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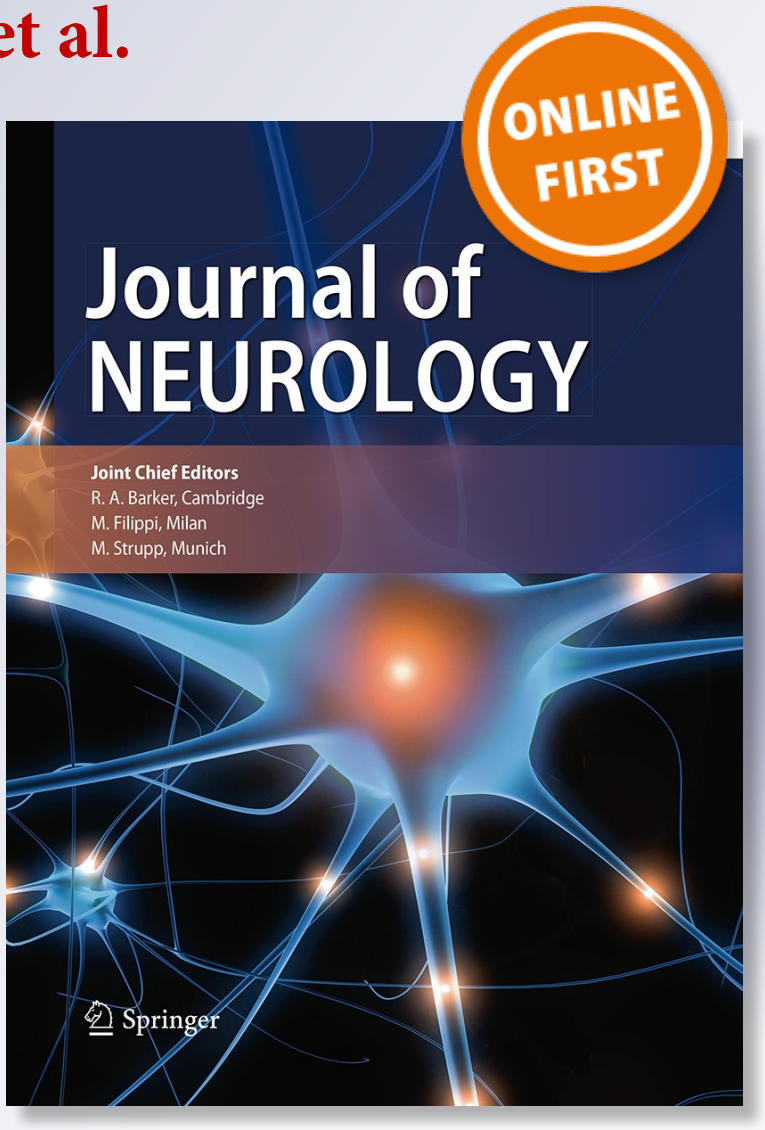

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ORIGINAL COMMUNICATION

Rituximab as first-line therapy in neuromyelitis optica: efficiency and tolerability

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Abstract Neuromyelitis optica (NMO) is a life-threatening disease without any validated treatment strategy. Recent retrospective studies suggested the efficacy of B cell depletion without any distinction between first-line or rescue therapy. To assess whether rituximab as first-line therapy in NMO could efficiently control the occurrence of relapses. A retrospective analysis of NMO patients from NOMADMUS network found 32 patients receiving rituximab as first-line therapy. Main measures were number of relapse-free patients, changes in the annualized relapse rate (ARR), and changes in the EDSS. Tolerance was reported. At baseline, NMO patients were 45 ± 12.1 years old, with a sex ratio of 5.4, and 87.5 % of them had AQP4 antibodies. The median disease duration was 6.5 months (1–410), the mean EDSS was 5.8 ± 2.4 and the mean ARR was 3.8 ± 4.3. After rituximab with a mean follow-up of 28.7 ± 21 months, twenty-seven patients (84.3 %) were relapse free. Patients presented a 97 % decrease of ARR ($p = 0.00001$). EDSS decreased significantly to 3.9 ± 2.6 ($p = 0.01$). No relevant side effect was noted. New retrospective data are presented on RTX use in NMOSD. When used as first-line therapy RTX is highly effective and well tolerated.

