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Effectiveness of immunotherapies in relapsing myelin oligodendrocyte glycoprotein antibody-associated disease

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Philippe Antoine Bilodeau, Anastasia Vishnevetsky, Negar Molazadeh, Itay Lotan, Monique Anderson, Gabriela Romanow, Rebecca Salky, Brian C Healy, Marcelo Matiello, Tanuja Chitnis and Michael Levy

Abstract

Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) can cause optic neuritis, transverse myelitis, or acute disseminated encephalomyelitis (ADEM). Immunotherapy is often used for relapsing disease, but there is variability in treatment decisions.

Objective: The objective was to determine the annualized relapse rates (ARRs) and incidence rate ratios (IRRs) compared to pre-treatment and relapse-freedom probabilities among patients receiving steroids, B-cell depletion (BCD), intravenous immunoglobulin (IVIG), and mycophenolate mofetil (MMF).

Methods: Retrospective cohort study of patients with relapsing MOGAD treated at Mass General Brigham. ARRs and IRRs compared to pre-treatment, and relapse-freedom probability and odds ratio for relapse-freedom compared to prednisone were calculated.

Results: A total of 88 patients met the inclusion criteria. The ARR on IVIG was 0.13 (95% confidence interval (CI) = 0.06–0.27) and the relapse-freedom probability after at least 6 months of therapy was 72%. The ARR on BCD was 0.51 (95% CI = 0.34–0.77), and the relapse-freedom probability was 33%. The ARR on MMF was 0.32 (95% CI = 0.19–0.53) and the relapse-freedom probability was 49%. In pediatric-onset disease, MMF had the lowest ARRs (0.15, 95% CI = 0.07–0.33).

Conclusion: IVIG had the lowest ARRs and IRRs compared to pre-treatment and the highest relapse-freedom odds ratio compared to prednisone, while BCD had the lowest. In pediatric-onset MOGAD, MMF had the lowest ARRs.

Keywords: Autoimmune diseases, neuroinflammatory diseases, demyelinating diseases, myelitis transverse, encephalomyelitis, acute disseminated, optic neuritis

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Correspondence to:
M Levy
Division of Neuroimmunology & Neuroinfectious Disease, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 15 Parkman Street, Wang 8th floor, Boston, MA 02114, USA.
mlevy11@mgh.harvard.edu

Philippe Antoine Bilodeau
Anastasia Vishnevetsky
Negar Molazadeh
Itay Lotan
Monique Anderson
Gabriela Romanow
Rebecca Salky
Marcelo Matiello
Michael Levy
Division of Neuroimmunology & Neuroinfectious Disease, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Brian C Healy
Tanuja Chitnis
Brigham Multiple Sclerosis Center, Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA

Itay Loan is also affiliated to Department of Neurology, Rabin Medical Center, Petah Tikva, Israel and Sackler Faculty of Medicine, Tel-Aviv University,Tel Aviv, Israel

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a demyelinating disorder that can cause optic neuritis, transverse myelitis, and, in children in particular, acute disseminated encephalomyelitis (ADEM).[1–4] The international diagnostic criteria include three additional core clinical demyelinating syndromes, namely cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, and cerebral cortical encephalitis.[2]

Since its initial description, various treatments have been proposed for MOGAD, including intravenous immunoglobulin (IVIG), rituximab, mycophenolate mofetil (MMF), azathioprine (AZA), and tocilizumab. An international survey reported that AZA (30.8%), mycophenolate (25.0%), and rituximab (17.3%) were the most used treatments[5] and treatment with immunosuppression reduces the risk of future relapses.[6] Several small studies have reported success with IVIG,[7,8] MMF,[9–11] rituximab,[12] and tocilizumab.[13] A large international study showed that rituximab reduces relapse rates by 63% when used first line and leads to relapse-freedom in 52.5% of patients after median 12.1 months.[14] This study is limited by the lack of comparison with other agents and the relatively short follow-up time. A

recent study reported higher efficacy with IVIG 2 g/kg monthly compared to other IVIG treatment regimens.[8] Most of these studies were limited by a small number of patients and variability in inclusion criteria and definitions. There is also some emerging data supporting the use of subcutaneous immunoglobulin (SCIG), with one case series ($n=6$) reporting no relapses and good tolerability.[15] Comparison of overall treatment efficacy across studies is complicated by the use of different treatment regimens and concurrent corticosteroids or other treatments.

In this study, we aimed to determine the effectiveness of the most used treatments: prednisone, MMF, IVIG, and B-cell depletion (BCD). We determined the incidence rate ratios (IRRs), annualized relapse rates (ARRs), and relapse-freedom probabilities for all therapies. Our patients were followed up for several years, more than 400 relapses were analyzed, and the number of patients and patient-years on various treatments was significantly higher than that of previous studies. Moreover, we considered combination therapy, monotherapy, and optimal dosing. All patients who met the inclusion criteria and did not meet the exclusion criteria were included in the study.

Methods

Study cohort

We performed a retrospective analysis of MOGAD relapses between 1981 and 2022 at Massachusetts General Hospital and Brigham and Women's Hospital. Patients were included if they had a positive MOG IgG test and met the 2023 MOGAD diagnostic criteria.[2] Cut-offs for high positive and low positive were determined based on individual assay guidelines.[2] For the Mayo live cell-based assay, clear positive included titers ⩾1:100, while low positive included titers from 1:20 to 1:40. For the fixed cell-based assay (ARUP, Athena, Quest), clear positive included titers ⩾1:100, while low positive included titers from 1:10 to 1:100. For clear positive, only Section A (core clinical demyelinating event) was used to determine if the patient met the criteria. For low positive, both Section A and supporting features were used to determine if the patient met the criteria. We excluded patients with an alternative diagnosis, less than 1 month of follow-up and monophasic disease (Figure 1).

