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RESEARCH ARTICLE

A meta-analysis comparing first-line immunosuppressants in neuromyelitis optica

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Abstract

Objective: As phase III trials have shown interest in innovative but expensive drugs in the treatment of neuromyelitis optica spectrum disorder (NMOSD), data are needed to clarify strategies in the treatment of neuromyelitis optica (NMO). This meta-analysis compares the efficacy of first-line strategies using rituximab (RTX), mycophenolate mofetil (MMF), or azathioprine (AZA), which are still widely used. **Methods**: Studies identified by the systematic review of Huang et al. (2019) were selected if they considered at least two first-line immunosuppressants among RTX, MMF, and AZA. We updated this review. The Medline, Cochrane Central Register of Controlled Trials, Embase, and ClinicalTrials databases were queried between November 2018 and April 2020. To be included, the hazard ratio (HR) [95% CI] for the time to first relapse after first-line immunosuppression had to be available, calculable, or provided by the authors. **Results**: We gathered data from 919 NMO patients (232 RTX-,

294 MMF-, and 393 AZA-treated patients). The risk of first relapse after first-line immunosuppression was 1.55 [1.04, 2.31] ($p = 0.03$) for MMF compared with RTX, 1.42 [0.87, 2.30] ($p = 0.16$) for AZA compared with RTX, and 0.94 [0.58, 1.54] ($p = 0.08$) for MMF compared with AZA. **Interpretation**: The findings suggest that RTX is more efficient than MMF as a first-line therapy. Even if the results of our meta-analysis cannot conclude that RTX has a better efficacy in delaying the first relapse than AZA, the observed effect difference between both treatments combined with the results of previous studies using as outcome the annualized relapse rate may be in favor of RTX.

Introduction

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS) that is described as an astrocytopathy leading to the loss of astrocytes associated with extensive tissue damage along with complement deposition and pro-inflammatory cytokine, macrophage, and granulocyte infiltrates.[1–7] This active and debilitating clinical entity leads clinicians to engage in the active management of attacks and to prevent further attacks with immunosuppressants.

Treatment strategies in the management of NMO and NMOSD patients are a popular topic, as several recent phase III clinical trials have shown the efficacy of inebilizumab (anti-CD19), eculizumab (anti-C5 fraction of complement), satralizumab (anti-IL6 receptor), and rituximab (anti-CD20).[8–12] All these innovative drugs were compared to placebo in sometimes add-on treatment strategies. Eculizumab and satralizumab have been recently approved in North America and by the European Medicines Agency for controlling NMOSD activity associated with anti-AQP4 antibodies.

Recommendations in the management of NMO and NMOSD are still not updated and remain to be discussed. Indeed, the recent development of innovative molecules left unsolved the clinical situation of NMO occurring without anti-AQP4 antibodies, as well as the risk of such new therapies in the long term, and raises the important public health question of the cost of such therapies in general and notably in low-income countries. It is interesting to highlight that in France, the French Health Administration called Haute Autorité de Santé (HAS) approved eculizumab for the treatment of active NMOSD refractory to off-label molecules such as AZA, MMF, and RTX (https://www.has-sante.fr/jcms/p_3202348/fr/soliris).

To help further discussions of the treatment strategies in NMO/NMOSD, a few studies have compared the use of RTX, MMF, and AZA to control disease activity. Huang et al.[13] published in 2019 a meta-analysis comparing the immunosuppressants previously used in the treatment of NMO (including cyclosporine, methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil and, in a few patients, rituximab).[13] They concluded that RTX and MMF were superior to AZA and may be recommended as optimal treatments to prevent relapses. This work provided interesting data but had several limitations. The authors considered all immunosuppressants and mixed first-line therapies and cumulative-line conditions. Moreover, the outcome they used was the annualized relapse rate (ARR), while the most recent studies, including phase III clinical trials, used the time to first relapse, which is more appropriate for the objective of disease-modifying drugs in the treatment of NMO. The main limitation was that they concluded that RTX and MMF may be equivalent based on the absence of a statistically significant difference concerning the efficacy of these two immunosuppressants, which could be misleading.

Thus, we designed an updated systematic review and meta-analysis to compare the efficacy of the major immunosuppressants administered, that is, RTX, AZA, and MMF, in the treatment of NMO using the time to first relapse as the main outcome.

Methods

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14]

Search strategy for the selection of eligible studies

First, we considered the studies identified by the systematic review of Huang et al.[13] Briefly, these authors considered all published and unpublished comparative studies, covering at least two interventions among immunosuppressive drugs and monoclonal antibodies, updated to 21 November 2018, in English.[13] We selected studies if they considered at least two immunosuppressants among RTX, MMF, and AZA only in first-line conditions.

Second, we updated this systematic review. The Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and ClinicalTrials databases were queried using the following search terms: (Neuromyelitis

optica spectrum disorder OR Neuromyelitis optica OR NMOSD OR NMO) AND (Rituximab OR Rituxan OR MabThera OR Azathioprine OR Imurel OR Mycophenolate mofetil OR Cellcept) between 21 November 2018, and 28 April 2020, for the time to first relapse literature search. Language was restricted to English or French.

Queries were reviewed by three authors (HZ, JZ, and MC) to assess appropriateness for inclusion; a fourth author (JG) arbitrated any disagreement until consensus was reached.

Inclusion and exclusion criteria

All comparative studies, from randomized controlled trials to prospective or retrospective cohort studies comparing at least two first-line immunosuppressants among RTX, MMF, and AZA in NMO or NMOSD patients, irrespective of the serological status or the outcome used for the comparison of the efficacy of immunosuppressants, were eligible for inclusion. Then, we contacted all the corresponding authors of eligible studies to offer them collaboration and obtain unpublished information. To be included in the analysis, the hazard ratio (HR) for the time to first relapse after first-line immunosuppression had to be available for comparisons between immunosuppressants.

We excluded publications considering specifically patients having MOGAD (MOG autoimmune disease).

