Received: 28 December 2020 | Revised: 10 January 2021 | Accepted: 12 January 2021

DOI: 10.1111/cen3.12630

REVIEW ARTICLE

Clinical & Experimental Neuroimmunology WILEY

Treatment of myelin oligodendrocyte glycoprotein immunoglobulin G–associated disease

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Abstract

Myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG)–associated disease (MOGAD) is increasingly recognized as a distinct nosological entity from aquaporin-4 antibody IgG–positive neuromyelitis optica spectrum disorder (AQP4-IgG NMOSD). The advent of highly specific MOG-IgG cell-based diagnostic assays have helped to refine our understanding of the clinical spectrum of MOGAD. To date, treatment approaches have been largely extrapolated from AQP4-IgG NMOSD experience, but there is growing evidence of distinct differences in treatment response between these conditions. This review summarizes the current status and understanding of acute and chronic treatments for MOGAD. Timing and duration of treatment, pregnancy, and emerging therapies are also discussed.

KEYWORDS

MOG, MOGAD, myelin oligodendrocyte glycoprotein, treatment

1 | INTRODUCTION

In recent years, myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG)–associated disease has gathered momentum as a distinct nosological entity, separate from aquaporin-4 antibody IgG–positive neuromyelitis optica spectrum disorder (AQP4-IgG NMOSD). The advent of cell-based assays, incorporating human MOG expressed in its native conformational state proved critical to the detection of disease relevant antibodies and has accelerated our understanding of MOG-IgG–associated disease (MOGAD).[1]

MOG is a component of the outer lamellae of the myelin sheath found in the central nervous system (CNS).[2] Its precise role in healthy nerve function is unclear, but it may be involved in the regulation of oligodendrocyte microtubule stability and modulation of interactions between myelin and the immune system.[3] The pathogenic role of MOG-IgG remains an area of intense research focus. A recent postmortem study described a MOGAD pathological signature with acute disseminated encephalomyelitis (ADEM)–like perivenous inflammatory demyelination and MOG-dominant myelin loss.[4] Distinct pathological differences between MOGAD and AQP4-IgG NMOSD were noted, with perivascular deposits of activated complement and immunoglobulins a more common finding in AQP4-IgG NMOSD. In vitro studies suggest complement-mediated mechanisms play a role, but passive transfer studies have shown only relatively mild neuronal injury.[5] Such models may be limited in their ability to recapitulate human disease due to differences between rodent and human MOG, a distinction that proved critical in the refinement of MOG antibody diagnostic assays. Broadly speaking, MOGAD is referred to as an oligodendrocytopathy while AQP4-IgG NMOSD is considered an astrocytopathy.[6]

Clinically, MOGAD is commonly associated with ADEM, optic neuritis (ON), longitudinally extending transverse myelitis (LETM), brainstem disease, cortical encephalitis, or a combination of these features.[7,8] Age appears to play an important role in attack topography; for instance, ADEM is particularly prevalent in pediatric cohorts.[9] Radiologically, MOGAD has a predilection for longitudinally extensive anterior optic nerve involvement and can be associated with perineural and periorbital fat enhancement.[7] In the spinal cord, T2-signal abnormality axially orientated as an "H" sign and conus medullaris involvement may be seen.[7]

From a prognostic perspective, a proportion of MOGAD cases is monophasic, which is comparatively rarer in AQP4-IgG NMOSD.[10,11] Currently there are no clinical or serological biomarkers that reliably predict the long-term course in MOGAD groups but age at first attack, attack topography, and persistently positive MOG-IgG may be associated with a higher risk of relapsing disease course.[12-14] Early relapses in the first 12 months are common[14] but, unsurprisingly, studies with longer follow-up have found higher rates of relapsing disease.[14,15] Disability in MOGAD is accrued through relapses; progressive disease has rarely been described.[16] Incomplete recovery can result in long-term disability including visual impairment, paralysis, sphincteric dysfunction, and cognitive impairment.[17] For this reason, MOGAD treatment centers on aggressive relapse management[18] and prevention.[16,19]

The treatment of MOGAD has been largely extrapolated from AQP4-IgG NMOSD and is currently unstandardized.[12] An increasing body of evidence suggests that AQP4-IgG NMOSD and MOGAD are dissimilar at a pathophysiological and clinical level indicating the need for MOGAD-specific treatment strategies. Despite the aforementioned differences, there remain a number of similarities between AQP4-IgG NMOSD and MOGAD, particularly because historically MOGAD was identified from cohorts of then "seronegative" NMOSD.[13,20-22] Conversely the proportion of MOGAD cases that fulfill 2015 International Panel for Neuromyelitis Optica criteria is small, between 33% and 42%.[21,23] For the purposes of this review, the term NMOSD is used only when referring to patients fulfilling the 2015 international panel for NMOSD diagnosis.[10] Herein, we review the current literature on acute and maintenance therapies for MOGAD. Treatment considerations including timing of treatment, pregnancy, and emerging therapies are also discussed (Figure 1).

1.1 | Untreated attacks and outcome differences between MOGAD and AQP4-IgG NMOSD

When considering the treatment of acute relapses, it is worth briefly reviewing the natural history of MOGAD attacks. Jarius et al.[13] reported the clinical outcomes of 14 untreated MOGAD attacks, mainly consisting of ON. Full recovery was observed in 9 of 14 (64%) and full or partial recovery in 12 of 14 (86%) cases. No recovery was observed in 2 cases, one of which was fatal (1 patient with ON and brainstem encephalitis and a second with ON). In the landmark Optic Neuritis Treatment Trial, MOG-IgG was detected in 3 of 177 (1.7%) of the original 448 patients included. Of these, 1 patient with severe ON at presentation (visual acuity reduced to hand movements) was randomized to receive placebo and at 15-year follow-up had complete recovery of visual acuity albeit with a residual field deficit (mean deviation −8.27 dB).[24] Other larger studies of MOGAD have not specifically focused on untreated outcomes.[14,15,25] These data highlight the potential for spontaneous recovery, an important consideration when interpreting unblinded retrospective accounts of MOGAD relapse treatments.

When comparing MOGAD and AQP4-IgG NMOSD outcomes, Kitley and colleagues[26] found that MOGAD attacks were often severe but demonstrated better overall recovery. MOGAD patients were more likely to present with simultaneous or rapidly sequential ON and transverse myelitis (TM). Median nadir EDSS score was similar, but MOGAD patients had greater median EDSS change and lower median EDSS scores at follow-up. Motor and visual disability were higher in AQP4-IgG NMOSD with spinal and optic nerve involvement respectively. Similarly, Sato et al.[22] reported better recovery after a single attack in patients with MOGAD vs AQP4-IgG NMOSD (median EDSS 2 (0-5) vs 6 (2-8.5); $P = .02$).

Taken together these studies suggest more favorable long-term outcomes in MOGAD compared to AQP4-IgG NMOSD, although the retrospective study designs and variation in acute treatment delivery must also be considered. It is also important to emphasize that a comparably more favorable outcome is not synonymous with a "favorable outcome" and it is widely recognized that MOGAD relapses can lead to severe and irreversible neurological disability.[7,12,14,15,22,27,28]

2 | ACUTE ATTACK TREATMENTS

2.1 | Methylprednisolone

Intravenous methylprednisolone (IVMP) is widely accepted an appropriate first-line treatment in MOGAD relapse.[29] As in other neuroinflammatory disorders, IVMP is thought to play an active role in reducing the production of antibodies, sealing the blood–brain barrier and reducing inflammation in MOGAD.[30] Information regarding dose, time to efficacy, adverse effects, and monitoring for all therapeutic options discussed can be found in Table 1. Although there is not yet an established duration or dosing regimen, a common strategy is to administer 1 g per day IVMP for 5 days.[12] Most studies of AQP4-IgG NMOSD and MOGAD have employed IVMP; however, studies have confirmed the noninferiority of bioequivalent doses of oral corticosteroids compared to intravenous administration in multiple sclerosis (MS) and ON, suggesting that oral corticosteroids may be an effective treatment alternative.[31,32]

We found one retrospective review[13] of 122 MOGAD attacks that specifically reported disability outcomes following IVMP in MOGAD.[13] Complete or near complete recovery was observed in 50% (61/122) of acute attacks following IVMP, partial recovery in 44.3% (54/122), and no or almost no recovery in 5.7% (7/122).[13] When considering attacks treated with both IVMP and plasma exchange (PLEX), the proportion of those requiring escalation to PLEX (suggesting a suboptimal IVMP response) was 58.5% (86/147). Although near complete recovery and partial recovery were not clearly defined, this study showed a beneficial role of IVMP for acute MOGAD treatment. However, as previously noted, retrospective analyses cannot control for the spontaneous improvement that can be seen with untreated MOGAD attacks. Another retrospective study also suggested that earlier treatment with IVMP was

associated with better visual outcomes in MOGAD, but the numbers treated were small (n = 9).[33]

IVMP efficacy can be variable even in patients with previous good responses to treatment.[13] The reasons for this are unclear and extend beyond important factors such as timing, which is discussed later in this review.[13] The definition of a "poor responder" has not been clearly defined but where there is clinical concern for suboptimal IVMP response options include an escalation of IVMP dose to 2 g or PLEX (our preference is usually the latter).[34,35] One retrospective study in an AQP4-IgG NMOSD cohort suggested that treatment with IVMP or PLEX within 14 days of symptom onset, younger age (<60 years old), and less severe attacks (EDSS change of <2.5) were associated with good responses to treatment.[36] This finding could potentially be extrapolated to MOGAD.

