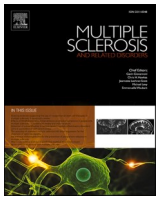
Multiple Sclerosis and Related Disorders 85 (2024) 105528

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Impact of rituximab treatment regime on time to relapse in aquaporin-4 antibody positive neuromyelitis optica spectrum disorder

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ARTICLE INFO

Keywords:
Neuromyelitis optica
Neuromyelitis optica spectrum disorder
NMO
NMOSD
Rituximab
Treatment regimens

ABSTRACT

Background: Aquaporin-4 (AQP4) antibody associated neuromyelitis optica (NMOSD) requires long-term immunosuppression. Rituximab is increasingly used worldwide, however the optimal regime is not established.
Methods: We retrospectively examined different rituximab regimens in AQP4-NMOSD. Standard monotherapy (SM; 6 monthly infusions), SM plus oral steroids (SM+*S*), extended interval dosing (EID; guided by CD19 repopulation) and EID with oral steroids (EID+*S*) were compared. The primary outcome was time to first clinical relapse. Potential confounders including age, gender, number of previous relapses, and onset phenotype were included.
Results: 77 patients were included: 67 females, median onset age 35.6, median DSS at rituximab initiation 5.0. 39 were on SM+*S*, 20 SM, 6 EID, and 12 EID+*S*. 25/77 patients relapsed during a median follow-up of 44.0 months. No significant difference in time to first relapse was observed between any rituximab regimen. Pooled analyses to compare regimens that use standard monotherapy (SM and SM+*S*) against those that use extended interval dosing (EID and EID+*S*) showed no significant difference. Pooled analysis of regimens using steroids with those not using steroids also showed no significant difference. Adjusted Cox proportional hazard model revealed no significant difference between rituximab regimens or influence of demographic factors. 9 significant adverse events were recorded, 5 in the SM group and 4 in SM+*S*.
Conclusions: This study provides some basis for further exploring EID as a viable option for long term treatment of AQP4-NMOSD. This may improve patient experience and consolidate use of hospital resources.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune condition that primarily affects the optic nerves, spinal cord and brainstem. It has a prevalence of 0.4–1.2 in 100,000 people worldwide with significant geographical differences (Hor et al., 2020). A substantial proportion of patients with NMOSD have positive anti-aquaporin 4 (AQP4) IgG antibodies. Persistent presence of the AQP4 IgG antibody confers a high risk of future relapse, leading to fixed disability in many patients (Matiello et al., 2008). For this reason, long term immunosuppression is usually initiated in a timely manner in patients with positive AQP4 antibodies in order to improve long term outcome.

There is now good evidence that rituximab is more effective at preventing relapses than both azathioprine and mycophenolate mofetil (Giovannelli et al., Oct; Velasco et al., 2021; Ma et al., 2022; Casallas-Vanegas et al., 2020). It is increasingly used first line internationally, in line with the single published randomised control trial (Tahara et al., 2020). In the UK, rituximab is predominantly used second line, following relapse or adverse events on azathioprine and/or

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https://doi.org/10.1016/j.msard.2024.105528
Received 2 July 2023; Received in revised form 23 January 2024; Accepted 26 February 2024
Available online 7 March 2024

Table 1
baseline characteristics of all patients included in study; median relapses = median relapses prior to starting rituximab therapy; median EDSS = median EDSS at time of starting rituximab; SAEs: significant adverse effects; * $p = 0.0012$ (Mann-Whitney U test).

Regimen or subset	n	Onset age (median years; range)	Disease duration (median months; range)	FU duration (median months)	Pre rituximab relapses (median; range)	Median EDSS (median; range)	Male to female ratio	SAEs
By rituximab regimen								
All patients	77	35.6 (3.0 – 78.6)	48.0 (0 - 336)	44.0	2.0 (0 – 12)	5.0 (0 – 9)	13.0 %: 87.0 %	9
Standard monotherapy (SM)	20	25.5 (10.0 – 78.6)	30.0 (0 - 336)		1.0 (0 – 6)	5.5 (1 – 7.5)	5.0 %: 95.0 %	5
Standard monotherapy + steroids (SM + *S*)	39	36.0 (3.0 – 75.0)	48.0 (0 – 264)		2.0 (0 – 12)	5.0 (0 – 9)	15.4 %: 84.6 %	4
Extended interval dosing (EID)	6	38.5 (14.8 – 55.2)	78.0 (12 – 180)		3.0 (0 – 11)	5.0 (0 – 7.5)	0 %: 100 %	0
Extended interval dosing + steroids (EID + *S*)	12	38.8 (9.0 – 65.7)	48.0 (0 – 180)		2.5 (0 – 7)	5.5 (0 – 7.5)	25.0 %: 75.0 %	0
By pooled rituximab regimen								
All standard monotherapy (SM and SM + *S*)	59	35.0 (3.0 – 78.6)	36.0 (0 – 336)		2.0 (0 – 12)	5.0 (0 – 9)	11.9 %: 88.1 %	9
All extended interval dosing (EID and EID + *S*)	18	38.8 (9.0 – 65.7)	66.0 (0 – 180)		3.0 (0 – 11)	5.5 (0 – 7.5)	16.7 %: 83.3 %	0
All regimen with steroids (SM + *S* and EID + *S*)	51	36.2 (3.0 – 75.0)	48.0 (0 – 264)		2.0 (0 – 12)	5.0 (0 – 9)	17.6 %: 82.4 %	4
All regimen without steroids (SM and EID)	26	30.5 (10.0 – 78.6)	42.0 (0 – 336)		2.0 (0 – 11)	5.5 (0 – 7.5)	3.8 %: 96.2 %	5
By neuroscience centre								
Oxford	34	34.5 (3.0 – 75.0)	36.0 (0 – 252)		1.5 (0 – 8) *	2.5 (0 – 9)	17.6 %: 82.4 %	6
Cardiff	9	31.0 (9.0 – 49.0)	60.0 (0 – 264)		1 (1 – 12)	6.5 (3 – 7.5)	11.1 %: 88.9 %	1
Liverpool	34	37.7 (14.6 – 78.6)	42.0 (0 – 336)		3 (0 – 12) *	6 (2 - 9)	8.8 %: 91.2 %	2

