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Review

Therapeutic approaches in adults with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): A review of current evidence

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ABSTRACT

Recent years have seen a considerable increase in knowledge pertaining to Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD). Nevertheless, a noteworthy degree of uncertainty remains within the neurological community, primarily due to the often highly heterogeneous nature of the disease and the absence of approved long-term treatment options. In this article, we undertake a comprehensive review of the various treatment strategies and drug options available for the pharmacological treatment of acute attacks and relapses in MOGAD.

1. Introduction

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) is a rare (prevalence of 0.5 to 3.4/100,000 [1]), antibody-associated autoimmune disease of the central nervous system (CNS) [2]. Initially classified as a variant of Neuromyelitis Optica Spectrum Disease (NMOSD) [3–5], recent advancements in understanding of the pathophysiology, phenotypes and course of the condition have facilitated a more precise characterization and comprehension of the disease [6,7]. Pathophysiologically, peripheral follicular T_H-cell-dependent production of MOG-IgG by B cells occurs, which seems to target oligodendrocytes, leading to subsequent demyelination. Disruption of the blood-brain barrier (BBB) is a prerequisite for this process, and is mediated by interleukin-6 (IL-6), among other factors. Recent findings indicate furthermore that MOG-specific T cells play a larger role than previously thought [8]. With this regard, MOGAD seems to be different as compared to NMOSD (where, in seropositive patients, the anti-Aquaporin 4 antibody itself mediates the disease alongside the appearance of specific T cells). Complement activation appears to be less pronounced in MOGAD than in NMOSD [1]. This may be because, in addition to anti-MOG IgG1 antibodies, IgG3 antibodies and IgA are present [9,10].

According to a recent review of almost 200 cohorts [11], adults diagnosed with MOGAD typically present with optic neuritis (ON, approximately 60 %) and transverse myelitis (approximately 20 %), while infratentorial symptoms (4 %), cortical encephalitis and other focal deficits are less common. These symptoms at the onset of the disease are comparable to earlier Caucasian data [12]. It should be noted that acute disseminated encephalomyelitis (ADEM) is less common in adults than in paediatric patients, while TM is more unusual in the latter. Relapsing courses typically present with recurrent ON and are equally prevalent in adults and children when follow-up intervals are extended beyond five years [11]. Since 2023, the diagnosis is made through Banwell's diagnostic criteria, with the detection of the MOG IgG antibody in serum via live-cell assay playing the central role [7]. Antibody testing in the cerebrospinal fluid (CSF) may only occasionally be helpful [13,14].

MOGAD patients frequently demonstrate more favorable outcomes

Abbreviations: AZA, Azathioprine; BBB, Blood-brain barrier; CAR, Chimeric antigen receptor; CNS, Central nervous system; EDSS, Expanded Disability Status Scale; FcRn, Neonatal Fc receptor; IA, Immunoadsorption; IgG/IgA, Immunoglobulin G / A; IL-6, Interleukin-6; IVIg, Intravenous immunoglobulins; IVMP, Intravenous methylprednisolone; MOGAD, Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease; MS, Multiple sclerosis; MMF, Mycophenolate mofetil; NMOSD, Neuromyelitis Optica Spectrum Disease; ON, Optic neuritis; PLEX, Plasmapheresis; RTX, Rituximab; TCZ, Tocilizumab.

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(as measured by Expanded Disability Status Scale (EDSS)), following relapses than patient with NMOSD. Nevertheless, suboptimal recovery is common, underscoring the imperative for expeditious access to therapeutic interventions [15,16]. Nevertheless, relevant unanswered questions remain with regard to the optimal therapeutic management. The timing for the initiation of long-term immunomodulatory therapy remains a subject of controversy and is not universally standardised [11]. Currently, there are no approved treatment options in this area, although clinical trials are underway. The present review aims to provide an overview of the available evidence for the handling of acute attacks and long-term immunomodulatory treatment in patients suffering from MOGAD.