Outcome measures and data extraction

In this meta-analysis, we considered the HR for the time to first relapse after first-line immunosuppression to be an outcome of efficacy. Thus, studies were included in the meta-analysis if we obtained the HR [95% confidence interval (CI)] for the time to first relapse. HRs [95% CIs] were obtained in different ways. First, we extracted the data directly when published in the included studies. Second, we computed the HR [95% CI] from Kaplan–Meier curves or plots representing individual data when possible. Third, several corresponding authors of eligible studies provided these statistics. Indeed, most studies, especially older studies, used the ARR as an outcome of efficacy, but data collected for the calculation of the ARR allow the calculation of the HR [95% CI] for the time to first relapse after the start of first-line immunosuppression.

In the same way, we extracted additional information (study design, patient phenotype, sample size, the number of events, follow-up time, anti-AQP4 positivity, age, sex ratio, pretreatment ARR, concurrent use of prednisone, and IS regimen) directly from published data when possible or obtained this information from the corresponding authors of the included studies. We also extracted or obtained data in subgroups including only NMO patients with anti-AQP4 antibodies when possible.

Quality assessment of included studies

Using the Newcastle–Ottawa Scale,[15] two reviewers (JC and MC) independently evaluated the risk of bias of the included study criteria covering selection, comparability, and outcome. A score of 5 or less (out of 9) corresponded to a high risk of bias. A third author (JG) arbitrated any disagreement until consensus was reached.

Statistical analysis

Pooled results were expressed as the HR for the time to first relapse after first-line immunosuppression comparing one IS with another (RTX vs. MMF, RTX vs. AZA, and AZA vs. MMF), with 95% confidence intervals (CIs). For each meta-analysis, the Der Simonian and Laird method was used.[16] Studies were considered a random sample from a population of studies. Statistical heterogeneity was tested for each analysis. The possibility of publication bias was assessed by funnel plot analysis and the Egger test.[17] We conducted meta-regressions to evaluate the impact of a moderator effect that may explain heterogeneity. The moderators studied were the proportion of anti-AQP4 antibody patients, female sex, concurrent use of prednisone, and the mean age and pretreatment ARR of the two-treatment group (except for the studies of Jeong et al.[18] and McCreary et al.[19] for which we used the mean of the pretreatment ARR medians pondered by the number of patients). Finally, we conducted a sensitivity analysis only in anti-AQP4-positive patients.

All analyses were performed using R software and the metafor package (R Development Core Team, 2011; R Foundation for Statistical Computing, Vienna, Austria).

Results

Description of included studies

First, the meta-analysis of Huang et al.[13] identified 10 comparative studies covering at least two interventions among immunosuppressive drugs and monoclonal antibodies in NMO patients updated to 21 November 2018. Among them, we excluded two studies because they did not consider at least two immunosuppressants among RTX, MMF, and AZA.[20,21] Thus, eight studies were eligible for inclusion in our meta-analysis based on the studies identified in the review of Huang et al. (Fig. 1). Second, we updated this review. A total of 373 records were identified from the Medline, CENTRAL, Embase, and ClinicalTrials databases search, including 366 nonduplicated

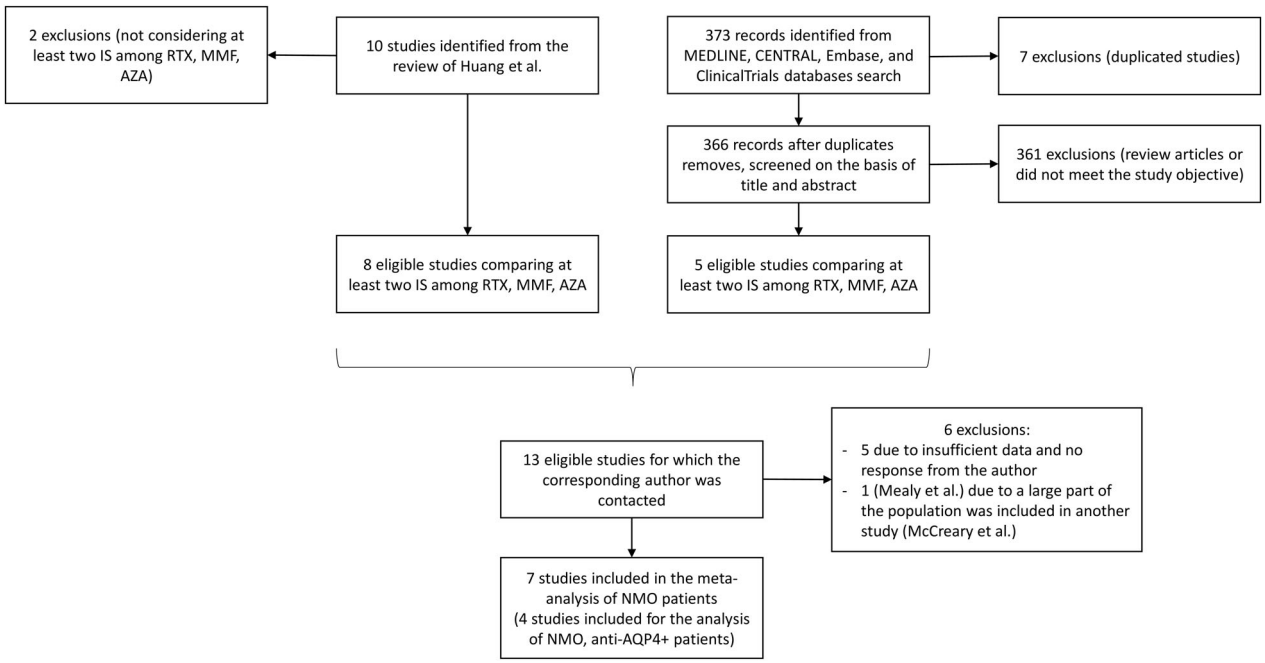

Figure 1. Flow diagram. RTX, rituximab; MMF, mycophenolate mofetil; AZA, azathioprine; NMO, neuromyelitis optica, anti-AQP4+, anti-aquaporin-4-positive.

studies, which were screened on the basis of title and abstract. Among them, we identified five eligible studies. In total, we identified 13 eligible, observational studies, and we contacted the corresponding authors.