mycophenolate mofetil. More recently there is clinical trial evidence to support the use of newer monoclonal antibodies, which are directed against the complement pathway (eculizumab), IL-6 (sartralizumab, tocilizumab), and CD19 (inebilizumab). Despite this, given its low cost and range of biosimilars, rituximab remains one of the most commonly used therapies for NMOSD. Prescribing conventions for rituximab for the treatment of AQP4 IgG positive NMOSD (AQP4-NMOSD) vary both between individual centres and internationally. Practice has historically been to use 6 monthly infusions of two doses of rituximab 1000 mg (referred to as 'standard monotherapy' in this paper). An increasing tendency is to use an 'extended interval dosing' regimen, as described by (Ellrichmann et al., 2019), where the interval between rituximab infusions is guided by the re-population of CD19 (or CD27) cell counts to above 1 %. Some patients have additional low dose corticosteroid cover for a limited or extended period (and in some cases other immunomodulatory medications) alongside rituximab.

However the optimal rituximab regimen to provide disease control whilst minimising potential risk of adverse events is not known. Additionally, it has not been established whether the use of concurrent corticosteroids alongside rituximab is beneficial or rather exposes patients to unnecessary side effects. We therefore set out to evaluate in a retrospective study whether any particular rituximab regimen is superior with respect to minimising future relapses in people with AQP4-NMOSD, and to evaluate whether there is a role for concurrent steroids alongside rituximab.

2. Methods

2.1. Participant cohort

This study included all patients with a diagnosis of AQP4-NMOSD who had received rituximab at any point during their disease course under the clinical care of participating tertiary and quaternary centres across England and Wales. Data were collected from three quaternary/tertiary neuroscience centres covering England and Wales: John Radcliffe Hospital (Oxford, UK), The Walton Centre NHS Foundation Trust (Liverpool, UK), and University Hospital Wales (Cardiff, UK). These centres are commissioned to provide care for patients with NMOSD across England and Wales, and so have records on the majority of patients with AQP4-NMOSD residing in these countries. Data were prospectively collected (and later retrospectively analysed) using patient records (either electronic or paper records) and relevant clinic letters, and stored in centralised databases at each site. Patient demographics, onset age, initial onset phenotype, clinical relapses, nadir disability, previous immunosuppression and its duration, current rituximab regimen, current use of other immunosuppression (e.g. prednisolone), and significant adverse effects potentially related to rituximab were recorded in a study-specific database. This study collected data from as far back as records were available. The first patient who received rituximab for AQP-4 positive NMOSD with data included in this study was in 2007. Data collection for this study ended in July 2021.

Patients included in this cohort study had been enrolled following informed consent and research ethics committee approval for each of the treating centres (ie, Oxford Research Ethics Committee C (Oxford; ref 10/H0606/56), London-Hampstead Research Ethics Committee (Walton Centre; ref 15/LO/1433), South East Wales Research Ethics Committee (Cardiff; ref 05/WSE03/111)) with data collected as part of standard care subsequently anonymized, pooled, and analysed.

2.2. Treatment regimens

Rituximab regimens were coded into 4 groups. One cycle of rituximab was taken to consist of two infusions of 1000 mg (1 g) of rituximab given two weeks apart, as per standard practice in the UK. The 4 rituximab regimens used in this study were: standard monotherapy (SM; one rituximab cycle every 6 months), standard monotherapy with steroids (SM + *S*; one rituximab cycle every 6 months with concurrent prednisolone at any dose), extended interval dosing (EID; interval between each rituximab cycle guided by CD19 repopulation to above 1 %), and extended interval dosing with steroids (EID + *S*; interval between each rituximab cycle guided by CD19 repopulation to above 1 % with concurrent prednisolone at any dose). As steroid dose varied during

Table 2
patients who switched from one regimen to another during the course of the study.

