Treatment of MOG-IgG-associated disorder with rituximab: An international study of 121 patients

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Abstract

Objective: To assess the effect of anti-CD20 B-cell depletion with rituximab (RTX) on relapse rates in myelin oligodendrocyte glycoprotein antibody-associated disorder (MOGAD).

Methods: Retrospective review of RTX-treated MOGAD patients from 29 centres in 13 countries. The primary outcome measure was change in relapse rate after starting rituximab (Poisson regression model).

Results: Data on 121 patients were analysed, including 30 (24.8%) children. Twenty/121 (16.5%) were treated after one attack, of whom 14/20 (70.0%) remained relapse-free after median (IQR) 11.2 (6.3–14.1) months. The remainder (101/121, 83.5%) were treated after two or more attacks, of whom 53/101 (52.5%) remained relapse-free after median 12.1 (6.3–24.9) months. In this 'relapsing group', relapse rate declined by 37% (95%CI=19–52%, p<0.001) overall, 63% (95%CI=35–79%, p = 0.001) when RTX was used first line (n = 47), and 26% (95%CI=2–44%, p = 0.038) when used after other steroid-sparing immunotherapies (n = 54). Predicted 1-year and 2-year relapse-free survival was 79% and 55% for first-line RTX therapy, and 38% and 18% for

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second-/third-line therapy. Circulating $CD19^+B$-cells were suppressed to <1% of total circulating lymphocyte population at the time of 45/57 (78.9%) relapses.

Conclusion: RTX reduced relapse rates in MOGAD. However, many patients continued to relapse despite apparent B-cell depletion. Prospective controlled studies are needed to validate these results.

Keywords

Myelin oligodendrocyte glycoprotein; MOG; Rituximab; Neuromyelitis optica; Optic neuritis

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1. Introduction

Autoantibodies targeting human myelin oligodendrocyte glycoprotein (MOG-IgG) have been identified in the sera of children and adults with a CNS inflammatory disease that is distinct from multiple sclerosis (MS) [O'Connor et al., 2007, Mader et al., 2011, Kitley et al., 2012]. 30–80% of patients relapse after an initial attack, [Lopez-Chiriboga et al., 2018, Jurynczyk et al., 2017, Cobo-Calvo et al., 2018, Jarius et al., 2016] and some fulfil diagnostic criteria for aquaporin-4 antibody (AQP4-IgG)-negative neuromyelitis optica spectrum disorders (NMOSD) [Jarius et al., 2016, Hamid et al., 2017]. A proportion of patients with MOG-IgG-associated disorder (MOGAD) accrue substantial disability and may benefit from long-term immunomodulatory treatment [Jurynczyk et al., 2017, Cobo-Calvo et al., 2018, Jarius et al., 2016, Hachohen et al., 2018, Ramanathan et al., 2018]. However, natural history and treatment responses in MOGAD are unclear.

Anti-CD20 B-cell depletion with rituximab (RTX) is effective in MS [Bar-Or et al., 2008, Hauser et al., 2008, Hauser et al., 2017, Montalban et al., 2017] and AQP4-IgG-NMOSD [Cree et al., 2005, Jacob et al., 2008, Pellkofer et al., 2011, Mealy et al., 2014, Kim et al., 2011, Kim et al., 2013, Kim et al., 2015, Radaelli et al., 2016, Damato et al., 2016, Cohen et al., 2017]. It is therefore hoped that RTX may be effective in MOGAD. However, its benefit is not yet defined, and several small case series suggest a lower efficacy than expected [Jarius et al., 2016, Hachohen et al., 2018, Ramanathan et al., 2018].

1.1. Objective

To examine the effectiveness of RTX in a large international cohort of MOGAD patients

1.2. Methods

Investigators submitted anonymised retrospective data on all patients in their care meeting the inclusion criteria: (1) At least one clinical and MRI-confirmed CNS inflammatory event; (2) MOG-IgG positive by cell-based assay (live or fixed) incorporating full-length human MOG in its conformational form and an IgG-specific secondary antibody; (3) AQP4-IgG negative by live or fixed cell-based assay; (4) treatment with RTX. Acceptable initial RTX dosing regimens were 1000 mg on day 0 and day 15 or a body surface area (BSA)-adjusted dose of 375 mg/m^2 weekly for 4 weeks. The interval between subsequent treatment courses was either fixed at 6-months or determined by periodic testing of circulating $CD19^+$B-cell or $CD19^+/CD27^+$ memory B-cell levels (maximum testing interval of 2 months). Both

approaches have been used successfully in large cohorts of AQP4-IgG-NMOSD patients [Cree et al., 2005, Jacob et al., 2008, Pellkofer et al., 2011, Mealy et al., 2014, Kim et al., 2011, Kim et al., 2013, Kim et al., 2015, Radaelli et al., 2016, Damato et al., 2016, Cohen et al., 2017].

Relapses were defined as a new or worsening symptomatic presentation, with a change in neurological examination, and confirmed by MRI as necessary.

Informed written consent and local ethics committee approval were mandatory for participation. All data were anonymised and were collected between August 2017 and September 2018.

1.3. Statistical analysis

Stata version 15 and SAS version 9.3 were used for data analysis. A Poisson regression model was fitted to the data, with a random effect by patient level, to compare the relapse rate before and after initiating RTX. We compared median annualised relapse rates (ARR) pre- and post-RTX using Wilcoxon signed rank tests. ARR is defined as the total number of attacks divided by the number of years of disease. Relapse-free survival on RTX was estimated with Kaplan-Meier survival curves. Several subgroup analyses were performed.

