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Association of Maintenance Intravenous Immunoglobulin With Prevention of Relapse in Adult Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease

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IMPORTANCE Recent studies suggest that maintenance intravenous immunoglobulin (IVIG) may be an effective treatment to prevent relapses in myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD); however, most of these studies had pediatric cohorts, and few studies have evaluated IVIG in adult patients.

OBJECTIVE To determine the association of maintenance IVIG with the prevention of disease relapse in a large adult cohort of patients with MOGAD.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study conducted from January 1, 2010, to October 31, 2021. Patients were recruited from 14 hospitals in 9 countries and were included in the analysis if they (1) had a history of 1 or more central nervous system demyelinating attacks consistent with MOGAD, (2) had MOG-IgG seropositivity tested by cell-based assay, and (3) were age 18 years or older when starting IVIG treatment. These patients were retrospectively evaluated for a history of maintenance IVIG treatment.

EXPOSURES Maintenance IVIG.

MAIN OUTCOMES AND MEASURES Relapse rates while receiving maintenance IVIG compared with before initiation of therapy.

RESULTS Of the 876 adult patients initially identified with MOGAD, 59 (median [range] age, 36 [18-69] years; 33 women [56%]) were treated with maintenance IVIG. IVIG was initiated as first-line immunotherapy in 15 patients (25%) and as second-line therapy in 37 patients (63%) owing to failure of prior immunotherapy and in 7 patients (12%) owing to intolerance to prior immunotherapy. The median (range) annualized relapse rate before IVIG treatment was 1.4 (0-6.1), compared with a median (range) annualized relapse rate while receiving IVIG of 0 (0-3) (t_{108} = 7.14; P < .001). Twenty patients (34%) had at least 1 relapse while receiving IVIG with a median (range) time to first relapse of 1 (0.03-4.8) years, and 17 patients (29%) were treated with concomitant maintenance immunotherapy. Only 5 of 29 patients (17%) who received 1 g/kg of IVIG every 4 weeks or more experienced disease relapse compared with 15 of 30 patients (50%) treated with lower or less frequent dosing (hazard ratio, 3.31; 95% CI, 1.19-9.09; P = .02). At final follow-up, 52 patients (88%) were still receiving maintenance IVIG with a median (range) duration of 1.7 (0.5-9.9) years of therapy. Seven of 59 patients (12%) discontinued IVIG therapy: 4 (57%) for inefficacy, 2 (29%) for adverse effects, and 1 (14%) for a trial not receiving therapy after a period of disease inactivity.

CONCLUSIONS AND RELEVANCE Results of this retrospective, multicenter, cohort study of adult patients with MOGAD suggest that maintenance IVIG was associated with a reduction in disease relapse. Less frequent and lower dosing of IVIG may be associated with treatment failure. Future prospective randomized clinical trials are warranted to confirm these findings.

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Supplemental content

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Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a distinct central nervous system (CNS) demyelinating disease that can relapse and has the potential to cause severe morbidity.[1-3] The clinical phenotype can include optic neuritis (ON), transverse myelitis (TM), acute disseminating encephalomyelitis (ADEM), and other manifestations.[1,4-8] A significant fraction of patients with MOGAD will experience recurrent demyelinating attacks, most frequently ON.[1,4,8] To our knowledge, there is currently no approved therapy to reduce the relapse frequency in MOGAD. Several traditional treatments used for multiple sclerosis have not been found to be effective for MOGAD,[9-11] and treatments used for neuromyelitis optica spectrum disorder, such as rituximab, have varying efficacy in retrospective studies.[9-13] Some recent observational studies suggest that maintenance intravenous immunoglobulin (IVIG) may be an effective treatment in preventing relapse in MOGAD, but these studies were predominantly performed in children.[10,12,14] There are very few studies evaluating maintenance IVIG in adults with MOGAD.[10,11,15] To better understand the association of IVIG therapy with the prevention of recurrent attacks in adults, we evaluated a large international multicenter cohort of adult patients with MOGAD who received maintenance IVIG.

Key Points

Question Is maintenance intravenous immunoglobulin (IVIG) associated with the prevention of relapses in adult patients with myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD)?

Findings In this cohort study of 59 adult patients with MOGAD, maintenance IVIG was associated with a significant reduction in disease relapse (median [range] annualized relapse rate of 0 [0-3]). More frequent relapses were observed in those who received lower and less frequent dosing.