2. Relapses and steroid tapering

The standard treatment for acute attacks of MOGAD is – similar to other autoimmune CNS diseases – primarily high-dose intravenous corticosteroids, mostly methylprednisolone (IVMP, 500 mg - 1 g/day for 3 to 5 days), which show good response rates [17,18]. One key to therapeutic success is undelayed administration to IVMP [19]. Recent data shows that, in a manner analogous to NMOSD, apheresis treatment (AT) with plasmapheresis (PLEX) or immunoadsorption (IA) seems to be highly effective [20]. First-line treatment leads to a higher degree of full remission than second-line AT, especially in conjunction with existing maintenance therapy. Advanced age and delayed initiation of plasma exchange are leading to reduced probability of improvement [20]. Typically, five apheresis cycles are targeted. The selection of procedure (PLEX vs. IA) does not appear to exert any influence [21]. Some authors also report the use of intravenous immunoglobulins (IVIg) [22], especially in children [22,23]. It is essential to initiate treatment for the first attack rapidly (< 5–7 days after symptom onset [19,24]); delaying treatment increases the risk of subsequent relapses and persistent disability [24].

It is widely accepted that the management of acute attacks should be followed by a phase of oral steroids, with a subsequent reduction in dosage ("steroid tapering") [25]. A number of recently published studies have postulated that administration of a dose of 12.5 mg/day or more over a period of at least three months significantly delay the time to first relapse [26,27].

In summary, intravenous corticosteroids appear to be an appropriate treatment of acute attacks for the majority of MOGAD patients. For patients displaying severe clinical symptoms (e.g., transverse myelitis, severe ON), administration of AT could be considered as first-line treatment. Subsequent oral steroid tapering according to the above-mentioned recommendations is obligatory.

3. When to start maintenance therapy?

In contrast to Multiple sclerosis (MS) and NMOSD, MOGAD appears to manifest as a monophasic course of disease in some cases. As a large international survey has shown, this leads to considerable disagreement among experts as to when maintenance therapy should be started [28]. Different approaches and concecutive risk of relapses are displayed in Fig. 1.

It is noteworthy that at least one third of patients do not experience further relapses over follow-up periods up to 5 years [11,29], even in the absence of long-term immunomodulatory therapy. Some studies even describe relapse rates as low as 50 %. However, it should be acknowledged that the follow-up periods in those studies reporting those relapse rates were relatively brief (≤ 24 months). Furthermore, relapses in MOGAD appear to result in a reduced degree of disability when compared to NMOSD [16]. These points prompted a deliberation on the

