Intravenous Immunoglobulin treatment for acute attacks in Myelin Oligodendrocyte Glycoprotein Antibody Disease

IVIG for acute MOGAD attacks

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Abstract

Objective

To describe the outcomes of intravenous immunoglobulins (IVIG) in the treatment of acute myelin oligodendrocyte glycoprotein antibody disease (MOGAD) attacks.

Methods

We report a retrospective observational study involving 7 tertiary neuroimmunology centers in 5 countries (USA, UK, Italy, Israel, and Germany). Data collection included: patients' demographics, Expanded Disability Status Scale (EDSS), and visual acuity (VA) before the attack, at the nadir of the attack before IVIG treatment, and at follow-up visits $\geq$ 3 months after treatment.

Results

Thirty-nine patients were included, of which 21 (53.8%) were female. The median age was 23 years (range 5-74 years; 21 (53%) $\geq$ 18 years old)), and the median disease duration was 4 months (range 0-93 months). The most common type of attack treated with IVIG was isolated optic neuritis (ON) (unilateral n=14, bilateral n=5), followed by acute disseminated encephalomyelitis (ADEM) (n=8), multifocal (n=7), transverse myelitis (TM) (n=3), brainstem (n=1), and other encephalitis (n=1). In 34 cases (87.2%), IVIG was administered as a second-line treatment due to lack of response to high-dose CS and/or plasma exchange. In 5 attacks (12.8%), IVIG was administered as first-line treatment. A significant improvement in both the EDSS and VA measures was observed at follow-up $\geq$ 3 months after treatment compared to nadir [median (range) EDSS at nadir=4(1-9.5), at follow-up=2 (0-7.5), p<0.0001; median (range) converted LogMar VA at nadir=2.1 (hand motion) (0.4-3), at follow-up= 0.15 (Snellen equivalent of 20/30) (0-3), p<0.0001].

Interpretation

IVIG may be an effective treatment option for acute MOGAD attacks. Further prospective studies are warranted to validate our results.

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an autoimmune disorder of the central nervous system (CNS), characterized by inflammatory demyelinating attacks in pediatric and adult patients. MOGAD presents with a variety of clinical manifestations including acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), and cortical and brainstem encephalitis syndromes. [1 2].

MOGAD has recently been recognized as a distinct clinical entity from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). The condition is considered rare, with reported incidence ranging from 1.6 to 3.4 per 1,000,000 person-years [3 4]. There are currently no FDA-approved medications, nor randomized controlled trials or evidence-based guidelines for the treatment of MOGAD, either in the acute setting or as maintenance therapy for relapse prevention.

The acute treatment strategy for MOGAD attacks is based on the experience gained in MS and AQP4-Ab positive NMOSD studies as well as retrospective observational studies conducted in relatively small cohorts of MOGAD patients[5 6]. Intravenous methylprednisolone (IVMP) is the commonly used first-line treatment for acute attacks in MOGAD patients, which is usually followed by an oral prednisone taper. In patients presenting with severe attacks such as complete visual loss, severe paralysis, or encephalopathy requiring intensive care admission, who do not improve after IVMP, escalation treatment is typically warranted. Escalation treatment options include therapeutic plasma exchange (TPE), immunoadsorption, intravenous immunoglobulin (IVIG), or TPE followed by IVIG [2 7]. Although supported by a theoretical rationale of removing and/or neutralizing the systemic antibodies responsible for the pathogenic process, the evidence supporting the therapeutic utility of these treatments in MOGAD is limited.

While the exact mechanism of action of IVIG has yet to be clearly defined, a growing body of evidence supports its immunomodulatory and anti-inflammatory effects in various inflammatory and autoimmune diseases [8]. Chronic administration of IVIG has recently shown effectiveness in relapse prevention in both pediatric and adult MOGAD patients [7 9-11]. Administration of

IVIG in the acute phase of MOGAD attacks, simultaneously or following IVMP, has only been reported in a small number of patients [12-14]. Hence, our aim was to investigate the treatment outcomes of IVIG in acute MOGAD attacks in a larger cohort of pediatric and adult patients.