2. Results

Data were obtained from 29 centres in 13 countries – Argentina, Austria, Brazil, France, Germany, Netherlands, India, Italy, Japan, South Korea, Switzerland, United Kingdom and United States of America. The total number of MOGAD patients attending all study centres was 875. RTX was administered to 132/875 (15.1%). We did not have the resources to also obtain and analyse data on the 743 patients who were not treated with RTX. Eleven patients were excluded due to incomplete data (6), inadequate treatment protocol (4) and diagnostic uncertainty (1) (Fig. 1).

2.1. Demographics

Data on 121 patients (71/121, 58.7% female) were analysed (Table 1). Median (interquartile range, IQR) age at onset attack was 24.8 (13.1–39.6) years and age at first RTX infusion was 29.7 (18.2–44.0) years. Race distribution was 103/121 (85.1%) White, 10/121 (8.3%) Asian, 1/121 (0.8%) Black, and 7/121 (5.8%) mixed race. Paediatric patients (age <18 years at RTX initiation) comprised 30/121 (24.7%).

The most common MOGAD phenotypes in adults were relapsing optic neuritis (ON) (27/91, 29.7%) and relapsing ON with transverse myelitis (TM) (25/91, 27.5%). Acute disseminated encephalomyelitis (ADEM) with relapses (13/30, 43.3%) was the predominant paediatric phenotype.

2.2. Relapses and immunotherapy prior to rituximab

For all patients, the median (IQR) disease duration prior to RTX initiation was 19.1 (5.9–55.0) months. RTX was started after the index attack in 20/121 (16.5%), and after at least two attacks in 101/121 (83.5%). The pre-treatment median (IQR) ARR was 1.82 (0.74–3.40)

for the 101 relapsing patients, of whom 54/101 (53.5%) had received one or more prior non-steroid maintenance immunotherapies (Table 1). These included azathioprine (26/101, 25.7%), mycophenolate mofetil (20/101, 19.8%), other immunosuppressive drugs (13/101, 12.8%), intravenous immunoglobulin (IVIg) (7/101, 6.9%), and MS disease-modifying therapies (MS-DMTs) (11/101, 10.9%, these are listed in the legend for Table 1). There was no standardised 'wash-out' period of prior immunotherapies.

2.3. Rituximab dosing

RTX was administered 6-monthly to 115/121 (95.0%). Others (6/121, 5.0%) were retreated according to repopulation of circulating $CD19^+$B-cells or $CD19^+/CD27^+$ memory B-cells. If only a single treatment course was given, treatment duration was considered as 6 months.

Most patients (79/121, 65.3%) received RTX 1000 mg, administered either once (day 0), or twice (day 0 and day 15) per treatment course. A BSA-adjusted dose of 375 mg/m^2 weekly for 4 weeks was given to 28/121 (23.1%) – predominantly paediatric patients. A minority of patients received a combination of both regimens (4/121,3.3%), or exact dosing was not specified (10/121, 8.3%).

2.4. The effect of RTX started after index attack (n = 20)

RTX was started after the index attack in 20/121 (16.5%) cases from 11/29 centres. Because a proportion of MOGAD patients appear not to relapse irrespective of treatment (i.e. "monophasic disease"), we analysed this group separately from those with an established relapsing phenotype (Fig. 1). After median (IQR) 11.2 (6.3–14.1) months on RTX, 14/20 (70%) remained relapse-free. Eleven relapses occurred in 6/20 (30.0%) patients, with a median (IQR) time to first relapse of 2.6 (1.3–4.5) months. The relapses comprised TM (6/11), ON (4/11) and simultaneous TM/ON (1/11).

2.5. The effect of RTX started after two or more attacks (n = 101)

RTX was started after two or more attacks in 101/121 (83.5%). The median (IQR) pre-treatment duration was 26.0 (9.8–70.9) months. After median (IQR) 12.1 (6.3–24.9) months on RTX, 53/101 (52.5%) remained relapse-free. 102 relapses occurred in 48/101 (47.5%) patients (Fig. 2) with a median (IQR) time to first relapse of 4.4 (1.8–8.5) months. The relapses comprised ON (73/102, 71.6%), TM (17/102, 16.7%), ADEM/encephalitis (5/102, 4.9%), cerebellitis/rhombencephalitis (5/102, 4.9%) and multifocal/unspecified relapses (2/102, 2.0%). The Poisson regression model showed a 37% (95%CI 19–52%, p<0.001) reduction in relapse rate following treatment with RTX. The Kaplan-Meier estimate of relapse-free survival was 55% (95%CI 44–65%) at 1 year of RTX therapy and 33% (95%CI 20–46%) at 2 years (Fig. 3a).

The effect of RTX on median ARR is shown in Table 2. For all patients (n = 101), median ARR declined after initiation of RTX from 1.82 to 0.00 (p<0.001; Wilcoxon signed rank test). Because calculation of ARR is dependent on pre- and post-treatment observation periods, we repeated the analysis after excluding patients with short observation periods (Table 2). In patients with at least 12 months observation both pre- and post-RTX treatment

(34/101, 33.7%), median ARR declined from 1.18 to 0.56 ($p = 0.002$; Wilcoxon signed rank test).

2.6. Early relapses after starting RTX (n = 97)

Some studies of RTX in AQP4-IgG-NMOSD have described a lag time of 3–4 weeks to the onset of relapse-preventing action, despite complete B-cell depletion occurring within days of RTX infusion [Kim et al., 2013, Lindsey et al., 2012]. We therefore re-analysed relapse rates after excluding relapses occurring within 1 month of RTX initiation (5/99,5.1%). With this adjustment, the Poisson regression model showed a 43% (95%CI 26–57%, $p<0.001$) reduction in relapse rate. Decline in median ARR was unchanged (Table 2). If relapses occurring within 3 months of RTX initiation (26/99, 26.3%) are excluded, relapse rate reduced by 55% (95%CI 40–67%, $p<0.001$) post-treatment.