Keywords Neuromyelitis optica · Rituximab · Immunosuppression · Aquaporin 4 · Relapse free · B Cell depletion

On behalf of SFSEP and NOMADMUS.

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Introduction

Neuromyelitis optica (NMO) is a life-threatening disease. Neurological disability is a direct consequence of acute attacks. It is postulated that avoiding attacks will diminish disability burden. In the same way attacks free patients may be considered in a remission state. In spite of a large body of retrospective studies suggesting that immunosuppression may benefit NMO patients, no treatment is currently validated as efficient [1]. Azathioprine is the most widely used therapy worldwide but, in the last decade, some case series have reported the potential interest of mitoxantrone, mofetil mycophenolate, rituximab, and tocilizumab [2–12]. The presence of aquaporin 4 (AQP4) antibodies as a specific pathological marker of the disease led researchers to consider the role of B cells in NMO pathology [13]. The potential effect of rituximab, an anti-

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CD20 monoclonal antibody, remains discussed [4, 5, 7–11] but, fortunately, randomized clinical trials with anti-CD20 and other biologics are ongoing (see clinicaltrial.org, NMO as key word).

Although the odds of confirming the interest of anti-CD20 therapy in NMO with those RCT are high, the question of the optimal strategy will not be solved, especially the interest of rituximab use as first-line therapy, and the need for long-term maintenance.

Here, we perform a retrospective study to test the hypothesis that rituximab efficacy is optimal when it is used as first-line therapy, especially when a systematic maintenance regimen is followed. Our results will be compared with published data.

Methods

As part of the NOMADMUS network (French collaborative network), we looked for NMO patients who had received RTX as first-line therapy between 2007 and 2014, irrespective of the regimen used. Wingerchuck's 2006 diagnosis criteria for NMO and NMOSD (NMO spectrum disorder) were used [14, 15]. A relapse was defined by a new neurological symptom that occurs 1 month after a previous relapse. An increase or at least 1 point of the EDSS scoring scale was required or an increase or 1 point of 2 functional score. Due to the time required for testing RTX efficacy any clinical relapses occurring in the first month after a first rituximab infusion were not considered as our study defined relapse. First-line therapy corresponded to the first immunosuppressant drug used for these patients. Patients having received intravenous corticosteroid pulses or plasma exchanges to manage relapses were not excluded. Receiving any potential modifying therapies, such as immunomodulating or immunosuppressant drugs or long-term oral prednisone before rituximab was an exclusion criterion. Biological status for AQP4 and myelin oligodendrocyte glycoprotein (MOG) antibodies was determined using a cell-based assay. The French data protection authority approved the study. All patients gave their written informed consent to participate in the study. This study has been perfomed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and its later amendment.

Two rituximab regimens were used: 375 mg/m^2 infused once per week for 4 weeks and 1000 mg infused twice, with a 2-week interval between the infusions. Consolidation regimens were 375 mg/m^2 infused once per week for 4 weeks, or 1000 mg infused twice with a 2-week interval between the infusions, or 1000 mg infused only once.

These regimens were based on the use of rituximab in rheumatology and haematology, and the previously reported series of patients with NMO [7, 16]. After rituximab, when relapse occurred, the patient received one pulse dose of methylprednisolone intravenously and/or plasma exchanges. No patient received long-term oral prednisone before or after rituximab introduction.

The primary objective of the study was to evaluate the effect of rituximab on relapse occurrence at maximal follow-up, using the percentage of relapse-free patients. Secondary objectives were to evaluate the annualized relapse rate (ARR calculated as the number of relapses from onset disease to rituximab introduction, divided by the duration disease in years) before and after rituximab, the EDSS variation, the delay to the first relapse after rituximab and the tolerance of the biotherapy.

Statistical analyses used Wilcoxon-rank tests to compare ARR and EDSS before and after rituximab, but also to compare disease duration between some subgroups of patients. Fisher's exact test was used to compare distribution between groups.