Regimen switches	Number	Duration before switch (median months)
All patients who switched regimens	30	38.5
SM + *S* to SM	1	85.0
SM + *S* to EID + *S*	13	38.0
SM + *S* to EID	6	41.0
SM to EID	6	50.5
EID + *S* to EID	2	22.0
EID + *S* to SM + *S*	1	36.0
EID to SM + *S*	1	100.0
Any steroid regimen to any non-steroid regimen	9	39.0

follow up, the absolute dose was not used in the analysis, and binary splitting (for example >10 mg vs <10 mg) was not feasible. Similarly, data on how quickly steroids were started or tapered was not included due to the small cohorts and substantial potential variation. Where patients switched from one rituximab regimen (such as standard monotherapy) to a different regimen (such as extended interval dosing, EID), their data were censored at the time of switch in order to avoid any carryover effects. 7 patients were also on other immunosuppression than rituximab and steroids. These patients were not excluded from the main analysis due to the small cohort size and the fact that they were spread across the groups.

2.3. Statistical analysis

The primary outcome was time to first relapse on rituximab. Demographic characteristics were compared between groups using *t*-test or Mann-Whitney-U test as appropriate. Survival analyses were used; Log-rank and Cox proportional hazard ratios were used to evaluate the effect of multiple variables (rituximab regimen, onset age, onset phenotype, number of previous relapses, gender, ethnicity) on time to first relapse. All statistical analysis were performed in R (R studio version 2021.09.01).

3. Results

Participant baseline characteristics are presented in Table 1. When baseline patient demographics were compared between neuroscience centres (Table 1), the only significant difference was between the number of prior relapses between Oxford and Liverpool ($p = 0.0012$). The Oxford cohort had a larger proportion of patients of Black African, Black Caribbean and Black British race compared to Liverpool and Cardiff (supplementary Table 1). Follow up data were available to a median of 44.0 months (Table 1).

There were no significant differences between age of onset, disease duration and prior relapses between any of the rituximab regimen groups. Similarly, there were no significant difference in the same three variables between patients on standard monotherapy (SM and SM + *S*) and extended interval dosing (EID and EID + *S*). There were also no significant differences between those receiving steroids (SM + *S* and EID + *S*) and those not receiving steroids (SM and EID). 4/39 (10 %) of those on SM + *S*, 2/12 (17 %) of those on EID + *S* and 1/20 (5 %) of those on

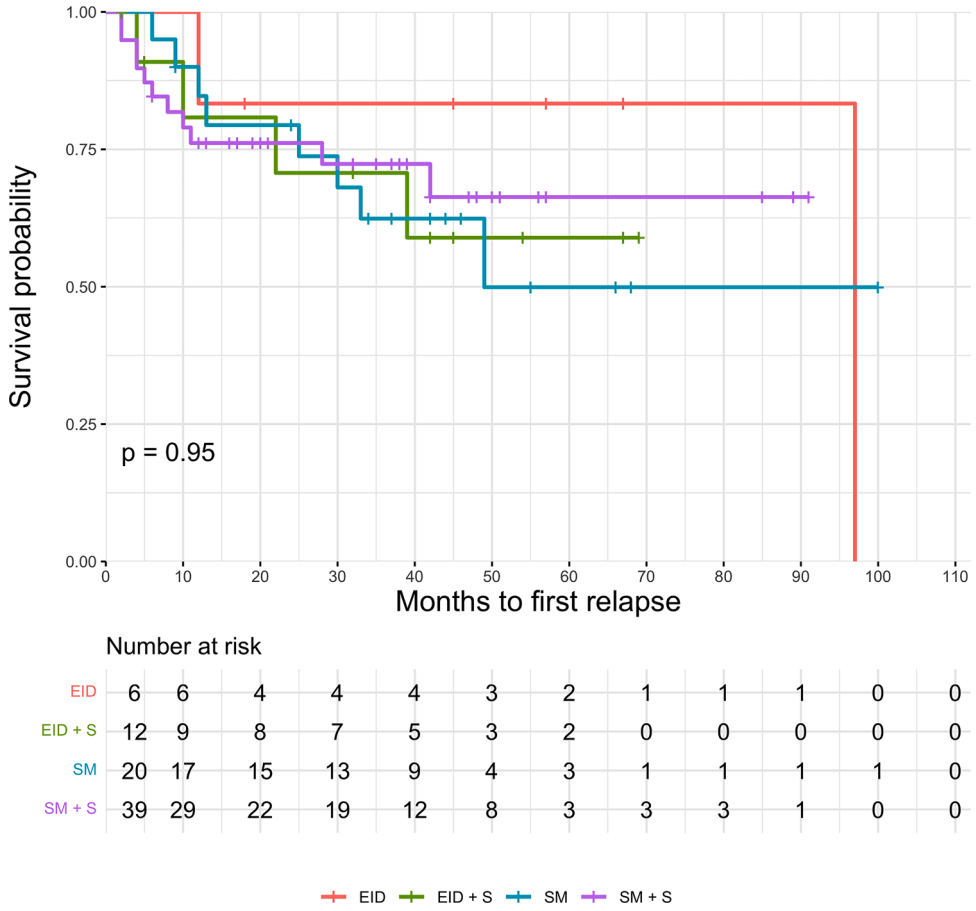

Fig. 1a. Kaplan-Meier curve showing time to first relapse for each of the primary rituximab regimen; SM = standard monotherapy; SM + *S* = standard monotherapy and steroids; EID = extended interval dosing; EID + *S* = extended interval dosing and steroids. Log-rank test used for comparison.