2.2 | PLEX and immunoadsorption

PLEX has been used in immune-mediated neurological disease since the 1970s, is an established treatment for acute attacks in AQP4-IgG NMOSD, and is often employed for severe steroid-refractory MOGAD attacks. PLEX is a highly efficient technique that removes antibodies and humoral factors from the circulation.[37] Conventionally, PLEX has been performed using a central line; however, peripheral access is increasingly used as techniques develop with improved safety profile.[37,38] An alternative to PLEX is immunoadsorption (IA). The mechanisms underlying the therapeutic effects of IA treatment are not fully understood but are thought to involve the removal of pathogenic humoral factors from circulating blood through a high-affinity adsorbent with tryptophan or phenylalanine.[39] IA availability is limited to specialized tertiary centers and is more cost prohibitive than PLEX. Comparable outcomes between IA and PLEX have been reported in AQP4-IgG NMOSD and refractory ON in MS.[35,40] IA may be more effective at removing circulating specific antibodies, but studies are required to determine whether this translates to clinical superiority over PLEX.

PLEX/IA has traditionally been used as an escalation therapy in the setting of steroid refractory relapses. In AQP4-IgG NMOSD, first-line use has been advocated by specialists based on a "time-is-tissue" principle, supported by a large retrospective analysis conducted by Kleiter and colleagues[35] and Levy.[41] At present there are insufficient data to make similar recommendations in MOGAD attacks but a large retrospective analysis or prospective study could help to address this. Factors concerning time to treatment are discussed in more detail later in this review. PLEX/IA may also be used as first-line therapy when methylprednisolone is contraindicated or if there has been previous poor response to methylprednisolone.[34]

There is one retrospective review of PLEX/IA as an acute treatment for MOGAD.[13] PLEX/IA monotherapy was associated with complete or near complete recovery in 20% (3/15), partial recovery in 73.3% (11/15), and no recovery in 6.7% (1/15) of attacks. When PLEX/IA was used after IVMP the authors reported complete or near complete recovery in 40% (10/25), partial recovery in 56% (14/25), and no recovery in 4% (1/25) of attacks. A limitation of this study was that outcomes such as "almost complete" and "partial" recovery were not clearly defined.

Both PLEX and IA require extensive training and equipment; therefore, widespread use and acute access can be limited. Some neurological centers rely on hematology and renal teams to provide access to PLEX, while others have established their own service.[37]

2.3 | Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) contains IgG (IgG3 and IgG4) as well as IgA, IgE, and IgM pooled from healthy donors. The mechanism of action is not well understood but is thought to involve the modulation of T- and B-lymphocytes, monocyte/macrophage system, dendritic cells, keratinocytes, and complement system[42] (please see Table 1 for more details). In recent years, an international shortage has led to an increase cost of IVIG. Accordingly, there has been more stringent regulation, although guidelines vary internationally.

Studies outlining the use of IVIG in acute attacks of MOGAD were not identified, but two studies have reported beneficial outcomes with its use in acute AQP4-IgG NMOSD attacks.[35,43] Improvement was noted in 5 of 11 (45.5%) of steroid and PLEX-refractory AQP4-IgG NMOSD relapses (bilateral ON, 4; LETM, 7); with median pretreatment EDSS of 7 (4-9) and posttreatment EDSS of 6.5 (3-9) approximately 2 months later.[43] One patient regained independent function 3 months after a severe cervical TM and respiratory failure when IVIG was started 14 days after onset. Three other severely disabled patients with steroid/PLEX-refractory relapses returned to their preattack baseline following IVIG administration. However, a delayed effect of IVMP and PLEX could not be excluded. Kleiter and colleagues[35] also reported 4 AQP4-IgG NMOSD attacks treated with IVIG, but therapy was combined with other treatments making interpretation of IVIG alone difficult. Disappointingly STRIVE, a randomized clinical trial, comparing IVMP vs IVMP and IVIG in acute TM, failed to recruit sufficient participants to reach its primary endpoint.[44] Further studies will be required to determine if IVIG is beneficial in MOGAD and other in CNS inflammatory disease.

3 | TIMING OF ACUTE THERAPY

Based on the pathophysiology of AQP4-IgG NMOSD, it is reasonable to presume that timing of relapse treatment delivery would have an impact on clinical outcome, and that this would also apply to MOGAD. Indeed, timing and escalation to second-line therapies such as PLEX have been shown to be an important factor in long-term outcome in several studies.[18,35,36,45] Bonnan et al.[18] studied

the outcome of 115 AQP4-IgG NMOSD ON attacks and reported maximal improvement in those patients where a delay to PLEX did not exceed 5 days. This time-is-tissue principle can be extrapolated to acute treatment of other CNS inflammatory conditions,[46] including MOGAD. It is important to note that several studies[47-50] with a median delay of 3 weeks to PLEX did not replicate these findings, but when one considers that the loss of retinal ganglion cell and inner plexiform layer occurs as early as day 8 from ON onset, the delays to treatment in these studies may have confounded interpretation of PLEX benefit.[51]

Stiebel-Kalish et al.[33] conducted a retrospective study to assess the impact of early treatment in AQP4-IgG NMOSD and MOGAD (n = 9) patients with ON. In the combined analysis of AQP4-IgG NMOSD and MOGAD patients, a treatment delay of >7 days to receiving IVMP for acute ON conferred an odds ratio of 5.50 (95% CI, 0.88-34.46; $P = .051$) of failure to regain 0.0 logMAR vision and an OR of 10.0 (95% CI, 1.39-71.9; $P = .01$) to regain 0.2 logMAR vision (20/30). Receiver operator curve characteristics showed the optimal time frame for delay to IVMP delivery was ≤4 days (sensitivity, 71.4%; specificity, 76.9%). A limitation of this study aside from its retrospective design was that MOGAD numbers were small and analysis was combined with AQP4-IgG NMOSD patients.

Our practice is to approach treatment of any significant AQP4-IgG NMOSD or MOGAD relapse in a hyperacute manner with early escalation to PLEX in steroid-refractory attacks. However, we acknowledge there is a lack of consensus on what constitutes a poor responder and the time frames in which escalation should be considered. Prospective studies are required to interrogate the time-is-tissue hypothesis further. Ideally these studies would include validated measures of not just visual acuity but contrast sensitivity, visual fields, and optical coherence tomography.

4 | MAINTENANCE THERAPIES

There is a lack of consensus on when to introduce maintenance immunosuppression in MOGAD, with equipoise between immunosuppression introduction after both first and second clinical events.[12] The rationale for treating after a first clinical attack is based on the observation from retrospective studies that patients with MOGAD, if followed for long enough, are likely to have a second attack and permanent disability is seen in half of patients.[13,14] Contrastingly, a study incorporating an incident cohort (which is not affected by relapse risk bias as are prevalence cohorts) reported a relapse risk of 36% over 16 months. The majority of relapses occurred within 6 months, the risk of which was reduced with a prolonged steroid taper >3 months.[14] The concern regarding unnecessary immunosuppression for potentially monophasic disease, the effective relapse risk reduction with a prolonged steroid taper, and generally favorable outcomes in MOGAD form the basis for initiating long-term non-steroidal immunosuppression only after a second MOGAD attack, which is our standard practice.

Overall, there is a lack of prospective clinical trial data for MOGAD treatments and many of the drugs discussed have been extrapolated from clinical experience in the management of AQP4-IgG NMOSD. Table 1 summarizes the key features of these medications.

4.1 | Prednisolone

Oral prednisolone can be used as a sole maintenance therapy or in combination with a nonsteroid immunosuppressant, as a taper following acute treatment of a relapse, or as a bridging therapy when introducing a nonsteroid immunosuppressant with latency to therapeutic effect. The mechanism of action is broadly similar to IVMP (please see Table 1 for further details).