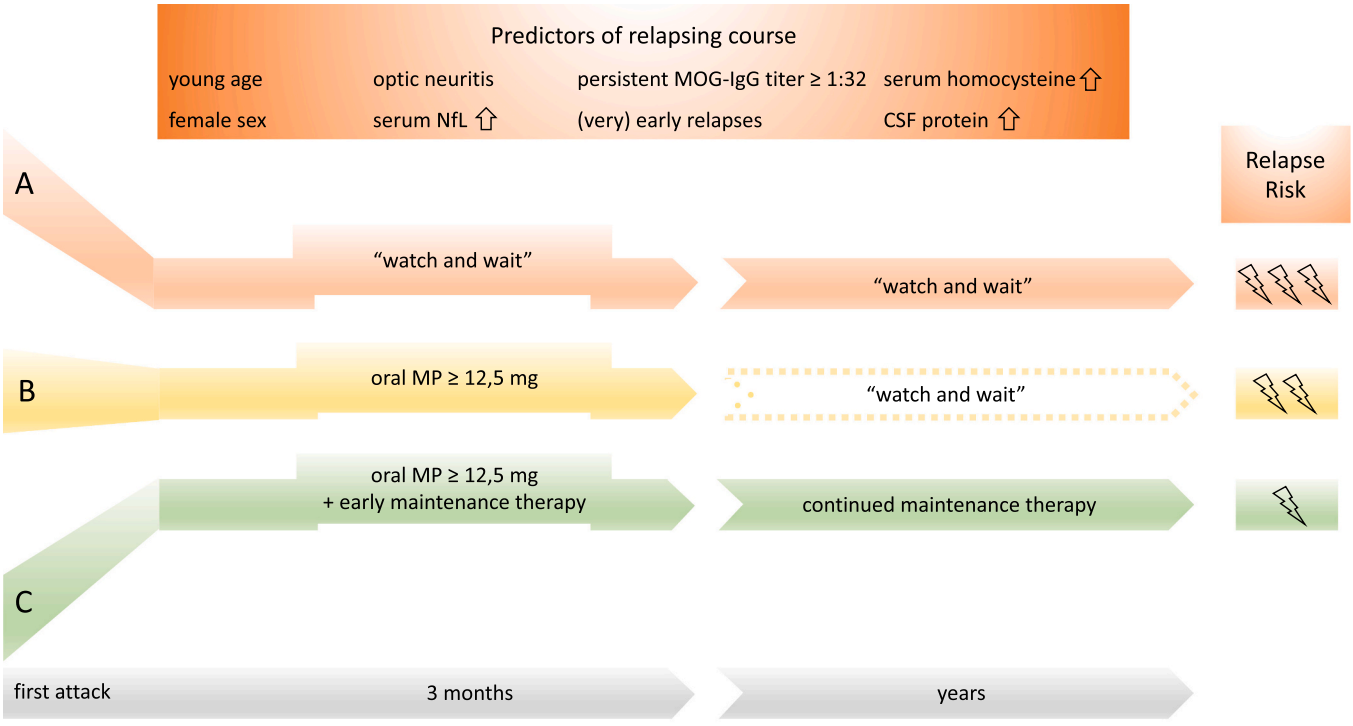

Fig. 1. Estimating relapse risk depending on the different treatment strategies in MOGAD. After initial treatment of acute attacks, different strategies of further therapy are possible. In the absence of immunosuppressive therapy, the relapse risk is at its highest **(A)**. The likelihood of relapsing course is diminished when the initial treatment is followed by a phase of oral steroid tapering (a minimum of 12.5 mg for a period of at least 3 months) **(B)**. The lowest risk of relapse is observed when maintenance treatment is initiated immediately in conjunction with steroid tapering **(C)**. The determination of an individualised treatment strategy should be informed by the consideration of specific risk factors associated with the potential for a relapsing course, as illustrated in the orange box.
IVMP = intravenous methylprednisolone, CSF = cerebrospinal fluid, PLEX = plasmapheresis, IA = immunadsorption, AT = Apheresis treatment, MP = methylprednisolone, NfL = Neurofilament light chain.

initiation of maintenance therapy during the course of the disease, and whether it should be commenced at this juncture. This approach is predicated on the knowledge that early maintenance therapy can significantly reduce the risk of relapse [24,30]; however, concerns have been raised that this may result in unnecessary exposure of patients to immunosuppression. Some authors advocate a more comprehensive approach, recommending the administration of these substances to all patients, on the basis of the purportedly favorable safety profile of the substances [31].

Therefore, the identification of reliable biomarkers is urgently needed - not only to predict disease course, but also to provide practical tools for monitoring, particularly since relapses tend to occur more frequently in the early stages. To date, all described biomarkers for prediction are experimental and have not been validated in independent cohorts. However, with their help, it could be possible to make an initial individual estimation of relapse risk in MOGAD patients. Patients who experience early relapses (within the first year [32]) or very early relapses (within the first 30 days, „polyphasic first attacks"[29]) are particularly vulnerable to developing a long-term relapsing course. The clinical presentation and age at initial diagnosis have been shown to be significant predictors of subsequent relapses. Presence of optic neuritis and a younger age (< 18–40 years) have been identified as prognostically unfavorable factors [33], as has female sex [34]. Nevertheless, it is imperative to acknowledge that advanced age and myelitis as the primary event are correlated with a diminished risk of recurrence, yet an augmented probability of future disability [16].

When looking at soluble biomarkers, the MOG-IgG serostatus is utilized as a prognostic maker: In instances where the antibody is detected on subsequent occasions for more than 6 months or with high serum titer (≥ 1:32), the probability of a relapsing course is increased [35,36]. The same applies to elevated CSF protein at initial diagnosis [29]. However, the prognostic relevance of MOG-IgG serostatus is still a matter of debate, with some authors even recommending against repeated testing [37]. A recently described biomarker that predicts relapsing disease and future disability is furthermore elevated serum homocysteine [38]. Additionally, a subtype with special epitope binding of the MOG-IgG antibody was identified, which was found to be associated with a particularly high risk of relapse [39]. Emerging biomarkers for MS include serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP). In MOGAD, both of these values are elevated at the onset of the disease. A high baseline sNfL value indicates a higher risk of subsequent relapses [40,41], changes in sNfL furthermore seem to correlate positively with change in MOG-IgG titers [42]. Further, more specific biomarkers are emerging (e.g., CD83 [43]).

