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EDITORIAL

Emerging drugs for the treatment of adult MOG-IgG-associated diseases

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1. Introduction

Myelin oligodendrocyte glycoprotein (MOG), a member of the immunoglobulin (Ig) superfamily, is a myelin protein expressed at the outermost lamellae of myelin sheaths and oligodendrocytes (OGD) membranes [1,2]. Since MOG expression starts later than other myelin proteins, it is considered a marker of OGD maturation and myelin compaction. Furthermore, its location in the surface of OGD makes it extremely immunogenic and brings antibody binding susceptibility [1,2].

Although in the past anti-MOG-IgG antibodies were related to multiple sclerosis (MS) pathogenesis and proposed as a biomarker of the disease, it was not possible to reproduce this association in subsequent studies, and was considered nonspecific. So far, the presence of serum MOG-IgG can distinguish patients with MOG-associated diseases (MOGAD) from MS and aquaporin-4(AQP4)-IgG-positive neuromyelitis optica spectrum disorders (NMOSD), evolving into a new central nervous system (CNS) inflammatory disease [1–3]. However, MOG-IgG have been found in the serum of up to 42% of AQP4-IgG-negative NMOSD patients [4]. The recent development of a reproducible cell-based assay (CBA), considered as the gold standard method for detecting MOG-IgG has improved the ability to correctly identify this entity [3]. Extensive studies in experimental autoimmune encephalomyelitis (EAE; an animal model of MS) models have shown that only antibodies that recognize folded MOG protein are pathogenic, whereas antibodies that solely bind to denatured protein or short synthetic peptides fail to induce demyelination [5]. Thus, CBA enable screening of native-folded MOG protein as an assay substrate [6]. Although titers observed varied significantly both intra- and interindividual, a serum dilution > 1:160 was selected to identify people with high-titers of MOG-IgG antibodies [7]. However, the use of MOG-IgG titers for treatment planning is under debate. Using the CBA technique with cells transfected with full-length human MOG (FL-MOG), it is possible to identify positivity in a few healthy individuals and in MS patients, even at relatively high serum dilutions (up to 1: 640). Waters and collaborators have shown that the use of cells transfected with C-terminal truncation of the MOG antigen reduces assay sensitivity, and that many of the low positive antibodies found to bind to FL-MOG result from cross-reactivity of the anti-human IgG (H + L) secondary antibody with IgM [3]. Moreover, flow cytometry data demonstrated an unspecific binding to the surface of MOG transfected cells at low levels in healthy subjects and patients with different diseases, that is detected by anti-human IgG (H + L) or IgM antibodies. The specificity of the test is substantially increased when an anti-human IgG1-specific secondary antibody is used in both flow cytometry and CBA instead of anti-IgG (H + L). Thus, IgG1 assay identifies not only the patients above the cutoff with the anti-IgG (H + L) secondary antibody, but also disease-relevant antibodies that fall below this cutoff [3]. Apart for the importance in the diagnosis, MOG-IgG also imply predictive capability in the course of the disease and further treatment.

Prevalence and incidence of MOGAD is higher in children than in adult patients [1,2]. The clinical phenotypes can be age dependent with acute disseminated encephalomyelitis (ADEM) and ADEM-like as the predominant presentation in young children, while optic neuritis (ON) and transverse myelitis (TM) is more common in children older than 11 years old and adults [1,2,8,9]. In addition, overlap syndromes with MOG-IgG and NMDAR antibodies have been described [8,9]. Classically, MOG-IgG were associated with fewer relapse rates and better functional outcomes than those with AQP4-IgG-positive NMOSD, particularly in pediatric MOGAD patients. However, longitudinal studies have reported relapses in up to 83% of adult MOGAD patients [1,2,10–12] and they present higher risk of relapse and worse functional recovery [13,14] compared to children [14].

