) with combined AZA treatment and continued oral prednisolone, and by 4.26 times (95% CI 1.09–16.61, $p = 0.037$) with RTX treatment [Kim *et al.* 2013b. Interestingly, the multivariate analysis did not find any association with AZA alone, mitoxantrone, MMF, IFNβ, cyclophosphamide or methotrexate.

Concern on the use of rituximab in neuromyelitis optica

An important point is that subsequent studies reported patients who experienced a severe relapse

Table 1. Main open-label studies on rituximab in neuromyelitis optica.

	Number of Patients	Patients with anti-aquaporin-4 antibodies	Patients naïve of any treatment before RTX[1]	Mean or median time of follow up	Mean or median ARR pre-RTX	Mean or median ARR post-RTX	Patients relapse free (%)	Median EDSS score pre-RTX	Median EDSS score post-RTX	Add-on therapy
Cree *et al.* [2005]	8	NA	4	12 (m)	2.6 (med.)	0	6 (75)	7.5	5.5	No
Jacob *et al.* [2008]	25	14	7	19 (med.)	1.7 (med.)	0	13 (52)	7	5	Yes
Pellkofer *et al.* [2011]	10	10	2	29 (m)	1.7 (m)	0.93 (m)	4 (40)	6.5	7	Yes
Bedi *et al.* [2011]	23	15	3	32.5 (med.)	1.87 (med.)	0	17 (74)	7	5.5	No
Kim *et al.* [2011]	30	21	20	24 (m)	2.4 (m)	0.3 (m)	21 (70)	4	3	No
Lindsey *et al.* [2012]	9	6	0	16.5 (med.)	2 (med.)	2 (med.)	3 (33)	3.5	4.5	Yes
Ip *et al.* [2013]	7	4	5	24 (med.)	1.38 (med.)	0.69 (med.)	5 (71)	8	7	No
Yang *et al.* [2013]	5	4	0	12 (m)	1.16 (m)	0	5 (100)	4.5	4	No
Kim *et al.* [2013]	30	23	20	60 (med.)	2.4 (m)	0.3 (m)	18 (60)	4	3	No
Kim *et al.* [2015]	100[2]	94	NA	67 (med.)	2.4 (m)	0.1 (m)	70 (70)	4	3	Yes[3]
Zephir *et al.* [2015]	32[2]	28	32	28.7 (m)	3.8 (m)	0.1 (m)	25 (78)	6	3.5	No
Radaelli *et al.* [2015]	21[2]	17	4	48 (m)	2	0.16	12 (57)	5.5	4	No
Collongues *et al.* [2015]	21	19	0	31 (m)	1.3 (m)	0.4 (m)	11 (52)	5	3	Yes[4]

RTX, rituximab; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; NA, not available; m, mean; med., median.
[1]Naïve patients include patients without any treatments or patients treated with immunomodulators (interferon β, glatiramer acetate or immunoglobulin) before RTX.
[2]It included definite 2006 neuromyelitis optica (NMO) patients but also limited forms of NMO with anti-aquarporin-4 antibodies.
[3]Three patients received mitoxantrone and one received cyclosporine and corticosteroids during RTX therapy.
[4]Two patients received corticosteroids or mycophenolate mofetil during RTX therapy.

3 months after the last RTX infusion [Capobianco *et al.* 2007; Nasir *et al.* 2009], or posterior reversible encephalopathy syndrome 24 hours after the first infusion [Sanchez-Carteyron *et al.* 2010; Berger *et al.* 2014]. These observations lead to the hypothesis that B cells could have an anti-inflammatory effect whereas the relapses were T-cell mediated. Another possibility is that RTX leads to anti-AQP4 release, and transiently enhances the pool of these pathogenic antibodies [Nakashima *et al.* 2011]. These data are offset by those of another study that showed a decrease in anti-AQP4 antibodies in three out of four patients treated with RTX; the fourth patient experienced a relapse 27 and 99 days after RTX and elevated anti-AQP4 antibodies [Jarius *et al.* 2008].

Monitoring

In the literature, a single-induction protocol is insufficient to suppress disease activity as shown by the high number of patients who experience relapses early after the first course of RTX. For example, in the Bedi study, among four patients who had induction with 4-weekly doses of RTX, two patients relapsed just short of their planned retreatment at 12 months. These two patients who relapsed short of 1 year have not been retreated at 6 months [Bedi *et al.* 2011]. In contrast, administration of RTX doses biweekly every 6 months has resulted in an impressive absence of relapses, and disease stability.

