MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Longitudinal evaluation of serum MOG-IgG titers in MOGAD after initiation of maintenance immunoglobulin: A case series

Multiple Sclerosis Journal

1–6

DOI: 10.1177/13524585231211119

Shuvro Roy, Eleni Vasileiou, Paula Barreras, Gelareh Ahmadi, Haiwen Chen, William Suslovic, Alexandra Kornbluh, Ilana Kahn and Elias S Sotirchos

Correspondence to:
ES Sotirchos
Department of Neurology, Johns Hopkins University, Johns Hopkins Hospital, 600 N. Wolfe St., Pathology 627, Baltimore, MD 21287, USA.
ess@jhmi.edu

Shuvro Roy
Eleni Vasileiou
Paula Barreras
Gelareh Ahmadi
Haiwen Chen
Elias S Sotirchos
Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

William Suslovic
Alexandra Kornbluh
Ilana Kahn
Children's National Hospital, George Washington University School of Medicine and Health Sciences, Washington, DC, USA

Abstract

Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a distinct demyelinating disease of the central nervous system. Immunoglobulin (Ig) has been used as a maintenance therapy to prevent relapses in MOGAD, but the impact of Ig on serum MOG-IgG titers is unclear.
Objective: To characterize the variation in serum MOG-IgG titers after initiation of Ig treatment in people with MOGAD.
Methods: We conducted a retrospective study of 10 patients with a diagnosis of MOGAD and available serum MOG-IgG titers before and after initiation of maintenance Ig treatment.
Results: We found that most of the patients remained MOG-IgG seropositive while on Ig treatment with a reduced or unchanged titer, despite a lack of disease activity.
Conclusions: This case series suggests that the mechanism of action of Ig therapy in MOGAD is not exclusively dependent on MOG-IgG titer reduction.

Keywords: Biomarkers, MOGAD, IVIg, disease-modifying therapies

Date received: 28 June 2023; revised: 1 October 2023; accepted: 14 October 2023.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is a distinct demyelinating disease of the central nervous system. Approximately 50%–60% of patients may develop a relapsing course.[1,2] Persistent and high-titer MOG-IgG seropositivity has been associated with a higher risk of relapse, and titers are higher in the setting of a relapse, though low or absent MOG titers do not preclude a relapsing course.[1–6] Importantly though, while this disorder is defined by the presence of MOG-IgG seropositivity (detected by use of a cell-based assay (CBA)) in patients with a compatible clinical phenotype, the specific mechanisms of disease and whether MOG-IgG is pathogenic in MOGAD remains unclear.[1,7] Immunoglobulin (Ig) has been used for the treatment of acute attacks, as well as a maintenance therapy to prevent relapses in MOGAD, with observational data supporting that maintenance Ig therapy reduces the risk of relapse in MOGAD.[8,9] Ig therapy exhibits a wide range of effects on the immune system. This includes modulating IgG-dependent autoimmune pathology by neutralizing auto-antibodies with anti-idiotypic antibodies, as well as increased clearance of auto-antibodies by saturating the neonatal Fc receptor. Notably, an ongoing phase 3 clinical trial in MOGAD (NCT05063162) is leveraging the latter mechanism by targeting the neonatal Fc receptor with a monoclonal antibody (rozanolixizumab).

However, the impact of treatment with Ig on MOG-IgG titers is unclear. Importantly, testing for auto-antibodies after intravenous immunoglobulin (IVIg) administration can potentially lead to false-positive serologic testing, though this seems to be related to the presence of antibodies directed against linear epitopes that may be detected with ELISA assays (and not CBAs).[10] On the other hand, it would be anticipated that MOG-IgG titers may decrease or convert to negative while on Ig treatment due to the mechanisms of action outlined above. In this study, we tracked changes in MOG-IgG titers after initiation of Ig treatment in a series of adult and pediatric MOGAD patients.

Table 1. Patient characteristics.