Considering that MOGAD is an antibody-mediated inflammatory demyelinating disorder of the CNS that may have a relapsing course, neurologists should consider ongoing treatment with immunosuppressant drugs to prevent future disability. Although there are no evidence-based guidelines for MOGAD treatment, the prognosis in each particular case is uncertain and variable, depending on demographics, clinical and paraclinical factors [1,2]. In this context, recurrent course was more frequently reported in patients with higher MOG-IgG titers at onset, particularly during the first months of the disease [13], as well as in patients who remain seropositive despite treatment. By contrast, transient low MOG-IgG titers or

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seroconversion to negativity during early disease course reliably predict a monophasic course (negative predictive value of 90% approximately) [10,13–15]. Clearly, this is another current point of debate. Indeed, other large study on 79 adult MOGAD patients could not confirm this observation as high MOG-IgG titers at onset were associated with a more severe presentation, but did not predict the future disease course [16]. Likewise, severe relapses with poor recovery should also be taken into account, as disability in MOGAD seems to be relapse-dependent [1]. Thus, severe disability was reported in 47% of adult MOGAD patients [13]. Importantly, >70% of this disability results from the onset attack [13].

The MOGAD treatment is largely adopted from experience in NMOSD and it is far from clear. To date, there are no approved drugs for long-term relapse prevention in adult MOGAD patients, so any prescription is done off-label. In clinical practice, decision-making to initial long-term relapse prevention treatment is based on the risk of further relapses and its potential recovery, as well as MOG-IgG persistency over time. In this regard, the most commonly used treatments for adult MOGAD patients include low-dose oral steroids, rituximab, human intravenous (IV) IgG, azathioprine (AZA) and mycophenolate mofetil (MMF) (Table 1) [1,2]. Similar to AQP4-IgG-positive NMOSD, MS treatments have not demonstrated usefulness in preventing relapses in MOGAD [1,2,8,17].

Efficacy of oral steroids was reported recently. Relapses were frequently observed with doses < 20 mg prednisone per day in adults and higher risk of relapses was observed in patients with a duration less than 3 months of treatment when compared with those patients treated for a longer time [12]. Patients whose treatment last for less than 3 months are twice as likely to relapse as those who are treated for a longer time. MOGAD patients on oral steroids in combination with immunosuppressive drugs experienced lower relapses as compared to the group treated with immunosuppressants only (5% vs. 38%; p = 0.016) [12]. In another study [18], when oral steroid dose was decreased (5–20 mg/day) or stopped within 30 days, 59% of patients experienced a relapse.

Either AZA (2–3 mg/kg/day divided into 2–3 doses) or MMF (1500–3000 mg/day divided into 2 doses) alone or in combination with oral steroids demonstrated to be effective and safe in adult MOGAD patients. AZA was evaluated in 17 articles (n = 117) from a systematic revision [19] documenting a reduction of both the mean/median of annualized relapse rate (ARR) and stabilization or improvement of the Expanded Disability Status Scale (EDSS) after AZA start [20]. The time from AZA start to the first relapse was reported with a median of 6 months (range: 3–9 months) [20]. MMF was reported to be effective in adult MOGAD patients (n = 96) in a systematic revision [19] due to a reduction of ARR and stabilization or slightly improvement in EDSS. A recent published prospective study [21] (n = 79) has shown a reduction of MOGAD-related relapse risk in patients on MMF, particularly in whose had isolated ON or high MOG-IgG titers. After a median of 400 days of follow-up, MMF treatment reduced the risk of relapse in 86% (HR = 0.14, [95%CI 0.05 to 0.45], p = 0.001) [21]. Failure and intolerance were the most frequent causes for AZA and MMF discontinuation. Of note, AZA might be used during pregnancy considering a risk-benefit balance, while MMF is contraindicated in pregnancy, so family planning may be relevant [1,2].