Materials and methods

Study Design and Data Collection. This was an international multicenter retrospective observational study conducted in 7 tertiary neuroimmunology centers in 5 countries (USA, UK, Italy, Israel, and Germany). All pediatric and adult MOGAD patients ascertained by cell-based assays and treated with IVIG during acute relapses were identified through the respective databases and included in this study. All decisions regarding patient selection and IVIG treatment protocol were made locally by the treating neurologist at each participating center. Demographic and clinical data were systematically extracted from medical records, including the following parameters: patients' age, sex, race, disease duration, number of attacks prior to the attack treated with IVIG, use of chronic immunosuppression, type of attack, IVIG treatment regimen during the attack, additional acute treatments, and adverse events during acute IVIG treatment. Expanded Disability Status Scale (EDSS) score and visual acuity (VA) were collected prior to the attack treated with IVIG, at the nadir of attack before IVIG treatment, at the end of IVIG treatment, at first follow-up visit, and at last follow-up visit.

All VA measures were converted to the Logarithm of the Minimum Angle of Resolution (LogMar) scale for statistical analysis. Non-numeric VA measures were converted to the LogMar scale based on the following conversion scheme: count fingers = 1.7, hand motion = 2.1, light perception = 2.3, no light perception = 3.0. In case of bilateral optic neuritis (BON), the VA of the worst affected eye was considered for analysis.

Study Outcomes. The main outcome measures included both the EDSS score and VA at the end of IVIG treatment, and at the first follow-up visit (performed at least 3 months after IVIG). The EDSS and VA at the last follow-up visit and the occurrence of adverse events during acute IVIG treatment were considered additional outcomes. VA measures were not considered as an outcome measure in cases without optic neuritis. Recovery from the attack was considered "complete" if the EDSS and VA measures at the first follow-up returned to the baseline values

before the attack onset. In cases where baseline EDSS and VA measures were not available (i.e., cases treated with IVIG during the first MOGAD attack), recovery was considered "complete" if the EDSS and VA at the first follow-up were zero. Recovery was considered "partial" if the EDSS and/or VA measures at first follow-up were higher compared to the baseline values, but lower compared to nadir. Where the baseline values were not available, recovery was defined as "partial" if the values at first follow-up were lower than nadir, or as "none", if the first follow-up values were equal or higher compared to nadir.

Patient selection. A total of 48 patients experiencing 49 attacks treated acutely with IVIG were screened for eligibility. Patients with insufficient data on the acute attack or without an available follow-up visit ≥ 3 months after the acute treatment as well as cases with an additional attack between the one treated with IVIG and the first follow-up visit were excluded from the study. Cases in which an additional attack occurred between the first and last follow-up visits were included in the analysis of EDSS and VA at the end of the first follow-up (≥3 months after the attack) and the safety analysis but excluded from the EDSS and VA analysis at the last follow-up to avoid inflation of the final outcomes by the subsequent attack. Based on these criteria, six cases were excluded due to an additional attack occurring before the first follow-up visit, three were excluded due to insufficient data on the acute treatment regimen, and one was excluded due to an unavailable first follow-up visit, leaving 39 attacks for the primary analysis. Nine patients included in the primary analysis experienced one or more attacks between the first and last follow-up and were therefore excluded from the analysis of EDSS and VA at the last follow-up. Figure 1 illustrates the patient selection process.

Standard Protocol Approvals, Registrations, and Patient Consents. The study was approved by the institutional review boards of all participating centers. Due to the retrospective study design and use of aggregate anonymous data, patients' informed consent was not obtained. Data was collected using a unified Excel database, which was shared anonymously with the lead site at the Massachusetts General Hospital (MGH).

Statistical Analysis. Descriptive statistics of continuous variables are presented by medians and ranges. Categorical variables are presented as total counts and proportions. Differences in

proportions between groups were analyzed using Fischer's exact test. Comparisons of non-parametric measures between groups were done with the Mann-Whitney test. Comparisons of paired non-parametric measures within each group were performed using the Wilcoxon matched pairs signed rank test. Two-tailed p-value <0.05 was considered significant. Due to the exploratory nature of the study, no adjustments for multiple comparisons were made. Statistical analysis was performed using GraphPad Prism 9 for MacOS (GraphPad Software, San Diego, CA, USA).

Data Availability. The data presented in this study will be made available to qualified investigators upon reasonable request to the corresponding author.