Patient	Age at disease onset (years), sex	Initial clinical phenotype	Ig route of administration and dose	Prior treatment(s)	Pre-Ig serum MOG-IgG titer	Post-Ig serum MOG-IgG titer	Number of attacks before Ig	Time between pre-Ig titer and post-Ig titer (weeks)	Duration of Ig treatment (weeks)	Time since Ig initiation for post-Ig titer (weeks)	Time since last attack at time of pre-Ig titer (weeks)	Time since last attack at time of post-Ig titer (weeks)
1	51, F	Bilateral ON	SCIg 0.4 g/kg weekly	Mycophenolate, rituximab	1:80	1:40	5	72	100	28	44	36
2	7, F	Bilateral ON	IVIg 1 g/kg monthly	Rituximab	1:1000	1:100	6	40	152	36	4	40
3	1, M	Unilateral ON	IVIg 1 g/kg monthly	None	1:40	Negative	2	32	72	24	0	32
4	1, F	ADEM	IVIg 1 g/kg monthly	None	1:1000	Negative	1	28	148	28	0	27
5	4, M	ADEM	IVIg 1 g/kg monthly	None	1:1000	1:1000	1	12	132	8	4	18
6	32, F	Bilateral ON	SCIg 0.4 g/kg weekly	Azathioprine, rituximab	1:100	1:40	3	88	48	20	68	104
7	11, F	ADEM	SCIg 0.4 g/kg weekly	None	1:100	1:40	2	60	56	56	0	4
8	2, M	ADEM	IVIg 1 g/kg monthly	None	1:100	1:20	1	8	96	8	1	8
9	55, M	Bilateral ON	IVIg 1 g/kg every 2 weeks	None	1:100	1:40	2	92	72	72	9	60
10	58, F	Unilateral ON	IVIg 1 g/kg every 2 weeks	None	1:100	1:100	2	24	40	40	12	52

ADEM: acute disseminated encephalomyelitis; ON: optic neuritis; Ig: immunoglobulin; IVIg: intravenous immunoglobulin; MOG: myelin oligodendrocyte glycoprotein; SCIg: subcutaneous immunoglobulin.