Meaning The study results suggest that maintenance IVIG was associated with a reduction in relapse frequency in adult patients with MOGAD.

Methods

This was an international retrospective, multicenter, cohort study conducted from January 1, 2010, to October 31, 2021, of patients with MOGAD who received maintenance IVIG therapy. Patients were recruited from 14 hospitals in 9 countries: Australia, France, Germany, Israel, Italy, South Korea, Spain, the UK, and the US. Patient race and ethnicity information was collected from the medical record to investigate the potential for race predilection toward more severe disease and response to IVIG therapy. Patients of the following races and ethnicities were included: Asian, Black, Hispanic, Lebanese, White, and mixed. Patient inclusion criteria were as follows: (1) a clinically documented history of CNS inflammatory demyelinating disease with phenotypes consistent with MOGAD,[16] (2) seropositivity for MOG IgG by cell-based assay, (3) IVIG treatment for 6 months or more (or a shorter duration if treatment was stopped owing to inefficacy or adverse effects), and (4) age 18 years or older at the initiation of IVIG therapy.

The Mayo Clinic institutional review board approved this study; in addition, written informed consent was obtained from patients at the Mayo Clinic to access their medical records for research purposes. For patient cases contributed from other medical centers, the pertinent institutional review boards approved the study with a waiver of informed consent owing to the retrospective nature of the study. Data were shared in a deidentified manner with the lead site through Excel (Microsoft) databases. The reporting of this research was done in conjunction with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

MOG-IgG Assay

All MOG IgG testing was performed on cell-based assays with full-length MOG in its native conformational form with the IgG-1 or IgG (H^+L) secondary antibody.[17] All centers used live cell-based assays, except for 2 centers that used a fixed cell-based assay (Euroimmun), for which 33 of 876 patients (4%) were screened.[17] Seropositivity was considered persistent when both the initial sample and a repeated sample were positive for 12 months or more.

Relapse Rate and Therapeutic Efficacy

All patients with MOGAD at each site who met eligibility criteria were included to avoid sampling bias. Age, sex, and race and ethnicity were documented. The patients' medical records were reviewed for number, dates, and types of CNS demyelinating events. A relapse was determined by all of the coauthors, who all have extensive experience in MOGAD; a relapse was defined as any new CNS sign or symptom lasting at least 24 hours, supported by clinical examination or radiologic findings, and occurring at least 1 month after a prior attack.[18] Immunotherapy modality, types, duration, number of relapses while receiving and not receiving treatment, and Expanded Disability Status Scale (EDSS) score were recorded.

Annualized relapse rate (ARR) was calculated as the ratio of the number of demyelinating attacks per year. To prevent artificial inflation of the pre-IVIG ARR, the index event was excluded,[11] and patients were excluded from the pre-IVIG ARR calculation if IVIG was started less than 6 months after the first attack. Patients were also excluded from the IVIG ARR calculation if they were receiving treatment for less than 6 months unless it was discontinued owing to adverse effects or other reasons.

Adjunct immunotherapies used in conjunction with IVIG were documented. In addition to other maintenance immunotherapies, such as rituximab, prednisone at a dosage of greater than 10 mg daily for longer than 6 months was also defined as adjunct immunotherapy.

Statistical Analysis

The overall time to first relapse end point was estimated using the Kaplan-Meier method. Baseline risk factors were related

Table 1. Distribution of Patients With MOGAD and Treatments From the Various Centers

Population, No.	Australia	France	Germany	Israel	Italy	South Korea	Spain	UK	US
Adult patients with MOGAD	32	238	19	14	15	53	16	234	255
Adult patients with MOGAD receiving long-term immunotherapy	18	94	16	4	5	47	16	188	123
Adult patients with MOGAD receiving maintenance IVIG	2	11	3	2	2	7	2	7	23

Abbreviations: IVIG, intravenous immunoglobulin; MOGAD, myelin oligodendrocyte glycoprotein antibody–associated disease.

to the time to first relapse using Cox proportional hazards models. Given the dosage changes in the follow-up period, the estimated risk of relapse within an individual dosage was evaluated using the dosage as a time-dependent covariate in a Cox proportional hazards model. Non–time-dependent comparisons between groups for categorical variables were completed with Fisher exact or χ^2 test. Simple ARRs under individual dosage levels were also completed for illustrative purposes. Statistics were performed using SAS, version 9.4 (SAS Institute). *P* values < .05 were considered statistically significant, and all *P* values were 2-sided.