Patients who were concurrently receiving more than one of the analyzed medications were included, given the frequency of relapses on multiple medications. All calculations were performed and reported for total patient-years on treatment, patient-years on monotherapy, and, in the case of MMF and IVIG, patient-years on optimal dosing. Other immunomodulatory therapies including glatiramer acetate, interferon β, natalizumab, methotrexate, and cyclophosphamide were not included in the analysis. The number of patient-years on tocilizumab was too small to be included in the statistical models.

Relapse definitions. Relapses were defined as new central nervous system (CNS) symptoms/signs compatible with a known MOGAD manifestation and lasting longer than 24 hours. Transient worsening due to other causes was excluded. Relapses prior to the first positive MOG antibody test result were included. Determination of relapses was done by reviewing the electronic medical record (EMR). Only established phenotypes from the 2023 diagnostic criteria were considered. In cases where a relapse could not be ascertained, for example, if the notes referred to "multiple relapses from 2010 to 2020" these were not included. Only relapses with some amount of clinical information and dates were included. Consequently, some of the retrospective data were missed. For all patients, relapse adjudication considered both MRI confirmation and objective change in exam (e.g. decreased visual acuity or worsening visual fields). In most patients with no MRI confirmation, no imaging was obtained rather than having a normal MRI. For the 10 historical relapses that occurred prior to 2000, information from the EMR was used and only established phenotypes from the 2023 Diagnostic Criteria were considered. To reduce bias, at least two different clinicians independently reviewed the information from the EMR and consensus was reached. In cases of disagreement, the senior author (Michael Levy) was used as the adjudicator. Follow-up time was defined as time from disease onset to the last clinical encounter. Follow-up time and patient-years on treatment were treated as continuous variables and reported as a mean and standard deviation or median and interquartile range (IQR).

Treatment definitions. Monotherapy was defined as being on a single immunomodulatory treatment, and carryover from prior immunotherapies was not considered. Patient-years pre-treatment included time following the first attack but prior to initiation of the first disease-modifying therapy (DMT). Off treatment time periods between immunotherapies were not included due to concern for variable carryover effects of prior immunotherapies. Patient-time on prednisone included time when prednisone dosage was maintained at 10 mg or higher. Patients who received BCD were included if they completed at least the initial loading dose. Dosing for rituximab was 1000 mg every 6 months. There were limited data on B cell

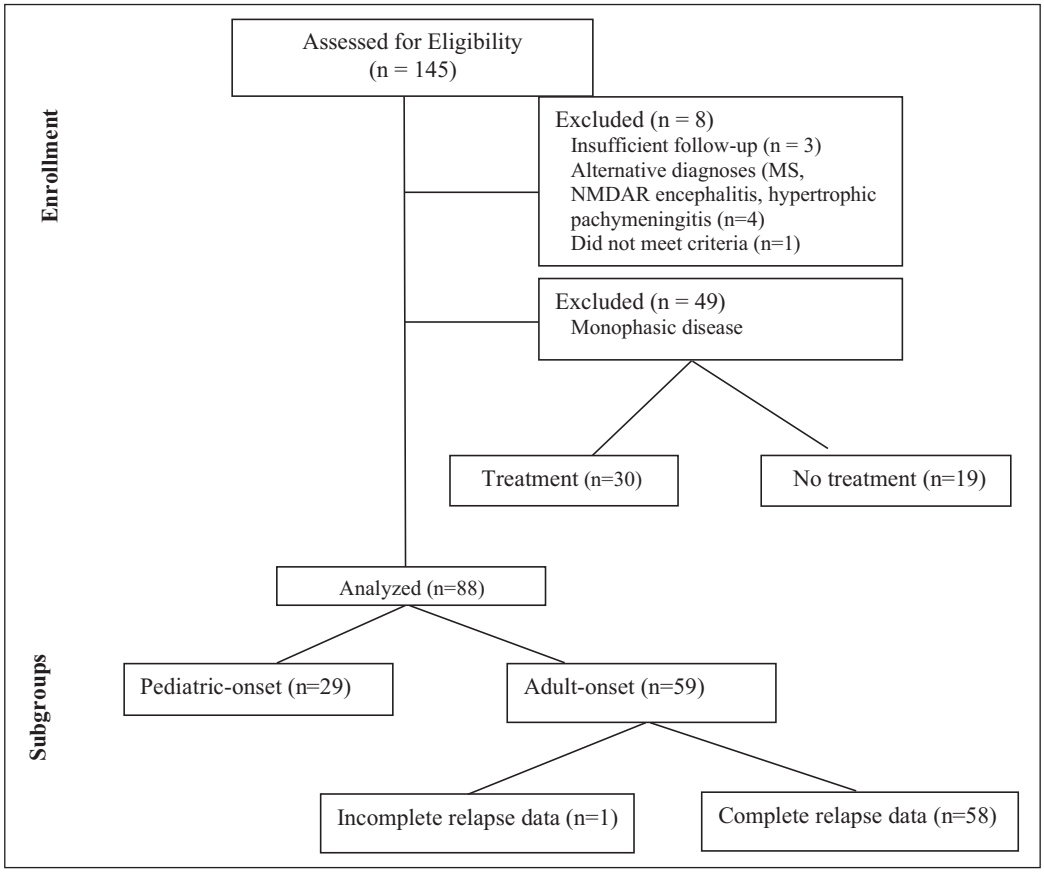

Figure 1. Consort diagram.

subsets at time of relapse. Relapses on BCD were included if they occurred more than 1 month after the initial dose, based on the fact that the half-life of IgG1 antibodies is 30 days.[16] BCD (rituximab, ocrelizumab) was considered to last for 6 months after the last dose. MMF and IVIG effects were considered to persist until the last dose, without carryover after discontinuation. MMF optimal dosing was defined as a dose of at least 1000 mg/m^2, or an absolute lymphocyte count of less than 1500/μL, based on guidelines from children, data showing lower relapse rates with higher doses and data from neuromyelitis optica spectrum disorder (NMOSD) studies.[9–11] MMF relapses on optimal dosing were included if they occurred after at least 3 months of treatment, while all relapses while on the final MMF dose were considered for total treatment. Optimal IVIG dosing was defined as 2 g/kg monthly.[8] For the pre-treatment, prednisone, and rituximab patient-year totals, time on optimal dosing was not defined or calculated.