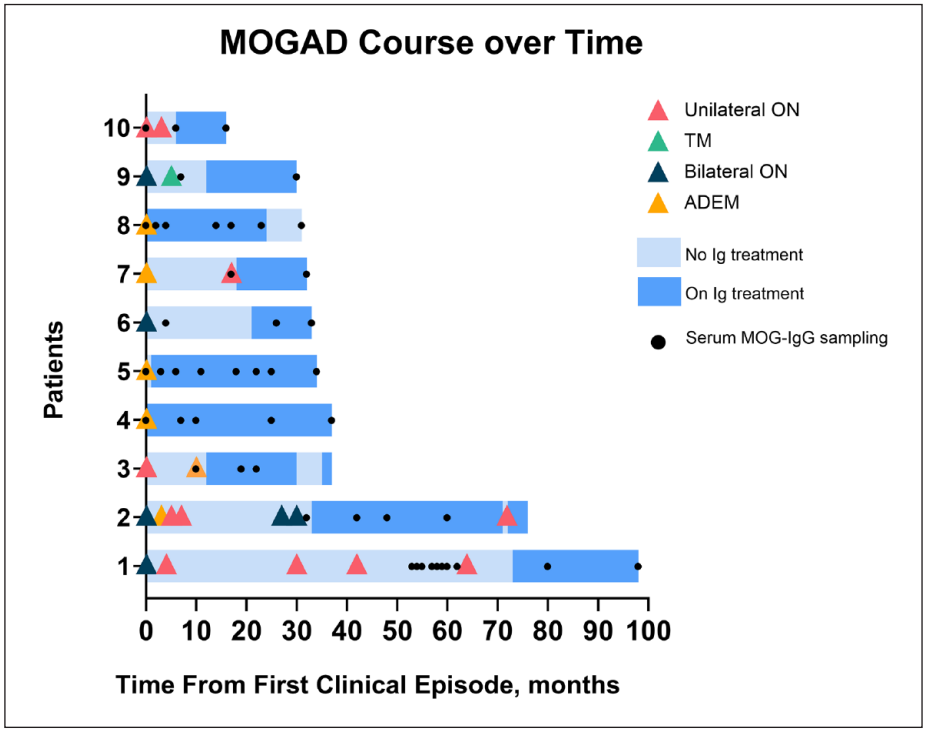

Figure 1. Serologic status over time in the 10 MOG-IgG-positive patients undergoing Ig treatment. Each bar represents an individual patient, with black dots representing antibody sampling time points. Dark blue bars indicate the period of time after initiation of immunoglobulin, and light blue bars indicate the period of time before initiation of immunoglobulin. Colored triangles represent different clinical attacks. Of note, patient 6 has one indicated relapse in the figure, but also reported two remote events decades beforehand concerning for relapse that could not be confirmed. Patients 4, 5, and 8 had one clinical attack each, but due to the severity of their attacks were started on IVIg. Due to maintained clinical stability, patient 8's IVIg therapy was discontinued after 24 months.

Cases

In this case series, we conducted a retrospective chart review of MOGAD patients followed at our two centers (Johns Hopkins University and Children's National Medical Center) and treated with Ig. MOG-IgG testing was performed using a live cell-based assay with detection by fluorescence-activated cell sorting (Mayo Clinic Laboratories). For this assay, sera are screened initially at 1:20 dilution, thus a negative result corresponds to a MOG-IgG titer of $<$1:20. All patients fulfilled the 2023 International MOGAD Panel proposed diagnostic criteria with core clinical demyelinating events, positive MOG-IgG testing, and exclusion of better diagnoses. In the cases of patients with low antibody titers (end-point titer $<$1:100) at the time of diagnosis, supporting clinical and magnetic resonance imaging (MRI) features were considered. It should be noted, however, that all patients had a positive MOG-IgG at a titer of $\geq$1:100 at some point in the disease course (Figure 2). Patients with a diagnosis of MOGAD and MOG-IgG testing results available before and after initiation of maintenance treatment with either IVIg or subcutaneous Ig (SCIg) were included. We identified 10 such patients. Four patients had adult-onset disease, and six had pediatric-onset disease. Attacks were determined based on the assessment of the treating clinician. The patients' demographics, clinical courses, MOG-IgG titers, and Ig treatment initiation timing/dosing are summarized in Table 1 and Figures 1 and 2.

The median pre-Ig MOG-IgG titer was 1:100 (range: 1:40 to 1:1000), and the median post-Ig MOG-IgG titer was 1:40 (range: $<$1:20 to 1:1000). Six patients experienced a relapsing course prior to initiation of Ig therapy. Two patients had an unchanged MOG-IgG at first assessment after initiation of Ig therapy, with one remaining at 1:100 ten months after Ig initiation, and another remaining at 1:1000 two months after Ig initiation (and 3 months removed from an initial clinical event of acute disseminated encephalomyelitis (ADEM)). Eight of the patients had a lower MOG-IgG titer after treatment with Ig. Two pediatric patients converted to negative ($<$1:20).