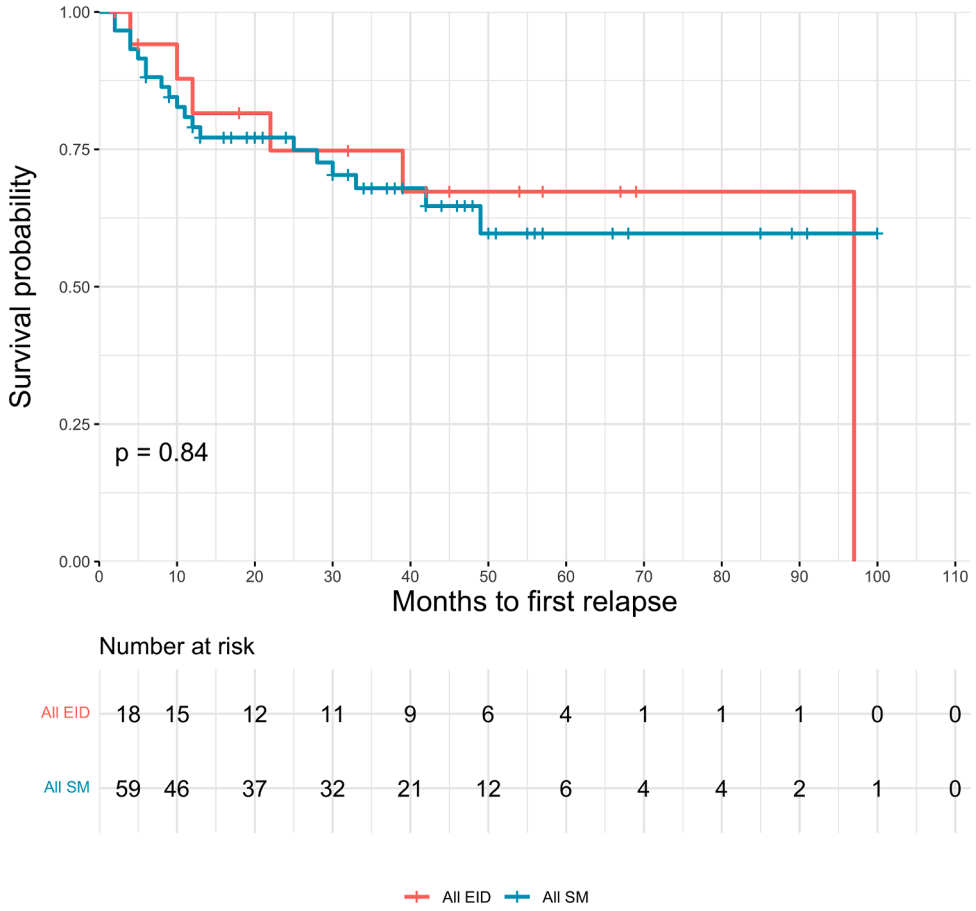

Fig. 1b. Kaplan-Meier curve showing time to first relapse for rituximab regimen using standard monotherapy (SM and SM + *S*) against those using extended interval dosing (EID and EID + *S*). Log rank test used for comparison.

SM were receiving additional immunosuppression (5 receiving mycophenolate mofetil, 1 azathioprine and 1 methotrexate weekly). Treatment switches at the time of censoring from the study are shown in Table 2. Data regarding CD19 count at dosing in the EID group were not included due to concerns regarding data completeness.

25/77 (33 %) patients relapsed during study follow up. We compared time to first relapse for each of the primary rituximab regimens using unadjusted Kaplan-Meier curves (Fig. 1a). These showed no significant difference in time to first relapse between any rituximab regimen ($p = 0.95$). Subsequently we conducted pooled analyses to compare regimens that use standard monotherapy (SM and SM + *S*) against those that use extended interval dosing (EID and EID + *S*). The unadjusted Kaplan-Meier plots of this comparison showed no significant difference in time to first relapse (Fig. 1b; $p = 0.84$). We then compared regimens that used steroids (SM + *S* and EID + *S*) with regimens that did not (SM and EID). Again, there was no significant difference in time to first relapse (Fig. 1c; $p = 0.93$).

Cox survival analysis (prespecified co-variates of onset age, gender, number of previous relapses prior to starting rituximab, onset phenotype and ethnicity) did not show any significant difference between rituximab regimen (Fig. 2a). None of the covariates had any significant effect on the adjusted hazard ratios. It is particularly notable that the number of relapses prior to starting rituximab did not appear to have any significant effect. Similarly, when patients who were on regimens that included steroids were compared with those not on steroids using the same cox survival model and the same co-variates (Fig. 2c) no significant differences in adjusted hazard ratios for relapse were seen ($p = 1.0$). Similarly, no significant difference was seen ($p = 0.8$) when all the extended interval dosing regimens (EID and EID + *S*) were pooled and compared with all regimen that involved standard monotherapy (SM and SM + *S*) (Fig. 2b). 9 significant adverse effects were recorded, 5 in the SM group (of which 4 of 5 were infections), and 4 in SM+*S* group (of which 4 of 4 were infections). One significant infection was recorded in a patient receiving additional immunosuppression. Due to low numbers and risk of ascertainment bias, statistical analysis was not performed.