We found two retrospective studies that assessed the utility of oral prednisolone in MOGAD (Table 2). Hacohen et al.[27] reported outcomes in 8 children treated with oral prednisolone for more than 6 months. Of these, 5 children experienced a relapse although 4 relapses were associated with steroid weaning or cessation. Ramanathan et al.[25] reported an annualized relapse rate (ARR) reduction from 2 (range, 0.5-6) to 0 (range, 0-1.57) over a median treatment duration of 10 (1-78) months. Compared to other nonsteroid immunosuppressants, treatment failure rates were lower with prednisolone (11/29, 38% vs 1/20, 5%). Relapses were more common when steroid doses were reduced below 10 mg, within 2 months of cessation, or with rapid tapering after a MOGAD attack. Although it is important to acknowledge the small sample size of prednisolone-treated patients in this study, this finding mirrors that of a large UK study of adult MOGAD patients where a steroid taper of >3 months was associated with a reduced risk of relapse.[14] Early disease activity upon rapid steroid taper may be due to fresh relapse activity or unmasking of residual inflammation and has led some groups including our own to recommend a slow taper of prednisolone over at least 6 months.[14]

Lower treatment failure rates have also been reported when corticosteroids are used as a bridging therapy with nonsteroid immunosuppression with a latency to therapeutic effect.[13,25] In addition, long-term low-dose corticosteroids in combination with nonsteroid immunosuppression as has been suggested for AQP4-IgG NMOSD may be helpful.[25] Taken together, these studies support a beneficial role for corticosteroids in reducing relapse risk in MOGAD and emphasize the importance of a prolonged steroid taper to prevent early relapses after an index event.

Oral corticosteroids are not without significant risks (Table 1). Various strategies have been employed to mitigate these risks such as the use of calcium supplements and bisphosphonates for bone density preservation, monitoring of glycemic control and weight, and alternate-day dosing regimens. The latter has been suggested to result in less suppression of the hypothalamic–pituitary–adrenal axis compared to daily dosing and is recommended for other neurological conditions such as myasthenia gravis.[52,53] Deflazacort is an oxazoline derivative of prednisolone with anti-inflammatory properties and immunosuppressive activity with proven efficacy in rheumatoid arthritis and Duchenne muscular dystrophy.

TABLE 1 Characteristics of acute and maintenance treatment options in MOGAD

Treatment	Mechanisms of action	Suggested dosing	Adverse effects or complications	Monitoring	Practical considerations	References
Acute treatments						
Intravenous and oral corticosteroids[a]	Reduce inflammation, help to seal blood–brain barrier, and reduce the production of antibodies	1 g for 3-7 days. Oral taper is recommended over minimum 6 mo	Weight gain, hypertension, thrombosis, osteoporosis, infection, hyperglycemia, gastritis and peptic ulcer disease, psychiatric disturbances, Cushing's syndrome, adrenal suppression	Surveillance for noted adverse effects if being used long term, for example, DEXA scanning	Consider bone and gastric protection awareness of adrenal insufficiency	6,29,30,34,35,115
IVIG[a]	Immunomodulation, blocking of Fc receptors, attenuation of secondary inflammation, protective antibodies[b]	Induction course of 2 g/kg with subsequent 1 g/kg infusions 4-weekly	Skin reaction, headaches, fever, muscle/joint pains, aseptic meningitis, exacerbation of preexisting congestive heart failure, anaphylaxis, thromboembolic events	Surveillance for noted adverse effects	Blood product; maybe unacceptable to certain populations, for example, Jehovah's witnesses. Considered safe in children	42,43
PLEX[a]	Removal of components of humoral immune system	5-7 exchanges of 1-1.5 plasma volumes , typically alternate days	Associated with vascular access complications: pneumothorax, hemothorax, vessel thrombosis, infection. Citrate toxicity can cause paresthesias and cardiac arrhythmia	Surveillance for noted adverse effects	Central line or reliable peripheral access needed. Considered safe in children	37,38,116
Maintenance treatments						
AZA	Antiproliferative and immunosuppressive effects via inhibition of lymphocyte differentiation	Slow escalation vs initiation at 2-3 mg/kg/day	Pancytopenia, infection, liver enzyme derangement, hepatotoxicity, nausea and vomiting, skin malignancy, PML, nephritis and pancreatitis	Regular full blood count and liver enzymes. Expected response of drop in lymphocyte count to 600-1000/μl and mean cell volume increase by approx. 5 fL from baseline. Thioguanine and 6-MPP metabolites to guide dosing	Check TPMT ↑↑/↓ due to risk of hypermethylation and bone marrow depression. Time to efficacy: 3-6 months. Prednisolone can be used as a bridging therapy	6,13,55
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase, reducing the proliferation of B- and T-lymphocytes	2-3 g/day	Leukopenia, diarrhea, vomiting, infection, PML. When combined with other immunosuppressants risk of malignancy and infection	Surveillance for noted adverse effects	Time to efficacy: 15 weeks. Prednisolone can be used as a bridging therapy	34,117-119
Methotrexate	Folate analog, inhibits dihydrofolate reductase and DNA / RNA synthesis	15-25 mg/wk	Nausea, diarrhea, bone marrow suppression, and liver enzyme elevation	Regular full blood count and liver function monitoring	Folic acid supplementation required, interaction with trimethoprim and co-trimoxazole	13,120,121

(Continues)

TABLE 1 (Continued)

Treatment	Mechanisms of action	Suggested dosing	Adverse effects or complications	Monitoring	Practical considerations	References
RTX	Chimeric monoclonal antibody targeting CD20 found on B-lymphocytes	Variable regimens exist. Example: 2-g induction with 1 g every 6 months or according to CD19 (B cells) or CD19/27 (memory B cells) counts repopulation	Infusion-related (28%): pruritis, headache, rash or fever, SJS, arrhythmia. Long-term hypogammaglobulinemia, infection, persistent leukopenia, posterior reversible encephalopathy	Immunoglobulin monitoring, laboratory and clinical surveillance due to increased risk of infection. Monitoring of B-cell subsets	Before initial dosing, viral screen and assessment for dormant TB. Reported lag to treatment time of 3-4 weeks. Prednisolone can be used as a bridging therapy	63,64,122
Mitoxantone	Synthetic anthracenedione inhibiting leukocytes and targeting CD19 B cells	12 mg/m^2 combined with 1 g of methylprednisolone given once/month for 3 mo, then 9-monthly courses of the same dose	Leukopenia, liver enzyme elevation, nausea, alopecia, blue discoloration of urine and nails, cardiotoxicity, leukemia (risk as high as 0.73%), infection	Surveillance for noted adverse effects	Monitoring of cardiotoxicity. Ceiling on cumulative lifetime dosing of	86,87,117,123
Cyclophosphamide	Nitrogen mustard drug exerting effect through alkylation of DNA.	As for vasculitis – pulse dosing of 15 mg/kg (max 1200 mg) every 2 wk for 3 doses, followed by maintenance pulses every 3 wk	Bladder and gonadal toxicity, hemorrhagic cystitis, amenorrhea, myelosuppression, alopecia, nausea and vomiting	Full blood count should be monitored, with regular urinalysis	Mesna should be administered to reduce the effects of haemorrhagic cystitis. Reduced dosing in renal and hepatic impairment. Ceiling on cumulative lifetime dosing	65,66
TCZ	Inhibitor of IL-6	8 mg/kg every 2-4 wk	Raised liver enzymes, infections, lipid elevation, anemia, leukopenia, fatigue, nausea	Surveillance for adverse effects	Consider administering prednisolone to manage infusion-related reactions	79-81
Ofatumumab	Fully humanized anti-CD20 monoclonal antibody	Monthly subcutaneous injection, 20 mg	Infusion reactions, infections	Surveillance for adverse effects	Consider loading doses for initiation	13,83,124

Abbreviations: AZA, azathioprine; IVIG, intravenous immunoglobulin; 6-MPP, 6-methylmercaptopurine; PLEX, plasma exchange; PML, progressive multifocal leukoencephalopathy; RTX, rituximab; SJS, Stevens-Johnson-Syndrome; TPMT, thiopurine methyltransferase.

[a]All acute treatments can potentially be utilized as maintenance therapies in addition to their roles in acute management.

[b]Mechanisms of IVIG treatment are not fully understood.