Optimizing maintenance therapy with rituximab

There is an absence of a standardized RTX protocol in NMO. In clinical practice, its use is driven by the experience acquired in each center by each physician. There is a general agreement that the induction phase should be based on the infusion of about 2 g during 1 month, consisting of either 1 g, 2 weeks apart or 375 mg/m^2 every week for 4 consecutive weeks. The maintenance regimen is a matter of debate, as it is not mentioned in most of the studies. Protocols differ from one another: reinfusion of RTX (375 mg/m^2) could be used when the CD27+ memory B-cell frequency was at least 0.05% in peripheral blood mononuclear cells [Kim *et al.* 2011, 2013b], or 2 g RTX divided into two biweekly infusions every 6–9 months or when the CD19 population was greater than 0.1% [Pellkofer *et al.* 2011; Mealy *et al.* 2014], or every 6–9 months based on clinical status and the patient's preference [Ip *et al.* 2013], or a 100 mg infusion once a week for 3 consecutive weeks depending on circulating B-cell repopulation [Yang *et al.* 2013]. In this last study, including 30 patients with MS or NMO, the mean number of days after a 100 mg dose of RTX until the CD19 population was greater than 2% was 99 ± 36 days (range 43–172), compared with 184 ± 72 days (range 106–288) after a 1000 mg dose of RTX. One study shows that the effect of altered body composition on drug disposition and therapeutic outcome could be associated with an increase in body mass index [Collongues *et al.* 2015]. These data are consistent with a previous study that showed that low doses of RTX were associated with a high rate of early B-cell repopulation [Greenberg *et al.* 2012]. As suggested by Kim and coworkers, repopulation of CD19+ B cells could not be a determining factor to ensure RTX efficacy [Kim *et al.* 2013a]. Nevertheless, CD19+/CD27+ memory B cells could be of interest in monitoring RTX pharmacodynamics. This approach is only used in Korea and further studies are needed to confirm these findings [Kim *et al.* 2011, 2013a] whereas in a large study including 100 NMOSD patients, 11 relapses in nine patients occurred during periods where memory B-cells were below the therapeutic target [Kim *et al.* 2015]. The same team has showed that the FcγR3A-158F allele, coding for FcγR present on immune cells, was associated with a risk of insufficient memory B-cell depletion and a short retreatment interval during the initial 2 years [Kim *et al.* 2015].

Interestingly, some studies have reported that nonresponse to RTX in patients with rheumatoid arthritis was correlated with higher circulating preplasma cell numbers at baseline and incomplete B-cell depletion [Dass *et al.* 2008; Vital *et al.* 2010]. At last, a recent study has shown that CD19+/CD24high/CD38high B cells' (regulatory B cells) quantities and functions were impaired during relapses in NMO [Quan *et al.* 2015]. In these patients, RTX led to the repopulation of B cells, which was characterized by the predominance of regulatory B cells. Therefore, RTX restored the numerical balance between regulatory and memory B cells in favor of regulatory B cells. This mechanism could be a way to research and closely monitor the efficacy of RTX in NMO.

Expert opinion

At this level of our knowledge and according to the pharmacodynamics of RTX, we could advise

to start with an induction phase consisting either of 1 g, 2 weeks apart, or 375 mg/m^2 every week for 4 consecutive weeks, which could have a rapid and profound effect on B-cell depletion.

Despite the absence of consensus, it seems reasonable to perform a count of CD19+ B cells every 3 months and to reinfuse the patients as soon as CD19+ B cells become detectable. The advantage of this approach is related to its feasibility in centers, contrary to the threshold of CD19+/CD27+ memory B cells corresponding to 0.05% of peripheral blood mononuclear cells (PBMCs), that requires being able to detect very few cells in the serum and needs technique standardization of flow cytometry. Furthermore, the count of CD19+ B cells includes the CD19+/CD27+ ones. The posology of the infusion for the maintenance therapy is a matter of debate. We propose to consider the posology of 1 g as a dose effect that has been suggested in many studies and seems to be a good compromise in preventing underdosing therapy. In the near future, new biomarkers like the FcγR3A-158F allele could impact the therapeutic strategy with RTX.

Safety

The tolerability of RTX is well established in several autoimmune diseases, especially rheumatoid arthritis. The main side effects are reaction to infusion, opportunistic and nonopportunistic infection. Infusion reactions are very common but can usually be managed by pretreatment with IV steroids, antihistamine and slow titration of RTX. A large number of infections has been reported, mostly herpetic rashes and tuberculosis, but also progressive multifocal leukoencephalopathy (PML). The risk of PML in rheumatoid arthritis is calculated to be 1/25,000 [Clifford *et al.* 2011]. To date, the only case of NMOSD reported was on AZA [Flanagan and Weinshenker, 2014]. Data concerning tolerability of RTX specifically in NMOSD are scarce. Overall, the adverse events profile of RTX in NMO appears to be consistent with the known safety profile of the drug. Only two studies recorded fatal outcomes in RTX-treated NMO patients: one patient died from septicemia [Jacob *et al.* 2008], and another to presumed cardiovascular failure that occurred 3 days after an RTX infusion [Pellkofer *et al.* 2011]. However, it is difficult to attribute this last side effect to RTX.

Efficacy and safety in children with neuromyelitis optica

There are few data concerning only NMO and RTX. However, several other diseases are frequently treated by RTX in children, especially juvenile arthritis and nephrotic syndrome [Basu *et al.* 2015; Sakamoto *et al.* 2015]. Tolerance is good in these different populations. Although there are different dose regimens, the recommended dose in children is 375 mg/m^2 weekly for 4 weeks, with additional infusions depending on the CD 19+B-cell count to maintain immunosuppression.