4. Discussion

Our study, which includes virtually all patients with AQP4 IgG antibody positive NMOSD receiving rituximab in the UK, shows no significant difference in time to first relapse between any of the rituximab regimens. It is important and reassuring to note that the majority of patients (66 %) remained relapse free for over 4 years. Breakthrough relapses in the EID group were not a notable phenomenon.

Comparing all EID rituximab regimens with grouped SM regimens revealed no significant difference in hazard of relapse. Similarly, there was no significant difference in hazard between regimens with steroids and regimens without steroids. Whilst these results provide interesting observations in that the standard monotherapy (SM or SM + *S*) was not immediately more effective than EID regimens (EID or EID + *S*), it is impossible to draw definitive conclusions for a number of reasons. Firstly, in this observational study, treatment decisions for a specific patient are likely to have taken into account their perceived hazard of relapse, and secondly, patient numbers were not balanced between groups. In the context of the relatively small numbers of patients and four different treatment approaches, demonstrating statistical significance would require a large effect. Proving a "null" effect requires higher statistical power, and so we are also unable to conclusively

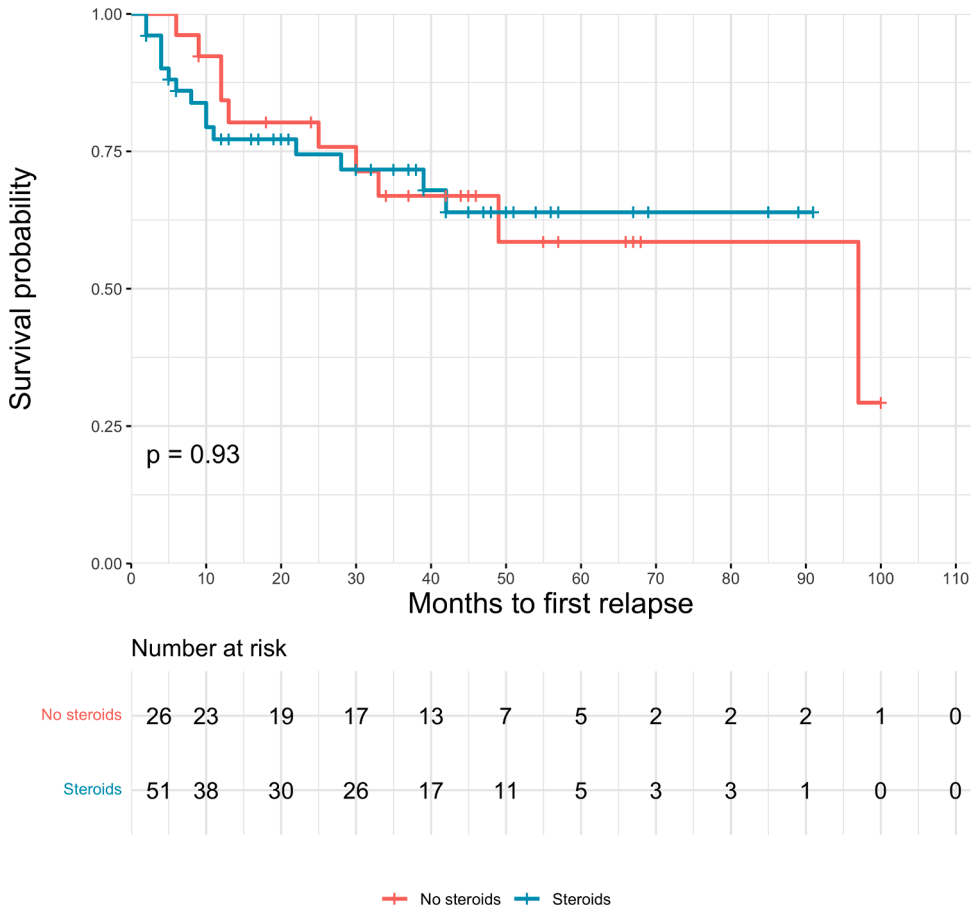

Fig. 1c. Kaplan-Meier curve showing time to first relapse for rituximab regimen with steroids (SM + *S* and EID + *S*) against those without steroids (SM and EID). Log rank test used for comparison.

demonstrate this. However, the similarities observed in the Kaplan Meir plots along with the lack of effect in either pooled analysis may provide some basis for further exploring EID as a potentially viable option in some patients with AQP4-positive NMOSD.

Interestingly, using a multi-segmental (rituximab dose determined by how high or low the CD19 count is) or low-dose treatment approaches to rituximab use have shown promise in both NMOSD and myasthenia gravis (Yang et al., 2022). For example, a recent retrospective study of 129 Chinese patients showed that rituximab used at lower doses (500 mg at first infusion only, followed by 100 mg at all subsequent infusions, guided by CD19 cell repopulation to 1 %) than would be typical for EID in the UK (two infusions of 1000 mg given 2 weeks apart per cycle; infusion interval guided by CD19 cell repopulation to >1 %) is still effective in relapse prevention (Yang et al., 2022). This low dose EID regimen (as well as other multi-segmental approaches) have the potential to be very effective whilst at the same time potentially conferring fewer side effects than expected with typical standard monotherapy. It is noteworthy, however, that east Asian AQP4-NMOSD patients may have milder disease as shown in a previous UK / Japanese study so it is unclear whether low dose EID protocols would be suitable in relatively higher risk British patients (Palace et al., 2019; Kim et al., 2018). Further studies are required to best understand treatment strategies that minimise the risk of adverse events whilst continuing to optimally control disease.