TABLE 2 Summary of studies of immunosuppression in MOG antibody–associated disease

Medication	Study	Methods	Population available for analysis	Time on treatment, median (range)	Median ARR (range)		Concomitant treatments	Additional information
					Pre	Post		
Prednisolone	Ramanathan et al. (2018)[25]	Retrospective multicenter study including adults and children[a]	n = 20 (adults and children)	10 (6-53) mo	2 (0.5-6)	0 (0-0.6)	MFM = 10, IVIG = 4, AZA = 3, RTX = 2, PLEX = 1, MTX = 1, cyclo = 1, IFN-β = 1)	—
	Hacohen et al. (2018)[27]	Pediatric prospective multicenter study	Children = 8	n/a	n/a	n/a	n/a	5 children experienced a relapse, 4 during steroid weaning or cessation
AZA	Ramanathan et al. (2018)[25]	Retrospective multicentre study including adults and children[a]	n = 7 (adults and children)	n/a	n/a	n/a	n/a	2/4 patients treated for ≥ 6 months relapsed. 3 patients intolerant of AZA
	Jarius et al. (2016)[13]	Retrospective multicentre study	n = 17	10 (2-101) mo	Unclear	0.99 overall, (0.92 after drug latency period)	Prednisolone = 8, PLEX = 1	—
	Cobo-Calvo et al. (2019)[16]	Retrospective multicentre study	Adults = 11	2.1 (0.5-12.6) y	Mean 1.05 (SD 1.2)	Mean 0.43 (SD 0.79)	n/a	AZA 150mg/day
	Chen et al. (2020)[19]	Retrospective multicentre study	Children = 8 Adult = 14	20.4 months	Children 0.9 (0-9.7) Adult 1.4 (0-6.9) Total 1.2 (0-9.7)	Children 0 (0-2.2) Adult 0.43 (0-3.4) Total 0.2 (0-3.2)	Prednisolone (>10 mg) = 10	Relapses not counted if within 3 mo of starting
	Hacohen et al. (2018)[27]	Pediatric prospective multicenter study	Children = 20	n/a	1.84	1.0	n/a	—
Methotrexate	Jarius et al. (2016)[13]	Retrospective multicenter study	n = 6	n/a	n/a	n/a	n/a	"effective in 5/6 patients"
RTX	Jarius et al. (2016)[13]	Retrospective multicenter study	n = 9	n/a	n/a	n/a	n/a	"decline in relapse rate in 3/9 patients" Varying regimens used
	Ramanathan et al. (2018)[25]	Retrospective multicentre study	n = 6 (adults and children)	n/a	n/a	n/a 1/6 treatment failures and 3/6 had repopulation relapses[c]	n/a	Regimen not specified
	Cobo-Calvo et al. (2019)[16]	Retrospective multicenter study	n = 26	1.7 (0.5-4.9) y	Mean 1.08 (SD 0.98)	Mean 0.43 (SD 0.89)	n/a	1 g of RTX 6-monthly
	Hacohen et al. (2018)[27]	Pediatric prospective multicenter study	Children = 9	n/a	2.12	0.67	IVIG (4-8 weekly) = 2	RTX regimen not specified
	Chen et al. (2020)[19]	Retrospective multicentre study	Children = 7 Adults = 30	1.2 years	Children 0.8 (0.1-3.4) Adults 2.4 (0-9.0) Overall 1.8 (0-9.0)	Children 0.86 (0-5.1) Adults 0.59 (0-6.8) Overall 0.59 (0-6.8)	5/36 received prednisolone > 10mg for > 6m	Relapses not counting if within 1 mo of starting Regimen not specified

(Continues)

TABLE 2 (Continued)

Medication	Study	Methods	Population available for analysis	Time on treatment, median (range)	Median ARR (range)		Concomitant treatments	Additional information
					Pre	Post		
	Whittam et al. (2020)[28]	Retrospective multicenter study	Children = 30 Adults = 91	12.1 (IQR 6.3-24.9) mo	Children 1.64 (0.76-2.92) Adults 1.84 (0.82-4.70) Overall 1.82 (0.74-3.40)	Children 0.00 (0.00-1.28) Adults 0.37 (0.00-1.12) Overall 0.00 (0.00-1.25)	Prednisolone = 32, MMF = 8, IVIG = 6, AZA = 3, MTX = 2, IVIG/AZA = 1, IVIG (0.2 mg/kg monthly), Alemtuzumab exposure = 1	6-monthly regimen = 115 Retreatment according CD19 or CD19/27 B cells = 6
Mycophenolate mofetil	Ramanathan et al. (2018)[25]	Retrospective multicentre study[a]	n = 16 (adults and children)	8 (1-76) mo	1.83 (0.47-6.0)	0.16 (0-4.00)	Corticosteroids = 16, RTX = 4, IFN-β = 1	MMF dose was calculated according to body weight
	Cobo-Calvo et al. (2019)[16]	Retrospective multicenter study	n = 11	1.7 (0.5-6.8)	Mean 1.20 (SD 1.11)	Mean 0.23 (SD 0.60)	n/a	MMF 2 g daily
	Hacohen et al. (2018)[27]	Pediatric prospective multicenter study	n = 15	n/a	1.79	0.52	n/a	
	Montcuquet et al. (2016)[118]	Retrospective multicenter study	n = 5	43 (7-67) mo	1 (1-1)	0 (0-0)	n/a	Relapses not counted if within 3 mo of starting
	Chen et al. (2020)[19]	Retrospective multicenter study	Children = 4 Adult = 15	1.1 y	Children 2.1 (0-9.7) Adult 1.9 (0.0-9.0) Total 1.9 (0-9.7)	Children 1.5 (0-3.4) Adult 0.4 (0-5.2) Total 0.67 (0-5.2)	Prednisolone > 10 mg > 6 mo in 2 patients	MMF 600 mg/m^2 or 1.5 g/d. Relapses not counted if within 3 mo of starting
	Li et al. (2020)[60]	Prospective observational study (children and adults)[a]	Children = 21 Adult = 33	472.5 (271.3-709.0) d	1.1 (0.1-2.4)	n/a Relapses in 4/54 (7.4%)	Corticosteroids = 47/54 (87%)	—
IVIG	Ramanathan et al. (2018)[25]	Retrospective multicenter study	n = 7 (adults and children)	16 (8-189) months	2 (0.8-2)	0 (0-0.75)	Corticosteroids = 6, RTX = 1, β-IFN = 1	2 g/kg then 1 g/kg monthly
	Hacohen et al. (2018)[27]	Children prospective multicenter study	Pediatric = 12	n/a	2.16	0.51	Not specified	IVIG 4- to 8-weekly
	Chen et al. (2020)[19]	Retrospective multicenter study	Children = 5 Adults = 5	18 months	Children 4.4 (0-7.2) Adult 1.0 (0-2.8) Total 2.8 (0-7.2)	Children 0 (0-0.2) Adult 0.2 (0-0.2) Total 0 (0-0.2)	Prednisolone > 10 mg > 6 mo in 2 patients	3-weekly = 3 and monthly = 7

Abbreviations: ARR, annualized relapse rates ; AZA, azathioprine; cyclo, cyclophosphamide; IFN-β, interferon-β; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; n/a, not available; PLEX, plasma exchange; RTX, rituximab.

[a]Figures represent a combined analysis of adults and children.

[b]AZA dose 150 mg.

[c]RTX failure defined as relapse between 2 weeks and 6 months after treatment and were considered separate from repopulation relapses which were defined as CD19 ≥10 × 10^6 cells/L.

[Correction added on 20 March 2021, after first online publication: The orientation of Table 2 has been changed from portrait to landscape]

Deflazacort may be as effective as prednisolone, but associated with less skeletal bone mineral density loss, fat accumulation, and adverse effect on lipid profile.[54] Deflazacort has not been studied in AQP4-IgG NMOSD or MOGAD but represents an interesting avenue for future research.

4.2 | Azathioprine

Azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) are purine analogs with antiproliferative and immunosuppressive effects. Before treatment is initiated, testing thiopurine methyltransferase levels is recommended to reduce the risk of myelotoxicity.[55] There is a latency of approximately 3 to 6 months prior to therapeutic effect.[55] A 5-fL rise in mean cell volume or mild absolute lymphocyte count suppression are useful indicators of this.[56] Measurement of the AZA metabolites 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) can be used for therapeutic drug monitoring and help to reduce the risk of myelotoxicity and hepatotoxicity. A serum 6-TG concentration greater than 400 pmol/8 $\times$ 10^8 red blood cells (RBC) correlates with myelosuppression and values within the range of 235 to 450 pmol/8 $\times$ 10^8 RBCs correlate with clinical efficacy. A serum concentration of 6-MMP above 5700 pmol/8 $\times$ 10^8 RBCs suggests an increased risk of hepatotoxicity.[55]

Four studies have retrospectively assessed the effect of AZA on MOGAD relapse risk (Table 2). The largest cohort included 22 MOGAD pediatric and adult patients.[19] AZA was used as first-line therapy in 77% of these patients, and the median ARR fell from 1.6 (range, 0-9.7) to 0.2 (range, 0-3.2). Overall, 59% (13/22) of patients on AZA had a relapse during a 1.7-year follow-up period. Half of patients also received prednisolone, but it was not clear how many relapses occurred in this subgroup or within the first 3 to 6 months after AZA initiation (attacks within the 3 months of AZA initiation were not counted). Three studies, including 48 patients in total, reported reductions in ARR from 1.2-2.0 to 0.43-1.0 (Table 2), with one study recording 41% of relapses in the first 6 months of AZA initiation.[13,16,27] Jarius et al.[13] reported that 41% (14/34) of relapses in 17 MOGAD patients occurred in the first 6 months of treatment in patients not receiving adjunctive prednisolone. This suggests that the latency period to AZA therapeutic effect is likely to be of clinical relevance. Accordingly, our practice has been to use prednisolone (10-20 mg) as a bridging therapy until a rise in the mean cell volume and/or drop in absolute lymphocyte counts is seen following AZA introduction. If this is not observed despite optimized metabolite parameters, a different nonsteroidal immunosuppression should be considered.