Results

Among 876 adult patients with MOGAD initially identified at all research centers (**Table 1**), 59 patients were treated with maintenance IVIG and met inclusion criteria, 7 (12%) of whom were included in earlier reports on MOGAD that were not focused on IVIG.[1,10,11] The median (range) age at initiation of IVIG was 36 (18-69) years; 33 patients were women (56%) and 26 were men (44%) (**Table 2**). A total of 8 patients (14%) were Asian, 46 (78%) were White, and 5 were (8%) other races or ethnicities (included 1 Black patient, 2 Hispanic patients, 1 Lebanese patient, and 1 patient of mixed race and ethnicity). Before starting IVIG treatment, 34 patients (58%) had ON, 25 (42%) had transverse myelitis, 4 (7%) had MOGAD with brainstem involvement, 3 (5%) had encephalitis, 8 (14%) had ADEM, and 2 (3%) had MOGAD with other areas affected. Among 47 patients with serial MOG antibody testing, 38 (81%) remained persistently seropositive.

Maintenance IVIG was initiated as first-line immunotherapy in 15 patients (25%) and as second-line immunotherapy in 37 patients (63%) owing to failure of prior immunotherapy and in 7 patients (12%) owing to intolerance to prior immunotherapy. Other than duration of disease before the initiation of IVIG therapy, there was no significant difference in the baseline characteristics between those treated with IVIG as first-line immunotherapy and those who failed prior immunotherapy (eTable in the Supplement). Among those who failed prior immunotherapy, patients failed a median (range) of 2 (1-4) prior treatments before starting IVIG, with 9 patients (23%) having failed 3 or more prior treatments. The median (range) duration of disease before starting IVIG therapy was 2.3 (0.1-19.8) years with a median (range) ARR of 1.4 (0-6.1). Treatment for most patients was initiated with IVIG owing to relapsing disease; 98% of patients (58 of 59) had relapsing disease before initiation of IVIG. The median (range) EDSS score at initiation of IVIG was 3 (0-6.5).

Maintenance IVIG was used initially at a frequency of every week to every 4 weeks with a dose ranging from 0.4 g/kg to 2 g/kg. A total of 20 patients (34%) received a dose of 0.4 g/kg at a frequency of every 4 weeks, 20 (34%) received a dose of 1 g/kg every 4 weeks or equivalent (2 [3%] received 0.4 g/kg every 2 weeks and were included in the 1 g/kg every 4 weeks), and 19 (32%) received a dose of 2 g/kg every 4 weeks or equivalent (2 [3%] received 0.4 g/kg every week and were included in the 2 g/kg every 4 weeks).

At final follow-up, 52 patients (88%) were still receiving maintenance IVIG with a median (range) treatment duration of 1.7 (0.5-9.9) years. Seven patients (12%) discontinued IVIG for the following reasons: 4 (57%) for inefficacy (2 were changed to rituximab owing to relapse, 1 had mycophenolate added to rituximab, and 1 was changed to tocilizumab), 2 (29%) for adverse effects (infusion reaction and fatigue/weight gain), and 1 (14%) for a trial not receiving therapy after a period of disease inactivity. One patient was transiently treated with IVIG because they developed aseptic meningitis and another stopped because of anxiety related to infusion, but details of their disease course were unavailable and were not included in the 59 patients with MOGAD who were included in this study. Among the 52 patients who were still receiving IVIG at last follow-up, 5 (10%) were taking a dose that was less than 0.4 g/kg every 4 weeks, 18 (35%) were taking 0.4 g/kg every 4 weeks, 17 (33%) were taking 1 g/kg every 4 weeks or equivalent, and 12 (23%) were taking 2 g/kg every 4 weeks or equivalent.