Relapse-freedom was defined as having had no relapses on a therapy after at least 6 months of treatment. Relapse-freedom probabilities were calculated as the total number of patients who were relapse-free at 6 months divided by the total number of patients who were relapse-free at 6 months plus the total number of patients who failed therapy.

Statistical analysis. A negative binomial mixed effects regression analysis was performed. Given that one patient could have been included in more than one treatment group, patient ID was included as a random effect to adjust for the correlation between relapses within each patient. To adjust for differences in disease acuity between treatment groups, the number of prior treatments was included as a fixed effect in the model, with the assumption that patients who failed multiple prior treatments had more aggressive disease. Prior treatments included any prior immunomodulatory treatment. Relapse IRRs relative to pre-treatment were computed. ARRs were derived from linear combinations of coefficients from the fitted negative binomial regression analyses. Separate negative binomial mixed effects regression analyses were conducted for total time on treatment, time on monotherapy (all dosing regimens), time on optimal dosing

(monotherapy and combination therapy), and time on optimally dosed monotherapy.

For relapse-freedom, a mixed effects logistic regression analysis was performed. Odds ratios (ORs) were computed relative to prednisone and 95% confidence intervals were calculated. A subgroup analysis of pediatric-onset MOGAD (defined as first attack when <18 years old) was performed using the methodology described above. All statistical analysis was performed using Stata (StataCorp. 2021).

Standard protocol approvals, registrations, and patient consents. Institutional review board approval was obtained from Mass General Brigham. Patient consent was not required since all data were de-identified.

Results

A total of 145 patients were identified. Eight ($n=8$) were excluded due to insufficient follow-up, or not meeting the diagnostic criteria. Forty-nine ($n=49$) were excluded due to monophasic disease, of which 30 ($n=30$) were started on maintenance treatment after initial attack and 19 ($n=19$) were observed off treatment. A total of 88 patients who met the inclusion criteria were included in the analysis. Data on relapses were available for all patients. Averaged baseline characteristics of patients who met the inclusion criteria are summarized in Table 1. There was a total of 442 relapses in the cohort: 42 relapses on prednisone, 24 relapses on IVIG, 114 relapses on BCD, and 54 relapses on MMF. Median follow-up time was 6.9 years (IQR = 4.0–11.9) for adult-onset and 6.3 years (IQR = 3.4–12.1) for pediatric-onset. Most patients had no oligoclonal bands. Pediatric-onset MOGAD patients were followed up for longer than adult-onset patients. Most patients were tested using a live cell-based assay. Demographic characteristics broken down by treatment groups are summarized in Table 2. Follow-up time and time on treatment were similar between the groups, except for shorter patient-time on prednisone. Patients who received IVIG at some point in their disease had the highest average number of prior treatments used, while BCD had the lowest average number of prior treatments used (Table 2). A total of 25 (56.8%) patients received BCD prior to IVIG, while 17 (36.9%) received BCD prior to MMF (Supplemental Table S1). The proportion of patients with high and low MOG IgG titers was similar between the treatment groups (Table 2).

ARRs and IRRs for total treatment and optimal total treatment

A total of 69 patients received prednisone at some point in their disease course, compared to 44 for IVIG, 51 for BCD, and 46 for MMF. Results of a negative binomial regression analysis with mixed effects (Table 3) on total treatment time showed an ARR of 1.05 (95% CI = 0.72–1.52) for pre-treatment, compared to 0.46 (95% CI = 0.28–0.77) for prednisone, 0.13 (95% CI = 0.06–0.27) for IVIG, 0.51 (95% CI = 0.34–0.77) for BCD, and 0.32 (95% CI = 0.19–0.53) for MMF (Figure 2). Corresponding IRRs compared to pre-treatment were 0.44 (95% CI = 0.26–0.76) for prednisone, 0.12 (95% CI = 0.06–0.27) for IVIG, 0.49 (0.31–0.78) for BCD, and 0.30 (0.17–0.53) for MMF (Table 3). A total of 26 patients received optimal IVIG therapy and a total of 39 patients received optimal MMF therapy. The ARRs on total treatment time, optimal dosing were 0.07 (95% CI = 0.02–0.22) for IVIG and 0.23 (95% CI = 0.12–0.44) for MMF. The corresponding IRRs were 0.07 (95% CI = 0.02–0.23) for IVIG and 0.25 (95% CI = 0.13–0.46) for MMF (Table 3).

For adult-onset patients, the ARRs on total treatment were 1.13 (95% CI = 0.69–1.83) for pre-treatment, 0.46 (95% CI = 0.25–0.84) for prednisone, 0.11 (95% CI = 0.04–0.31) for IVIG, 0.54 (95% CI = 0.33–0.87) for BCD, and 0.46 (95% CI = 0.24–0.88) for MMF. The ARRs on optimal total treatment are available in Table 6.