Among the 13 eligible studies, 5 were excluded because insufficient data for the calculation of the HR [95% CI] for the time to first relapse were obtained, with no response from the corresponding author.[22–26] One study was excluded, Mealy et al. 2014,[27] because a large part of the population was already included in another study, McCreary et al., 2018,[19] included in this meta-analysis and because of the inability to retrieve data from nonduplicated patients. Finally, seven observational studies comparing at least two first-line immunosuppressants among RTX, MMF, and AZA were included in the meta-analysis of NMO patients: Xu et al., 2016,[28] Chen et al., 2017,[29] Jeong et al., 2016,[18] McCreary et al., 2018,[19] Yang et al., 2018,[30] Stellmann et al., 2017,[31] and Poupart et al., 2020,.[32] Four studies were included for the analysis of NMO and anti-AQP4$^-$positive patients: Jeong et al., 2017,[18] McCreary et al., 2018,[19] Stellmann et al., 2018,[31] and Poupart et al., 2020.[32] For three studies, the HR [95% CI] for the time to first relapse was provided by the corresponding author: Jeong et al., 2016,[18] McCreary et al., 2018,[19] and Stellmann et al., 2018.[31] The data of the publications of Jeong et al.[18] and McCreary et al.[19] were updated in 2020 with additional patients for the meta-analysis. For two studies, HRs were obtained directly from published data: Xu et al., 2016[28] and Poupart et al., 2020.[32] For two studies, HRs were calculated from the published Kaplan–Meier curve, Yang et al., 2018,[30] or published figure showing plots representing individual data, Chen et al., 2017.[29]

The characteristics of the included studies are described in Table 1. The level of evidence was grade 3 for these observational studies. These studies included 919 NMO patients (232 RTX-, 294 MMF-, and 393 AZA-treated patients). Among them, 717 (83.9%) were positive for anti-AQP4.

Quality of included studies

The overall quality of the included studies is summarized in Table 2. Three studies received eight stars, and four studies received nine stars, indicating a very good quality of the observational studies included in the meta-analysis.

Comparison of the efficacy of first-line immunosuppressants

The pooled HR [95% CI] for the time to first relapse after the start of first-line immunosuppression was estimated for every comparison of immunosuppressants. Five studies were used for the comparison between RTX and MMF. We observed a higher risk of first relapse in MMF-treated patients than in RTX-treated patients (HR = 1.55

Table 1. Characteristics of the studies included in the meta-analysis.

Reference	Year	Study design	Level of evidence	Phenotype	IS	Sample size	Number of events, n (%)[b]	Follow-up (months)	Anti-AQP4 positivity, n (%)	Age (years)	Female gender, n (%)	Pretreatment ARR	Concurrent use of prednisone, n (%)	Regimen
Jeong, et al.[18] (Korea)[a]	2015	Monocentric, retrospective cohort	3	NMOSD	RTX	52	18 (34.6)	41 [63]	52 (100)	33.8 ± 13	46 (88.5)	2.0 [1.65]	0 (0)	375 mg/m² infused once/w for 4 w or 1000 mg infused twice at a 2-week interval for induction, then for maintenance 375 mg/m^2 when memory B cells reemerged
					MMF	45	13 (28.9)	31[32]	45 (100)	36.3 ± 10.4	40 (88.9)	1.0 [1.4]	0 (0)	1.5 g–2 g/d
					AZA	47	26 (55.3)	17 [23]	47 (100)	32.8 ± 12.3	39 (83)	1.0 [0.94]	0 (0)	1.75–2.5 mg/kg/d
Chen, et al.[29] (China)	2016	Multicenter, prospective cohort	3	NMO, NMOSD	MMF	105	46 (43.8)	11 [13]	89 (84.8)	44.0 ± 12.1	97 (92.4)	1.2 (0.1–7.0)	49 (46.7)	20 mg/kg/d
					AZA	105	50 (47.6)	16.5 [28.5]	91 (86.7)	41.6 ± 11.9	99 (94.3)	1.4 (0.2–14.6)	89 (84.8)	2 mg/kg/d
Xu Y, et al.[28] (China)	2016	Monocentric, prospective cohort	3	NMOSD	MMF	38	NA	15.2	33 (86.8)	31.6 ± 14	32 (84.2)	0.8 (0.0–3.8)	38 (100)	11.5 g/d
					AZA	119	NA	16.3	110 (92.4)	39.7 ± 13.9	110 (92.4)	0.8 (0.0–8.0)	119 (100)	100 mg/d
Stellmann et al.[31] (Germany)	2017	Multicenter, retrospective cohort	3	NMOSD	RTX	62	23 (37.1)	6.0 [7.8]	54 (87.1)	43.7 ± 14.9	51 (82.2)	NA	0 (0)	Median dose 1000 mg [375–3000] every 6 months
					MMF	8	5 (62.5)	1.9 [6.2]	7 (87.5)	48.1 ± 14.2	5 (62.5)	NA	0 (0)	Median dose 1.5 g/d [1.5–2]
					AZA	42	11 (26.2)	8.2 [13.4]	36 (85.7)	39.2 ± 13.6	38 (90.5)	NA	0 (0)	Median dose 150 mg [50–300]
Yang et al.[30] (China)	2018	Monocentric, prospective cohort	3	NMOSD	RTX	20	7 (35)	28.5 [11.5]	10 (50.0)	40.7 ± 11.4	19 (95.0)	0.9 (0–5.2)	20 (100)	100 mg/w during 4 w for induction and maintenance when memory B cells reappeared
					MMF	30	14 (46.7)	26.5 [15.3]	13 (43.3)	42.6 ± 11.7	26 (86.7)	0.9 (0–5.0)	30 (100)	1 g/d
					AZA	22	12 (54.5)	24 [9.8]	8 (36.4)	39.6 ± 12.0	20 (90.9)	0.8 (0–4.5)	22 (100)	2 mg/kg/d
McCreary et al.[19] (USA)[a]	2018	Multicenter, retrospective cohort	3	NMO, NMOSD	RTX	36	13 (36.1)	8 [20.5]	30 (83.3)	44.4 ± 16.9	31 (86.1)	0.71 [1.9]	0 (0)	NA
					MMF	26	13 (50)	12.5 [26.25]	23 (88.5)	40.8 ± 14.9	23 (88.5)	0.28 [0.82]	5 (19.2)	NA
					AZA	35	21 (60)	12 [28.5]	28 (80)	40.7 ± 16.1	31 (88.6)	0.75 [1.35]	13 (37.1)	NA

(*Continued*)

Table 1 Continued.

