Multiple Sclerosis and Related Disorders 57 (2022) 103462

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Correspondence

Treatment of myelin oligodendrocyte glycoprotein antibody associated disease with subcutaneous immune globulin

SUMMARY

Myelin oligodendrocyte glycoprotein (MOG)-antibody associated disease (MOGAD) is a distinct demyelinating disease of the central nervous system that often exhibits a relapsing course. Immune globulin (Ig) therapy has been proposed as maintenance therapy to prevent relapses in MOGAD, but existing reports are limited to the use of intravenous Ig (IVIG). Subcutaneous Ig (SCIG) may exhibit several advantages over IVIG, including self-administration and less systemic adverse effects. Herein, we report six patients with MOGAD who were treated with subcutaneous Ig (SCIG) with good tolerability and without any relapses during follow-up. This supports the rationale for prospective randomized studies of SCIG in MOGAD.

Short Report

Myelin oligodendrocyte glycoprotein (MOG) antibody associated disease (MOGAD) is a distinct demyelinating disease of the central nervous system. (Reindl and Waters, 2018) The clinical course can often be relapsing, especially in adults, and a variety of therapies have been proposed to reduce the risk of relapses, including various immunosuppressive therapies (such as rituximab, azathioprine and mycophenolate mofetil) and maintenance intravenous immune globulin (IVIG). (Hacohen et al., 2018, Ramanathan et al., 2018, Cobo-Calvo et al., 2019, Chen et al., 2020) There are no randomized clinical trials reported to date in MOGAD and data regarding the efficacy of these therapies are derived from observational studies, however existing evidence suggests that IVIG may be highly effective in preventing relapses in MOGAD. (Hacohen et al., 2018, Chen et al., 2020) Notably, immune globulin (Ig) therapy may also be administered subcutaneously (SCIG), and SCIG formulations have been approved for treatment of primary immunodeficiency and chronic inflammatory demyelinating polyneuropathy (CIDP). (Ness, 2019) SCIG has several potential advantages over IVIG, including the ability to self-administer at home, cost-effectiveness, and lower risk of systemic adverse effects. (Ness, 2019) Importantly, IVIG and SCIG differ in their pharmacokinetics, with relatively steady-state serum Ig levels achieved with SCIG, whereas with IVIG there is significant variation between the peak and trough concentrations. (Bonilla, 2008) These differences, in addition to impacting the risk of systematic adverse effects, may conceivably also impact clinical efficacy, and reports of SCIG use for treatment of MOGAD are lacking. Herein, we aim to report our joint clinical experience using SCIG for treatment of MOGAD.

In this case series, we included patients with a diagnosis of MOGAD that were treated with SCIG. We identified six patients (three with adult-onset and three with pediatric-onset MOGAD). The patients' clinical courses and Ig treatment regimens are detailed in Table 1. All patients had clinical phenotypes consistent with MOGAD and were MOG-IgG seropositive by live cell-based assay (with detection using fluorescence-activated cell sorting [FACS] or indirect immunofluorescence [IIF] using anti-human IgG1 secondary antibody). Four patients had experienced multiple breakthrough relapses while on other steroid-sparing therapies prior to starting Ig therapy, while SCIG was used as a first-line therapy for one patient and another patient was switched to SCIG due to intolerance to azathioprine and rituximab. Two patients were treated initially with IVIG and then transitioned to SCIG maintenance therapy. None of the patients experienced relapses after starting SCIG and all have remained on SCIG therapy as of their last follow-up, with the duration of therapy ranging from 1 to 7 years. Expanded Disability Status Scale (EDSS) remained stable or improved at last follow-up after starting Ig therapy in all patients. SCIG formulations used included Hizentra (20% immune globulin) or HyQvia (10% immune globulin with recombinant human hyaluronidase), with similar dosing across patients (0.4g/kg/week or 2g/kg/month). No significant adverse effects were observed, with the exception of headaches associated with the infusions in one patient that resolved after switching from monthly HyQvia to weekly Hizentra infusions.

This case series, while limited due to the small sample size and the observational nature of the study, supports that SCIG may be a highly effective therapy to prevent relapses in MOGAD and may be considered as a direct alternative to IVIG at the time of treatment initiation or as a maintenance therapy following an initial induction period with IVIG (as was the case in two patients in this series). Notably, these findings are in line with reports in other autoimmune neurological diseases, including autoimmune peripheral neuropathies and myasthenia gravis, in which SCIG appears to exhibit similar efficacy to IVIG, with potential reductions in systemic adverse effects. (Racosta, Sposato, and Kimpinski, 2017, van Schaik et al., 2018, Alcantara et al., 2021) Our findings support the rationale for additional studies to investigate the efficacy of SCIG for relapse prevention in MOGAD, including observational studies with larger numbers of participants and longer follow-up duration, as well as prospective randomized studies investigating the efficacy of SCIG for relapse prevention in MOGAD.

AUTHOR DISCLOSURES

Elias Sotirchos has received speaker honoraria from Viela Bio and Biogen and has served on scientific advisory boards for Viela Bio, Alexion and Genentech. Eleni Vasileiou, Rebecca Salky and Saif Huda

https://doi.org/10.1016/j.msard.2021.103462
Received 21 October 2021; Received in revised form 7 December 2021; Accepted 10 December 2021
Available online 13 December 2021