2.7. B-cell depletion (n = 121)

A CD19$^+$B-cell count <1% of circulating lymphocytes is a commonly used indicator of effective B-cell depletion by RTX [Kimbrough et al., 2012]. B-cell counts were available at the time of 57/113 (50.4%) relapses. In 12/57 (21.1%) relapses the CD19$^+$B-cell count was ≥1%, indicating that the effect of RTX had waned. However, circulating CD19$^+$B-cells were supressed <1% in 45/57 (78.9%), indicating disease activity despite effective B-cell depletion. In 22/57(38.6%) relapses, B-cells were completely undetectable.

2.8. The effect of RTX on treatment naïve patients (n = 47, 46.5%) versus those with prior exposure to non-steroid immunotherapies (n = 54, 53.5%)

A greater decline in median ARR ($p = 0.015$, Mann Whitney U test) was observed in treatment naïve patients. Relapse rate declined by 63% (95%CI 35–79%, $p = 0.001$, Poisson regression) in this group. After 1 and 2 years, 79% (95%CI 62–89%) and 55% of patients treated first-line with RTX are predicted to be relapse-free respectively (Kaplan-Meier analysis, Fig. 3b).

When RTX was given second- or third-line, relapse rate declined by 26% (95%CI 2–44%, $p = 0.038$, Poisson regression). After 1 and 2 years, 38% (95%CI 25–52%) and 18% (95% CI 7–34%) are predicted to be relapse-free respectively (Kaplan-Meier analysis, Fig. 3b). Repeat analysis after excluding the 11 patients with MS-DMTs exposure obtained similar results, though the 25% (95%CI−3–46%, $p = 0.077$, Poisson regression) decline in relapse rate was not statistically significant. In the 11 patients exposed to MS-DMTs, median ARR declined from 2.19 pre-treatment (median observation period 49 months) to1.79 after RTX initiation (median observation period 13 months). For the 7 patients with at least 12 months observation pre- and post-RTX, median ARR declined from 1.71 to 0.89.

2.9. The effect of RTX in adults (n = 71) versus children (n = 30)

All 30 children experienced two or more attacks prior to starting RTX. We therefore compared the effect of RTX in 30 children versus 71/91 (78.0%) adults, who had established relapsing disease pre-RTX (Table 2). Median duration on RTX was 12.7 months for adults and 11.8 months for children, in which 31/71 (43.7%) adults and 17/30 (56.7%) children relapsed. Relapse rate declined by 42% (95%CI 20–59%, $p = 0.001$, Poisson regression) in

adults and by 29% (95%CI−7–53%, p = 0.103) in children. Treatment naïve patients comprised 40/71(56.3%) adults versus 7/30 (23.3%) children. CD19$^+$B-cell counts were available for 22/62 (35.5%) relapses in adults and 30/40 (75.0%) relapses in children, and were suppressed <1% in 19/22 (86.4%) and 21/30 (70.0%) respectively.

2.10. Use of corticosteroids and steroid-sparing immunotherapies (n = 121)

Maintenance corticosteroid therapy, defined as daily or alternate day dosing of oral prednisolone, was used in 32/121 (26.4%) of patients while receiving RTX, of which 17/121 (14.0%) received continuous treatment, 7/121 (5.8%) were gradually tapered to cessation, and 8/121 (6.6%) restarted maintenance corticosteroids after relapse. Maintenance corticosteroid dosing did not follow a set protocol, so was individualised and variable throughout the observation period. It was therefore not possible to analyse corticosteroid use in greater detail. Maintenance corticosteroids were not used in 78/121 (64.5%). Information about steroid use was not available in 11/121 (9.1%).

Continuation or addition of other immunotherapies with RTX occurred in 20/121 (16.5%) patients: mycophenolate mofetil (8), IVIg (6), azathioprine (3), methotrexate (2), IVIg with azathioprine (1). One patient received low dose IVIg (0.2 mg/kg monthly) for RTX-induced hypogammaglobulinemia, which developed after 35 months of treatment. One patient had recent exposure to alemtuzumab (33 and 21 months pre-RTX).

Exclusion of all patients co-treated with maintenance corticosteroid and steroid-sparing immunotherapies left 61/101 (60.4%) patients (those who started maintenance corticosteroid only after a relapse were included in this analysis, but their follow-up was censored at the point of starting corticosteroid). For this group, the median (IQR) treatment duration was 11.3 (5.3–22.3) months. The Poisson regression model showed a 42% (95%CI 15–60%, p = 0.005) reduction in relapse rate following treatment with RTX. Median ARR declined from 1.54 to 0.00 (p<0.001; Wilcoxon signed rank test).

2.11. Treatment switches (n = 121)

Twenty-two/121 (18.2%) patients discontinued RTX due to relapses (16/22, 72.7%), de-escalation of immunotherapy (5/22, 22.7%), and infection (1/22, 4.5%). They switched to mycophenolate mofetil (4), tocilizumab (3), azathioprine (3), IVIg (4) or multi-drug regimens.

2.12. Expanded disability status scale (EDSS) scores (n = 121)

We compared EDSS at RTX initiation and at last review or on RTX discontinuation. EDSS data were available for 97/121 (80.2%) patients, but scores were not assessed at defined time points with respect to relapses. Median (IQR) EDSS score improved from 3.0 (2.0–3.5) at RTX initiation to 2.0 (1.0–3.0) at follow-up (z = 3.36, p = 0.001; Wilcoxon signed rank test).