Reference	Year	Study design	Level of evidence	Phenotype	IS	Sample size	Number of events, n (%)[b]	Follow-up (months)	Anti-AQP4 positivity, n (%)	Age (years)	Female gender, n (%)	Pretreatment ARR	Concurrent use of prednisone, n (%)	Regimen
Poupart J, et al.[32] (France)	2020	Multicenter, retrospective cohort	3	NMOSD	RTX	62	11 (17.7)	31 [29]	48 (77.4)	41.8 ± 14.3	55 (88.7)	0.99 ± 1.46	3 (4.8)	1 g repeated at 15 days for induction and 1 g for maintenance every 6 months (or anticipated maintenance perfusions every 2–5 months, *n* = 4 according to memory B cells reappearance)
					MMF	42	16 (38.1)	35 [38]	35 (83.3)	41.4 ± 17.6	31 (73.8)	0.71 ± 1.17	8 (19.1)	1 g–2 g/d
					AZA	23	6 (26.1)	25 [26]	12 (52.2)	39.1 ± 14.2	16 (69.6)	0.67 ± 1.46	9 (39.1)	1–2 mg/kg/d

Follow-up, age, and ARR pre-treatment are described as mean ± standard deviation, median [interquartile range] or median (range).

AQP4, aquaporin-4; ARR, annualized relapses rate; AZA, azathioprine; CI, confidence interval; d, day; HR, hazard ratio; IS, immunosuppressant; MMF, mycophenolate mofetil; NA, not available; NMO: neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; RTX, rituximab; w, week.

[a]Data updated using the same methodology as published, provided by the authors.

[b]Number of patients presenting at least one attack after initiation of immunosuppressive treatment.

Table 2. Risk of bias assessment for observational studies.

	Selection				Comparability	Outcome			
Author, Year	1	2	3	4	1	1	2	3	Total score
Jeong et al., 2016[18]	*	*	*	*	**	*	*	*	9
Chen et al., 2017[29]	*	*	*	*	*	*	*	*	8
Xu et al., 2016[28]	*	*	*	*	*	*	*	*	8
Stellmann et al., 2017[31]	*	*	*	*	**	*	*	*	9
Yang et al., 2018[30]	*	*	*	*	*	*	*	*	8
McCreary et al., 2018[19]	*	*	*	*	**	*	*	*	9
Poupart et al., 2020[32]	*	*	*	*	**	*	*	*	9

[1.04, 2.31], $p = 0.032$, p for heterogeneity = 0.31) (Fig. 2). Five studies were used for the comparison between RTX and AZA. We did not observe a difference between groups (pooled HR = 1.42 [0.87, 2.30], $p = 0.16$, p for heterogeneity = 0.10, RTX as reference) (Fig. 3). Seven studies were used for the comparison between AZA and MMF. We did not observe a difference between groups (HR = 0.94 [0.58, 1.54], $p = 0.82$, p for heterogeneity = 0.004, AZA as reference) (Fig. 4).

Publication bias was investigated through funnel plots. We did not observe a significant Egger test for any comparison between immunosuppressants (data not shown).