ARRs and IRRs for monotherapy and optimal monotherapy

A total of 59 patients were on prednisone monotherapy, compared to 38 for IVIG, 44 for BCD, and 36 for MMF. The ARRs on monotherapy were 0.66 (95% CI = 0.33–1.29) for prednisone, 0.09 (95% CI = 0.03–0.26) for IVIG, 0.71 (95% CI = 0.42–1.21) for BCD, and 0.27 (95% CI = 0.14–0.52) for MMF (Figure 2). The corresponding IRRs compared to pre-treatment were 0.61 (95% CI = 0.29–1.26) for prednisone, 0.08 (95% CI = 0.03–0.23) for IVIG, 0.66 (95% CI = 0.36–1.18) for BCD, and 0.25 (95% CI = 0.13–0.50) for MMF (Table 2). A total of 23 patients received optimal IVIG monotherapy compared to 29 for MMF. ARRs on optimal dosing monotherapy were 0.00 (95% CI = 0.01–0.03) for IVIG and 0.07 (95% CI = 0.02–0.21) for MMF (Table 4). The corresponding IRRs were 0.00 (95% CI = 0.00–0.03) for IVIG and 0.07 (95% CI = 0.02–0.20) for MMF (Table 4). The ARR and IRR for adult-onset patients only are available in Table 6.

Table 1. Demographic characteristics.

	Total	Adult-onset	Pediatric-onset	*p* value
	N=88	*N*=59	*N*=29	
Age of onset	29.4 (18.9)	39.5 (14.7)	9.0 (4.5)	<0.001
Sex				0.47
Female	56 (63.6%)	36 (61.0%)	20 (69.0%)	
Male	32 (36.4%)	23 (39.0%)	9 (31.0%)	
Race				0.57
White	63 (71.6%)	44 (74.6%)	19 (65.5%)	
African American or Black	11 (12.5%)	6 (10.2%)	5 (17.2%)	
Asian	6 (6.8%)	3 (5.1%)	3 (10.3%)	
Other or unknown	8 (9.1%)	6 (10.2%)	2 (6.9%)	
Ethnicity				0.46
Hispanic/Latino	13 (14.8%)	7 (11.9%)	6 (20.7%)	
Not Hispanic/Latino	73 (83.0%)	51 (86.4%)	22 (75.9%)	
Other or unknown	2 (2.3%)	1 (1.7%)	1 (3.4%)	
Oligoclonal bands				0.66
Negative	55 (62.5%)	35 (59.3%)	20 (69.0%)	
Positive	3 (3.4%)	2 (3.4%)	1 (3.4%)	
Unknown	30 (34.1%)	22 (37.3%)	8 (27.6%)	
Type of cell-based assay				0.71
Live CBA	75 (85.2%)	49 (83.1%)	26 (89.7%)	
Fixed CBA	4 (4.5%)	3 (5.1%)	1 (3.4%)	
Unknown	9 (10.2%)	7 (11.9%)	2 (6.9%)	
Total follow-up (years)	6.7 (3.7–12.0)	6.9 (4.0–11.9)	6.3 (3.4–12.1)	0.77

IQR: interquartile range; CBA: Cell-based assay.
Total follow-up time was defined as time between the first attack and the last follow-up. Data are presented as mean (SD) or median (IQR) for continuous measures, and *n* (%) for categorical measures. Patients who received more than one treatment during their disease course could be included in multiple categories. Adult-onset and pediatric-onset groups were compared using Pearson's chi-square test for categorical variables and two-sample *t* test for continuous variables.

Relapse-freedom probabilities

Relapse-freedom probabilities and ORs compared to prednisone were calculated. Relapse-freedom probabilities on total treatment were 47% for prednisone, 72% for IVIG, 33% for BCD, and 49% for MMF (Table 4). Results of a mixed effects logistic regression analysis showed ORs compared to prednisone of 3.74 (95% CI = 1.11–12.58) for IVIG, 0.45 (95% CI = 0.17–1.19) for BCD, and 1.33 (95% CI = 0.46–3.83) for MMF (Table 4). Using optimal dosing, relapse-freedom probabilities increased to 85% for IVIG and 60% for MMF, with an OR relative to prednisone of 13.97 (95% CI = 3.09–63.17) for IVIG and 2.59 (95% CI = 0.84–7.97) for MMF (Table 5).

A total of six patients received tocilizumab for a total of 7.59 patient-years. Two of those patients had two relapses each, while the other four remained relapse-free.

Comparison of treatments in pediatric-onset MOGAD

The different treatments were compared in patients with pediatric-onset MOGAD. Monotherapy was used for the comparison. A total of 24 patients received prednisone, compared to 6 for IVIG, 9 for BCD, and 16 for MMF. The ARRs were 0.54 (95% CI = 0.22–1.32) for prednisone, 0.18 (95% CI = 0.02–1.54) for IVIG, 0.55 (95% CI = 0.23–1.28) for BCD, and 0.04 (95% CI = 0.01–0.16) for MMF (Table 6).

Discussion

In our multi-center cohort of 88 patients with relapsing MOGAD seen between 1981 and 2022, treatment with IVIG was associated with the lowest ARR (0.13) and highest relapse-freedom probability (72%). MMF had the second lowest ARR (0.32) and second lowest relapse-freedom probability (49%). BCD had the

Table 2. Demographic characteristics by treatment group.