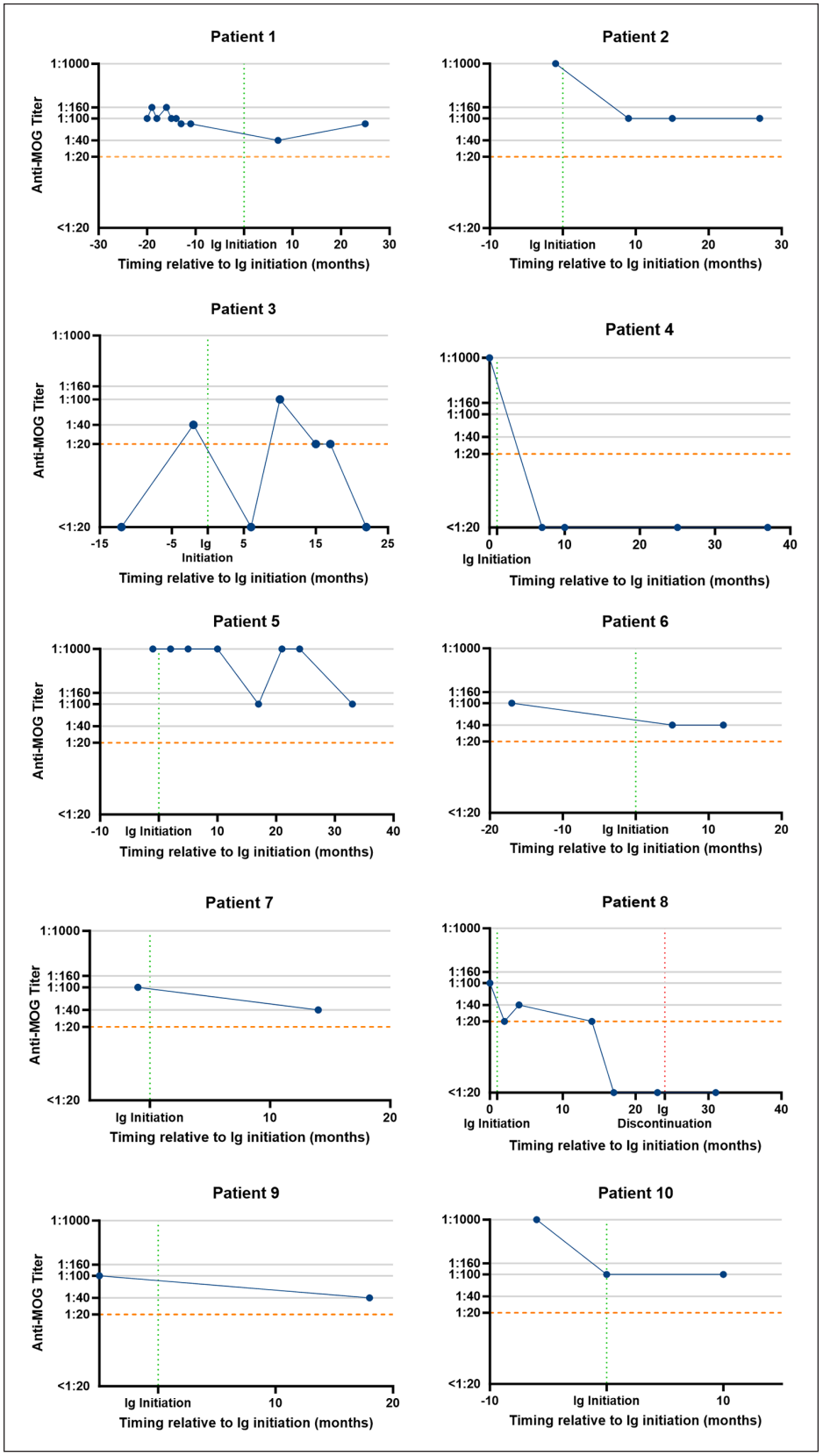

Figure 2. Antibody titers for each patient during their course, relative to the initiation of Ig (0, green dashed line), in months. Seropositive cutoff is represented by the orange dashed line in each individual graph.

Titers for all patients are presented in Table 1 and Figure 2. Six patients had their pre-Ig titers drawn within 3 months of a relapse with three (patients 3, 4, and 7) having them drawn at the time of an attack. Multiple post-Ig MOG-IgG titers were available in seven patients, and all remained at a lower or equal titer compared to before Ig treatment, with the exception of one patient (patient 3). Of the six pediatric patients, three either converted to negative (<1:20) or had an unchanged titer, and all six had their pre-Ig titer drawn within 3 months of an attack. Three of four adult patients had reduced titers after Ig, with the remaining patient having an unchanged titer. Despite persistent seropositivity in most patients, only one (patient 2) experienced a relapse after starting Ig, in the setting of a delayed IVIg infusion. Another (patient 3) developed an asymptomatic enhancing lesion after discontinuation of IVIg, which prompted re-initiation of therapy.