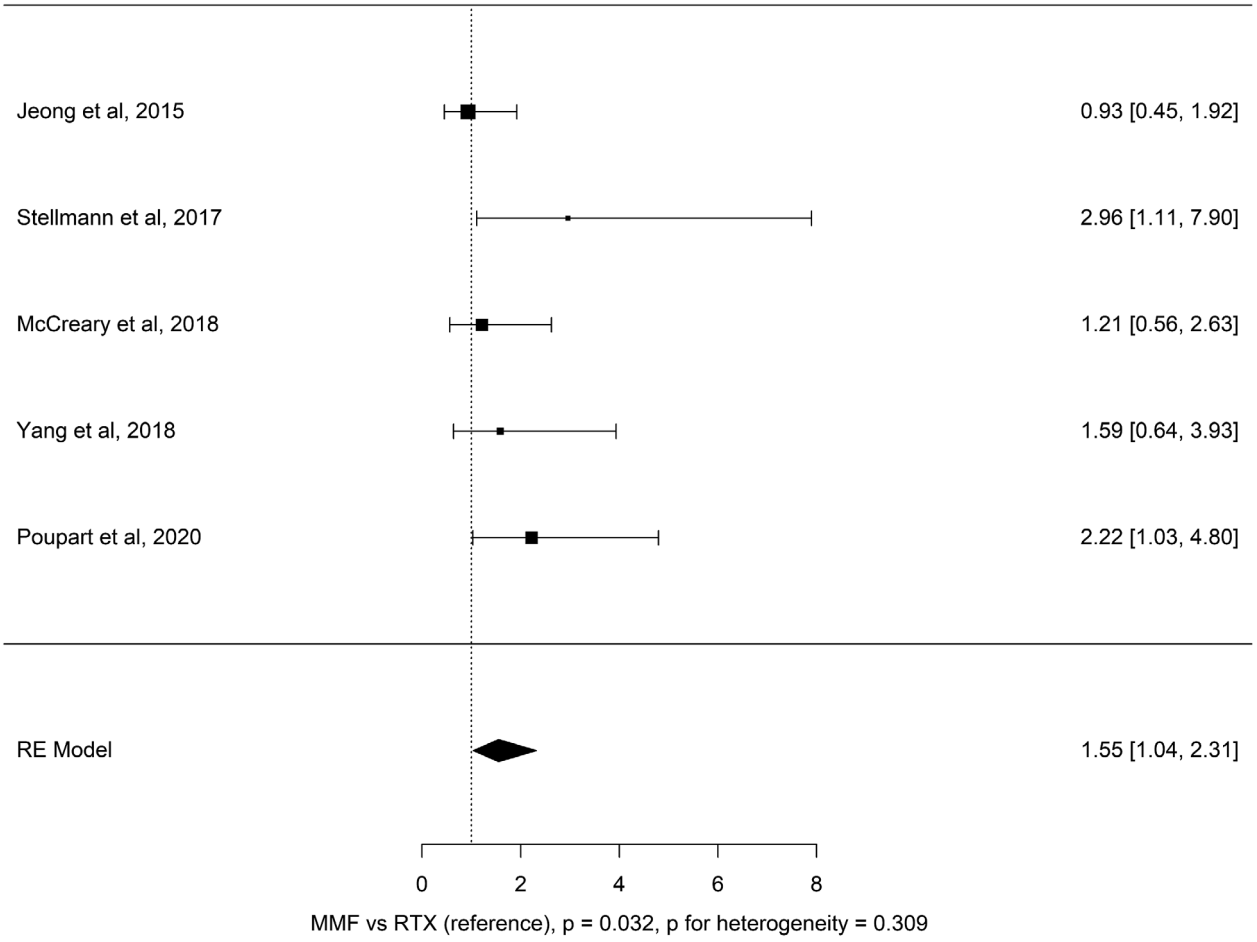

Figure 2. Forest plot of the hazard ratio for the association between the time to first relapse and first-line immunosuppression using mycophenolate mofetil (MMF) or rituximab (RTX) (as reference) in NMO patients.

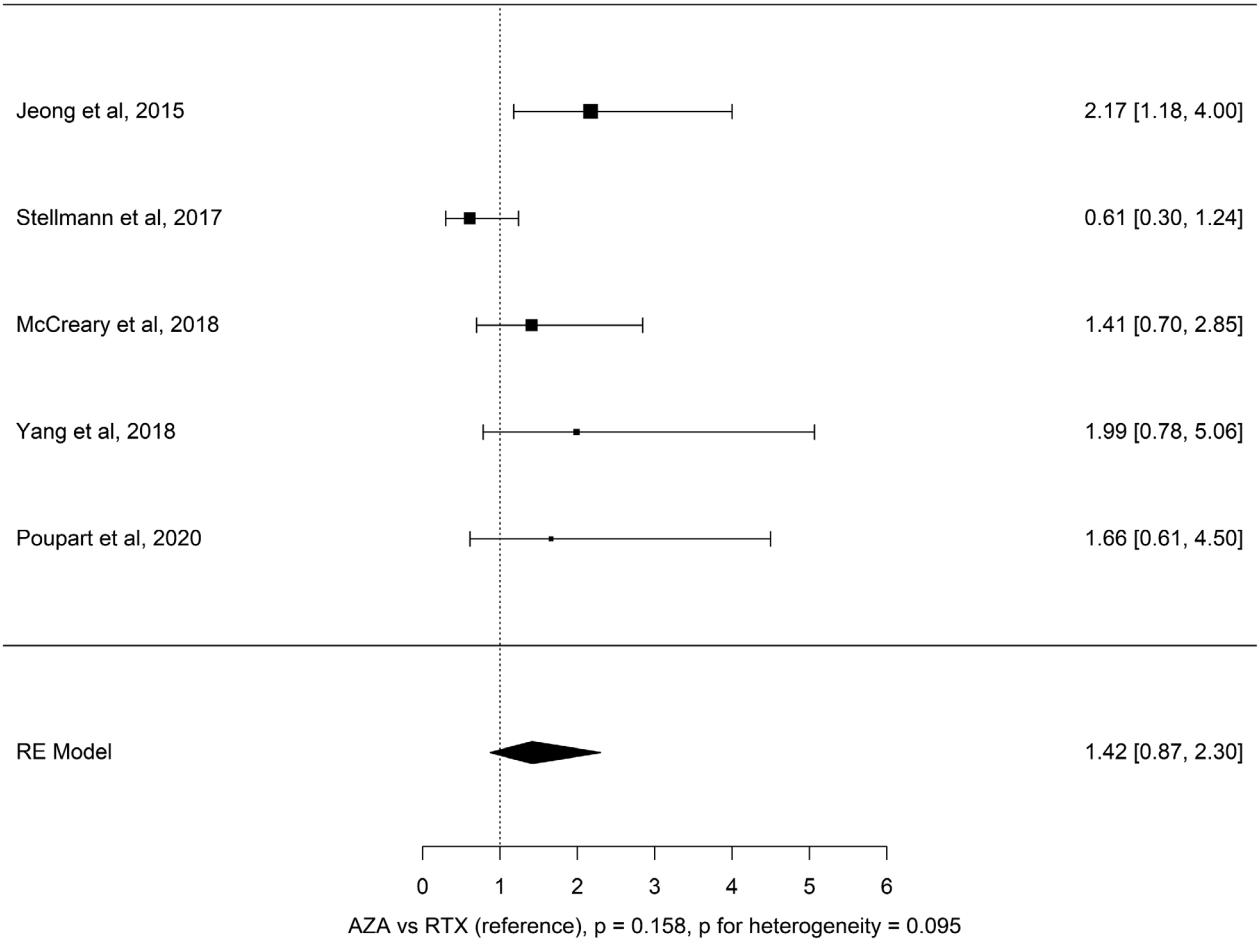

Figure 3. Forest plot of the hazard ratio for the association between the time to first relapse and first-line immunosuppression using azathioprine (AZA) or rituximab (RTX) (as reference) in NMO patients.