In terms of tolerability, AZA is generally well tolerated but can cause gastrointestinal upset. In these cases, 6-MP can be trialed but up to 33% may still have ongoing adverse effects.[57] In many of the reported studies, AZA formed the largest drug group for analysis, likely a reflection of physician preference. Retrospective studies to date have shown modest reductions in ARR, but AZA efficacy as a monotherapy remains questionable and the latency to therapeutic effect is also a limitation. Future prospective studies addressing these factors and comparing AZA with other nonsteroidal immunosuppression and control groups would be helpful.

4.3 | Mycophenolate mofetil

Mycophenolate mofetil has frequently been used in the treatment of AQP4-IgG NMOSD and has comparable efficacy with AZA with fewer side effects.[58,59] Five retrospective studies have assessed the effect MMF on MOGAD relapse risk.

To date the largest MMF experience comes from a recently published prospective observational study that compared MMF treatment in 21 children and 33 adults vs an MMF (–) group (n = 25).[60] The MMF dose was 1.5 g/day (lower than other studies that have used 2 g/day as standard) or 600 mg/m^2. Over a median of 400 days, relapse rates were 7.4% (4/54) and 44% (11/25) in MMF-treated and untreated groups, respectively. This equated to an 86% reduction in relapse risk and a number needed to treat of 2.7. Importantly 87% (47/54) of patients also received prednisolone, reducing by 2.5 mg/wk till a maintenance dose of 7.5 mg/d was reached. In contrast Chen et al.[19] noted relapses in 74% (14/19) of patients over a 1.1-year follow-up period. Pre- and posttreatment median ARRs were 1.9 (0-9.7) and 0.67 (0.5.2), respectively. Only two patients received concomitant oral corticosteroids. Ramanathan et al.[25] reported a median ARR reduction from 1.83 (0.5-6) to 0.0 (0-1.57) in 16 patients treated with MMF. Importantly all patients received concurrent corticosteroids but almost half (7/16; 44%) experienced a relapse within the 8-month follow-up period (range, 1-76 months). While the ARR reduction was numerically more impressive, as with the study by Li and colleagues,[60] the contribution of corticosteroids after the bridging period confounds the interpretation of MMF treatment as a monotherapy. Notably 4 of 10 relapses occurred during tapering of adjunctive prednisolone, implying that MMF monotherapy may well be less effective. Hacohen et al.[27] reported outcomes of 15 children on MMF, of whom 53.5% (8/15) relapsed during treatment. Pre- and posttreatment ARRs were 1.79 and 0.52, respectively, with no change in EDSS observed. Details regarding concomitant prednisolone use were not given. Cobo-Calvo et al.[16] reported high rates of relapse suppression, with relapse freedom observed in 72.7% (8/12) of MMF-treated patients. EDSS progression was not seen with MMF, which was associated with a reduction in mean ARR from 1.20 to 0.23. Concomitant steroid use was not detailed and a set MMF dose of 2 g/d was used. MMF was also found to be better tolerated than AZA.

Although data from these studies are somewhat conflicting, factors such as steroid bridging, use of maintenance steroids, and MMF dosage may explain some the variability seen. With regard to the latter the study by Li and colleagues[60] suggests that high doses of MMF may not be needed (up to 3 g/d can be given), and perhaps it is the combination with low-dose prednisolone that is important for relapse risk reduction. A large prospective multicenter study addressing these factors would help to clarify MMFs role in MOGAD treatment.

4.4 | Rituximab

The effectiveness of rituximab (RTX) in AQP4-IgG NMOSD has been acknowledged for some time and is now supported by a randomized double-blind placebo-controlled trial that demonstrated complete suppression of relapses in the 19 patients receiving RTX compared to placebo.[61,62] There are several regimens that have been suggested for AQP4-IgG NMOSD and more recently MOGAD: 1 or 2 g RTX 6-monthly; low-dose RTX regimens; RTX according to body surface area, for example, 375 mg/m^2 weekly for 4 weeks and retreatment timed to B-lymphocyte subset repopulation (eg, CD19 and CD27); and combinations of the above[28,63,64] (Table 1). The purported benefits of B-lymphocyte monitoring include the detection of patients who repopulate early and are thus at higher risk of relapse, a reduction in cumulative RTX dose and side effects, and reduced cost.[65] A latency to B-cell depletion of 3 to 4 weeks following RTX administration is recognized[64] and there have also been a few reports of RTX-induced worsening of AQP4-IgG NMOSD relapse, possibly related to an increase in B-cell–activating factor or BAFF.[66]

There are 6 retrospective studies of RTX use in MOGAD. To date, Whittam et al.[28] have reported on the largest cohort of RTX-treated MOGAD patients that included 101 adults and children. RTX treatment was associated with a 37% reduction in relapse rate and an ARR reduction of 1.18 to 0.56 in those with at least 12 months' follow-up. If latency to RTX effect was considered, and relapses within the first 3 to 4 weeks were excluded, regression analysis demonstrated a 43% reduction in relapse rate. A similar rate of relapse reduction (42%) was observed when patients on long-term maintenance prednisolone or other nonsteroid immunosuppression were excluded, with an ARR reduction of 1.54 to 0.00. Of 113 relapses, B-cell counts were available in 57, and of these 78.9% (45/57) of samples showed suppression of circulating CD19+ B cells during relapse, indicating RTX failure. In keeping with this study the second largest RTX experience was reported by Chen et al.[19] and included RTX outcomes in 37 adults and children. Of these, 62% (23/37) had a relapse over 1.2 years of follow-up. Overall pre- and post-RTX ARRs were 1.8 (0.0-9.0) and 0.59 (0-6.8), respectively. Five patients received concomitant prednisolone for >6 months but relapse data were not reported in this subgroup. Details of RTX regimen and B-cell monitoring were also not available. Contrastingly, Cobo-Calvo et al.[16] found that 73% (19/26) of patients treated with RTX achieved relapse freedom with a mean ARR reduction of 1.08 to 0.43. Freedom from EDSS progression was also noted in 88.5% (23/26) of patients. The relapses that were seen occurred within 6 months of infusion. Ramanathan and colleagues[25] reported outcomes in 6 RTX treated MOGAD patients of whom 1 patient had 2 relapses in spite of adequate B-cell depletion. Other relapses were related to B-cell repopulation. Jarius et al.[13] reported outcomes of 9 MOGAD patients treated with RTX. Reminiscent of the AQP4-IgG NMOSD experience, the majority of the 33% of patients who relapsed did so within months of their infusion; 2 others were classed as end-of-dose relapses. Finally, Hacohen et al.[27] reported relapses in 66.7% (6/9) of children receiving RTX. Two of the children also received IVIG, which may have contributed to their relapse freedom. Overall, mean pre- and post-ARR were 2.12 and 0.67, respectively, with no significant change in EDSS observed (mean EDSS prior to treatment, 2.4; during treatment, 3.2).

Other RTX considerations include attacks on initiation and withdrawal of RTX, safety of treatment, and cost. In AQP4-IgG NMOSD, attacks have been reported in RTX-treated patients within weeks of first infusion, possibly due to a temporary increase in B-cell–activating factor and autoantibody levels[29,67] as well as rebound relapses following discontinuation.[68] Whether steroid-bridging therapy should be routinely considered at initiation and withdrawal of RTX requires further study. Our practice is to continue corticosteroids for at least the first 4 weeks following RTX introduction.

In terms of safety, a recent meta-analysis of RTX use in AQP4-IgG NMOSD patients reported 5 deaths in 528 patients (<1%) due to serious illness and related complications. Two of those deaths were associated with adverse reactions to RTX.[69] A further meta-analysis including 438 AQP4-IgG NMOSD patients demonstrated a 10% rate of infusion-related adverse effects, 9% rate of infection, 4% rate of persistent leukopenia, and 0.5% rate of posterior reversible encephalopathy.[62] Hypogammaglobulinemia has been reported in 64% (32/50) of AQP4-IgG NMOSD patients following maintenance RTX therapy with severe infection associated with secondary antibody deficiency occurring in 10% (5/50).[65] Risk factors predisposing patients to hypogammaglobulinemia and infections post–RTX maintenance therapy included low immunoglobulin levels prior to treatment, prior immunosuppression, concomitant use of purine analogs, and chronic lung or heart disease.[70] The cost of RTX and day-case infusion-related costs also require consideration. However, biosimilars are now available and depending on local and regional arrangements can be more competitive in cost.