	Total	Pre-treatment	Prednisone	IVIG	BCD	MMF	*p* value
	N=286	*N*=76	*N*=69	*N*=44	*N*=51	*N*=46	
Age of onset	29.5 (18.5)	27.8 (18.4)	29.8 (19.9)	30.0 (17.6)	33.4 (17.3)	27.2 (18.8)	0.45
Sex							0.65
Female	184 (64.3%)	47 (61.8%)	43 (62.3%)	29 (65.9%)	31 (60.8%)	34 (73.9%)	
Male	102 (35.7%)	29 (38.2%)	26 (37.7%)	15 (34.1%)	20 (39.2%)	12 (26.1%)	
Race							0.91
White	209 (73.1%)	55 (72.4%)	49 (71.0%)	37 (84.1%)	37 (72.5%)	31 (67.4%)	
African American or Black	28 (9.8%)	8 (10.5%)	7 (10.1%)	3 (6.8%)	3 (5.9%)	7 (15.2%)	
Asian	22 (7.7%)	6 (7.9%)	6 (8.7%)	2 (4.5%)	5 (9.8%)	3 (6.5%)	
Other or unknown	27 (9.4%)	7 (9.2%)	7 (10.1%)	2 (4.5%)	6 (11.8%)	5 (10.9%)	
Ethnicity							0.97
Hispanic/Latino	37 (12.9%)	9 (11.8%)	8 (11.6%)	5 (11.4%)	6 (11.8%)	9 (19.6%)	
Not Hispanic/Latino	242 (84.6%)	65 (85.5%)	59 (85.5%)	38 (86.4%)	44 (86.3%)	36 (78.3%)	
Other or unknown	7 (2.4%)	2 (2.6%)	2 (2.9%)	1 (2.3%)	1 (2.0%)	1 (2.2%)	
Total follow-up (years)	9.7 (8.3)	11.0 (9.7)	8.9 (7.0)	9.1 (7.4)	9.6 (8.4)	9.7 (8.6)	0.60
Time on treatment (years)	3.0 (5.3)	5.2 (9.2)	1.0 (1.2)	2.1 (1.9)	3.4 (2.2)	3.0 (2.8)	<0.001
Number of prior treatments							<0.001
None	222 (77.6%)	76 (100.0%)	69 (100.0%)	10 (22.7%)	41 (80.4%)	26 (56.5%)	
One (1)	41 (14.3%)	0 (0.0%)	0 (0.0%)	20 (45.5%)	8 (15.7%)	13 (28.3%)	
Two (2)	16 (5.6%)	0 (0.0%)	0 (0.0%)	10 (22.7%)	0 (0.0%)	6 (13.0%)	
Three prior treatments	7 (2.4%)	0 (0.0%)	0 (0.0%)	4 (9.1%)	2 (3.9%)	1 (2.2%)	
Highest MOG IgG titer							0.98
⩽1:20	43 (15.0%)	12 (15.8%)	8 (11.6%)	7 (15.9%)	7 (13.7%)	9 (19.6%)	
1:40	41 (14.3%)	13 (17.1%)	10 (14.5%)	7 (15.9%)	4 (7.8%)	7 (15.2%)	
⩾1:100	95 (33.2%)	27 (35.5%)	22 (31.9%)	12 (27.3%)	18 (35.3%)	16 (34.8%)	
1:1000	74 (25.9%)	17 (22.4%)	20 (29.0%)	12 (27.3%)	15 (29.4%)	10 (21.7%)	
N/A	33 (11.5%)	7 (9.2%)	9 (13.0%)	6 (13.6%)	7 (13.7%)	4 (8.7%)	

IVIG: intravenous immunoglobulin; BCD: B-cell depletion; MMF: mycophenolate mofetil; MOG: myelin oligodendrocyte glycoprotein; N/A: not applicable; IQR: interquartile range; ANOVA: analysis of variance.
Total follow-up time was defined as time between the first attack and the last follow-up. Data are presented as mean (SD) or median (IQR) for continuous measures, and *n* (%) for categorical measures. Patients who received more than one treatment during their disease course could be included in multiple categories. Treatment groups were compared using Pearson's chi-square test for categorical variables and ANOVA for continuous variables.

highest ARR (0.54) and the lowest relapse-freedom probability (33%).

The use of IVIG 2 g/kg monthly (optimal IVIG) was associated with an even lower ARR (0.00) and higher relapse-freedom probability (85%). This is similar to a recent study by Chen et al.[8] showing a median ARR of 0 (0–3, $p < 0.001$) on IVIG and higher relapse rates in patients treated with less than 2 g/kg every 4 weeks. MMF significantly decreased the relapse rate but relapse-freedom probability was lower than that for IVIG. The ARR of 0.32 for total treatment MMF and 0.23 for optimal dosing MMF were similar to the relapse rate on high-dose MMF reported by Li et al.[9] and much lower than the French pediatric cohort (0.52).[17] These differences may be due to differences in dosing and differences in the definition of a relapse. For optimal dosing, we only included time on optimally dosed MMF and did not consider relapses that occurred in the first 3 months of therapy. Some groups have shown that patients receiving high-dose MMF (defined as equal to or more than 2000 mg/day) had a significantly reduced risk of relapses compared to patients receiving low-dose MMF (less than 1000 mg/day).[10] Similarly, there was an improvement in ARR with optimal dosing in our cohort. The relapse-freedom probability for MMF was 49%, which is lower than what was found by Li et al.[9] (50/54 relapse-free) and Montcuquet et al.[18] (4/5 relapse-free). This may be due to differences in study design, patient characteristics, and statistical analysis. Interestingly, MMF was the most effective treatment in pediatric-onset MOGAD, consistent with a recent study that reported an ARR of 0 (95% CI = 0–1.72) in their pediatric

Table 3. IRRs (95% CI) and ARRs for total treatment and optimal treatment.