Overall, treatment decisions currently remain individual. Recently, a Chinese team published a score that predicts the risk of relapse by taking various factors into account, such as age, sex category, use of oral steroids, maintenance therapy and the phenotype of the initial attack [34]. Tools like this and artificial intelligence-supported decision-making aids will help to identify patients at high risk in future.

4. Maintenance therapy

As mentioned above, all substances used in long-term immunosuppressive therapy for MOGAD are **off-label treatments**. There is still no class 1 evidence for any of them, but good data exists on the various drugs. Relapses are reported under all types of these. An overview of the evidence for each substance is provided below. Additionally, Fig. 2 summarises different treatment strategies in the pathophysiology of MOGAD.

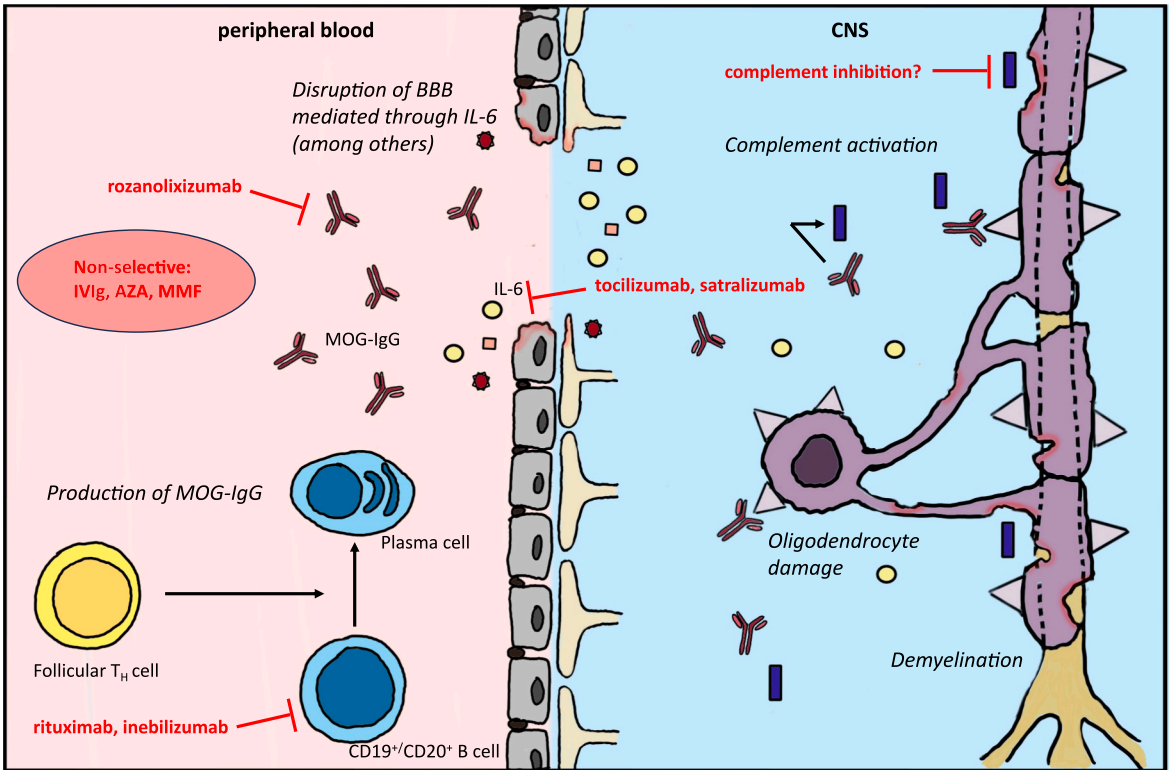

Fig. 2. Different treatment strategies based on the pathophysiology in MOGAD. **Rituximab** and **inebilizumab** intend to reduce production of MOG-IgG by depleting of CD20+ and CD19+ B cells, respectively. **Rozanolixizumab** is blocking the neonatal Fc-receptor, leading to reduced antibody levels via altered IgG recycling. **Tocilizumab** and **satralizumab** are antagonists at the IL-6 receptor, reducing damage of BBB. **IVIg, AZA** and **MMF** are non-selective immunosuppressants.
IVIg = intravenous immunoglobulins, AZA = azathioprine, MMF = mycophenolate mofetil, IL-6 = interleukin-6, CNS = central nervous system, BBB = blood brain barrier.