2.13. Tolerance and adverse events

We did not systematically acquire data on adverse events. However, the following serious adverse events were reported: anaphylactoid infusion reaction (1), hypogammaglobulinemia (1) and cryptococcal meningoencephalitis (1). The latter occurred a 13-year-old boy on RTX

for 2 years, with prior exposure to azathioprine and prednisolone. No patients died during treatment with RTX.

3. Discussion

This is the first study examining the effectiveness of RTX in a large MOGAD cohort. RTX led to a 37% decline in relapse rate, and after 2 years, 33% of patients are predicted to remain relapse-free. This is a less beneficial effect than observed with anti-CD20 B-cell depletion in MS and AQP4-IgG-NMOSD [Bar-Or et al., 2008, Hauser et al., 2008, Hauser et al., 2017, Montalban et al., 2017, Cree et al., 2005, Jacob et al., 2008, Pellkofer et al., 2011, Mealy et al., 2014, Kim et al., 2011, Kim et al., 2013, Kim et al., 2015, Radaelli et al., 2016, Damato et al., 2016, Cohen et al., 2017]. Where data were available, 79% of relapses occurred despite apparent robust B-cell depletion. The greatest treatment effect (63% decline in relapse rate) was observed in patients who received RTX as a first-line maintenance immunotherapy (see further discussion below). Patients receiving RTX second- or third-line experienced only a 25% decline in relapses. Separate analyses of adults and children suggested a better response in adult patients (42% versus 29% reduction in relapse rates).

The true benefit of RTX in MOGAD may be even less than that observed in this study, when one considers the potential influence of regression to the mean (the tendency of a group to return to the average, rather than to sustain an above average relapse rate). For example in randomised controlled MS trials, regression to the mean can account for up to 40% of the reduction in relapse rate observed in both treatment and placebo arms [Martínez-Yélamos et al., 2006]. In MOGAD cohorts, estimates of median ARR vary greatly and have been prejudiced by testing bias, variable treatment paradigms and short observation periods. It is therefore difficult to quantify the effect of regression to the mean in this study, but given that the observed treatment effect is relatively small, it is particularly important to consider this phenomenon.

Previous studies of MOGAD treatment responses included smaller numbers of RTX-treated patients. They also observed reduced relapse rates following RTX treatment. Some described frequent early relapses: A German study reported that 6/9 patients relapsed on RTX therapy [Jarius et al., 2016]. An Australasian study included six RTX-treated patients, one of whom relapsed twice despite B-cell depletion [Ramanathan et al., 2018]. Finally, in a European paediatric study, 6/9 RTX-treated children relapsed, including one life-threatening relapse despite confirmed B-cell depletion. Of the three RTX responders, two were additionally receiving maintenance IVIg [Hachohen et al., 2018].

It is not clear why RTX appears less effective for MOGAD than for MS and AQP4-IgG-NMOSD. Phase I and II trials of RTX and phase III trials of ocrelizumab (another anti-CD20 therapy) in relapsing MS, [Bar-Or et al., 2008, Hauser et al., 2008, Hauser et al., 2017] and retrospective studies of RTX in NMOSD, [Cree et al., 2005, Jacob et al., 2008, Pellkofer et al., 2011, Mealy et al., 2014, Kim et al., 2011, Kim et al., 2013, Kim et al., 2015, Radaelli et al., 2016, Damato et al., 2016, Cohen et al., 2017] have consistently reported high efficacy. The largest meta-analysis of 46 NMOSD studies, including 438 predominantly AQP4-IgG positive patients, calculated a 79% reduction in relapse rate

[Damato et al., 2016]. RTX has therefore become a dependable maintenance therapy for AQP4-IgG-NMOSD in many countries.

One explanation for apparently poor efficacy is that this study has selected out a subgroup of highly active treatment-refractory MOGAD patients from specialist centres. Only 15.1% of all MOGAD patients at the participating centres were treated with RTX. The pre-treatment median ARR (1.09 for those with >12 months of pre-treatment observation) was relatively high in our study, as compared to unselected incident MOGAD cohorts [Jurynczyk et al., 2017, Cobo-Calvo et al., 2018]. A treatment paradox, in which higher relapse rates and poorer outcomes are seen in those receiving more therapy, reflects the a priori threshold for initiating such treatments and has been observed in other neuroinflammatory disorders [Titulaer et al., 2013, Deiva et al., 2015]. In line with this, we observed a much better response in treatment-naïve patients versus those who had failed an alternative steroid-sparing maintenance therapy (63% reduction in relapses versus 25%). We also saw a paradoxical improvement in RTX effectiveness (42% reduction in relapses versus 37%) when excluding patients co-treated with maintenance corticosteroid and steroid-sparing immunotherapies.

We explored if early relapses may account for poor treatment response, by excluding the 5% of relapses occurring within one month of RTX initiation. The decline in relapse rate increased slightly from 37% to 43%. The validity of this adjustment is uncertain in MOGAD, but stems from experience in AQP4-IgG-NMOSD, where a lag time of 3–4 weeks to achieve relapse-preventing effect has been described, despite complete B-cell depletion within days of RTX infusion [Kim et al., 2013, Lindsey et al., 2012]. Relapse risk may in fact be paradoxically high during this lag period, [Perumal et al., 2015, Nakashima et al., 2011] but most consider this not to reflect truly RTX-refractory disease [Kimbrough et al., 2012]. An even greater delay to therapeutic effect is possible: Decline in relapse rate improved to 55% when relapses within three months of RTX initiation were excluded. However, a more pro-longed median follow-up than 12.1 months would be required to properly discriminate between delayed therapeutic onset and lack of efficacy.