Table 1
Summary of MOGAD patients treated with subcutaneous immune globulin

Case	Age/ Sex (onset)	Pre-Ig therapy serum MOG-IgG result (assay)	Summary of clinical history prior to initiation of immune globulin therapy	IVIG induction prior to starting SCIG	SCIG Formulation and Dosing	Duration of Therapy with Maintenance SCIG at last follow-up	Number of relapses since starting SCIG	EDSS at Ig therapy start-> last follow-up
1	51 F	1:100 (CBA-FACS)	Onset in 2014 with bilateral ON. Multiple recurrent attacks of unilateral and bilateral ON (2014 × 2, 2016, 2017, 2019) and TM (2015, 2017) despite treatment with mycophenolate (2014, 2018-2020) and rituximab (2014-2018). Course complicated by hypogammaglobulinemia with recurrent infections (pneumonia, otitis and urinary tract infections). Started SCIG in 2020.	No	Hizentra 0.4g/kg SC weekly	1.5 years	None	3.5 -> 3.5
2	5 F	Positive (no titer; CBA-IIF)**	Onset in 2015 with ADEM with recurrent attacks of ADEM (2016 × 2, 2017) and ON (2016) despite treatment with mycophenolate (2016-2017) and rituximab (2017). Started immune globulin therapy in 2017.	IVIG 2g/kg monthly for 5 months	HyQvia 2g/kg SC monthly*	4 years	None	4.0 -> 3.0
3	11 F	1:100*** (CBA-FACS)	Onset in 2017 with seizures in setting of cortical encephalitis, followed by unilateral ON in 2019. SCIG was initiated as first-line therapy when MOGAD diagnosis was made in 2019 after episode of ON. Started SCIG in 2020.	No	HyQvia 2g/kg SC monthly* for 2 months (switched due to headaches), followed by Hizentra 0.4g/kg weekly	2 years	None	1.5 -> 1.5
4	63 F	1:100*** (CBA-FACS)	Presented in 2019 with bilateral ON, also noted to have a non-enhancing thoracic spinal cord lesion. Reported history of diagnosis of TM 30 years prior and episode of left-sided weakness 2 years prior diagnosed as a TIA. Treated initially with azathioprine (2019) and rituximab (2019-2020) but discontinued due to intolerance (GI complaints, fatigue). Started SCIG in 2020.	No	Hizentra 0.4/kg SC weekly	1 year	None	2.0 -> 2.0
5	52 M	1:40 (CBA-FACS)	Onset in 2017 with unilateral ON, with multiple recurrent attacks of ON (2018 × 2, 2019) despite treatment with mycophenolate (2018-2019) and rituximab (2019). Started SCIG in 2020.	No	HyQvia 0.4g/kg SC weekly	2 years	None	0.0 -> 0.0
6	14 F	Positive (no titer; CBA-IIF)	Onset in 2002 with bilateral ON, followed by multiple attacks of unilateral or bilateral ON (2005, 2006, 2007, 2009 × 4, 2010, 2011, 2012) and TM (2009) despite treatment trials with azathioprine, mycophenolate, rituximab, methotrexate and mitoxantrone (in conjunction with corticosteroids). Started immune globulin therapy in 2012.	IVIG 2g/kg every 12 weeks for 2 years	Hizentra 0.4g/kg SC weekly	7 years	None	4.0 -> 4.0

*Dosing split over 2 consecutive days
**Repeat MOG-IgG testing by CBA-FACS 4 years after initiation of Ig therapy was positive (titer 1:100).
***Repeat MOG-IgG CBA-FACS testing for cases 3 and 4 at one year after initiation of Ig therapy remained positive at 1:40.
ON: optic neuritis, TM: transverse myelitis, ADEM: acute disseminated encephalomyelitis, CBA-FACS: live cell-based assay with detection by fluorescence-activated cell sorting, CBA-IIF: live cell-based assay with detection by indirect immunofluorescence; IVIG: intravenous immune globulin; SCIG: subcutaneous immune globulin; EDSS: expanded disability status scale

report no disclosures. Sara Mariotto reports speaker honoraria from Biogen and Novartis and has received research funding from Euroimmun. John Chen reports consulting for UCB and Roche. Michael Levy has received personal compensation from Alexion, Horizon, Genentech/Roche, Sanofi, and UCB for work on advisory boards and his lab has received grant funding from Alexion, Horizon, Genentech/Roche and Bluerock.

REFERENCES

Alcantara, M., Sarpong, E., Barnett, C., Katzberg, H., Bril, V., 2021. Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol 28, 639–646.

Bonilla, F.A., 2008. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immunol Allergy Clin North Am 28, 803–819 ix.

Chen, J.J., et al., 2020. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology 95, e111–e120.

Cobo-Calvo, A., et al., 2019. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. J Neuroinflammation 16, 134.

Hacohen, Y., et al., 2018. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. JAMA Neurol 75, 478–487.

Ness, S., 2019. Differentiating characteristics and evaluating intravenous and subcutaneous immunoglobulin. Am J Manag Care 25, S98–S104.

Racosta, J.M., Sposato, L.A., Kimpinski, K., 2017. Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis. Muscle Nerve 55, 802–809.

Ramanathan, S., et al., 2018. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 89, 127–137.

Reindl, M., Waters, P., 2018. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nature Reviews. Neurology. https://doi.org/10.1038/s41582-018-0112-x.

van Schaik, I.N., et al., 2018. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 17, 35–46.

Elias S. Sotirchos[1,*], Eleni S. Vasileiou[1], Rebecca Salky[2], Saif Huda[3], Sara Mariotto[4], John J. Chen[5], Michael Levy[2]

[1] *Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

[2] *Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

[3] *Walton Centre NHS Foundation Trust, Liverpool, UK*

[4] *Neurology Unit, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy*

[5] *Departments of Ophthalmology and Neurology, Mayo Clinic, Rochester, MN, USA*

[*] **Address Correspondence and reprint requests to:** Elias S. Sotirchos, Department of Neurology, Johns Hopkins Hospital, 600 N. Wolfe St., Pathology 627, Baltimore, MD 21287, USA

E-mail address: ess@jhmi.edu (E.S. Sotirchos).