4.1. Rituximab and inebilizumab

The anti-CD20 monoclonal antibody rituximab (RTX), administered intravenously every six months, works by depleting B cells in the peripheral blood, thereby is intended to reduce anti-MOG IgG, even though plasma cells are not depleted. Relapse-free survival rates of around 55 % can be achieved when treating MOGAD [44–46]. Most relapses occur within the first 12 weeks of treatment [17]. Compared with NMOSD, its effectiveness in MOGAD appears to be somewhat lower [47]. As with B cell depletion therapy in general, major safety concerns include infusion reactions and increased susceptibility to infections, mainly due to lymphopenia and hypogammaglobulinemia [47]. Of note, inebilizumab, an anti-CD19 antibody delivering a broader B cell depletion than RTX and approved for AQP4-IgG+ NMOSD, showed clinical efficacy in a small group of MOGAD patients recruited in N-MOmentum, the corresponding phase 3 trial [48,49]. This observation was later confirmed in an independent real-world study [50] and may indicate that deep B cell depletion beyond RTX [51,52] may have a therapeutic role in MOGAD as well.

4.2. Azathioprine

Azathioprine (AZA, 2–3 mg/kg/day) is utilized globally for the long-term management of MOGAD. Interference with purine metabolism has been demonstrated to result in a reduction in the annual relapse rate (ARR), with observations indicating a shift from >1 to 0.25 [53]. Relapse-free status can be achieved in up to 70 % of patients [45,54]. A considerable number of relapses have been observed to occur prior to the anticipated commencement of the pharmaceutical agent's efficacy (within the initial 3–6 months [17,18]). Adverse events include nausea, fatigue, hepatotoxicity and bone marrow suppression. Furthermore, there is a significant increase in the risk of malignancy (especially skin camcer) after long-term treatment, with a factor of 4.4 observed after more than 10 years of therapy.

4.3. Mycophenolate mofetil

Another conventional immunosuppressant in treatment is the lymphocyte proliferation inhibitor mycophenolate mofetil (MMF, 1–2 g/day). Its efficacy is comparable to that of the previously mentioned substances, with a relapse-free rate of up to 73 % and an ARR reduction of more than 1.25 [18,54]. The duration of action after the start of therapy is 8–12 weeks. Overall tolerability is good, most events are gastrointestinal side effects, infection and hematological changes.

4.4. Intravenous immunoglobulins

The majority of extended data on IVIg in MOGAD therapy is derived from paediatric cohorts, thus precluding a comprehensive evaluation. However, the results observed in adult patients appear to be analogous, exhibiting a high level of efficacy and good tolerability (relapse-free rate > 75 %, ARR reduction >1.75) [18,54–56]. Furthermore, a rapid onset of action is to be expected. Therefore, as previously stated, IVIg may also be used in the setting of acute attacks [22]. It is imperative to consider financial constraints and accessibility issues, particularly in low-income settings, that are associated with this treatment.

4.5. Tocilizumab

Recent studies have demonstrated the excellent efficacy of the IL-6 inhibitor tocilizumab (TCZ) in the long-term treatment of MOGAD. The majority of published cases were treated by intravenous administration (8 mg/kg body weight every four weeks), while reliable data on subcutaneous administration are not available for MOGAD. Reductions of the median ARR to 0 are described, with a relapse-free rate of >75 %. Severe adverse events were not reported [57]. For the latter study, it is important to note that all described subjects were patients with drug-resistant conditions, with the majority having failed on rituximab before. These patients exhibited a consistent reduction in both clinical and morphological disease activity following the initiation of treatment with TCZ [57,58]. The promising data on TCZ forms the basis for a current Phase 3 trial investigating the use of satralizumab in MOGAD (see below).

4.6. Direct comparisons

There is a single open comparative study between RTX and AZA, which showed comparable efficacy of the two substances [45]. To date, there have been no other controlled comparative studies conducted between the individual substances mentioned above. Two substantial meta-analyses comprising a total of more than 41 included studies have described that IVIg is significantly more efficacious and better tolerated than RTX, AZA and MMF [54,59]. The same applies to TCZ, although no large numbers of cases are available at present [54]. Furthermore, IVIg and TCZ seem to have a significantly faster onset of action than the other substances.