Relapses While Receiving IVIG

While receiving maintenance IVIG, 20 of 59 patients (34%) had at least 1 relapse with an overall median (range) number of attacks of 0 (0-7) and a median (range) ARR of 0 (0-3), which was lower than the median pre-IVIG ARR of 1.4 ($t_{108} = 7.14$; $P < .001$). Among the 37 patients whose prior long-term immunotherapies failed, the median (range) ARR while receiving treatments before IVIG was 1.6 (0.4-6.6), whereas the median (range) ARR while receiving IVIG was 0 (0-3) ($t_{71} = 7.28$; $P < .001$). Relapses occurred at a median (range) of 1 (0.03-4.8) year after initiation of IVIG (**Figure**). Only 5 of 29 patients (17%) treated at a dose of 1 g/kg of IVIG every 4 weeks or more (including 1 patient treated with 0.4 g/kg every 2 weeks) had a relapse with a mean (SD) ARR of 0.12 (0.34), whereas 15 of

Table 2. Clinical Characteristics of the Adult MOG Antibody-Associated Disease Cohort Treated With Maintenance IVIG

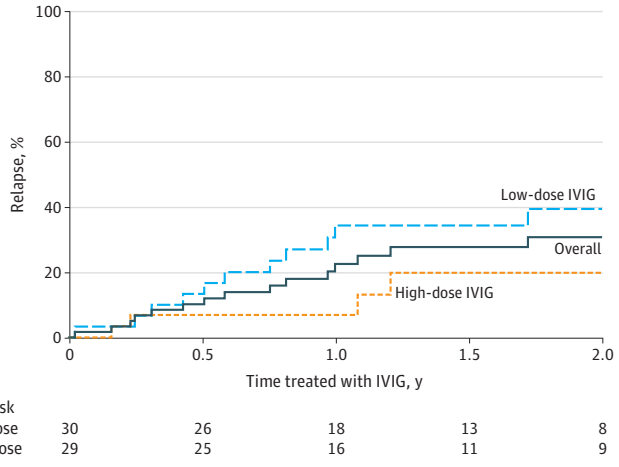
Characteristic	Median (range)			Hazard ratio (95% CI)	*P* value
	Total MOGAD cohort (n = 59)	Relapsing while receiving IVIG (n = 20)	No relapses while receiving IVIG (n = 39)		
Age at IVIG initiation, y	36 (18-69)	29.5 (18-57)	38 (19-69)	0.99 (0.95-1.02)	.45
Sex, No. (%)					
Female	33 (56)	13 (65)	20 (51)	1.00 (0.38-2.62)	.99
Male	26 (44)	7 (35)	19 (49)		
Race and ethnicity, No. (%)					
Asian	8 (14)	5 (25)	3 (8)	0.37 (0.14-0.97)	.04
White	46 (78)	13 (65)	33 (84)		
Other[a]	5 (8)	2 (10)	3 (8)		
Pre-IVIG ARR	1.4 (0-6.1)	1.5 (0-6.1)	1.3 (0-5.6)	1.07 (0.81-1.43)	.63
Disease duration before starting IVIG, y	2.3 (0-19.8)	2.4 (0.1-16.5)	2.3 (0-19.8)	0.95 (0.84-1.06)	.34
ARR while receiving IVIG	0 (0-3.0)	0.6 (0.1-3.0)	0 (0-0)	NA	NA
IVIG used as first-line therapy, No./total No. (%)	15/59 (25)	6/20 (30)	9/37 (24)	1.35 (0.52-3.53)	.56
Concomitant immunotherapy with IVIG, No. (%)	17 (29)	7 (35)	10 (26)	1.65 (0.65-4.18)	.29
EDSS score at time of initiating IVIG	3 (0-6.5)	3 (0-6.5)	2.75 (0-6.5)	0.92 (0.70-1.22)	.57
EDSS score at final follow-up	2 (0-6)	1.5 (1-4)	2 (0-6)	NA	.39
Persistent MOG antibody seropositivity, No./total No. (%)	38/47 (81)	15/19 (79)	23/28 (82)	0.69 (0.23-2.14)	.52
Dose and frequency of IVIG at time of relapse or last follow-up, No. (%)					
<0.4 g/kg Every 4 wk	6 (10)	4 (20)	2 (5)	NA	NA
0.4 g/kg Every 4 wk[b]	21 (36)	8 (40)	13 (33)		
>1 g/kg But less frequent than 4 wk	6 (10)	3 (15)	3 (8)		
1 g/kg Every 4 wk	15 (25)	5 (25)	10 (26)		
2 g/kg Every 4 wk[b]	11 (19)	0	11 (28)		

Abbreviations: ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IVIG, intravenous IgG; MOGAD, myelin oligodendrocyte glycoprotein antibody–associated disease; NA, not applicable.