Results

The whole cohort

Thirty-two NMO patients were included. All patients were immunomodulatory or immunosuppressant treatment-naïve and satisfied the criteria for NMO and NMOSD [14, 15]. The sex ratio was 5.4 females per male and 27 NMO patients (87.5 %) had serum anti-AQP4 antibodies. Among the 5 patients presenting a negative status for anti-AQP4, 3 had serum anti-MOG reactivity. The characteristics of patients according to their status for AQP4 IgG are shown in Table 1.

Demographic features of the whole cohort are displayed in Table 1. The mean number of relapses was 2.7 ± 1.8 before receiving rituximab treatment. In the year before rituximab initiation, the mean number of relapses was 2 ± 1. Twenty patients (62.5 %) received 1 g of rituximab intravenously twice at an interval of 15 days at baseline and 12 patients (37.5 %) received 375 mg per m^2 per week during 4 weeks at baseline. One patient died 1 month after the first infusion of rituximab, all the other patients were followed for at least 6 months: 90.6 % of the patients ($n = 29$) were followed for at least 12 months, 65.6 % ($n = 21$) for 18 months and 43.7 % ($n = 14$) for more than 24 months. Five patients (15.6 %) had only one relapse after rituximab with a median delay of 6 (0.4–22) months. Two patients presented 1 relapse 15 days after first rituximab infusion and were not considered as study defined relapses. If we did not consider these relapses as failure therapy because B cell depletion could not have been efficient yet, the percentage of disease-free patients is

Table 1 Clinical characteristics of the patients according to their biological status for AQP4 antibodies

	Whole cohort ($n = 32$)	AQP4 Ab negative status ($n = 5$)	AQP4 Ab positive status ($n = 28$)	p value*
Sex ratio	5.4	4	5.75	ns
Mean age ± SD (years)	45 ± 12.1	34 ± 16	42.5 ± 14.2	ns
Median disease duration (months)	6.5 (1–410)	10 (5–148)	5 (1–410)	ns
Mean ARR ± SD at baseline	3.8 ± 4.3	2.91 ± 1.7	3.93 ± 4.68	ns
Mean EDSS ± SD at baseline	5.8 ± 2.4	4.9 ± 2	5.95 ± 2.48	ns
Mean follow-up ± SD (months)	28.7 ± 21	15.8 ± 4.9	31.2 ± 22	ns
Relapse-free patients (%)	25 (78)	5 (100)	21 (75)	ns
Mean ARR ± SD at last follow-up	0.1 ± 0.2	0.01 ± 0.02	0.13 ± 0.25	ns
Mean EDSS ± SD at last follow-up	3.9 ± 2.6	4.9 ± 3.4	3.7 ± 2.4	ns

Ab antibody, *AQP4* aquaporin 4, *ARR* annualized relapse rate, *EDSS* expanded disability status scale, *ns* not significant