4.7. Supportive pharmacological treatments

The role of vitamin D in the pathogenesis and treatment of MS has been studied extensively. While low serum levels are thought to increase the risk of developing MS and of experiencing higher disease activity, therapeutic effectiveness is controversial, but promising [60–62]. The underlying pathophysiological mechanisms are various: It has been demonstrated that vitamin D induces pleiotropic immune regulations, decreasing differentiation of effector T and B cells, promoting regulatory subsets, modulating innate immune cells, and reducing immune cell trafficking at the BBB and microglial and astrocytic activation [62–64]. Data on vitamin D in MOGAD is much more rare, with some small studies reporting low serum levels in MOGAD patients and in ON patients in general [65]. When considering these facts, and given the generally good tolerance of vitamin D supplementation, it may be reasonable to offer vitamin D supplementation to patients with MOGAD in cases of apparent deficiency.

4.8. Treatments to avoid

There is evidence to suggest that various agents employed in the treatment of MS (including beta interferons, teriflunomide, glatiramer acetate, and alemtuzumab) may demonstrate no efficacy, or even negative efficacy, in the treatment of MOGAD. It appears that the conventional immunosuppressants methotrexate and cyclophosphamide are also ineffective and should be avoided [17,59,66,67]. However, it is noteworthy that the number of cases analysed for all substances mentioned was very small.

4.9. Special situations

4.9.1. Pregnancy

There is a paucity of data on the disease activity of MOGAD in pregnant women. These findings indicate that the relapse rate decreases significantly during pregnancy, with a distinct renewed increase observed in the post-partum period [68,69]. None of the aforementioned medications are approved for use during pregnancy, with the exception of IVIg. In most cases, maintenance therapy should be paused; however, in individual cases or with very high disease activity, continuation with oral steroids. Based on large case series in rheumatology [70], IVIg, AZA, TCZ or RTX may be considered, but MMF as a confirmed teratogen associated with an increased rate of spontaneous abortion in general must not be used in MOGAD.

4.9.2. Comorbidities

Autoimmune comorbidities are significantly less prevalent in MOGAD than in NMOSD [71]. The most common is anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, followed by autoimmune thyroiditis. Double-positivity of MOG-IgG and AQP4-IgG have been reported. These patients appear to be more likely to experience a refractory course [72]. RTX is considered an appropriate therapy for patients with NMDAR encephalitis/MOGAD overlap. The same is likely to apply to other autoantibody-mediated comorbidities.

When looking at non-autoimmune comorbidities, special attention is warranted regarding obesity. Although larger studies on this topic are still pending, individual studies indicate an association between elevated body mass index (> 30 kg/m^2) and the development of MOGAD [73].

4.10. Future / rescue options

Three phase 3 trials are currently underway, with the objective of obtaining class 1 evidence for the treatment of MOGAD. AZA (*MOGwAI* study, *NCT05349006*), the blocker of the neonatal Fc receptor (FcRn), rozanolixizumab (*COS-MOG* study, *NCT05063162*) and the IL-6 receptor antagonist satralizumab (*METEROID* study, *NCT05271409*) are each being tested against placebo. The endpoint in each trial is defined as the time to first relapse. In view of the clinical benefits demonstrated by TCZ in MOGAD patients, it is reasonable to hypothesize that satralizumab (with an even higher binding affinity to the IL-6 receptor) will show at least comparable level of efficacy. Rozanolixizumab is currently employed in the treatment of seropositive myasthenia gravis, with outcomes that have been found to be highly satisfactory; the reduction of autoantibodies is achieved through the process of FcRn blockade. However, it should be noted that *COS-MOG* and *METEROID* only include patients with confirmed relapsing disease.

In the context of refractory disease courses, positive case reports for the use of autologous haematopoietic stem cell transplantation [74] and CD19-directed chimeric antigen receptor (CAR) T cells [75] exist. In addition, preclinical research regarding induction of immune tolerance in MOGAD is ongoing [76]. At the present time, these rescue treatments are reserved for individual cases.

4.11. Treatment duration

There is an absence of evidence-based recommendations regarding the duration of maintenance therapy for MOGAD. In the context of paediatric MOGAD, it is recommended that therapy be discontinued following a period of two years with absence of relapses [23]. The few available data on treatment discontinuation in adults suggests that the likelihood of further relapses seems to decrease following several years of immunotherapy (i.e. 2–3 years) without clinical instability [25,30]. Larger, controlled studies are also needed here in the future.

Table 1 provides a synopsis of the relevant current and future drugs used for maintenance therapy in MOGAD.