[a] Other race and ethnicity included 1 Black patient, 2 Hispanic patients, 1 Lebanese patient, and 1 patient of mixed race and ethnicity. *P* value is for the comparison between the cohort that relapsed and did not relapse while receiving maintenance IVIG.

[b] Approximate dosage.

Figure. Kaplan-Meier Estimates of Time to Relapse While Receiving Intravenous Immunoglobulin (IVIG)



Kaplan-Meier curves showing time to relapse for patients treated with maintenance IVIG, which is also separated into low-dose and high-dose IVIG.

30 (50%) treated with lower or less frequent IVIG dosing had a relapse with a mean (SD) ARR of 0.45 (0.73) (t_{57} = −2.24; *P* = .03). None of the 11 patients treated with 0.4 g/kg every week or 2 g/kg of IVIG every 4 weeks relapsed; however, 3 of 8 patients (38%) relapsed at a dose of approximately 2 g/kg every 6 weeks. Thus, the overall risk of relapse was increased in

patients treated with either a lower dose or less frequent dosing (hazard ratio [HR], 3.31; 95% CI, 1.19-9.09; P = .02).

There was no difference in relapse rates among patients treated with IVIG as first-line therapy (6 of 15 [40%]) compared with those in which IVIG was not used as first-line therapy (14 of 44 [32%]) (HR, 1.35; 95% CI, 0.52-3.53; P = .56). There was also no difference in age, pre-IVIG ARR, or EDSS score at the time of initiating IVIG in those who relapsed compared with the subcohort without relapses while receiving IVIG (Table 2). Most patients had persistent MOG antibodies, which was not significantly different between the patients who relapsed (15 of 19 [79%]) and those who did not (38 of 47 [81%]; HR, 0.69; 95% CI, 0.23-2.14; P = .52), although a conversion to seronegativity was seen more commonly in those treated with IVIG as first-line treatment (4 of 10 [40%]) compared with those treated owing to failure of other medications (2 of 30 [7%]; Pearson χ^2_1 = 6.54; P = .01). White race was associated with a lower relapse rate (median [range] ARR: White patients, 0 [0-3]; Asian patients and those of other race and ethnicity, 0.3 [0-1.8]) with an HR of 0.37 (95% CI, 0.14-0.97; P = .04); however, there was a nonsignificantly higher IVIG dosing in the cohort of White patients (25 of 45 White patients [56%] vs 4 of 13 Asian patients and those of other race and ethnicity [31%]; Pearson χ^2_1 = 2.48; P = .11).

While receiving IVIG, 20 of 59 patients (34%) experienced disease relapse. A total of 15 relapses (75%) were in the form of ON, 1 (5%) TM, 2 (10%) brainstem MOGAD, and 2 (10%) ADEM. Among the patients with relapses of ON, the median (range) nadir of visual acuity loss was 20/40 (20/25-20/400) in the eye with worse visual acuity while receiving IVIG, compared with a median (range) nadir of visual acuity loss of counting fingers (20/20 to no light perception) in the worse eye in ON attacks before starting IVIG (t_{55} = 5.16; P < .001). The median (range) nadir EDSS score at time of relapse was 3.0 (1.0-6.0), and the final EDSS score at last follow-up was 2.0 (0-6.0), which did not differ between those who relapsed and those who did not (Table 2). Only 2 patients (3%) had a worse EDSS score at final follow-up compared with the EDSS score at the time of initiation of IVIG.