* Comparison between AQP4 negative and AQP4 positive populations

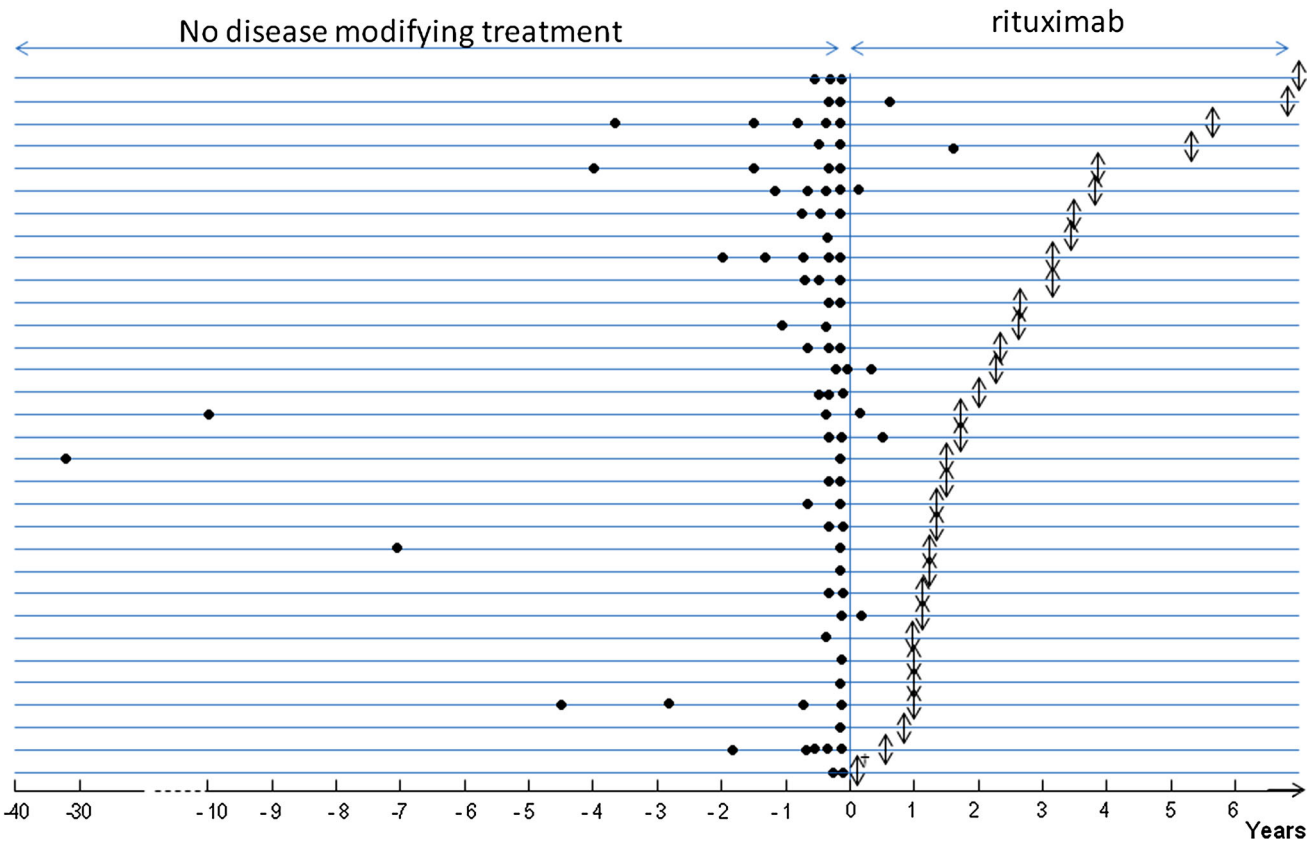

Fig. 1 History of relapses before and after rituximab initiation for the whole cohort of NMO patients. Each *line* corresponds to one patient and illustrates his/her history from the first NMO relapse to the end of follow-up after rituximab initiation. Relapses are indicated by *black dots* and the end of follow-up is marked by *black arrows*. One patient died 1 month after rituximab initiation *tagger*

84.3 %. Figure 1 shows the relapse history of each patient before rituximab and at maximum follow-up after treatment. Rituximab dramatically reduced the mean ARR (97 %; $p < 0.00001$). The EDSS score was significantly reduced after rituximab therapy ($p = 0.01$). The treatment was well tolerated. No serious infectious complications were noticed, but 1 patient died. That death occurred 1 month after the first rituximab infusion was related to

cardiac and respiratory failure due to very extensive myelitis reaching the medulla oblongata but not to an infectious side effect. No serious side effect was notified as being related to the immunosuppressive therapy.

Comparison between patients who received rituximab after the first relapse and the others

Most of the patients received rituximab after at least 2 relapses, 7 among them (22 %) received it after the first relapse. All of these 7 NMO patients presented NMO-IgG reactivity. Table 2 shows the characteristics of both subgroups. Patients who received rituximab after at least 2 relapses presented a mean of 3.2 ± 1.7 relapses before the baseline. There were no differences between these 2 subgroups in terms of follow-up duration, biological or clinical (ARR, EDSS) parameters (before and after rituximab). For patients receiving rituximab after the first relapse, the ARR dropped by 99 % ($p = 0.00001$) and in those who received rituximab after at least 2 relapses it dropped by 97 % ($p = 0.00001$). The variations of EDSS score were not significantly reduced in both groups.