Notwithstanding the above considerations, the obvious explanation may be that anti-CD20 B-cell depletion is indeed not as effective in MOGAD compared to MS and AQP4-IgG-NMOSD. It is notable that most relapses occurred in the context of apparent robust B-cell depletion.

Despite their overlapping phenotypes, many differences have been identified between the immunopathogenic mechanisms underpinning these disorders. Both AQP4-IgG and MOG-IgG are immunoglobulin G1 antibodies, but the evidence that MOG-IgG is directly pathogenic to the CNS is less assured than for AQP4-IgG. It appears that the pathogenicity of human MOG-IgG is dependent on interactions with cognate T-cells [Spadaro et al., 2018]. Additionally, the abundance of circulating MOG-specific B-cells differs greatly between MOGAD patients, and does not correlate with serum titres of MOG-IgG [Winklmeier et al., 2019]. It may therefore be that the predominant source of MOG-IgG production in some patients is by CD20$^-$ long-lived plasma cells in the bone marrow (which are not depleted effectively with RTX), rather than by continuous activation and differentiation of CD20$^+$

MOG-specific B-cells in the peripheral circulation. Systematic longitudinal assessment of MOG-IgG titres and B-cell populations were not available in this study but would be informative in future studies of RTX, particularly with respect to treatment failure.

The children in this study experienced only a 29% ($p = 0.103$) reduction in relapse rates on RTX, compared to the 42% decline observed in adults. Children comprised only a quarter of the cohort, and a much smaller proportion of children (23% versus 56% of adults) were treatment naïve prior to RTX. This may have confounded the comparison between adults and children, given that treatment-naïve patients appeared to respond more favourably to RTX. Finally, of all relapses known to have occurred in the context of inadequate B-cell depletion, 9/12 (75%) occurred in children. This may suggest that children may benefit from closer B-cell monitoring. While possible, it seems unlikely that use of the BSA-adjusted dosing regimen in children accounts for the lesser efficacy observed, as this is a conventional dosing protocol that is proven to cause complete circulating B-cell depletion with established efficacy in numerous autoimmune and haemato-oncological disorders.

Although 45% of the cohort relapsed on RTX, only 18% switched to an alternative immunotherapy. This could be because relapses were mild or responded well to acute therapy. We could not explore this as EDSS data (which did show a trend towards improving disability) were available for only 80% of the cohort and were not calculated at designated time points with respect to relapses. Alternatively, neurologists may continue RTX despite ongoing MOGAD relapses due to limited third-line therapy options. Paediatric studies have suggested possibly superior responses to either IVIg or oral corticosteroid, but this requires further study [Hachohen et al., 2018, Wong et al., 2018]. Tocilizumab (interleukin-6 blockade) has been used effectively in some patients with RTX-refractory MOGAD [Novi et al., 2019, Hayward-Könnecke et al., 2019, Ringelstein et al., 2020].

Important limitations of this study include its retrospective design and the inclusion of many patients with relatively short duration of treatment. The latter will bias analysis of ARR, often utilised in this type of study, which is why we used Poisson regression to provide a more meaningful analysis of treatment effect. Other limitations include the absence of a relapse adjudication committee, and the heterogeneity of the cohort in terms of patient ages, MOGAD phenotypes and prior drug exposure. Furthermore, some patients received concomitant corticosteroid treatment at changing doses, there was no standardised washout from prior steroid-sparing medications and a minority of patients continued these treatments alongside RTX therapy. These limitations are inherent to real-world, retrospective studies of this nature and the inclusion of all cases improves the generalisability of the study and reflects the challenge of managing this rare and unpredictable disorder.

In summary, this is largest study of RTX effectiveness in MOGAD. RTX seems less beneficial than expected for MOGAD, when compared with AQP4-IgG-NMOSD, supporting observations from small case series. Prospective studies in well-defined cohorts of adults and children are needed to confirm or refute our findings and to better understand the role of anti-CD20 therapy in the treatment of MOGAD.