Whilst more work needs to be done to evaluate the safety and efficacy of EID regimens, it is clear that there are potential logistical advantages of extended interval dosing regimens over 6 monthly infusions. These would principally include greater convenience for patients and a significant saving of hospital resources in terms of clinician time (both doctors and nurses), medication costs and availability of neurology wards and day units (Kelly et al., 2019). In our cohort the mean interval between the first and second rituximab infusions in patients receiving either EID or EID + *S* was 15.6 months. It is therefore reasonable to extrapolate that cost of rituximab could be approximately 2.5 times lower (15.6 / 6 = 2.6) than if the same patients were receiving 6 monthly dosing. However, being unable to plan ahead may not always be convenient for patients and it can be challenging admitting patients at short notice when their CD19 count starts to rise especially when there are large numbers of patients on this regime. This is of particular concern given the potential risk of disabling breakthrough relapses in the context of increasing CD19 counts and antibody titres.

Our data does not demonstrate any substantial additional protection of concurrent steroids alongside rituximab (either standard monotherapy or extended interval) against future relapses compared to rituximab alone. However, the relatively small sample sizes, selection biases (such as corticosteroid responsiveness leading to such patients being kept on/off steroids), and collider biases mean that we are unable to make definitive recommendations on whether adjunctive steroids confer additional protection against relapses or not. Only an RCT would be to answer this question definitively.

This study incorporated patients from three national referral centres for NMOSD. The studied population should theoretically include patients from all geographical regions of England and Wales with a range of demographic backgrounds; it should therefore be relatively representative of the British population. A further strength of our study is the presence of near complete data for all variables of interest. However, despite these strengths, we acknowledge that the overall number of patients analysed is relatively modest (n = 77). The rarity of AQP4-

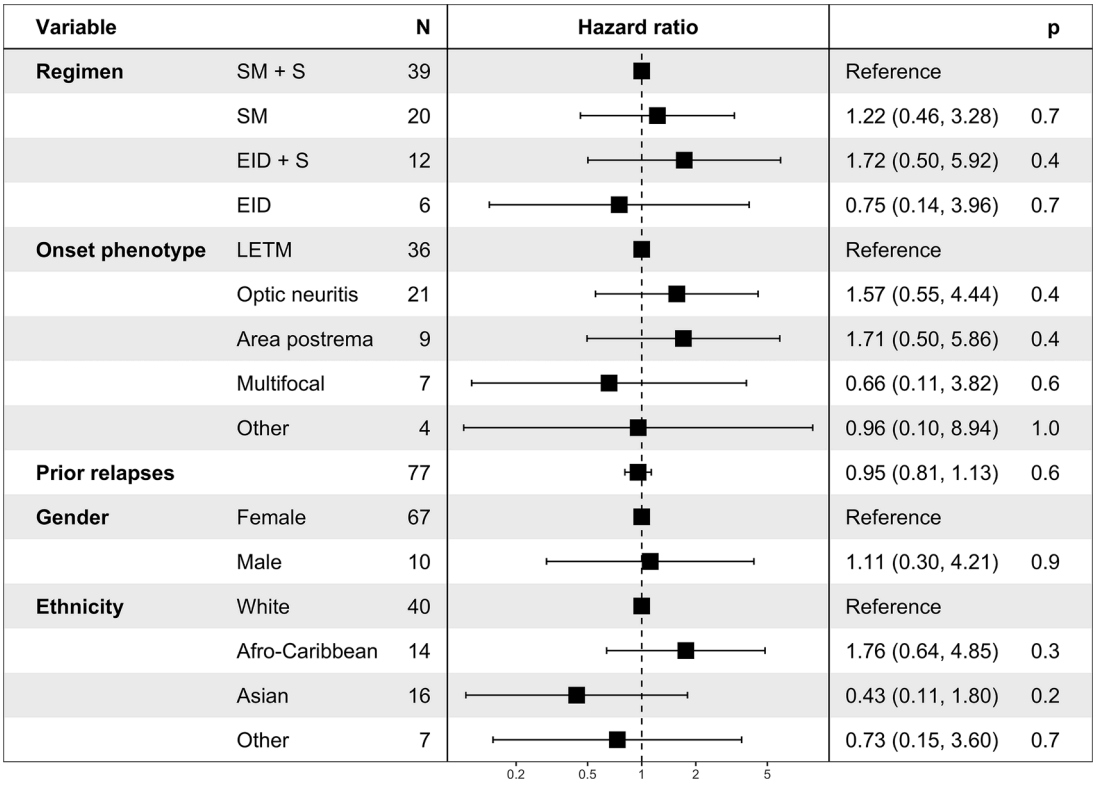

Fig. 2a. Comparison of adjusted hazard ratios for time to first relapse for each of the individual rituximab regimen using multiple regression analysis. LETM = longitudinally extensive transverse myelitis.