Subgroup of NMO patients receiving rituximab within 24 months of disease onset

Considering the subgroup of NMO patients who received rituximab within 24 months of the disease onset ($n = 24$) compared to those who received it later ($n = 8$), the only different feature was the ARR at baseline (Table 3), which was higher in the first subgroup. The number of relapses that occurred in the year before rituximab did not differ between the two subgroups. Comparisons showed similar significant percentages of relapse-free patients. The ARR dropped significantly in both groups after treatment but more dramatically in the group receiving the treatment earlier. The variations of EDSS score in both groups were not significant.

Patients receiving maintenance infusions of rituximab

Most patients received maintenance infusions of rituximab ($n = 29$, 94 %). Maintenance infusions were performed between 6 and 9 months. We collected 53 results of B cell counts in 25 patients, performed before the maintenance infusions of rituximab: 39.6 % ($n = 21/53$) showed no CD19 cells. The other B cells counts showed a median value of 19 (1–299). The B cells count of the 7 patients who relapsed after rituximab initiation were not available. At maximum follow-up, none of these 29 patients had switched from rituximab to another disease-modifying drug. They received a mean of 4.2 ± 2.2 curses of rituximab. Only 2 patients from the whole cohort (6 %) received an oral immunosuppressive drug without any maintenance infusion. These 2 patients switched from rituximab to azathioprine for personal convenience 6 months after the introduction of rituximab and not because of side effects or the occurrence of new relapses. Another patient switched to azathioprine but after 24 months of rituximab therapy with maintenance infusion. He presented one relapse 9 months after rituximab initiation but infusions were maintained up to 24 months before switching to azathioprine. Excluding the 2 patients who switched from rituximab early and considering patients who received at least one maintenance infusion of rituximab every 6–9 months after baseline, the effect of rituximab on the decrease of ARR remains highly significant

Table 2 Characteristics at baseline and outcome parameters for patients who received rituximab after the first relapse and those who received rituximab after second relapses

	Patients who received rituximab after 1st relapse ($n = 7$)	Patients who received rituximab after at least 2 relapses ($n = 25$)	p value
Sex ratio	5	5.2	ns
Number of AQP4 positive patients (%)	5 (100)	17 (68)	ns
Mean disease duration ± SD (months)	3 ± 2.2	46.6 ± 87	ns
Mean ARR ± SD before rituximab	2.8 ± 1.8	4.5 ± 5.3	ns
Mean EDSS ± SD before rituximab	5.8 ± 3.4	5.7 ± 1.8	ns
Mean duration of follow-up ± SD (months)	17 ± 9.6	32.2 ± 22.2	ns
Number of relapse-free patients (%)	6 (86)	19 (76)	ns
Mean ARR ± SD after rituximab at maximum follow-up	0.09 ± 0.25	0.12 ± 0.2	ns
Mean EDSS ± SD after rituximab at maximum follow-up	3.4 ± 3.4	4.0 ± 2.3	ns

AQP4 aquaporin 4, *ARR* annualized relapse rate, *EDSS* expanded disability status, *SD* standard deviation

Table 3 Comparison of the subgroups of patients who received rituximab early as first-line therapy, and those who received it later as first-line therapy

	Patients receiving rituximab within 24 months of disease onset			Patients receiving rituximab more than 24 months after disease onset		
Number of patients (%)	24 (75)			8 (25)		
Number of women (%)	20 (83)			7 (87.5)		
Positive status for AQP4 antibodies (%)	17 (70)			7 (87.5)		
Mean age at baseline ± SD (years)	43.3 ± 12			43.3 ± 18		
Mean disease duration ± SD (months)	6.45 ± 5.5			129 ± 120		
Mean number of relapses 1 year before rituximab ± SD	2.1 ± 0.9			1.8 ± 1.2		
Mean duration of follow-up (months ± SD)	29.4 ± 22			26.7 ± 18.5		
Number of patients with ≥1 maintenance infusion (%)	23 (96)			8 (100)		
Number of disease-free patients (%)	19 (79)			6 (75)		
	At baseline	At last follow-up	*p* value	At baseline	At last follow-up	*p* value
Mean EDSS ± SD	5.7 ± 2.6	4 ± 2.7	ns	6 ± 1.7	3.5 ± 2.3	ns
Mean ARR ± SD	4.8 ± 4.5	0.1 ± 0.2	<0.0001	0.62 ± 2.5	0.1 ± 0.3	0.04

AQP4 aquaporin 4, *ARR* annualized relapse rate, *EDSS* expanded disability status

(3.10 ± 2.4 before treatment and 0.1 ± 0.2 after treatment, $p < 0.00001$). In this subgroup of patients, the EDSS also had decreased significantly at last follow-up (from 5.6 ± 2.4 to 3.9 ± 2.7 after rituximab, $p = 0.01$) and 24 of these patients (80 %) remained relapse free at last follow-up.