Meta-regression did not show a significant effect of anti-AQP4 positivity ($p = 0.58$, $p = 0.77$, and $p = 0.74$), age ($p = 0.11$, $p = 0.20$, and $p = 0.07$), sex ($p = 0.06$, $p = 0.61$, and $p = 0.60$), pre-treatment ARR ($p = 0.42$, $p = 0.42$, and $p = 0.80$), or concurrent use of prednisone ($p = 0.92$, $p = 0.51$, and $p = 0.36$) for the comparisons RTX versus MMF, RTX versus AZA, and AZA versus MMF, respectively.

Meta-analysis in anti-AQP4-positive patients

We did not observe a difference between RTX and MMF (pooled HR = 1.45 [0.89, 2.39], $p = 0.14$, p for heterogeneity = 0.23, RTX as reference), RTX and AZA (pooled HR = 1.32 [0.70, 2.51], $p = 0.39$, p for heterogeneity = 0.047, RTX as reference), or AZA and MMF (pooled HR = 1.07 [0.42, 2.76], $p = 0.89$, p for heterogeneity = 0.003, AZA as reference) (Fig. 5A–C).

Discussion

We showed that in the whole NMO population, the risk of first relapse after the start of first-line immunosuppression was (i) 1.55 [1.04, 2.31] for MMF compared with RTX, (ii) 1.42 [0.87, 2.30] for AZA compared with RTX, and (iii) 0.94 [0.58, 1.54] for MMF compared with AZA.

Methodological issues

As the meta-analysis of Huang et al.[13] used a systematic review of all publications comparing immunosuppressants in the treatment of NMO, regardless of the treatment line, we updated this quality systematic review and selected papers comparing at least two treatments among AZA, MMF, and RTX in first-line conditions.

Given the paucity of the population, the strength of this study is based on the high number of NMO patients

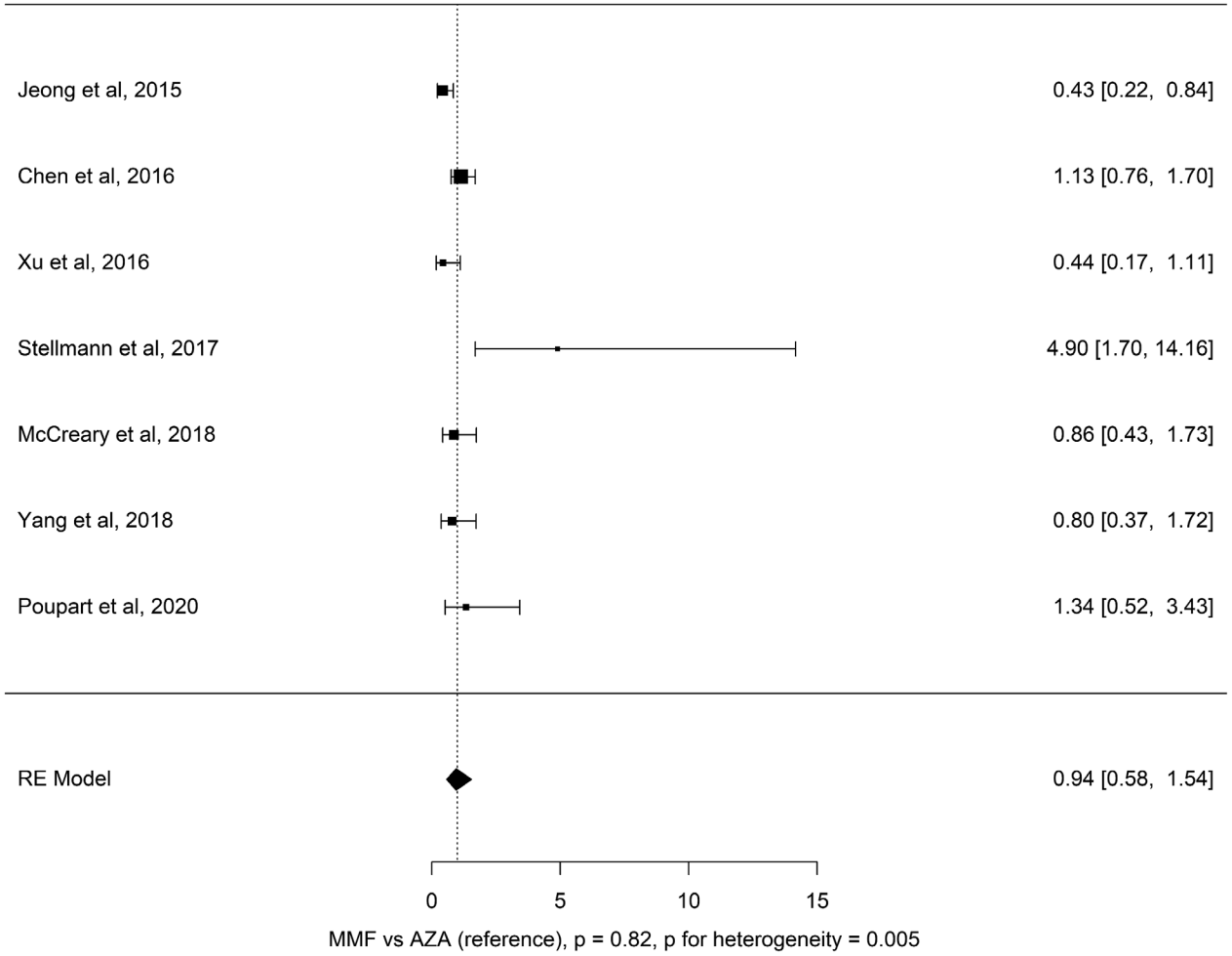

Figure 4. Forest plot of the hazard ratio for the association between the time to first relapse and first-line immunosuppression using mycophenolate mofetil (MMF) or azathioprine (AZA) (as reference) in NMO patients.

treated by either RTX, MMF, or AZA. Moreover, we chose to compare the treatments with each other using the relapse-free condition as the primary outcome. This outcome is more relevant than the ARR in NMO pathology, as clinical prognosis in NMO is directly related to relapse. This outcome was used for the primary objective in recent phase III trials in the treatment of NMO.[8–12] In addition, we chose to focus on first-line therapies to avoid the cumulative effect of immunosuppressants. Another strength was the comparison of the main immunosuppressants used today worldwide. This study could be complementary to the phase III trials comparing different molecules with placebo to discuss future treatment strategies.