Overall, the reduction in relapses rates with RTX is less impressive in MOGAD compared to the AQP4-IgG NMOSD. While there are methodological considerations that can be considered in the reported studies it seems unlikely if addressed that relapse-freedom rates are to match those that have been observed in AQP4-IgG NMOSD. The experience of RTX in MOGAD underscores the need for MOGAD-specific treatment strategies.

4.5 | IVIG

IVIG has been studied as a maintenance therapy in 3 retrospective studies. Hacohen et al.[27] reported clinical outcomes in 12 children given IVIG every 4 weeks. IVIG was superior to MMF, AZA, RTX, and cyclophosphamide with respect to ARR (2.61 → 0.51) and EDSS (2.2 → 1.2). Overall, 4 of 12 (33%) patients relapsed. Two patients also received RTX and in 2 patients IVIG frequency was reduced to 8-weekly. The exact IVIG doses were not included. In an Australian study that used an induction dose of 2 g/kg followed by monthly 1 g/kg infusions, ARR decreased from 2 (0.8-2) to 0 (0-0.75) in 7 patients over a 12-month period. Half of relapses coincided with either a reduction in monthly IVIG dose or an increase in the dosing interval. Relapses associated with IVIG weaning have also been noted in other studies.[25]

In another study, 10 patients (including 5 children) treated with IVIG had a decrease in median ARR from 2.8 (0-7.2) to 0 (0-0.2) over a 1.2-year period. Doses were not reported but infusion intervals varied between patients (3 weekly to 7 monthly). Relapses were observed in 2 patients, and a further 2 patients received concomitant prednisolone for >6 months.[19] On balance, these studies reflect a positive role for maintenance IVIG in MOGAD. Furthermore, in the studies of Ramanathan et al.[19] and Chen et al.,[25] treatment with IVIG resulted in the lowest relapse rates of all assessed treatments.

A handful of case reports have also been reported on the utility of IVIG in MOGAD. Jarius et al.[13] reported the progress of a patient who achieved relapse freedom during 11 months of IVIG treatment and for 12 months following its discontinuation. Other case reports in IVIG and MOGAD have demonstrated reductions in mean ARR (ARR, 2-3 to 0-0.5) and EDSS stability with 3- or 12-weekly IVIG treatment.[71,72] These data provide encouraging signals to the efficacy of IVIG as a maintenance treatment in MOGAD. Collaborative efforts are underway to pool international retrospective experience of IVIG for MOGAD, which, if in keeping with the aforementioned positive results, could help provide the necessary impetus for a prospective clinical trial.

4.6 | Methotrexate

Methotrexate (MTX) has been used in a number of inflammatory and autoimmune conditions including inflammatory bowel disease, rheumatoid arthritis, and AQP4-IgG NMOSD.[73] MTX is a generally safe and well tolerated medication (Table 1).

Jarius et al.[13] reported disease stabilization in 5 of the 6 MOGAD patients treated with MTX. Over a treatment period of 22.5 years, 5 attacks were recorded equating to an ARR of 0.22, which was less than the cumulative ARR of 0.95 of the 34 patients with relapsing disease. Two patients were on MTX for coexistent rheumatoid disease and in one of these patients, treatment suspension (due to infection) was associated with a relapse after a 40-year interval.

In another retrospective study a single patient was treated with MTX as a second-line therapy after cyclophosphamide. When grouped together with other less frequently used treatments (cyclophosphamide and mitoxantrone) no change in ARR was noted.[16] To date there are insufficient data to draw clear conclusions about the efficacy of MTX as a treatment for MOGAD.

4.7 | Cyclophosphamide

Cyclophosphamide is a potent immunosuppressant commonly used to manage immune mediated CNS processes such as CNS vasculitis (Table 1). Previous studies of its use in AQP4-IgG NMOSD have suggested either a lack of or minimal benefit.[74-76] Only small numbers of MOGAD patients have been reported following treatment with cyclophosphamide.

Chen and colleagues[19] reported 3 children treated with IV cyclophosphamide. Two relapsed and were later treated with RTX. Jarius et al.[13] reported one patient treated with IVMP and IA and IV cyclophosphamide for an acute ON but visual acuity improved only marginally (0.05-0.16 at discharge). Further studies are needed to establish whether cyclophosphamide is effective as either an acute or maintenance treatment in MOGAD.

4.8 | Tocilizumab

Tocilizumab (TCZ) is an inhibitor of the IL-6 signaling pathway and its use in AQP4-IgG NMOSD has been associated with a reduction in disease activity in both pilot studies and open-label multicenter randomized trials.[77-80] Data regarding TCZ use are available in 5 MOGAD patients. Two patients achieved relapse freedom with TCZ; 1 had previously been refractory to RTX;[81] and another achieved relapse following ongoing disease activity with natalizumab, RTX, and cyclophosphamide.[79] A case series also identified 3 MOGAD patients who had disease activity despite RTX. All 3 patients had a reduction in ARR from 1 to 0 and stable MRI appearances at 5 and 29 months following treatment with TCZ.[82] Larger prospective studies will be needed to determine if TCZ an effective long-term treatment strategy in MOGAD.

4.9 | Ofatumumab

Ofatumumab is a fully humanized anti-CD20 monoclonal. As part of the second generation of monoclonal antibodies, ofatumumab has been designed to be better tolerated and of a lower level of immunogenicity.[83] It is administered as a once-monthly subcutaneous injection with clinical trials ongoing to assess its potential use. Ofatumumab has been used for one patient with MOGAD. In this case, ARR decreased from 2.1 to 0.66 and no adverse effects were documented.[13] Further studies of ofatumumab are needed to better understand its efficacy and tolerability in MOGAD.

4.10 | MS treatments

The higher prevalence of MS and its similarities with MOGAD means that patients with the latter may inadvertently be exposed to conventional MS disease-modifying therapies (DMTs). In AQP4-IgG NMOSD, interferon-β (IFN-β), glatiramer acetate, natalizumab, and alemtuzumab are ineffective or result in disease exacerbation.[13,27,79,84]

Several groups have reported their experience of DMT exposure in MOGAD. Chen and colleagues[19] found that 9 patients receiving DMTs (interferon-β, n = 5; glatiramer acetate, n = 4) as first-line treatment relapsed. Cobo Calvo et al.[16] reported 9 MOGAD patients on MS DMTs, of whom 7 discontinued due to treatment failure, intolerance, physician decision, and conception planning. Treatment

failure and intolerance has also been noted in children.[27] Jarius et al.[13] also found no change in ARR in 16 patients who received MS treatment. We did come across one report of disease stabilization in a patient with an MS phenotype and detectable MOG-IgG following alemtuzumab, but the antibodies were detected with a non–IgG-specific secondary antibody so false positivity due to IgM cannot be excluded.[1,85]

Mitoxantone was approved for the management of patients with relapsing–remitting and early secondary progressive MS in 1999.[86] Details regarding dosing, mode of action, and adverse effects can be found in Table 1. An 80% reduction in ARR and improvement in EDSS was reported in a multicenter observational study of 51 patients with AQP4-IgG NMOSD.[87] The authors suggested that the benefits of treatment in aggressive AQP4-IgG NMOSD may outweigh the significant risks of the drug. However, there remain insufficient data to draw meaningful conclusions about its efficacy as a maintenance therapy in MOGAD. Overall, it is too early to exclude the use of MS DMTs in MOGAD altogether; the reported signals of efficacy to date have not been encouraging.

4.11 | Duration of treatment

Once commenced, there is a lack of consensus on how long patients should receive immunosuppression. Commonly considered factors include duration of relapse freedom, severity and frequency of prior attacks, and MOG-IgG serostatus.[12] Interestingly similar questions are now also being asked in AQP4-IgG NMOSD.[88] Without a suitable biomarker to inform impending or ongoing disease activity there is difficulty quantifying relapse risk in patients with either disease.