Comparison of other subgroups of patients

The characteristics of AQP4 IgG positive patients are presented and compared with those of AQP4 IgG negative patients in Table 1. No significant difference in clinical features or outcome parameters was found between the two subgroups. Table 4 reports the clinical characteristics of patients having presented at least one relapse after rituximab initiation ($n = 7$) and those who remained relapse free after rituximab ($n = 25$). No significant difference was found between these two subgroups, although the mean ARR at baseline appeared higher (but not significantly so) in the subgroup of patients with relapse after rituximab.

Discussion

In this multicentre study, we confirmed the potential efficacy of rituximab as a first-line disease-modifying immunosuppressant drug when NMO or NMOSD was diagnosed. A high proportion of patients received maintenance infusions every 6–9 months. This efficacy was reflected by a high proportion of relapse-free patients (84.3 %) and a dramatic decrease (more than 97 %) of the ARR at maximum follow-up. We also underline a beneficial effect of rituximab on EDSS score.

To date in NMO, no treatment is supported by class I evidence. B cell depleting biotherapies have been tested in case studies since there is a specific NMO-IgG activity. Nevertheless, the mechanism by which this potentially beneficial effect occurs is not clearly understood. Previous studies testing rituximab in NMO included 57–100 % of NMO-IgG positive patients and a preponderance of females. We found a high proportion of NMO-IgG positive patients (87.5 %) and a female to male ratio of more than 5.

Because the consequence of the disease is directly related to the relapses occurrence we choose to appreciate the efficacy of this first-line therapy by firstly the percentage of patients who remained relapse free at last follow-up and only secondarily the ARR. We found a particularly high percentage of relapse-free patients and the ARR decrease was one of the highest reported in the literature, 84.3 vs 15.7 % of treatment failure. As compared to previous studies our cohort included the higher number of patients and displayed a higher inflammatory activity. It may explain differences with reported disease efficacy (60–100 % of disease-free patients in cohorts with 5–30 NMO patients) [8–10]. A retrospective comparison between azathioprine, mycophenolate mofetil (MMF) and rituximab was made by Mealy et al. in NMO patients who had similar ARR when first immunosuppression was considered, but some of these patients had received

Table 4 Patients who presented at least one relapse compared with those who were relapse free after rituximab

	Patients with at least one relapse after rituximab (22 %, $n = 7$)	Patients relapse free after rituximab (78 %, $n = 25$)	p value
At baseline			
Percentage of women	100	80	ns
Positive status for AQP4 antibodies (%)	85	92.8	ns
Mean age at baseline ± SD (years)	42.7 ± 13.3	40.7 ± 15.1	ns
Mean disease duration ± SD (months)	32.3 ± 54.3	38.44 ± 85	ns
Mean EDSS at baseline ± SD	6.5 ± 1.4	5.6 ± 2.5	ns
Mean ARR at baseline ± SD	6.9 ± 7.9	2.9 ± 2.2	ns
Mean number of relapses one year before rituximab ± SD	2 ± 1	2.03 ± 0.9	ns
At last follow-up			
Number of patients with ≥1 maintenance perfusion (%)	1 (86)	2 (88)	ns
Mean ARR at last FU ± SD	0.46 ± 0.71	0	ns
Mean EDSS at last FU ± SD	4.5 ± 2.14	3.9 ± 2.93	ns

immunomodulating drugs or prednisone treatment before [11]. In our NOMADMUS cohort RTX seems to be more efficacious than MMF since in 64 patients, 63 % remained relapse free (MMF was used as first-line therapy, sometimes with prednisone in the first 6 months). After a median follow-up of 18 months, one death after septicaemia was observed and one patient stopped the treatment after a breast cancer diagnosis [16].