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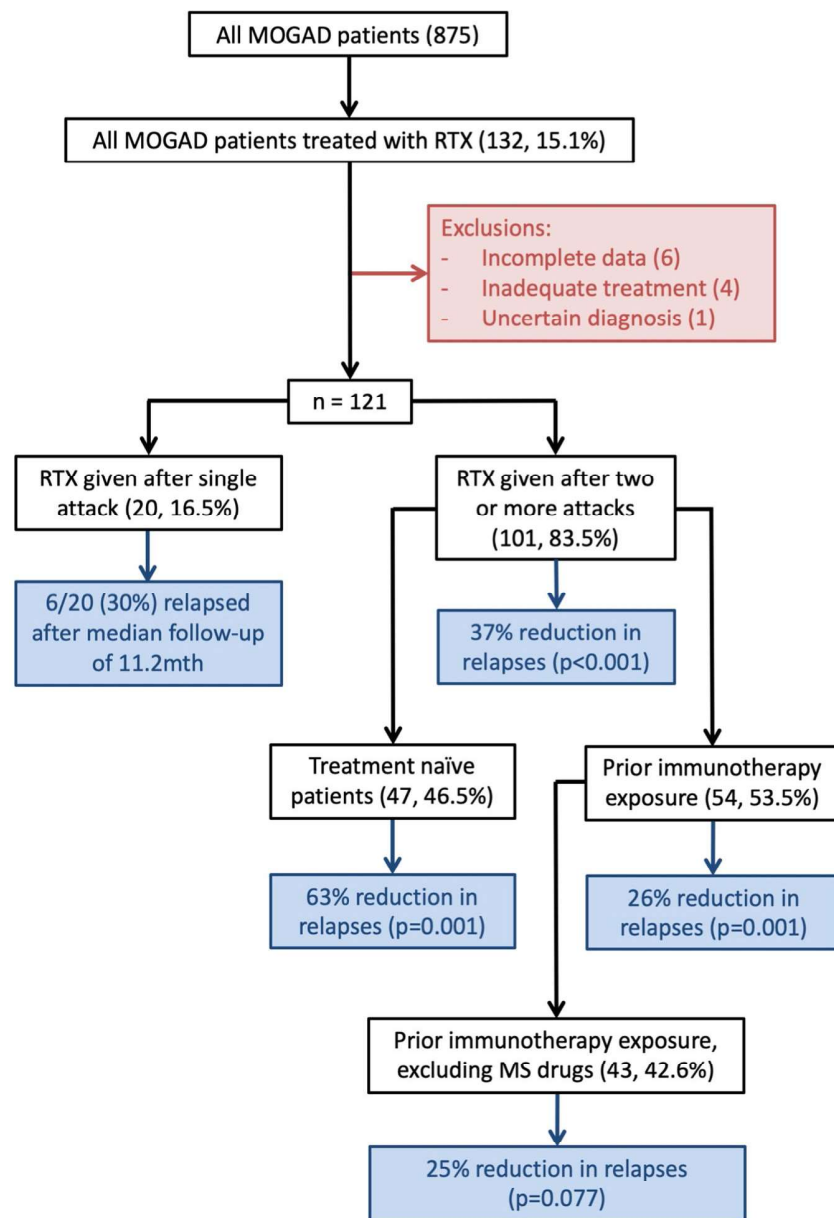
Fig. 1.
Flow diagram demonstrating data analysis.
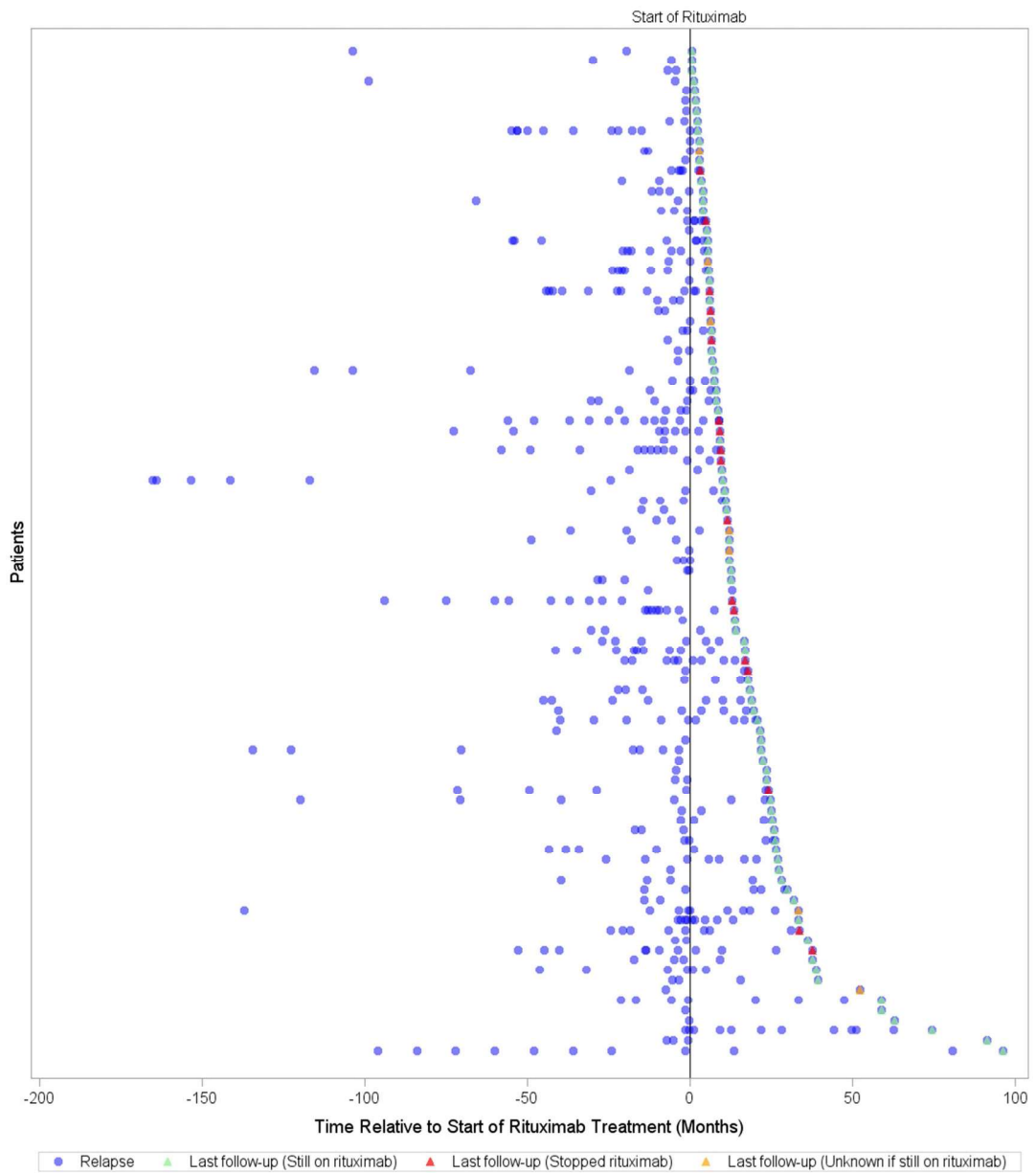
Fig. 2.
MOGAD relapses occurring before and after treatment with rituximab.