That being said, MOG-IgG serostatus in adults can be helpful, and relapses appear uncommon following MOG-IgG negative seroconversion.[14,89] One study followed the serostatus of 57 adult patients and of those 41 of 57 (72%) remained positive (median disease duration, 37 months; range, 17-57), 14 of 57 (25%) became negative, and 2 (3%) had a fluctuating serostatus (median disease duration, 9 months; range, 1-16).[14] No patients who became MOG-IgG negative experienced further relapses. Importantly, this observation does not hold true for children where relapses can be seen irrespective of serostatus. MOG-IgG serological reversion also remains a possibility as recently noted in a MOGAD relapse with COVID-19.[90] On longitudinal MOG-IgG testing, 1 study found that MOG-IgG seroreversion occurred in 3% of cases.[14] In an international survey 17.3% (9/52) of respondents contemplated treatment cessation following negative MOG-IgG testing, and 40.4% (21/52) considered discontinuation when taking MOG-IgG serostatus and other factors (duration of relapse freedom and prior attack severity/frequency) into account.[12,14,91]

The duration of steroid treatment after an index MOGAD event appears critical to the risk of early relapse or perhaps also the recrudesce of subclinical inflammatory activity. In large UK and Australian studies, a prolonged steroid taper (>3 and 2 months, respectively) was associated with a lower risk of relapse. In the UK study an index TM attack was associated with a poor outcome, but if having recovered well from the index attack it was not possible to predict which patients were at risk of a subsequent poor outcome. In the UK, MOG-IgG serostatus at months 6 and 12 is used to guide treatment duration after the index attack. If MOG-IgG becomes negative after 6 months, treatment is tapered, but if not treatment may be continued to 12 months depending on factors such as index attack severity, relapse activity, and medication tolerability. Following this time point, irrespective of MOG-IgG serostatus, treatment is commonly tapered.[91]

Cobo-Calvo et al.[92] recently reported on the relapse risk in 336 cases of children and adults with MOGAD. Adults were at higher risk of relapse and had worse functional outcomes compared to children. In addition, index ADEM or TM attacks were associated with a higher relapse risk in adults. Interestingly females also had a higher risk of relapse. Higher disability at onset was associated with a lower risk of relapse, but as the authors point out, this latter finding may relate to a tendency to use long-term immunosuppression in these cases.

Although further studies are required to better predict the long-term clinical course of patients following an index MOGAD event, prognostic clinical factors that help to predict risk of relapse are starting to come to fruition. It is hoped that in the future a personalized approach involving risk stratification with MOG-IgG serostatus and other biomarkers will help guide when best to start and stop chronic immunotherapy.

4.12 | Pregnancy

A detailed review of pregnancy and MOGAD is beyond the scope of this review. The interested reader is directed to a recent comprehensive review by Mao-Draayer and colleagues.[93]

Data on MOGAD and pregnancy are limited. Two published case series have included 10 and 30 patients with pregnancies.[13,94] Attacks during pregnancy were reported in 10% to 20% of patients and in approximately 40% of patients during the postpartum period. Compared to prepregnancy relapse rates, attacks were less frequent during pregnancy but increased in the postpartum period.[94] ARRs, particularly in the postpartum period, were lower in those treated with immunotherapy. It is difficult to draw firm conclusions on the available data but larger studies ideally involving pregnancy registries could be utilized to better understand interactions between MOGAD and pregnancy.

A summary of key treatment considerations in pregnancy is provided in Table 3. From a practical perspective, preconceptual planning is ideal, with careful discussions of topics such as risks and benefits of treatment, mode of delivery, and anesthesia. Ideally, this should involve a multidisciplinary approach in for instance an obstetric neurology clinic. If immunosuppression during pregnancy is mutually agreed upon, options are limited, and drugs such as mycophenolate and methotrexate must be avoided due to their teratogenicity. Table 3 summarizes key aspects of chronic immunosuppression in pregnancy. In comparison to MMF and MTX, AZA has a more favorable safety

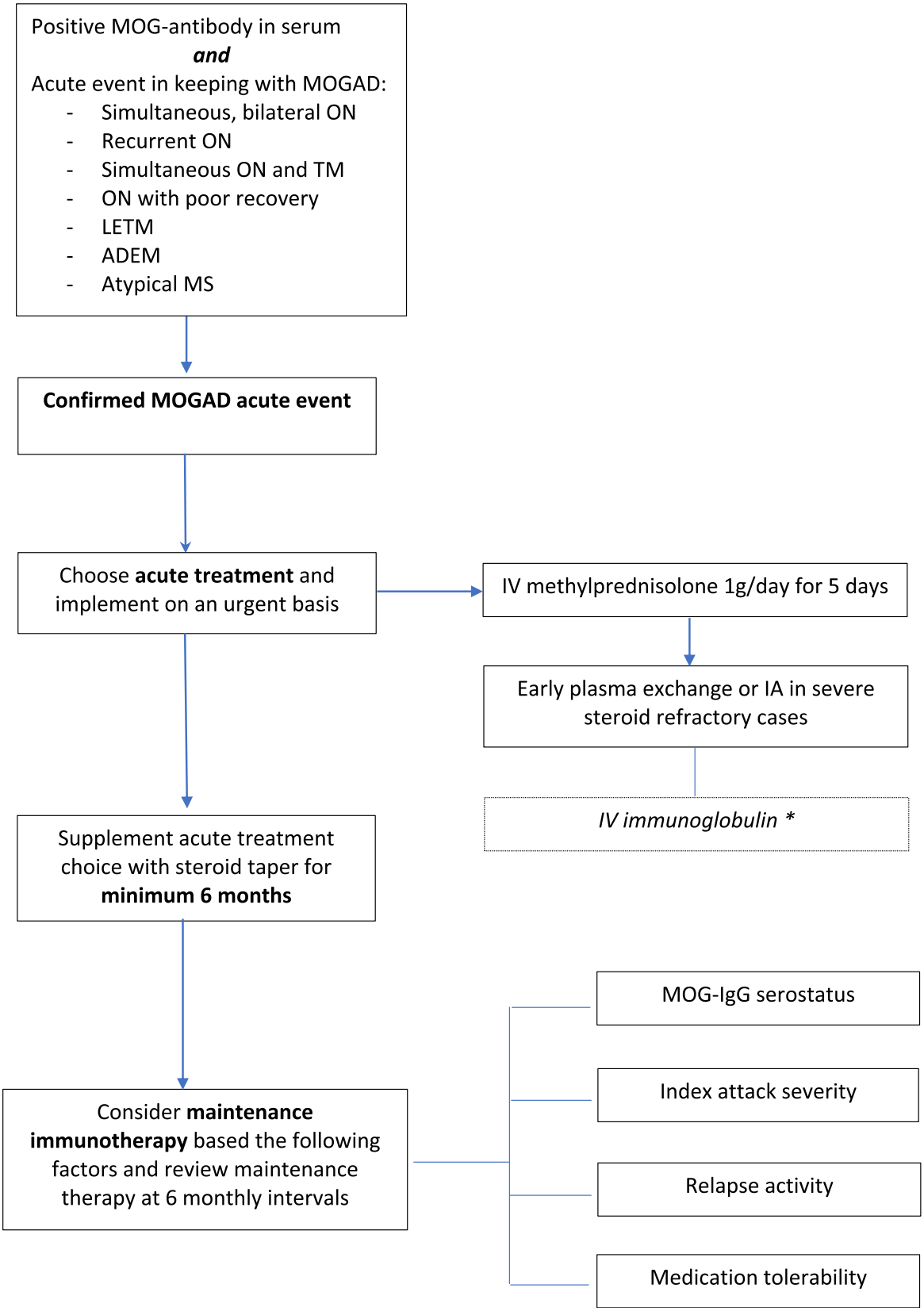

FIGURE 1 An algorithm of proposed acute treatment options and considerations regarding continued immunotherapy. *There is limited information on efficacy of IVIG in acute MOGAD attacks, however, based on studies in AQP4-IgG NMOSD it may be an efficacious treatment. ADEM, acute disseminated encephalomyelitis; IA, immunoadsorption; IVIG, intravenous immunoglobulin; LETM, longitudinally extending transverse myelitis; MOGAD, myelin oligodendrocyte glycoprotein immunoglobulin G–associated disease; MS, multiple sclerosis; ON, optic neuritis; TM, transverse myelitis [Correction added on 30 April 2021, after first online publication: Figure 1 caption and image have been placed on the same page in this current version]

TABLE 3 Associations between therapeutics, contraception, use in pregnancy and breastfeeding, and teratogenicity

Drug	Teratogenicity	Contraception	Use in pregnancy and specific considerations	Breastfeeding
Corticosteroids	Conflicting literature regarding association with cleft palate, low birth rate, and preterm birth[105]	No confirmed interaction with hormonal contraceptives.[125] Barrier methods and intrauterine devices advised	Consider on an individual basis	Considered safe[93]
IVIG	Teratogenicity not reported[126]	No confirmed interaction with hormonal contraceptives. Barrier methods and intrauterine devices advised	Risk of hyperviscosity[108,126]	Considered safe[127]
PLEX	Teratogenicity not reported	No confirmed interaction with hormonal contraceptives.[128] Barrier methods and intrauterine devices advised	Risk of hypovolemia, removal of prophylactically administered RhIG[109]	Insufficient literature on this area
AZA	Associated with prematurity, intrauterine growth retardation, low birthweight, fetal infection, and blood dyscrasia[129,130]	No evidence that hormonal contraceptives interact with 5-ASA drugs[131]	Consider on an individual basis	Can be excreted in low concentrations 4-6 h after a dose.[55] Consider counselling on risk of immunosuppression and blood dyscrasias in the newborn with mothers considering breastfeeding[129]
Mycophenolate mofetil	Corpus callosum agenesis, limb abnormalities, cardiac abnormalities, cleft palate, high rates of spontaneous abortions[129,132]	Reduces the effectiveness of hormonal contraceptives,[133] advised to combine hormonal contraceptives with barrier methods	Contraindicated in pregnancy, contraception recommended on MMF and 6 wk after discontinuation[130]	Unclear if MMF is excreted in breast milk, avoid breastfeeding with MMF
Methotrexate	Increased risk of neural tube defects including anencephaly[134]	Hormonal contraception does not appear to interact with MTX[131]	Contraindicated in pregnancy	Excreted in breast milk, avoid breastfeeding with MTX[134]
RTX	Associated with low birthweight and prematurity[129]	Hormonal contraception does not appear to interact with RTX[135]	Known to cross the placenta after 20 weeks' gestation, associated with transient B-cell depletion and risk of infection in newborns[129]	One study reported safety in breastfeeding,[107] other studies suggests avoidance of breastfeeding[93]