Consecutively to its use as first-line therapy, the disease duration before rituximab was frequently less than 1 year. Therefore, the ARR is not a real but calculated one [for instance, if 2 relapses occur in 6 months the calculated ARR (cARR) is $2 \times 2 = 4$]. It is indeed possible that calculated ARR overestimates the ARR as opposed to the real ARR (rARR). This may explain why we found less efficacy in patients with RTX used after 24 months, and why we preferred to use % of disease-free patients as primary evaluation criteria.

We found 97 % decrease in the ARR. Other authors found between 25 and 95 % reduction of ARR after rituximab [4, 7–11]. The large range in the literature may probably been explained by the heterogeneity of the studies mixing different proportion of NMO patients receiving rituximab as first-line immunosuppressant therapy or as rescue therapy after using immunomodulation, oral prednisone or immunosuppressant drugs [4, 7–11]. We advocate that our homogenous study gives a percentage closer to the reality. Longer follow-up of our patients would have been useful, but more than 90 % of them were followed for more than 1 year.

Because our study and the previous ones were retrospective and uncontrolled, conclusions are subject to caution even though the general view is that B cell depleting therapy could be efficient to delay the next relapse. We did not find any difference of efficacy between patients who received rituximab after only one relapse and those who received it after at least 2 relapses. The NMO patients who received rituximab after only one relapse were all positive for AQP4 IgG antibodies, which made it easy to diagnose the disease faster and lead to start faster the treatment. Kim et al. showed that a longer time to the next relapse was associated with a longer disease duration in their NMO population followed for about 5 years after the disease onset [17]. Moreover, they showed how the use of rituximab also led to a longer time to next relapse, independently of the natural course of NMO and independently of the cumulative number of attacks.

Rituximab was well tolerated and no serious infectious side effects were reported as mentioned in the literature [7, 11]. However, Pellkofer et al. reported more upper respiratory tract infections and VZV recurrences, and 2 deaths due to septic status a few months after rituximab infusions [5]. The greatest experience in the use of rituximab comes from rheumatologists and is based on the management of rheumatoid arthritis [18]. The global rituximab Rheumatoid Arthritis (RA) clinical trial programme reported data from more than 3000 RA patients who had received up to 17 infusions over 9.5 years. They found comparable serious infectious events in patients treated with rituximab plus methotrexate and those treated with methotrexate only. The death rate in the rituximab group was consistent with the death rate expected in the age- and sex-matched general population. In our study, one death was reported 1 month after the first infusion of rituximab. We concluded that death was disease related (vital deficiency due to bulbar lesion) and not RTX related. Whether or not this patient was a RTX non-responder is unknown since the death occurred in the

1 month range where it is difficult to consider that the drug is fully efficacious.

Regarding when and how to prescribe a consolidation treatment, previous studies raised the potential interest of the CD27 cell count [7]. B cell repletion has been measured to occur 6–9 months after rituximab infusion. Some authors wait for B cell repletion or a relapse to re-treat. Moreover, some relapses are described to occur in spite of B cell depletion. Our data suggest that systematic 6–9 months maintenance infusions with rituximab lead to a significant decrease of relapses occurrence and to a significant EDSS decrease. However, our retrospective study did not allow to clearly decide when to perform the maintenance infusions and how to monitor B cells count. This 6–9 month interval between rituximab maintenance infusions came from the usual regimen protocol implemented by rheumatologists and corresponds to the time habitually found for B cell repletion [1]. Using a more sensitive flow cytometry technique Dass et al. assumed that incomplete B cell depletion after 1 perfusion of rituximab was associated with a poorer clinical prognosis [19]. In the present study, we showed that using maintenance infusion between 6 and 9 months is efficient on NMO disease and is associated with good tolerability.

Overall, we highlight the interest of rituximab used as first-line immunosuppressant therapy in NMO and NMOSD to decrease the occurrence of new relapses. Moreover, considering the high risk of disability after relapse and the good tolerance profile when a risk management plan is implemented, we suggest that systematic retreatment after 6–9 months leads to the best benefit to risk ratio.

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Compliance with ethical standards

Conflicts of interest None of authors have conflict of interest with this study.

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