Results

Demographics. Thirty-nine patients were included in the final analysis, of which 21 were adults (≥18 years; 53.8%), 21 (53.8%) were females, and 25 (64.1%) were Caucasians. The median age was 23 years (range 5-74 years), and the median disease duration at the time of the attack treated with IVIG was 4 months (range 0-93 months). The median time from attack onset to IVIG treatment initiation was 9 days (range 1-51 days). Nineteen patients (48.8%) received IVIG during the first MOGAD attack. In 12 patients (30.8%), IVIG was given during the second attack. In 3 (7.7%) – at the third attack, in 2 (5.2%) - at the fourth attack, in 1 (2.6%) – at the fifth attack, and in 2 (5.2%) - at the sixth attack. Thirty-two patients (82.1%) were not receiving immunosuppressive medications at the time of the attack that was treated with IVIG; three patients (7.7%) were using oral corticosteroid (CS) maintenance therapy at the time of the attack. Table 1 summarizes the demographic and disease-related characteristics of the study population.

Attack phenotype and treatment regimen. The most common clinical phenotype of the acute attacks treated with IVIG was ON (unilateral [n=14], bilateral [n=5], associated with myelitis [n=1]), followed by ADEM (n=8), multifocal (n=7), TM (n=3), brainstem (n=1), and other types of encephalitis (n=1) (Table2).

In most cases, IVIG was given at a high dose (i.e., total dose ≥2 gr/kg; n=32, 82%). In 7 attacks, a low dose of IVIG (i.e., a total dose of 0.8-1.6 gr/kg) was used.

In 34 attacks (87.2%), IVIG was administered as a second-line treatment due to lack of response to high-dose CS and/or TPE. In 5 attacks (12.8%), IVIG was administered as a first-line treatment (Table 2).

Treatment outcomes. The median time between the attack onset and the first follow-up visit was 4 months (range 3-12). The median time between attack onset and last follow-up visit was 13.5 months (range 5-82 months). Figure 2 illustrates the variation in the EDSS and VA scores between nadir, end of treatment, and first follow-up visit for the entire study population. A detailed description of the clinical outcomes for each of the cases included in the study is provided as supplementary material.

For both the EDSS and the VA measures, a significant improvement was observed at the end of IVIG treatment compared to nadir [median (range) EDSS at nadir = 4 (1-9.5), at the end of treatment = 3 (0-9.5), $p < 0.001$; median (range) VA at nadir = 2.1 (0.4-3), at the end of treatment = 0.65 (0-3), $p < 0.0001$]. At first follow-up, a significant improvement in both the EDSS and VA scores was observed compared to the end of IVIG treatment [median (range) EDSS at the end of treatment = 3 (0-9.5), at first follow-up = 2 [0-7.5], $p < 0.0001$; median (range) VA at the end of treatment = 0.65 (0-3), at first follow-up = 0.15 (0-3), $p < 0.0001$].

At the first follow-up, 13 cases (33.3%) achieved complete recovery, 23 (59%) had partial recovery, and 3 (7.7%) had no recovery. An improvement in the EDSS compared to nadir was observed in 27 of the 39 cases (69.3%) at the end of treatment, and in 36 of the 39 cases (92.3%) at first follow-up visit. For the VA measures, an improvement in the worst affected eye compared to nadir was observed in 16 of 20 cases (80%) at the end of treatment, and in 18 cases (90%) at the first follow-up visit.

Considering the clinical outcomes at the final follow-up for patients who did not experience additional attacks (n=30), the EDSS remained stable compared to the first follow-up in 16 (53.3%) cases, while in the remaining 14 cases (46.7%), a further improvement in the EDSS compared to the first follow-up was observed. The median (range) EDSS at the last follow-up

was 1 (0-7), showing a significant improvement compared to the EDSS at nadir (p<0.0001) and at the first follow-up (p=0.0001). In patients presenting with ON, the VA at last follow-up remained stable in 11 out of 14 (78.6%) cases, improved from LogMar 1.3 to 0.5 in 1 case (7.1%), and worsened from 0 to 0.1 and 0 to 0.2 in 2 cases (14.3%). The median LogMar VA at the last follow-up was similar to that recorded at the first follow-up, i.e., 0.15 (range 0-3).