Concomitant Immunotherapy With IVIG

Seventeen of 59 patients (29%) continued to receive concomitant maintenance immunotherapy and/or high-dose prednisone (daily dose of >10 mg) at time of initiation of IVIG, including rituximab (6 patients [10%]), azathioprine (3 patients [5%]), high-dose prednisone (7 patients [12%]: 5 received prednisone; 2 received prednisone with concomitant maintenance immunotherapy), and mycophenolate mofetil (2 patients [3%]) and tocilizumab (1 patient [2%]). Seven of 17 patients (41%) received concomitant immunotherapy or high-dose prednisone (1 patient [14%] received 35 mg of prednisone, 1 [14%] received mycophenolate and 20 mg of prednisone, 1 [14%] received azathioprine, 3 [43%] received rituximab, and 1 [14%] received tocilizumab) and had at least 1 disease relapse whereas 13 of 42 patients (31%) who received IVIG alone (33 patients [79%]) or low-dose prednisone (9 patients [21%]) had a relapse, which provided a nonsignificant HR of 1.65 (95% CI, 0.65-4.18; P = .29). The median (range) ARR before starting IVIG was 1.6 (0.2-4.0) for patients who received concomitant immunotherapy and 1.3 (0-6.1) for patients who received IVIG alone or low-dose prednisone. The median (range) EDSS score before starting IVIG treatment was 3.0 (1.0-5.0) for patients who received concomitant immunotherapy and 2.5 (0-6.5) for patients who received IVIG alone or low-dose prednisone (t [46] = −1.13; 2-tailed P = .26). Dosing of IVIG was similar between the 2 groups, with 8 of 17 patients (47%) who received concomitant immunotherapy treated at a dose of 1 g/kg or greater every 4 weeks compared with 18 of 42 patients (43%) who received IVIG alone or low-dose prednisone (Pearson χ^2_1 = 0.09; P = .77). Four additional patients were administered a concomitant immunotherapy after experiencing a relapse while taking IVIG, which included 1 patient taking rituximab who had 2 further relapses, and 1 patient taking ocrelizumab and 2 patients taking mycophenolate who did not have further relapses.

Among the 9 patients who received concomitant low-dose prednisone (≤10 mg), 2 (10.5%) experienced disease relapse compared with 11 of 33 patients (34%) who received IVIG alone, which provided an HR of 0.43 (95% CI, 0.65-4.18; P = .28). There were 2 patients with MOGAD who were treated with subcutaneous immunoglobulin therapy (SCIG; 1 patient received 0.4 g/kg every week, and 1 patient received 0.4 g/kg every 4 weeks) for an average duration of 1.1 years; neither patient experienced a relapse.

Discussion

Results of this large multicenter cohort study of adult patients with MOGAD suggest that maintenance IVIG treatment was associated with a reduction in recurrent demyelinating attacks. Although some of the decrease in relapses observed in patients who received IVIG could be attributed to regression to the mean, most patients had numerous relapses and failed multiple medications before starting IVIG therapy, which has previously been shown to be associated with a higher risk of relapse on subsequent treatment with other therapies.[13]

Prior smaller case series have suggested that maintenance IVIG is associated with a reduction in attacks in MOGAD.[10,12,14] Hacohen et al,[12] in a retrospective pediatric MOGAD study, suggested that IVIG was associated with the largest reduction in relapses among common immunotherapies. Chen et al[10] previously reported that a reduction in relapses were experienced by 10 patients with MOGAD while receiving IVIG therapy, of which only 4 were adults. Ramanathan et al[11] reported a relapse in 3 of 7 patients receiving IVIG therapy, but 2 of these patients had a relapse when treatment frequency was extended from every 4 weeks to every 6 weeks. Tsantes et al[15] reported an adult patient with MOGAD and a history of continued disease relapses who responded to IVIG treatment at intervals of 3 weeks despite prior relapses when treated with interferon beta 1A, fingolimod, and rituximab.

Most patients who received IVIG did not experience worsening disability (EDSS score). It remains unclear if this was primarily because of a reduction in relapses, or if relapses were less severe while receiving IVIG therapy. In this cohort, ON attacks

in patients receiving IVIG were less severe at nadir than before starting IVIG treatment. However, patients with known MOGAD are typically given earlier steroid treatment in the setting of a recurrent attack, which may prevent the attack from getting to its natural nadir.[19,20]

The optimal dose and frequency of maintenance IVIG therapy for patients with MOGAD is unclear. Patients were typically started at a higher dose and frequency and then tapered to a lower dose and/or frequency. The higher rate of disease relapse in patients who received lower or less frequent IVIG dosing suggests a dose response with fewer relapses at higher doses. However, some MOGAD disease courses were stable in patients who received lower doses of IVIG, and therefore, the optimal dose is likely different for each patient. Lengthening the interval between IVIG dosing could potentially create unstable peaks and troughs and may result in "end of dose wear off" as seen in other diseases, such as chronic inflammatory demyelinating polyneuropathy.[21,22] A prior study on chronic inflammatory demyelinating polyneuropathy using symptoms to individualize dose/frequency of IVIG treatment determined that the mean dose required to control disease was 1.4 g/kg with a mean dosing interval of 4.3 weeks, but the dose and frequency greatly varied for each patient, ranging from 0.5 to 10 weeks.[23] Thus, it would be reasonable to start at higher or more frequent dosing and then taper patients with disease that is quiescent because of the high cost and limited resources of IVIG.