5. Conclusion and “take-home” messages

Acute attacks in MOGAD are frequently effectively managed with IVMP and AT. Subsequent to this, initiation of oral steroid tapering at a dose of 12.5 mg/day over a period exceeding three months seems reasonable. Relapse rates reported in studies differ depending on the length of follow-up period and individual risk factors (see below). Early maintenance therapy leads to a reduced risk of relapse and should be initiated after the first event if unfavorable prognostic factors are present. These include optic neuritis as a clinical phenotype, young age, female gender, early relapses, but also biomarkers such as high CSF protein, high serum homocysteine and persistently high MOG-IgG titers. Positive data on maintenance therapy is available for the following substances: RTX, AZA, MMF, IVIg and TCZ. IVIg and TCZ appear to be particularly efficacious, with TCZ demonstrating particular promise in the treatment of refractory patients. Randomised controlled trials are

Table 1
Overview of relevant current and future drugs used for maintenance therapy in MOGAD.

Immunotherapy	Mode of action	Application route	Dosage	Main side effects
Rituximab	B cell depletion (anti-CD20)	i.v.	500 mg – 1000 mg semiannually	infusion reactions, infections
Inebilizumab	B cell depletion (anti-CD19)	i.v.	300 mg semiannually	infusion reactions, infections
Azathioprine	interference with purine metabolism	p.o.	2–3 mg/kg/day	nausea, fatigue, hepatotoxicity, bone marrow suppression
Mycophenolate mofetil	lymphocyte proliferation inhibition	p.o.	1–2 g/day	gastrointestinal, infections, hematological changes
Intravenous immunoglobulins	pleiotropic	i.v.	0.4–2 g/kg every 4 weeks	infusion reactions, kidney failure, thrombosis
Tocilizumab	IL-6 inhibition	i.v.	8 mg/kg	Infections, nausea, liver damage
INVESTIGATIONAL DRUGS OF CURRENT RCTs				
Azathioprine (*MOGwAI*)	see above	see above	see above	see above
Rozanolixizumab (*COS-MOG*)	FcRn blockade	s.c.	body weight-adapted 1/week for 6 weeks, afterwards individual cycles	headache, fever, diarrhoea
Satralizumab (*METEROID*)	IL-6 inhibition	s.c.	120 mg every 4 weeks	headache, injection reactions, leucopenia

i.v. = intravenous; p.o. = per os; s.c. = subcutaneous; RCTs = randomised controlled trials; IL = interleukin; g = gram; mg = milligram; kg = kilogram.

currently being conducted for various drugs with the objective of achieving Class 1 evidence in pharmacological treatment of relapsing MOGAD. Due to the uncertain disease course compared with NMOSD or MS, therapeutic efforts must be accompanied by intensive biomarker analyses to both predict future progression and enable practical monitoring in clinical practice.

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Declaration of competing interest

JS received travel support and personal fees from Alexion, Neuraxpharm and Novartis. M.P. reports no conflicts of interest related to this study. He has received honoraria for lecturing and travel expenses for attending meetings from Alexion, ArgenX, Bayer Health Care, Biogen, Hexal, Merck Serono, Neuraxpharm, Novartis, Roche, Sanofi-Aventis, Takeda, and Teva. His research is funded by ArgenX, Biogen, Hexal, and Novartis, all outside the scope of this study. S.G.M. reports no conflicts of interest related to this study. He has received honoraria for lecturing and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, ArgenX, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Neuraxpharm, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS, and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology, and by Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche, and Teva, all outside the scope of this study. OA reports grants from the German Ministry of Education and Research (BMBF) and the German Research Foundation (DFG); and travel support and personal fees from Alexion, Almirall, Amgen, AstraZeneca, Roche, and Sanofi. He is co-coordinator of the German Neuromyelitis optica study group (NEMOS) and member of the associated board of FV NEMOS e.V.. SG received Research funding from patient groups, BMBF, DFG (SPP2177 Radiomics), UM Mainz, Abbott, Boston Scientific, Böhringer Foundation, Magventure, National MS Society, Precisis, Innovationsfond GBA (01NVF22107, INSPIRE – PNRM+) and lectures fees from Abbott, Abbvie, Bial, BVDN, IPSEN, Stada, UCB. The other authors report no conflicts of interest.

Data availability

No data was used for the research described in the article.

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