Comparison between low and high-dose IVIG regimens. Thirty-two attacks (82%) were treated with a high dose (i.e., total dose ≥2 g/kg) and seven (18%) were treated with a low dose IVIG regimen (total dose of 0.8-1.6 gr/kg). The median EDSS and VA at nadir were similar in the two groups. In the high-dose group, a significant decrease in the EDSS and the VA scores was observed at the end of treatment compared to nadir, with an additional decrease observed at first follow-up. In the low-dose group, the EDSS and VA scores at the end of treatment were not statistically different compared to nadir. At the first follow-up, the median EDSS score was significantly lower compared to nadir, while the median VA score was not significantly different (Tables 3 and 4).

Ten patients treated with high-dose (31.3%) and 3 patients treated with low-dose IVIG (42.9%) achieved complete recovery at the first follow-up [odds ratio (OR) = 0.60, 95% confidence interval (CI): 0.14-2.8, p=0.666], and 19 patients (59.4%) in the high-dose group and 4 (57.2%) in the low-dose group achieved partial recovery (OR = 1.07, 95% CI = 0.24-4.65, p>0.999). Three patients in the high-dose group (9.4%) and none in the low-dose group had no recovery.

Comparison between pediatric and adult patients. Our study included 18 (46.2%) pediatric (<18 years old) and 21 (53.8%) adult (≥18 years old) patients. The median EDSS and VA at nadir were similar in the two groups. In the adult group, a significant improvement in both the EDSS and the VA was observed at the end of IVIG treatment, and at the first follow-up compared to nadir. At last follow-up, the median EDSS was significantly lower compared to nadir and first follow-up. In the pediatric group, the median EDSS and VA were significantly lower at the end of treatment and at the first follow-up compared to nadir. The median EDSS and VA at the last

follow-up visit were not significantly different compared to the first follow-up visit (Tables 3 and 4).

At the first follow-up visit, 8 patients in the adult group (38.1%) and 5 in the pediatric group (27.8%) achieved complete recovery (OR= 1.6, 95% CI: 0.4-6.2, p=0.73). Eleven patients in the adult group (52.4%) and 12 in the pediatric group (66.7%) achieved partial recovery (OR = 0.55, 95% CI: 0.17-1.97, p=0.52), while 2 patients in the adult group (9.5%) and 1 in the pediatric group (5.6%) had no recovery (OR = 1.8, 95% CI: 0.19-27.28, p>0.9999).

Comparison between early (≤7 days) and late (>7 days) treatment groups. Sixteen patients (41.1%) were treated with IVIG ≤7 days from the onset of the attack (early treatment group), and 23 (58.9%) were treated >7 days from the attack onset (late treatment group). The median EDSS and VA at nadir were similar in the two groups. In the early treatment group, the median EDSS was significantly lower at the end of treatment and at the first and last follow-up compared to nadir. The median VA at the end of IVIG treatment was not significantly different compared to nadir, while at the first and last follow-up, the median VA was significantly lower compared to nadir. In the late treatment group, the median EDSS at the end of treatment was not significantly different compared to nadir, while at the first and last follow-up visit, the median EDSS was significantly lower compared to nadir. The median VA in the late treatment group was significantly lower at the end of treatment, at the first and at the last follow-up compared to nadir (Tables 3 and 4).

Seven patients (43.8%) in the early treatment group and six patients (26.1%) in the late treatment group achieved complete recovery at the first follow-up (OR=2.2, 95% CI=0.52-7.73, p=0.32). Eight patients (50%) in the early treatment group and 14 patients (60.9%) in the late treatment group achieved partial recovery (OR=0.53, 95% CI=0.16-2.37, p=0.53), while three patients (13.1%) in the late treatment group and none in the early treatment group had no recovery (OR=0.25, 95% CI= 0-1.61, p=0.25). The timing of IVIG treatment initiation was not correlated with the clinical outcomes (Spearman r= 0.26, 95% CI= -0.07- 0.54, p=0.12).

Outcomes of IVIG as a first-line treatment. Five patients were treated with IVIG as a single first-line treatment. Two were < 18 years old (ages 14 and 15), and three were ≥ 18 years old (ages 36, 44, and 45). Four of the five patients (80%) achieved a complete recovery at the first follow-up, and the remaining patient achieved partial recovery. In all cases, an improvement in the EDSS score was observed from the nadir to the end of IVIG treatment and to the first follow-up. In two patients with bilateral ON, an improvement in the VA of the worst affected eye was observed (Figure 3).