Most patients in this cohort had persistently positive MOG antibodies, which other studies have suggested confers a higher risk of disease relapse.[1,16,24,25] Unfortunately, MOG serostatus alone does not appear to be helpful in estimating the need for IVIG because in our IVIG MOGAD cohort, there was no difference in MOG serostatus among patients with disease relapse and those who did not experience disease relapse. It is possible that IVIG treatment could transiently affect the MOG serostatus, which contributed to the lack of difference in relapses.

Maintenance IVIG used as first-line therapy or as second-line rescue therapy appeared to produce similar results. Furthermore, concomitant immunotherapy (other than perhaps steroid therapy) with IVIG did not appear to be associated with lower rates of relapses compared with IVIG monotherapy. There was a nonsignificant trend toward fewer relapses among those treated with concomitant low-dose prednisone (≤10 mg). Prior retrospective studies have shown that prednisone is associated with a reduction in relapses in patients with MOGAD.[1,11] Thus, concomitant prednisone may be considered in patients with MOGAD, especially if they continue to experience disease recurrence on IVIG.

Only 2 patients were treated with maintenance SCIG, and neither experienced a relapse. This number is too low to determine whether SCIG has a similar association with a reduction in relapses compared with IVIG, but a recent case series that evaluated MOGAD, in addition to several studies of other neurologic diseases, suggests that treatment with SCIG and IVIG results in similar reductions in relapses.[26-28] Weekly SCIG provides a more steady-state concentration of immunoglobulin and has the benefit of avoiding large swings in peaks and troughs that can occur with IVIG therapy.[29] SCIG also has the benefit of self-administration. Therefore, SCIG may be a treatment option for patients with MOGAD, but this will need to be explored more in the future.

Limitations

Limitations to this study include its retrospective and open design, the variable periods of follow-up, and the selection of therapy by treating physician (potentially biasing assignment of therapy by personal practice experience), and patient or disease characteristics, including cost and convenience of therapy. Disease relapses were determined by the coauthors who all are all experts in MOGAD, but there was not an independent adjudication to confirm the relapse attacks. Being drawn from tertiary care centers, the cohort was likely biased to more severe and recurrent disease, and therefore, these findings are most applicable to patients with MOGAD and relapsing disease. In addition, patients have variable individual disease courses; therefore, our results may have limited generalizability to all patients with MOGAD. Concomitant treatments may also influence the potential outcomes of IVIG therapy. Lastly, there is a potential that the measured IVIG treatment outcomes were a result of regression toward the mean, but we believe that this is less likely owing to the (1) significant reduction in ARR when IVIG was initiated, (2) multiple treatment failure in many patients before becoming quiescent on IVIG, and (3) presence of an IVIG dose response.

If a patient has relapsing MOGAD and requires maintenance immunotherapy, treatment selection has to be weighed between outcomes, adverse effects, and costs. A benefit of IVIG is that it is not an immunosuppressive treatment and, therefore, does not increase the risk of infection or malignancy.[30] However, maintenance IVIG requires frequent intravenous infusions. There are rare complications of IVIG, such as aseptic meningitis and thrombosis.[31] In addition, IVIG therapy is costly, its approval by insurance companies is difficult, and it has limited availability in some countries.

Conclusions

Results of this retrospective cohort study suggest that maintenance IVIG was associated with a reduction in relapse frequency in adult patients with MOGAD. Future prospective randomized clinical trials of IVIG are required to confirm these findings.

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Author Contributions: Dr Chen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Chen, Huda, Lotan, Wilf-Yarkoni, Stiebel-Kalish, Hellmann, Sotirchos, Henderson, Pittock, Bhatti, Eggenberger, Di Nome, H. Kim, S. Kim, Saiz, Paul, Dale, Ramanathan, Palace, Camera, Leite, Lam, Bennett, Mariotto, Hodge, Audoin, Maillart, Deschamps, Pique, Flanagan, Marignier.
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