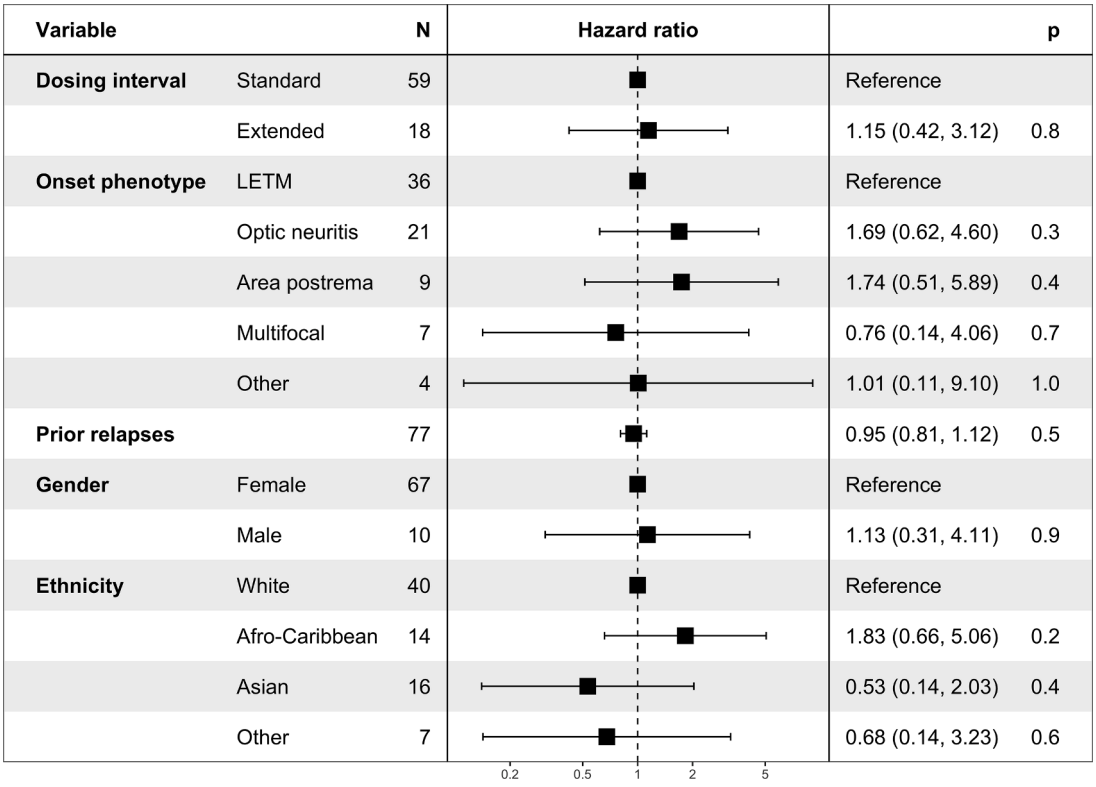

Fig. 2b. Comparison of adjusted hazard ratios for time to first relapse for rituximab regimen using standard monotherapy (SM and SM + *S*) against those using extended interval dosing (EID and EID + *S*) using multiple regression analysis.