Treatment	Total				Optimal			
	ARR (95% CI)	IRR (95% CI)	*n*	Median treatment years (IQR)	ARR (95% CI)	IRR (95% CI)	*n*	Median treatment years (IQR)
Pre-treatment	1.05 (0.72–1.52)	Reference	76	1.03 (0.34–5.68)	N/A	Reference	76	1.03 (0.34–5.68)
Prednisone	0.46 (0.28–0.77)	0.44 (026–0.76)	69	0.53 (0.24–1.31)	N/A	N/A	69	0.53 (0.24–1.31)
IVIG	0.13 (0.06–0.27)	0.12 (0.06–0.27)	44	1.90 (0.72–2.91)	0.07 (0.02–0.22)	0.07 (0.02–0.23)	26	1.41 (0.57–1.96)
BCD	0.51 (0.34–0.77)	0.49 (0.31–0.78)	51	3.00 (1.67–4.64)	N/A	N/A	51	3.00 (1.67–4.64)
MMF	0.32 (0.19–0.53)	0.30 (0.17–0.53)	46	2.05 (0.87–4.83)	0.23 (0.12–0.44)	0.25 (0.13–0.46)	39	1.65 (0.85–3.42)

ARR: annualized relapse rate; CI: confidence interval; IRR: incidence rate ratio; IVIG: intravenous immunoglobulin; BCD: B-cell depletion; MMF: mycophenolate mofetil; N/A: not applicable; IQR: interquartile range.
Two separate negative binomial mixed effects regression analyses were performed for total treatment and optimal dosing. The number of prior treatments was included as a fixed effect and patient ID was included as a random effect. Estimated IRRs relative to pre-treatment are shown along with 95% CIs. The estimated IRR and ARR on optimal treatment were not included for pre-treatment, BCD, and prednisone, given that optimal therapy was not defined for those treatments.

cohort.[19] Across all groups, BCD was consistently inferior to both MMF and IVIG. Unlike an earlier multi-center analysis by Chen and colleagues, in our cohort, rituximab was much less effective than MMF.[7] The relapse-freedom probability on rituximab was lower in our cohort (33%) than what was reported in a recent meta-analysis (55%, $n = 238$), despite the fact that it was most likely to be used first line.[12,14] This is likely due to the long follow-up time in our study. The BCD ARR in pediatric-onset MOGAD (0.58) was similar to the French pediatric cohort.[17] BCD is not trivial in children, given the risk of inadequate humoral responses to vaccinations. Similar to Ringelstein et al.,[20] we found that four of the six patients remained relapse-free on tocilizumab. One of the patients who had two relapses on tocilizumab had extremely refractory disease, with more than 20 relapses.

This retrospective effectiveness analysis compares four of the most used MOGAD treatments. While previous studies have investigated individual immunotherapies, our analysis of over 400 relapses allows us to determine the efficacy of different treatment regimens in a statistically robust fashion, albeit with the biases inherent to observational studies. While Chen et al.[7] showed similar results, there were few patients on some of the treatments, particularly IVIG, which precluded performing a regression analysis. A strength of this analysis is that we used a negative binomial regression modeling approach, which can be applied to count outcomes with significant overdispersion, or variability and outliers in the distribution. In multiple sclerosis (MS), significant subject heterogeneity in the number of relapses has been shown to lead to overdispersion.[21] Moreover, at the patient level, the occurrence of a relapse increases the risk for a subsequent one—a phenomenon called contagion.[21] Cox models assume that the hazard ratio between treatment groups is constant over time. When there is subject heterogeneity, this assumption is often violated, and the Cox model may not be suitable for estimating treatment effects.[21] Given the drawbacks of Cox models, and the fact that negative binomial models are simple and efficient, the latter have been the preferred method of analysis for relapses in MS.[21] Since MOGAD patients may have similar or potentially even greater heterogeneity, with relapses on various therapies ranging from none to over 20 in our dataset, we chose the negative binomial regression analysis to account for this variability. A follow-up study of the first and second attacks using Cox regression is currently under review and preliminarily confirms our findings.

There are several limitations to this retrospective study. First, the fact that many patients were on multiple and overlapping therapies can complicate the attribution of outcomes to a specific treatment, making it challenging to distinguish the individual treatment effects from potential synergistic effects between therapies and carryover effects of earlier treatments.