Discussion

This case series, while limited by the small sample size, variable serum sampling time points, and its retrospective, observational nature, supports that Ig maintenance treatment for MOGAD was not associated with conversion to seronegative status in most patients, though all patients did demonstrate either unchanged or reduced titers immediately after treatment. While drawing pre-Ig samples in close proximity to a relapse (thus increasing likelihood for high-titer seropositivity) may also account for decreases in MOG-IgG during longitudinal sampling in a subset of these patients, a decrease in MOG-IgG titers occurred in most patients. Of note, despite persistent seropositivity in most patients after treatment initiation (including with high titers), disease activity occurred only in 2 patients, either in the context of treatment delay or Ig discontinuation. This suggests that the mechanism of action of Ig therapy in MOGAD is not exclusively dependent on reduction in MOG-IgG titers, but should not be misinterpreted as implying that MOG-specific antibodies are not pathogenic in MOGAD. These findings support the rationale for additional studies investigating the relationship between Ig treatment and MOG-IgG titers. Additionally, further investigation is needed on the mechanisms by which maintenance Ig therapy may reduce relapse risk in MOGAD, which may also include effects not dependent on auto-antibody neutralization/reduction, such as cytokine neutralization, T- and B-cell regulation, and complement system modulation.[11]

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.R. has served on scientific advisory boards for Horizon Therapeutics. E.V., P.B., G.A., H.C., W.S., A.K., and I.K. have nothing to disclose. E.S.S. has received speaker honoraria from Alexion and Viela Bio, and has served on scientific advisory boards for Alexion, Viela Bio, Horizon Therapeutics, and Genentech.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by the Caring Friends NMO Research Fund.

ORCID iDs

Shuvro Roy https://orcid.org/0000-0002-3240-7441
Eleni Vasileiou https://orcid.org/0000-0002-8639-8405
Gelareh Ahmadi https://orcid.org/0000-0002-5315-4498
Alexandra Kornbluh https://orcid.org/0000-0002-7880-918X
Elias S Sotirchos https://orcid.org/0000-0002-8812-1637

References

1. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. *Lancet Neurol* 2021; 20(9): 762–772.
2. Sechi E, Cacciaguerra L, Chen JJ, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): A review of clinical and MRI features, diagnosis, and management. *Front Neurol* 2022; 13: 885218.
3. Waters P, Fadda G, Woodhall M, et al. Serial anti–myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. *JAMA Neurol* 2020; 77(1): 82–93.
4. Cobo-Calvo A, Sepúlveda M, D'Indy H, et al. Usefulness of MOG-antibody titres at first episode to predict the future clinical course in adults. *J Neurol* 2019; 266(4): 806–815.
5. Gastaldi M, Foiadelli T, Greco G, et al. Prognostic relevance of quantitative and longitudinal MOG antibody testing in patients with MOGAD: A multicentre retrospective study. *J Neurol Neurosurg Psychiatry* 2023; 94(3): 201–210.

6. Hennes EM, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. *Neurology* 2017; 89(9): 900–908.
7. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *Lancet Neurol* 2023; 22(3): 268–282.
8. Chen JJ, Huda S, Hacohen Y, et al. Association of maintenance intravenous immunoglobulin with prevention of relapse in adult myelin oligodendrocyte glycoprotein antibody–associated disease. *JAMA Neurol* 2022; 79(5): 518.
9. Sotirchos ES, Vasileiou ES, Salky R, et al. Treatment of myelin oligodendrocyte glycoprotein antibody associated disease with subcutaneous immune globulin. *Mult Scler Relat Disord* 2022; 57: 103462.
10. Dimitriadou MM, Alexopoulos H, Akrivou S, et al. Anti-neuronal antibodies within the IVIg preparations: Importance in clinical practice. *Neurotherapeutics* 2020; 17(1): 235–242.
11. Dalakas MC. Mechanistic effects of IVIg in neuroinflammatory diseases: Conclusions based on clinicopathologic correlations. *J Clin Immunol* 2014; 34(Suppl. 1): 120–126.