In the few studies focused on NMOSD, children treated with RTX demonstrated significant reductions in the relapse rate, with 60–70% of patients remaining relapse free, and stabilization or improvement of disability [Mahmood *et al.* 2011; Kimbrough *et al.* 2012; Kavcic *et al.* 2013; Longoni *et al.* 2014]. The main question remains what to use for maintenance therapy, as for adults. There is no clear identified strategy on NMO, but in nephrotic syndrome, Basu and colleagues recently recommended a treatment with MMF following induction with RTX. Such strategies could be proposed in NMOSD [Basu *et al.* 2015].

Questions unresolved and futures directions of research

Gender effect

Several studies on lymphoma have shown a gender-dependent difference in RTX PK [Jager *et al.* 2012; Muller *et al.* 2012]. It is characterized in females by a higher minimal concentration and area under the curve than in males, both in the induction and maintenance phases. Modification of PK was also followed by a better quality of response. Interestingly, these effects were observed only in premenopausal and not postmenopausal women and occur independently of weight [Gisselbrecht *et al.* 2012]. Further studies are needed to confirm these data on PK and efficacy.

Subcutaneous route

IV administration is related to a prolonged infusion time and a reduced autonomy for patients. A more convenient administration would be the oral route, but is limited by the degradation of RTX in the gastrointestinal tract and its inefficient diffusion through the intestinal epithelium.

The subcutaneous (SC) administration fulfills criteria to improve acceptability in patients compared with the IV route, including a shorter infusion time (~5 min *versus* 150 min or more) and the possibility to treat at home, facilitating a better autonomy for patients. The SC doses for RTX are fixed doses ranging from 1400 to 1600 mg, to compensate for the portion lost during the absorption phase (~40%). This formulation has been tested in patients with follicular lymphoma and chronic lymphocytic leukemia with comparable PK and tolerability with the IV route [Davies *et al.* 2014; Salar *et al.* 2014; Assouline *et al.* 2015].

New monoclonal antibodies targeting B cells

New generations of anti-CD20 antibodies that have enhanced immune-mediated activities are now under development in clinical trials for hematologic neoplasm or relapsing–remitting MS. Ocrelizumab is a humanized mAb, which binds to the large loop of the CD20 molecule. The epitope is overlapping with the binding site of RTX and depletes B cells by ADCC, whereas RTX acts more in a CDC manner, which is due to differences in the Fc portion of the antibodies. Positive results in a phase II trial in MS [Kappos *et al.* 2011] have allowed procedure of two phases III studies that are in progress [ClinicalTrials.gov identifiers: NCT01247324 and NCT01194570]. The fully human anti-CD20 antibody is called ofatumumab. It binds to an epitope distinct from that of ocrelizumab or RTX, located in both the small and large loops of the CD20 molecule. Ofatumumab increased complement activation potential, particularly in the presence of low CD20 expression levels [Teeling *et al.* 2006]. The cytotoxicity *in vitro* is superior to RTX, since ofatumumab was able to deplete RTX-resistant B-cell lines [Wierda *et al.* 2011; Bologna *et al.* 2013; Barth *et al.* 2015]. Two phase II studies are ongoing to establish the relation between the dose and efficacy after IV or SC administration in the field of MS [ClinicalTrials.gov identifiers: NCT00640328 and NCT01457924]. At last, obinutuzumab (GA101), a humanized and glyco-engineered mAb, shows increased binding to FcγR3A, enhanced NK-mediated ADCC and increased direct cell-death induction [Mossner *et al.* 2010]. This drug is tested in a phase II study in the maintenance treatment of patients with a central nervous system lymphoma [ClinicalTrials.gov identifier: NCT02498951].

Another innovative drug called MEDI-551 is a humanized mAb that binds to the B-cell-specific antigen CD19. Contrary to RTX, it results in depletion from pre-B cells to plasmablasts, these last being responsible for the production of autoimmune antibodies involved in NMOSD. Furthermore, the affinity-optimization and α-fucosylation of CD19 enhanced the ADCC resulting in a lower effective dose than RTX [Ward *et al.* 2011]. This product is in entered in a phase IIb in NMOSD and phase I in the relapsing form of MS [ClinicalTrials.gov identifiers: NCT02200770 and NCT01585766].

Conclusion

This review underlines the efficacy and tolerance of RTX in NMOSD. This treatment is widely recognized as the best second-line therapy in this rare disease despite lack of class A evidence from therapeutic trials. Due to the severity of the disease, placebo-controlled trials appear unethical. However, several questions remain open, including the use of this treatment as a first-line therapy, especially after the first relapse in patients with AQP4-positive antibodies. We have also to better understand the maintenance therapy program and the surveillance dosage in order to detect and prevent a possible new relapse. Finally, new anti-CD20 drugs such as ocrelizumab or ofatumumab should be tested, as fewer side effects, especially infusion reactions, have been described with these humanized monoclonal antibodies.

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