Abbreviations: 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; IVIG, intravenous immunoglobulin; MTX, methotrexate; MMF, mycophenolate; PLEX, plasma exchange; RTX, rituximab.

profile. A meta-analysis of 1201 pregnant women on thiopurines and 4189 controls found a higher risk of preterm birth with thiopurine exposure but no difference in other adverse pregnancy outcomes.[95] Reassuringly several other studies of AZA in pregnancy have not found increased rates of birth defects.[96-101] If AZA is used, monitoring of white cell and platelet counts as well as regular ultrasound assessment has been suggested.[102]

Corticosteroids are another useful option in pregnancy but rationalization of maintenance doses prior to conception is advisable due to associated low birthweight, maternal hypertension, and diabetes. Another important consideration is the possible link between orofacial clefts and corticosteroid exposure in the first trimester though data on this are conflicting.[103-105]

RTX is emerging as another treatment option in pregnancy though there are fewer studies of its use in pregnancy compared to AZA. A recent systematic review found no significant safety concerns in 102 pregnancies with RTX exposure within 6 months of conception.[106,107] It is worth noting that in 39% (9/23) of neonates transient B-cell suppression was seen with normalization of levels by 6 months. Due to the prolonged action of RTX, one strategy that has been suggested is conception as close to the last RTX infusion as possible with consideration of retreatment in the early postpartum phase.[93]

Acute relapses in pregnancy are managed similar to those in the nonpregnant state. Typically, one of or a combination of IVMP, IVIG, and PLEX are used. IVIG and PLEX are not known to adversely affect fetal development, although there are risks of hypovolemia with PLEX and hyperviscosity with IVIG, which require monitoring.[37,108,109]

4.13 | Emerging treatments

In the past 2 years there has been a rapid expansion in the armamentarium of drugs available for the treatment of AQP4-IgG NMOSD.

Existing drugs such as RTX and TCZ and newer drugs such as eculizumab, satralizumab, and inebelizumab have all reported positive results in large multicentre trials, the majority of which were conducted in a double-blind placebo-controlled manner.[110-112] In the Inebelizumab trial 7 MOGAD patients were included and 1 MOGAD patient was included in the TCZ trial,[80,112] but separate outcomes for MOGAD were not specifically reported. Importantly the rationale for the selection of these drugs in AQP4-IgG NMOSD was backed by robust preclinical research underpinned by the pathophysiological mechanisms of NMOSD and AQP4-IgG. While it is certainly possible that some of these drugs may be of benefit in MOGAD, the success of the AQP4-IgG NMOSD "blueprint" would suggest that emphasis be placed on drugs with a mechanistic rationale that is MOGAD specific.

5 | DISCUSSION

Improvement in the accuracy of MOG antibody detection has allowed for the distinction of MOGAD from other CNS-demyelinating illnesses. Although there are similarities with AQP4-IgG NMOSD, the differences in histopathological, clinical, and prognostic characteristics separate MOGAD as a distinct disease entity. The importance of this is underlined by the contrasting efficacy of treatments in AQP4-IgG NMOSD and MOGAD.

When assessing existing and novel treatments, the identification of an at-risk population most likely to benefit from long-term treatment will be important. Several key factors warrant consideration and further study: (a) the risk of relapsing disease, (b) time periods of elevated relapse risk, (c) the risk of disabling relapses, and (d) overall duration of relapse risk.

1. Risk of relapsing disease—There is variability in the reported proportion of patients affected by relapsing disease, with large studies indicating that up to 50% of patients may relapse within the first 2 years, increasing to 80% over 5 years.[14,15] Unsurprisingly, studies with longer follow-up periods have identified a greater proportion of relapsing cases.[13] However, caution should be applied when interpreting disease course in retrospective cohorts in which patients with higher relapse rates and disability are more likely to remain under long-term follow-up. The use of incident cohorts and prospectively identified MOGAD cases should help to address these issues. In addition, prognostic markers that predict patients at higher relapse risk will be helpful for long-term treatment decisions as well as clinical trials.
2. Time periods of elevated relapse risk—In 2 large studies, MOGAD relapse risk was highest in the 2 to 6 months following an index event. In a further study, 20% of index attacks were preceded by infection, suggesting that MOGAD may be a precipitated event and as result associated with a more transient disruption of immunological tolerance.[15] Importantly steroid treatment during this period was associated with a reduction in relapse risk.[14,25] It is conceivable that corticosteroids allow for a reduction in relapse risk while the restoration of immunological tolerance takes place. However, it remains unclear if corticosteroids early on in the course of MOGAD has a long-term prognostic benefit on risk of relapsing disease.
3. Risk of disabling relapses—As illustrated in accounts of untreated MOGAD, even severe attacks may be associated with a good functional recovery.[13] Furthermore, potentially long periods between relapses make rationalization of chronic immunosuppression difficult. Based on these observations and a comparatively better prognosis compared to AQP4-IgG NMOSD, an argument can be made for a reactionary treatment paradigm, whereby treatment is only instituted when relapse activity is clinically present. However, although the prognosis of MOGAD is better than AQP4-IgG NMOSD this does not necessarily equate to a good long-term outcome, and in one study 47% of MOGAD patients were left with severe disability.[14] It would therefore be helpful to further study factors such as the importance of time to treatment, reversibility of relapse associated disability, and whether there is clinically silent or subtle disease activity. This, along with the identification of factors that predict patients at risk of disabling relapse, could help lead to a more precision-based approach to MOGAD treatment.[13]
4. Overall duration of relapse risk—In adults, a decline in relapse risk has been associated with negative MOG-IgG seroversion.[14] In contrast, relapses can be seen in children irrespective of MOG-IgG serostatus and there remains a pressing need to identify biomarkers to guide treatment duration in this group.[113] In adults, our practice is to discontinue immunosuppression in patients who become persistently MOG-IgG negative by live cell-based assay.[1] Whether negative seroversion should be defined as MOG-IgG that is persistently undetectable or below an accepted cutoff remains unclear. The clinical relevance of this distinction was highlighted in a recent report of a MOGAD relapse with SARS-CoV-2 infection associated with MOG-IgG serological reversion despite prior persistently subthreshold MOG-IgG levels.[90]

Thus far, retrospective studies assessing the efficacy of traditional immunosuppressants such as AZA and MMF have yielded conflicting results, in part due to study design, sample size, heterogeneity of study sample (eg, combined analyses of adults and children), and concomitant use or lack of other immunotherapies (eg, bridging strategies for drugs with a delayed therapeutic action). In spite of these limitations, these studies have consistently confirmed the steroid-sensitive nature of MOGAD, and more tolerable alternatives could be explored such as deflazacort or even intramuscular administration.[114] There are also encouraging signals of IVIG efficacy in MOGAD treatment. Pooling together of international treatment experience and prospective randomized clinical trials should address the role of these drugs in the MOGAD treatment armamentarium. In the case of RTX, it appears probable that even if studied in a prospective randomized manner, this medication is unlikely to be as effective as for AQP4-IgG NMOSD. This striking difference in efficacy highlights the importance of a mechanistic

understanding of a condition when selecting and developing new treatments, as has eloquently been demonstrated in the story of C5 inhibition–eculizumab in AQP4-IgG NMOSD. In many ways we are with MOGAD where we were 10 years ago with AQP4-IgG NMOSD, but as with AQP4-IgG NMOSD, there is considerable scope for rapid advancement in our understanding of the disease and its treatment if we can adopt a similar approach.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Healy S, Elhadd KT, Gibbons E, Whittam, D, Griffiths, M, Jacob, A et al. Treatment of myelin oligodendrocyte glycoprotein immunoglobulin G–associated disease. *Clin Exp Neuroimmunol*. 2021;12:22–41. https://doi.org/10.1111/cen3.12630