A study limitation was that only 7 out of 13 eligible studies were included because of the lack of data in publications and that some corresponding authors did not reply to our request for collaboration. This meta-analysis was based on observational studies, which implied heterogeneity between studies and a level of evidence lower than that of clinical trials. In addition, although the doses of AZA and MMF were similar between the included studies, RTX was used at low-dose in one study. An important limitation was that the results were not adjusted for potential confounding factors, as we did not have any access to individual data. To identify a potential factor biasing the results, meta-regressions were performed for several parameters of interest, such as anti-AQP4 positivity, disease activity before treatment, or concomitant use of prednisone. No univariate test was significant; however, meta-regression results should be interpreted with caution due to the low number of studies. We could not include several variables in a single statistical model due to this low number of studies. The evaluation of publication bias from funnel plots and Egger tests should also be interpreted with caution due to the low number of studies.

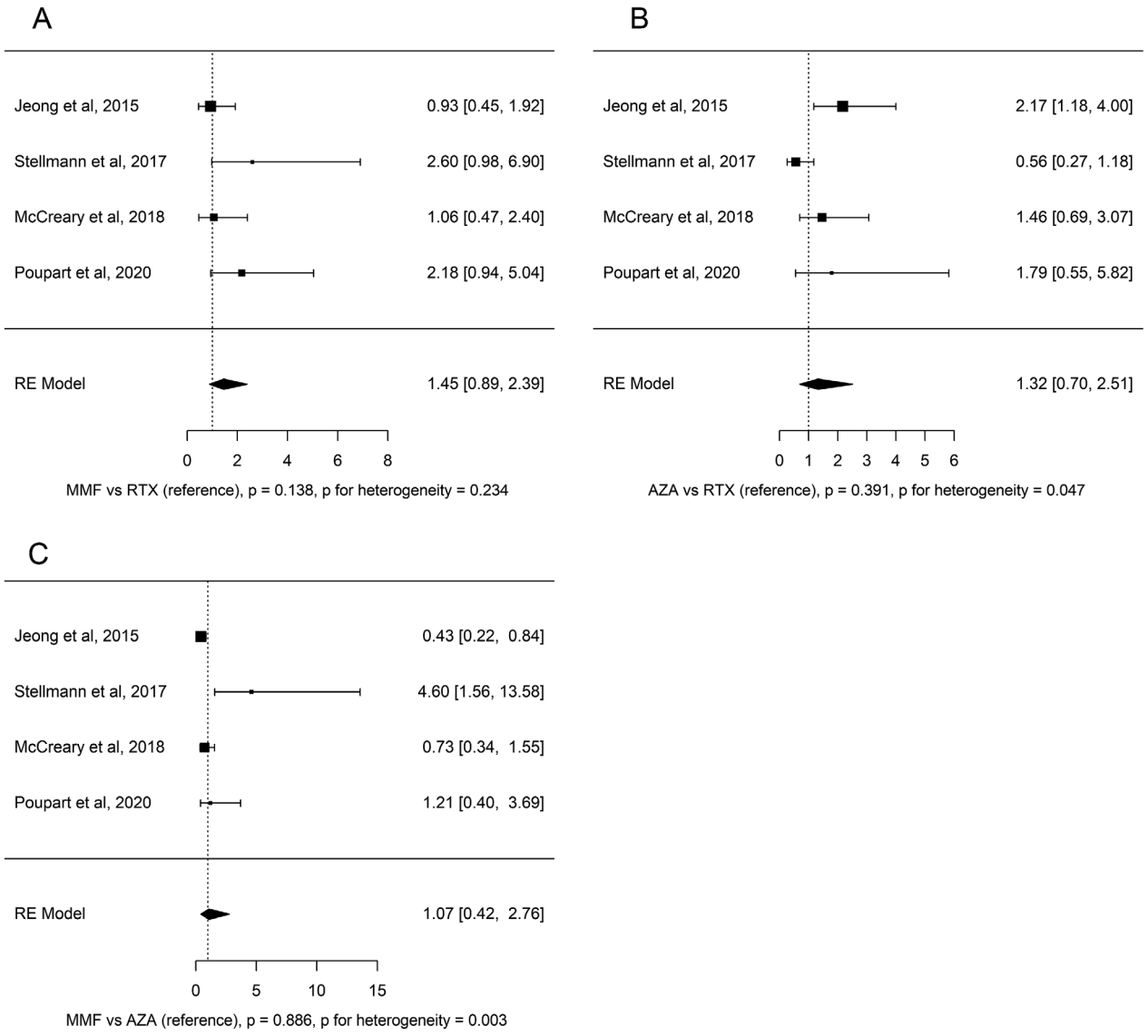

Figure 5. Forest plot of the hazard ratio for the association between the time to first relapse and first-line immunosuppression using (A) mycophenolate mofetil (MMF) or rituximab (RTX) (as reference), (B) azathioprine (AZA) or rituximab (RTX) (as reference), (C) mycophenolate mofetil (MMF) or azathioprine (AZA) (as reference), in NMO in patients positive for anti-aquaporin-4 antibodies.

Moreover, for two publications,[29,30] we calculated the HR from published graphs, which might lead to very slightly imprecise calculated values but without biasing our results. Finally, we chose not to limit the meta-analysis to only publications considering NMOSD patients, as the criteria for this disorder are recent,[33] and we could not exclude papers that did not measure anti-MOG activity to exclude MOGAD patients, as the criteria for this disease are also recent.[34–36] Thus, we performed a sensitivity analysis in NMO patients with anti-AQP4 positivity when data were available. However, the results of this analysis were difficult to interpret. We did not observe any significant difference between groups, but the HRs in the NMO population and in the anti-AQP4-positive patients were close as most patients (84%) in the NMO population were anti-AQP4-positive, and the results of the meta-regression did not support a major effect of anti-AQP4 status on the treatments, as found in our previous study.[32] Interpreting these findings as a better effect of RTX than MMF on NMO, but not on NMO in patients with anti-AQP4 positivity, maybe due to a decrease of the power, would be misleading.