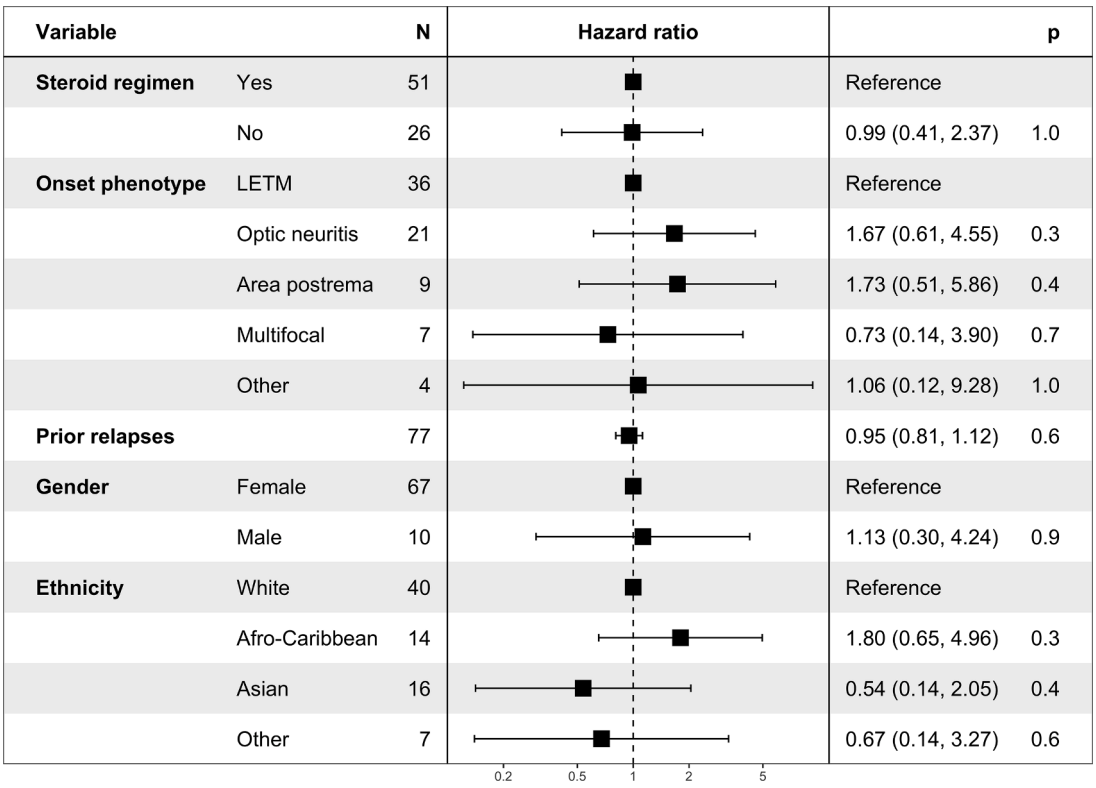

Fig. 2c. Comparison of adjusted hazard ratios for time to first relapse for rituximab regimen with steroids (SM + *S* and EID + *S*) against rituximab regimen without steroids (SM and EID) using multiple regression analysis.

NMOSD and the even smaller subset of these patients receiving rituximab in the UK makes gathering data on this matter very difficult. In the UK, rituximab is primarily a second line therapy, meaning that a smaller number of people with higher risk disease receive this therapy. Secondly, whilst the efficacy of rituximab leading to relatively few events (relapses) demonstrates its benefit for patients, it limits the conclusions that can be drawn from these analyses. Thirdly, there were a small number of patients ($n = 7$) who were also on immunosuppression other than rituximab and prednisolone.

As this is a retrospective analysis we were not able to adjust for selection biases (such as why specific regimens were chosen for individual patients). It is possible that those patients who were not receiving steroids were judged by their treating clinicians to be at lower relapse risk than those who continued on steroids; similarly those selecting EID rituximab may have made this choice due to perceived risk of adverse events, or as a result of prolonged disease remission. We collected data on adverse events associated with immunosuppression, but did not collect prior data; however such events would be expected to be rare. Our data (supplementary Table 1) suggests that differing prescribing cultures exist between physicians and between institutions. This could quite plausibly mean that two patients of similar perceived risk of relapse and/or complications could be assigned two different treatment regimens. For example, we note that none of the Cardiff cohort were prescribed EID, whilst around 38 % of the Liverpool cohort and around 14 % of the Oxford cohort were receiving EID. Furthermore, neither the steroid dose nor rituximab timing (or CD19 monitoring intervals) in the EID cohort were standardised across the cohort, although the "no steroid" group was homogenous in their lack of current exposure, and the standard interval rituximab dose group had a set 6-monthly dose interval. Lastly, whilst we endeavoured to control for the major relevant and potentially influential co-variates within our Cox regression model it is possible that we have inadvertently omitted other important variables; correcting for all potential mediators was not possible due to sample size considerations.

These results must be interpreted in the context of these limitations and should not be overinterpreted as providing guidance on either ideal rituximab dosing interval or optimal steroid dose. Additionally, group level findings such as our data must be treated with caution when extrapolating to individual patients. It is worth noting, however, that the realistic prospect of seeing a RCT in the future directly addressing the questions addressed in this study seems very low. Our real-world data, whilst clearly imperfect, may provide some gauge on the overall effect size of various rituximab regimen and steroid use. We were not able to address the optimal frequency for CD19 testing or threshold for treatment. Repopulation to 1 % is generally used as the threshold for redosing; however data from ocrelizumab trials in MS demonstrates that there is considerable variation to the time of repopulation (Baker et al., 2022). The kinetics of repopulation are relatively poorly understood, and so balancing frequency of testing against the cost of testing requires further investigation.

In conclusion, our data showed no difference in time to first relapse between patients on standard monotherapy regimens (SM or SM + *S*) and extended interval dosing regimens (EID or EID + *S*). Additionally, there was no difference in time to first relapse in patients on regimens with steroids (SM + *S* or EID + *S*) and regimens without steroids (SM or EID). Given the limitations of the data, however, it is not possible make definitive recommendations on whether one dosing regimen is favourable to another, although the data does provide some basis for further exploring whether extended interval dosing could be a viable option for AQP4-positive NMOSD patients. Further studies are required to evaluate these questions.

CRediT authorship contribution statement

Moneeb Nasir: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Luke Hone:** Data curation, Investigation, Methodology, Writing – review & editing. **Emma Tallantyre:** Data curation, Writing – review & editing.

Patricia Kelly: Data curation, Writing – review & editing. **Maria Isabel Leite:** . **Neil Robertson:** Data curation, Writing – review & editing. **Jonathan Bestwick:** Formal analysis, Methodology, Writing – review & editing. **Saif Huda:** Data curation, Writing – review & editing. **Jacqueline Palace:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Ruth Dobson:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

N/A.

Acknowledgements

The authors would like to thank all of the patients who consented for their data to be used as part of this study.

Author disclosures

Nil.

Funding statement

Not applicable.

Data availability

Not available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105528.

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