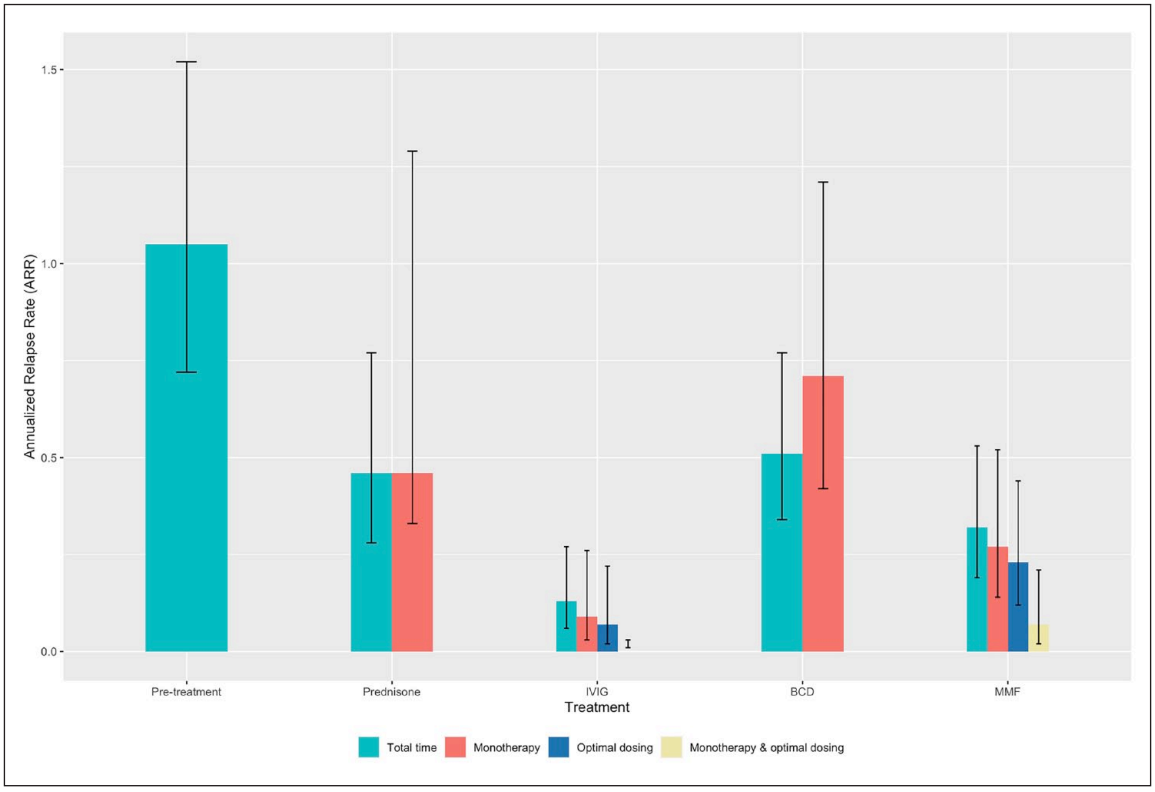

Figure 2. Annualized relapse rates were derived from linear combinations of coefficients from the fitted negative binomial regression analyses. A total of four regression analyses were performed (total time, monotherapy, optimal dosing, and monotherapy and optimal dosing) and the results are compared here. ARRs for prednisone and BCD optimal dosing and monotherapy and optimal dosing are not shown since optimal dosing is not defined for those treatments.

Table 4. IRRs (95% CI) and ARRs for monotherapy and optimal monotherapy.

Treatment	Monotherapy				Optimal monotherapy			
	ARR (95% CI)	IRR (95% CI)	*n*	Median treatment years (IQR)	ARR (95% CI)	IRR (95% CI)	*n*	Median treatment years (IQR)
Pre-treatment	N/A	Reference	76	1.03 (0.21–4.3)	N/A	Reference	76	1.03 (0.21–4.3)
Prednisone	0.66 (0.33–1.29)	0.61 (0.29–1.26)	59	0.20 (0.056–0.47)	N/A	N/A	59	0.20 (0.056–0.47)
IVIG	0.09 (0.03–0.26)	0.08 (0.03–0.23)	38	0.92 (0.49–1.95)	0.00 (0.01–0.03)	0.00 (0.00– 0.03)	23	0.86 (0.40–1.66)
BCD	0.71 (0.42–1.21)	0.66 (0.36–1.18)	44	1.67 (1.00–3.72)	N/A	N/A	43	1.67 (1.00–3.72)
MMF	0.27 (0.14–0.52)	0.25 (0.13–0.50)	36	1.66 (0.97–3.26)	0.07 (0.02–0.21)	0.07 (0.02 - 0.20)	29	1.10 (0.52–2.72)

ARR: annualized relapse rate; CI: confidence interval; IRR: incidence rate ratio; IVIG: intravenous immunoglobulin; BCD: B-cell depletion; MMF: mycophenolate mofetil; N/A: not applicable; IQR: interquartile range.
Two separate negative binomial mixed effects regression analyses were performed for optimal dosing and monotherapy and optimal dosing. The number of prior treatments was included as a fixed effect and patient ID was included as a random effect. Estimated IRRs relative to pre-treatment are shown along with 95% CIs. The estimated IRRs and ARRs for pre-treatment monotherapy were not included, given that monotherapy was not defined for this group. The estimated IRRs and ARRs on optimal therapy and optimal monotherapy were not included for pre-treatment, BCD, and prednisone, given that optimal therapy was not defined for those treatments.

Table 5. Comparison of relapse-freedom probabilities.

Treatment	Relapse-freedom probabilities (%)	OR for relapse-freedom (95% CI)	*N*
Prednisone	39	Reference	69
IVIG	72	3.74 (1.11–12.58)	44
IVIG optimal	85	13.97 (3.09–63.17)	26
BCD	33	0.45 (0.17–1.19)	51
MMF	49	1.33 (0.46–3.83)	46
MMF optimal	58	2.59 (0.84–7.97)	39

OR: odds ratio; CI: confidence interval; IVIG: intravenous immunoglobulin; BCD: B-cell depletion; MMF: mycophenolate mofetil. A mixed effects logistic regression analysis was performed. ORs were computed relative to prednisone and 95% CIs were calculated.

Second, for the early relapses in the 1980s and 1990s, medical records were limited, MRI use was inconsistent or difficult to confirm, and MOGAD was not a known diagnostic entity. Even for patients with detailed information, relapse adjudication in retrospective studies can be fraught, given the inconsistent use of MRI and a lack of certainty, particularly for patients presenting with non-specific symptoms. To address this issue, we considered radiographic confirmation and objective change in exam to determine relapses and had two independent clinicians review each relapse. For future studies, we will collect detailed information on how relapse adjudication was determined for each patient, including whether there was radiographic confirmation and whether there was a change in the neurological exam. This will allow us to establish levels of confidence for relapse adjudication. Ultimately, objective rules for relapse adjudication are the gold standard and can only be achieved in a clinical trial. Third, there was significant heterogeneity in individual relapse rates. The pre-treatment ARR was likely biased by patients who had an interval of years between the first and second inflammatory events. Similarly, some particularly refractory patients relapsed on every treatment, which could have biased the ARR. Moreover, the pediatric-onset subgroup analysis was limited by the low number of patients on the various treatments. Fourth, patients who were started on treatment after the index event and never relapsed again were excluded; as a result, the ARR may have been overestimated. We were unable to include patients on tocilizumab and AZA in the statistical analysis, given that the numbers were too low. Patients were considered on prednisone if they were on 10 mg or more chronically; consequently, the efficacy of higher doses of prednisone was likely underestimated. Finally, we did not collect information regarding several important considerations that impact treatment selection, including patient preferences and satisfaction, costs, reasons for treatment transitions, adverse effects, and long-term safety. A recent study by our group showed that 30 of the 257 patients on BCD for MS, NMOSD, and MOGAD had hypogammaglobulinemia, which was corrected by IVIG/SCIG,[22] and we are currently collecting more in-depth data on these other factors for a follow-up study.