Adverse events. Two patients (both adults) experienced mild-moderate headaches during IVIG treatment. Both cases responded favorably to simple analgesics and did not require a change in the treatment. No other infusion-related adverse events were reported during acute IVIG treatment in our cohort.

Discussion

This study reports real-world observational treatment outcomes of IVIG in the acute setting of MOGAD attacks. This retrospective analysis showed improvement in the EDSS and VA following IVIG treatment used either as a first-line or as an add-on second-line treatment in both children and adults. Our data suggest that IVIG should be further explored as a potential treatment option for acute MOGAD attacks.

Although MOGAD was initially conceptualized as a relatively milder disease, accumulating data shows that a proportion of patients present with an aggressive disease course, characterized by severe recurrent demyelinating attacks. Similar to NMOSD, the accumulation of disability is primarily driven by attacks [15 16]. Some degree of permanent neurological disability has been reported in as many as 47% of adult MOGAD patients [17], with up to 60% resulting from the onset attack [18]. While high-dose CS treatment is generally used as a first-line treatment for acute attacks, Jarius et al. reported complete or almost complete recovery in only 50% of 122 attacks treated with IVMP as a sole treatment, with the remaining having partial (44%) or no or almost no recovery (6%). When TPE or immunoadsorption (IA) was added as a second-line treatment, complete or almost complete recovery was observed in 40% of 25 attacks, partial

recovery in 56%, and no or almost no recovery in 4% [19]. Therefore, there is still a need to identify additional treatment strategies that would prevent residual disability after each attack.

While many MOGAD patients show a rapid and complete clinical response to high-dose CS, a subgroup of patients may not achieve adequate treatment response and require additional escalation treatments to prevent permanent neurological disability. The inadequate response to CS may be due to a state of glucocorticoid resistance or insensitivity, similar to what has been described in other autoimmune and inflammatory conditions, where it is thought to be induced by proinflammatory cytokines [8]. In this context, IVIG may suppress the production of proinflammatory cytokines and improve glucocorticoid-receptor binding and the response to glucocorticoids [8 20]. This mechanism of action may explain the beneficial effect of IVIG given as an add-on treatment after failure of high-dose CS and/or TPE, which applied to the majority of patients included in our study. Still, we report a beneficial therapeutic effect in five patients who were treated with IVIG as a single first-line treatment, suggesting that other immunomodulatory and anti-inflammatory mechanisms are likely involved as well. Moreover, the fact that favorable outcomes were observed not only shortly after the end of treatment but also at the follow-up visits, implies that the effects of IVIG are likely more complex than simply enhanced passive clearance or interference with pathogenic antibodies.

Different regimens of IVIG treatment were used to treat MOGAD attacks in our cohort, ranging from 0.8 g/kg administered over two days, to 2.4 g/kg over six days (Table 2). Although the proportion of patients who achieved complete or partial recovery was similar between the cases treated with a lower dose (0.8-1.6 g/kg) and those treated with a higher dose ($\geq$ 2 g/kg), we observed a trend toward a more significant improvement in the EDSS and VA scores in the latter group. Although the lack of significant improvement in the low-dose group may be driven by the small number of patients treated with this regimen, this observation is in line with prior evidence showing more potent anti-inflammatory activities of IVIG when used in higher doses [8]. A total dose of 2 g/kg IVIG given in 2-5 days is the recommended dose in several other acute neurological conditions, like Guillain-Barré syndrome and myasthenia gravis, as well as in the induction phase of chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and paraproteinemic demyelinating polyneuropathy [21]. Considering the favorable

adverse events profile observed in our cohort, it seems reasonable to consider using a similar treatment protocol in MOGAD attacks.

In AQP4-positive NMOSD, early initiation of high-dose CS and/or TPE is associated with better clinical outcomes[6 14 22-25]. In MOGAD, a similar association has been reported in patients presenting with ON, where early steroid treatment initiation has been associated with better visual outcomes[22 26 27]. Timing of TPE is also correlated with better visual outcomes in MOGAD-ON (Chen et al., under review). While high-dose CS and TPE are reportedly beneficial in other types of MOGAD attacks[6 14], the impact of the timing of treatment on clinical outcome measures in non-ON-MOGAD attacks is currently unknown. In our cohort, the clinical outcomes of patients treated with IVIG ≤ 7 days from attack onset were not significantly different compared to patients treated after 7 days. However, a higher proportion of patients in the early treatment group (43.8%) achieved complete recovery at the first follow-up compared to the late treatment group (26.1%), and it is possible that the lack of statistical significance is due to the relatively small number of patients in our cohort. Larger prospective studies are needed to determine the impact of timing of IVIG treatment on the clinical outcomes following acute MOGAD attacks.