Fig. 3.
Kaplan-Meier plots of relapse-free survival following initiation of rituximab for (a) all relapsing patients (*n* = 101); and (b) comparing treatment-naïve patients (blue line, *n* = 47) and those with previous exposure to non-steroid immunotherapies (red line, *n* = 54).

Table 1

Cohort demographics, clinical phenotypes and previous immunotherapies.

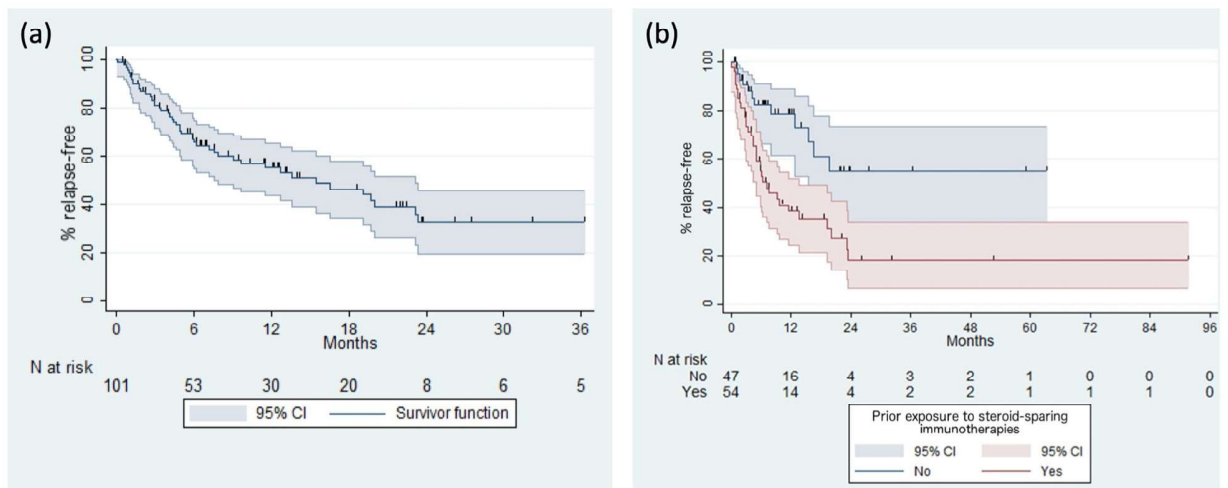|	Whole cohort	Adults	Children	Single attack pre-RTX (all ages)	Multiple attacks pre-RTX (all ages)
Patients, n	121	91	30	20	101
Female, n (%)	71 (58.7)	56 (61.5)	15 (50.0)	14 (70.0)	57 (56.4)
White, n (%)	103 (85.1)	84 (92.3)	19 (63.3)	19 (95.0)	84 (83.2)
Median (IQR) onset age, yrs	24.8 (13.1–39.6)	33.0 (22.7–43.5)	7.6 (4.0–9.9)	31.9 (22.5–40.9)	23.2 (10.9–38.8)
Median (IQR) RTX start age, yrs	29.7 (18.2–44.0)	37.7 (25.5–48.5)	11.7 (8.3–14.0)	32.1 (22.7–41.5)	27.2 (16.4–44.1)
Disease onset <18years, n (%)	39 (32.2)	9 (9.9)	30 (100)	0	39 (38.6)
RTX initiation <18years, n (%)	30 (24.7)	0	30 (100)	0	30 (29.7)
Median (IQR) disease duration pre-RTX, mths	19.1 (5.9–55.0)	12.8 (5.0–49.1)	33.0 (16.3–69.6)	3.3 (1.7–5.1)	26.0 (9.8–70.9)
Median pre-RTX ARR	2.25	2.34	1.64		1.82
Phenotypes pre-RTX, n (%):					
Monophasic (all attack types)	20 (16.5)	20 (22.0)	0	20 (100)	
Monophasic ON	6 (5.0)	6 (6.6)		6 (30.0)	
Monophasic TM	9 (7.4)	9 (9.9)		9 (45.0)	
Monophasic ON with TM	5 (4.1)	5 (5.5)		5 (25.0)	
Relapsing (all attack types)	101 (83.5)	71 (78.0)	30 (100)		101 (100)
Relapsing ON	29 (24.0)	27 (29.7)	2 (6.7)		29 (28.7)
Relapsing TM	6 (5.0)	5 (5.5)	1 (3.3)		6 (5.9)
Relapsing ON and TM	29 (24.0)	25 (27.5)	4 (13.3)		29 (28.7)
Relapsing ADEM/ADEM-like	15 12.4	2 (2.2)	13 (43.3)		15 (14.9)
Other relapsing phenotypes / brain involvement	22 (18.2)	12 (13.2)	10 (33.3)		22 (21.8)
No. of steroid-sparing ITs prior to RTX, n (%):					
0	66 (54.5)	59 (64.8)	7 (23.3)	19 (95.0)	47 (46.5)
1	35 (28.9)	19 (20.9)	16 (53.3)	1 (5.0)	34 (33.7)
2	13 (10.7)	9 (9.9)	4 (13.3)	0	13 (12.9)
3+	7 (5.8)	4 (4.4)	3 (10.0)	0	7 (6.9)
Types of prior steroid-sparing ITs prior to RTX, n (%):					
None	66 (54.5)	59 (64.8)	7 (23.3)	19 (95.0)	47 (46.5)
AZA	27 (22.3)	13 (14.3)	14 (46.7)	1 (5.0)	26 (25.7)