Comparing treatment groups is challenging in retrospective analyses, given the heterogeneity of the groups. For example, patients who were treated prior to the first IVIG studies were more likely to be treated with rituximab. While we adjusted for this by including the number of prior treatments as a proxy for disease severity in a mixed effects model, future studies should consider using statistical methodologies such as propensity score matching and marginal structural models to address indication bias. Propensity score matching helps balance the observed covariates between treatment groups, while marginal structural models allow for the estimation of treatment effects while accounting for time-varying confounding and treatment history. Using these techniques would mitigate confounding and indication bias, which would allow for causal inference. Beyond non-interventional causal inference, we strongly advocate for prospective randomized controlled trials (RCTs) of IVIG and other treatments in MOGAD. Establishing the efficacy of these treatments with rigorous Class 1 evidence is of paramount importance.

In conclusion, our large cohort of MOGAD patients with long follow-up time showed that all analyzed treatments lowered relapse rates compared to the pre-treatment group. IVIG had the lowest ARR and IRR, while BCD had the highest. In pediatric-onset

Table 6. ARRs and IRRs, adult- and pediatric-onset MOGAD.

Treatment	Adult-onset			Pediatric-onset		
	ARR (95% CI)	IRR (95% CI)	*n*	ARR (95% CI)	IRR (95% CI)	*n*
Total treatment						
Pre-treatment	1.13 (0.69–1.83)	Reference	49	0.80 (0.43–1.46)	Reference	27
Prednisone	0.46 (0.25–0.84)	0.41 (0.22–0.77)	45	0.62 (0.26–1.47)	0.66 (0.25–1.76)	24
IVIG	0.11 (0.04–0.31)	0.10 (0.03–0.29)	31	0.19 (0.07–0.53)	0.23 (0.07–0.72)	13
BCD	0.54 (0.33–0.87)	0.48 (0.28–0.82)	42	0.52 (0.24–1.14)	0.63 (0.27–1.51)	9
MMF	0.46 (0.24–0.88)	0.41 (0.20–0.84)	28	0.15 (0.07–0.33)	0.18 (0.07–0.43)	18
Optimal dosing						
Pre-treatment	N/A	Reference	49	N/A	Reference	27
Prednisone	N/A	0.40 (0.21–0.77)	45	N/A	N/A	24
IVIG	0.06 (0.02–0.26)	0.05 (0.01–0.23)	20	0.18 (0.02–1.54)	0.24 (0.03–2.15)	6
BCD	N/A	0.47 (0.27–0.81)	42	N/A	N/A	9
MMF	0.44 (0.21–0.91)	0.37 (0.17–0.82)	23	0.04 (0.01–0.16)	0.05 (0.01–0.23)	16
Monotherapy						
Pre-treatment	N/A	Reference	49	N/A	Reference	27
Prednisone	0.76 (0.34–1.67)	0.62 (0.26–1.45)	38	0.54 (0.22–1.32)	0.72 (0.27–1.92)	24
IVIG	0.08 (0.02–0.31)	0.06 (0.02–0.24)	26	0.18 (0.02–1.54)	0.24 (0.03–2.15)	6
BCD	0.69 (0.36–1.32)	0.56 (0.28–1.14)	34	0.55 (0.23–1.28)	0.73 (0.29–1.82)	9
MMF	0.43 (0.17–1.07)	0.35 (0.14–0.88)	21	0.04 (0.01–0.16)	0.05 (0.01–0.23)	16
Monotherapy, optimal dosing						
Pre-treatment	N/A	Reference	49	N/A	Reference	27
Prednisone	N/A	N/A	38	N/A	N/A	21
IVIG	0.00 (0.00–0.08)	0.00 (0.00–0.06)	17	0.11 (0.00–17.13)	0.14 (0.0–21.99)	6
BCD	N/A	N/A	34	N/A	N/A	9
MMF	0.15 (0.03–0.74)	0.12 (0.02–0.62)	14	0.02 (0.00–0.13)	0.02 (0.00–0.17)	15

ARR: annualized relapse rate; CI: confidence interval; IRR: incidence rate ratio; IVIG: intravenous immunoglobulin; BCD: B-cell depletion; MMF: mycophenolate mofetil; N/A: not applicable; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease. Separate negative binomial mixed effects regression analyses were performed for pediatric-onset and adult-onset for each category. Estimated IRRs relative to pre-treatment are shown along with 95% CIs. The estimated IRRs and ARRs for pre-treatment monotherapy were not included, given that monotherapy was not defined for this group. The estimated IRRs and ARRs on optimal therapy and optimal monotherapy were not included for pre-treatment, BCD, and prednisone, given that optimal therapy was not defined for those treatments.

MOGAD, MMF had the lowest ARR and IRR, but interpretation is limited by the small number of patients.

While we await Class 1 data, IVIG and mycophenolate could be considered in relapsing MOGAD.

Other information

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

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ORCID iDs

Philippe Antoine Bilodeau https://orcid.org/0000-0002-2672-554X
Itay Lotan https://orcid.org/0000-0002-4015-9783
Michael Levy https://orcid.org/0000-0002-7969-8346

Supplemental material

Supplemental material for this article is available online.

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