Comparison of RTX versus MMF

The results showed a higher risk of first relapse under MMF versus RTX. We have included all the studies comparing these two immunosuppressants, except the study of Mealy et al.[27] to avoid duplicates as a large part of the population was already included in the study of McCreary et al.[19] The meta-analysis of Huang et al.[13] did not show a difference between MMF and RTX, using the ARR as an outcome, from the traditional pairwise meta-analysis (standardized mean differences [95% CI] = 0 [−0.57, 0.57]), including only one study, Yang et al.,[30] or the network meta-analysis (standardized mean differences = −0.70 [−1.62, 0.26]).

Comparison of RTX versus AZA

Our findings did not find a significant difference between AZA and RTX, with a pooled HR of 1.42 [0.87, 2.30], $p = 0.16$. This finding could obviously mean that there is no difference between these two immunosuppressants. However, this result could also reflect a lack of power. Moreover, the results of the study of Stellmann et al.[31] seemed discordant with those of other studies and could explain the absence of an observed difference. We stress that we did not identify any explanation to understand this conflicting result.

Using the ARR as an outcome (and not the time to first relapse), previous studies pointed out that the efficiency of RTX was better than that of AZA. In the study of Nikoo et al.,[22] the decrease in the ARR after immunosuppression was significantly higher in the RTX group than in the AZA group (mean (standard deviation) = 1.09 (0.72) vs. 0.49 (0.59), $p < 0.001$). In the study of Torres et al.,[26] the median ARR decreased from 1.17 to 0.25 on RTX ($p < 0.01$) and from 0.92 to 0.56 on AZA ($p = 0.475$); however, a comparison of the decrease in the ARR after immunosuppression between these two immunosuppressants was not performed. Huang et al.[13] described a significant difference in favor of RTX in the control of the ARR from the traditional pairwise meta-analysis (standardized mean differences = −0.91 [−1.78, −0.038]) or the network meta-analysis (standardized mean differences = −0.86 [−1.60, −0.11]). Even if the meta-analysis cannot conclude that RTX has a better efficacy in delaying the first relapse than AZA, the difference in the effect between the two treatments may be in favor of RTX. On the basis of these data together with data from studies that could not be included in our work and that we reported above, we could suggest that RTX might be more efficacious than AZA to control the clinical activity in NMO patients.

Comparison of AZA versus MMF

We did not find a difference between these two immunosuppressants. The difference effect was close to 1 (pooled HR = 0.94 [0.58; 1.54]), with the larger groups included in this meta-analysis. In the study of Huang et al., no difference in the control of the ARR was observed between groups from the traditional pairwise meta-analysis (standardized mean differences = 0.007 [−0.20, 0.21]) or the network meta-analysis (standardized mean differences = −0.15 [−0.89, 0.57]). All these results suggest a similar effect of AZA and MMF in the control of the disease.

Tolerance

Although the safety question is a key question, we chose not to analyze adverse effects (AEs), as data for this parameter are difficult to collect in retrospective, observational studies. No AZA-, MMF-, or low-dose RTX-treated patients discontinued the treatment in Yang's cohort[30]; similarly, no MMF- and AZA-treated patients discontinued the treatment in Chen's cohort,[29] and no low-dose RTX- and AZA-treated patients discontinued the treatment in Zhang's cohort.[23] Nikoo et al. counted 3/33 AZA- and 1/35 RTX-treated patients who discontinued the treatment owing to gastroenterological intolerance (AZA) and allergy (RTX).[22] Xu et al. reported 28.6% of AZA- and 5.3% of MMF-treated patients who discontinued the treatment owing to intolerance.[28] Huang et al., in their meta-analysis, concluded that the lowest number of AEs was observed for MMF, without any significant difference compared to RTX, but with a significant difference compared to AZA.[13] However, they did not distinguish AEs from serious AEs. Despite the similar percentage of side effects in AZA-, RTX-, and MMF-treated patients in Torres' cohort, they counted one death in each AZA and RTX group due to sepsis.[26] In our previous study, we chose to focus on serious infectious events (SIEs) to ensure retrospective data collection.[32] We found SIEs in 8.1% of RTX- and 11.9% of MMF-treated patients and no SIEs in AZA-treated patients after a median duration of treatment of 2.6 ± 2.4 years.[32] Data concerning the tolerance of AZA, MMF, and RTX as first-line therapy in NMO remain scarce, but this may suggest that no significant tolerance concern can be raised in one IS compared to the others.

In conclusion, the results of this updated systematic review and meta-analysis of the most widely used immunosuppressants in first-line strategies for NMO suggest that RTX is more efficient than MMF in delaying relapses. Even if the results of our meta-analysis cannot

conclude that RTX has a better efficacy in delaying the first relapse than AZA, the observed effect difference between both treatments combined with the results of previous studies using as outcome the annualized relapse rate may be in favor of RTX. These results aim to help future first-line treatment strategies that will have to consider (i) seronegative NMOSD, (ii) the place of the treatments that are most largely used today and that were not used as comparators in phase III trials, and (iii) the public health cost.

Authors Contributions

HZ, JG, JC, MC, and LD contributed to conception of the study. JG, JC, MC, HJK, SHK, JPS, IK, MM, BG, RD, BA, EM, CP, NC, BB, DL, XA, FDD, AR, SV, RM, LD, and HZ contributed to the acquisition and analysis of data; JG, JC, MC, LD, and HZ contributed to drafting the text or preparing the figures and tables.

Conflict of Interest

None of the co-authors have any disclosure related to the submitted work.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Co-investigators of the Neuromyelitis Optica Study Group (NEMOS) in alphabetical order.
Table S2. CO-investigators of the French Neuromyelitis Optica Study Group (NOMADMUS) and Observatoire Français de la Sclérose en Plaques (OFSEP).