	Whole cohort	Adults	Children	Single attack pre-RTX (all ages)	Multiple attacks pre-RTX (all ages)
MMF	20 (16.5)	14 (15.4)	6 (20.0)	0	20 (19.8)
Other IS *	13 (10.7)	9 (9.9)	4 (13.3)	0	13 (12.9)
IVIg	7 (5.8)	1 (1.1)	6 (20.0)	0	7 (6.9)
Maintenance PLEX	2 (1.7)	1 (1.1)	1 (3.3)	0	2 (2.0)
Any MS-DMT	11 (9.1)	8 (8.8)	3 (10.0)	0	11 (10.9)
Injectable MS-DMT **	9 (7.4)	6 (6.6)	3 (10.0)	0	9 (8.9)
Oral / infusible MS-DMT ***	5 (4.1)	5 (5.5)	0	0	5 (5.0)

*
Other IS comprised cyclophosphamide (6), mitoxantrone (3), methotrexate (2), tacrolimus (1) and ciclosporin (1).

**
Injectable MS-DMT comprised beta-interferon(8) and glatiramer acetate (4).

***
Oral / infusible MS-DMT comprised natalizumab (5), dimethyl fumarate (1), alemtuzumab (1) and fingolimod (1). Abbreviations: ADEM, acute disseminated encephalomyelitis; ARR, annualised relapse rate; AZA, azathioprine; IS, immunosuppressive drug; IT, immunotherapy; IQR interquartile range; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MS-DMT, multiple sclerosis disease modifying therapy; ON, optic neuritis; PLEX, plasma exchange; RTX, rituximab; TM, transverse myelitis.

Table 2

The effect of rituximab on relapse rates in MOGAD.

	Number of patients, n	Median (IQR) disease duration pre-RTX	Median (IQR) follow-up time on RTX	Reduction in relapse rate after RTX (95%CI), Poisson regression	Median (IQR) ARR pre-RTX	Median (IQR) ARR on RTX	Median change in ARR	Change in ARR, significance, Wilcoxon signed rank test
Whole cohort (all patients with ≥ 2 attacks pre-RTX):								
All patients	101	26.0 (9.8–70.9)	12.1 (6.3–24.9)	37% (19–52%)p<0.001	1.82 (0.74–3.40)	0.00 (0.00–1.25)	−1.09	p<0.001
Patients with ≥12mths observation pre-RTX	71	49.2 (23.1–99.0)	11.4 (6.0–21.9)		1.09 (0.64–1.90)	0.00 (0.00–1.26)	−0.46	p<0.001
Patients with ≥12mths observation post-RTX	51	25.2 (8.4–71.2)	24.9 (18.1–33.5)		1.84 (1.02–3.87)	0.43 (0.00–1.02)	−1.26	p<0.001
Patients with ≥12mths observation pre- and post-RTX	34	49.1 (27.5–80.0)	22.0 (16.7–29.9)		1.18 (0.73–1.68)	0.56 (0.00–1.17)	−0.40	p = 0.002
Exclusion of early relapses:								
Exclusion of the first 1 month post-RTX	97	25.5 (9.4–70.0)	12.0 (6.4–25.1)	43% (26–57%) p<0.001	1.84 (0.84–3.47)	0.00 (0.00–1.25)	−1.09	p<0.001
Exclusion of the first 3 months post-RTX	88	25.7 (9.1–70.5)	13.7 (7.8–26.1)	55% (40–67%) p<0.001	1.83 (0.84–3.51)	0.00 (0.00–1.11)	−1.27	p<0.001
Exclusion of patients co-treated with maintenance corticosteroid or steroid-sparing immunotherapies:								
Patients on RTX monotherapy	61	29.3 (9.4–76.0)	11.3 (5.3–22.3)	42% (15–60%) p=0.005	1.54 (0.64–3.50)	0.00 (0.00–1.00)	−1.09	p<0.001
Treatment naïve patients versus those with prior exposure to steroid-sparing immunotherapies:								
Treatment naive patients	47	14.8 6.6–64.2)	10.0 (5.2–22.3)	63% (35–79%) p=0.001	2.36 (0.53–4.82)	0.0(0.00–0.15)	−2.13	p< 0.001
Prior immunotherapy exposure (including MS-DMTs)	54	36.0 (18.8–72.3)	13.8 (8.0–26.8)	26% (2–44%) p=0.038	1.45 (1.01–2.51)	0.90 (0.00–1.79)	−0.61	p<0.001
Prior immunotherapy exposure (excluding MS-DMTs)	43	30.0 (18.0–71.2)	16.7 (8.0–27.5)	25% (−3–46%) p = 0.077	1.23 (0.92–2.62)	0.62 (0.00–1.44)	−0.70	p< 0.001
Adults versus children:								
Adults	71	26.0 (8.0–74.1)	12.7 (6.1–24.4)	42% (20–59%) p=0.001	1.84 (0.82–4.70)	0.00 (0.00–1.28)	−1.13	p<0.001
Children	30	33.0 (16.3–69.6)	11.8 (6.6–27.1)	29% (−7–53%) p = 0.103	1.64 (0.76–2.92)	0.37 (0.00–1.12)	−0.75	p<0.001

Abbreviations: ARR, annualised relapse rate; 95%CI, 95% confidence interval; IQR, interquartile range; MS-DMT multiple sclerosis disease modifying therapy; RTX, rituximab.