Several limitations of this study should be considered. First, its retrospective design and relatively small sample size call for validation in larger prospective trials. Second, in many cases, IVIG was given as a second-line treatment after failure of IVMP and/or TPE was adjudicated by the treating neurologist. In these cases, the positive final treatment outcome observed cannot be attributed solely to IVIG. Thirdly, this study lacked a control group that did not receive attack treatment, and reports of spontaneous improvement exist [27 28]. However, there are ethical concerns with having a placebo arm for studying acute MOGAD attacks, and the retrospective analysis in this study suggested possible benefits. A future randomized controlled trial comparing the treatment outcomes in MOGAD patients treated with CS alone versus IVIG (alone or in combination with CS) can better define the place of IVIG as a first-line treatment in acute MOGAD attacks. In patients with inadequate treatment response to IVMP, a randomized control trial that will assign some to receive IVIG and others to receive TPE will allow a better characterization of IVIG as a second-line treatment.

In conclusion, this study describes safety and efficacy outcomes of IVIG in acute MOGAD attacks. Our observations suggest that IVIG may be a potential therapeutic option for MOGAD attacks, either as a first- or second-line treatment. Prospective randomized-controlled studies are warranted to validate our findings and to better characterize the place of IVIG in the treatment of MOGAD attacks.

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Table 1- Demographics and clinical characteristics of the study population

	Number of patients (%)
Total number	39
Age, median (range), years	23 (5-74)
Age <18	18 (46.2)
Age ≥18	21 (53.8)
Female sex	21 (53.8)
Disease duration, median (range), years	4.16 (0.75-15.5)
Ethnicity	
White	25 (64.1)
Asian	11 (28.2)
Black	1 (2.6)
Other	2 (5.2)
Number of prior attacks	
None	19 (48.8)
One	12 (30.8)
Two	3 (7.7)
Three	2 (5.2)
Four	1 (2.6)
Five	2 (5.2)
DMTs	
None	32 (82.1)
MMF	2 (5.2)
MTX	1 (2.6)
RTX	3 (7.7)
Chronic IVIG	1 (2.6)
Oral CS	
Yes	3 (7.7)
No	36 (92.3)

DMTs= disease modifying treatments; AZA= azathioprine; MMF= mycophenolate mofetil; MTX= methotrexate; RTX= rituximab; IVIG= intravenous immunoglobulin; CS= corticosteroids

Table 2- Characteristics of MOGAD attacks treated with IVIG

	Number (%)
Attack Phenotype (N, %)	
Unilateral ON	14 (35.9)
Bilateral ON	5 (12.8)
TM	3 (7.7)
Brainstem syndrome	1 (2.6)
Encephalitis	1 (2.6)
ADEM	8 (20.5)
Multifocal	7 (17.9)

IVIG Treatment Dose (protocol) (N, %)	
0.8 g/kg (0.4g/kg x 2 days)	1(2.6)
1 g/kg (1 g/kg x 1 day)	1(2.6)
1.2 g/kg (0.4g/kg x 3 days)	3 (7.7)
1.32 g/kg (0.66g/kg x 2 days)	1(2.6)
1.6 g/kg (0.4 g/kg x 4 days)	1 (2.6)
1.98 g/kg (0.66g/kg x 3 days)	
2 g/kg (0.4g/kg x 5 days)	2(5.2)
2 g/kg (1 g/kg x 2 days)	17 (43.6)
2.4 g/kg (0.4g/kg x 6 days)	12 (30.8)
	1(2.6)
Additional Treatments (N, %)	
IVMP	15 (38.5)
IVMP + oral CS	5 (12.8)
IVMP + TPE	9 (23.1)
IVMP + oral CS + TPE	5 (12.8)
None	5 (12.8)

ON=optic neuritis; ADEM=acute demyelinating encephalomyelitis; IVIG= intravenous immunoglobulin; IVMP=intravenous methylprednisolone; CS=corticosteroids; TPE=therapeutic plasma exchange

Table 3- EDSS values at various time points throughout the study

EDSS Median (range) Patients/treatment	Nadir	End of Treatment	P value	First follow-up visit	P value	Last follow-up visit	P value
Entire study population	4 (1-9.5)	3 (0-9.5)	p<0.0001	2 (0-7.5)	p<0.0001 (vs end of Tx)	1 (0-7)	p<0.001 (vs nadir) p=0.0001 (vs first follow-up)

Adult patients	3.5 (1-9.5)	2.5 (0-8)	p<0.0001	2.25 (0-7.5)	p<0.0001 (vs nadir)	2 (0-7)	p<0.001 (vs nadir) p=0.004 (vs first follow-up)
Pediatric patients	4 (3-9.5)	3 (0-9.5)	p=0.001	1.25 (0-4)	p<0.0001(vs nadir)	1 (0-4)	p=0.031 (vs nadir) p=0.063 (vs first follow-up)
High dose IVIG	4 (1-9.5)	3 (0-9.5)	p<0.0001	2 (0-7.5)	p<0.0001 (vs nadir)	1.25 (0-7)	p<0.001 (vs nadir) p=0.005(vs first follow-up)
Low dose IVIG	3.5 (3-7)	2 (0-7)	p=0.063	1 (1-4)	p=0.016 (vs nadir)	1 (1-4)	p=0.016 (vs nadir) p>0.9999 (vs first follow-up)
Early IVIG treatment group	4.5 (3-9.5)	3 (1-6.5)	p=0.006	1.25 (0-4)	0<0.0001 (vs nadir)	1 (0-4)	P<0.0001 (vs nadir) p=0.078 (vs first follow-up)
Late IVIG treatment group	4 (1-9.5)	3 (0-9.5)	P=0.112	2 (0-7.5)	P=0.0003 (vs nadir)	2 (0-7)	P<0.0001 (vs nadir) p=0.52 (vs first follow-up)

EDSS= expanded disability status scale; IVIG= intravenous immunoglobulins.

Table 4- Visual acuity values at various time points throughout the study

VA Median (range) Patients/treatment	Nadir	End of IVIG Treatment	P value	First follow-up visit	P value	Last follow-up visit	P value
Entire study population	2.1 (0.4-3)	0.65 (0-3)	p<0.0001	0.15 (0-3)	p<0.0001 (vs end of Tx)	1 (0-7)	p<0.001 (vs nadir) p=0.0001 (vs first follow-up)
Adult patients	1.7 (0.2-3)	0.5 (0-1.7)	p=0.03	0.15 (0-1.7)	p=0.004 (vs nadir)	0.15 (0-1.7)	p=0.004 (vs nadir) p>0.9999 (vs first follow-up)
Pediatric patients	2.1 (1.7-3)	1.3 (0-3)	p=0.03	0.1 (0-3)	p=0.008 (vs nadir)	0.1 (0-3)	p=0.03(vs nadir) p>0.9999 (vs first follow-up)
High-dose IVIG	2.1 (0.2-3)	0.65 (0-3)	p=0.001	0.2 (0-1.7)	p=0.0002 (vs nadir)	0.2 (0-1.4)	p=0.0002 (vs nadir) p>0.9999 (vs first follow-up)
Low-dose IVIG	1.7 (1.7-3)	0.55 (0-3)	p= 0.13	0.05 (0-3)	p=0.13 (vs nadir)	0.05 (0-3)	p=0.13 (vs nadir) p>0.9999 (vs first follow-up)
Early IVIG treatment group	2.350 (1.7-3)	1.7 (0-3)	P=0.03	1 (0-3)	P=0.035 (vs nadir)	0.55 (0-3)	P=0.03(vs nadir) P=0.89 (vs first follow-up)

| Late IVIG treatment group | 2.1 (0.2-3) | 1 (0.1-1.7) | P=0.006 | 0.2 (0-1.7) | p=0.0001 (vs nadir) | 0.2 (0-1.2) | p=0.0001 (vs nadir) p>0.9999 (vs first follow-up) |

VA= visual acuity; IVIG= intravenous immunoglobulins