Regarding rituximab, some studies and one systematic revision [19] (n = 253 adult MOGAD) were published recently. Similar to AQP4-ab-positive NMOSD patients, new relapses within the few weeks after the first rituximab infusion were observed in about 30% of MOGAD patients despite a correct biological effect, with a median time from the most recent infusion to the first relapse of 2.6 (range: 0.6–5.8) months [22]. The median EDSS declined significantly from 2 (0–6.5) to 1.75 (0–4) [22]. Additionally, other study (n = 26) [12] reported a decreased ARR (from 1.08 [± 0.98] to 0.43 [± 0.89], p = 0.012) and EDSS (from 3.0 [2.0–3.5] to 2.0 [1.0–3.0], p = 0.001) after rituximab start. In another study [23] (n = 71; 56% treated naïve) the reduction in the EDSS median (from 1.84 [0.82–4.70] to 0.00 [0.00–1.28], p < 0.001) and relapse rates was observed in 42% of adults MOGAD patients on RTX (median follow-up time on RTX: 12.7 [6.1–24.4] months). Notably, MOG-specific B cells were only detected in about 60% of these patients, indicating that MOG-specific B cells are not linked to levels of serum MOG-Abs. Therefore, whether anti–MOG-positive patients are good candidates for B cell depleting therapy, this needs to be assessed in future studies [24].Tocilizumab (interleukin-6 blockade) was used with varied effectivity in some patients with RTX-refractory MOGAD [19].

Table 1. Most relevant case series including adult patients with MOG-IgG associated diseases.

Drug	Author	Study design	Number of adults treated	Follow up in years (median)	ARR post treatment (range or SD) or relapse rate reduction
Prednisone	Ramanathan et al[12]	Retrospective	20*	5	0 (0–1.57)
Azathioprine	Jarius et al[25]	Retrospective	18	6.25	0.99 (0–6)
	Chen et al[17]	Retrospective	14	1.8	0.43 (0–3.4)
	Cobo-calvo et al[20]	Retrospective	19	2.1	0.43 (0.79)
Mycophenolate mofetil	Cobo-Calvo et al[20]	Retrospective	12	1.7	0.23 (0.60)
	Chen et al[17]	Retrospective	15	1.1	0.4 (0–5.2)
	Li et al[21]	Retrospective	33	1.3	Reduced the relapse risk (HR = 0.11)
Rituximab	Cobo-Calvo et al[20]	Retrospective	30	1.7	0.43 (0.89)
	Chen et al[17]	Retrospective	30	1.2	0.59 (0–6.8)
	Whittam et al[23]	Retrospective	71	1.1	0 (0.00–1.25)
IVIG	Chen et al[17]	Retrospective	5	1.2	0.1 (0–0.2)

*It is not assessed how many adult patients were treated with steroids.

Finally, IVIgG response was analyzed after an acute relapse in a large European retrospective cohort of MOG-IgG-positive patients with ON and/or TM [25]. Fifty percent of patients experienced complete (or almost complete) recovery as measured by visual acuity and EDSS and partial recovery was observed in 44%[25]. A limitation can be its high cost, particularly in lower-income countries. Notably, the efficacy could not be as proper as that for pediatric patients. In another study [17] evaluating small groups of patients treated with different steroids-sparing maintenance strategies, IVIgG demonstrated to have the lowest ARR as compared to AZA, MMF and rituximab. In this line, in adults MOGAD patients on long-term treatment, the proportion of patients with relapse was 59% for azathioprine, 73% for MMF, 62% for rituximab and 20% for IVIgG. The IVIgG group contained the greatest proportion of children with only 5 adults, suggesting that adults and children may need to be treated differently [12]. Future studies are needed to determine whether IVIgG is effective in adult MOGAD patients or not.

In the NMOmetum trial (Phase III), comparing NMOSD (positive and negative) on inebelizumab vs. placebo, 7 adult MOGAD patients were enrolled, but separate outcomes for MOGAD patients were not specifically reported [26].

2. Expert opinion

MOG-IgG testing by CBA is recommended in patients who present with the clinical and/or radiological phenotypes suggestive of MOGAD, in order to avoid MS or NMOSD misdiagnosis particularly in those with overlapping syndromes, and help to identify patients who are most likely to experience a relapse [1,2]. Treatment for adult MOGAD patients is still based on clinical experience and observational studies (Class IV evidence), since there are no randomized controlled trials. Thus, trials with specific targeted drugs are needed immediately.

Studies from different cohorts strongly argue against the previous concept that MOGAD is a mild and usually monophasic disease. However, compared to pediatric, adult MOGAD patients may have a higher risk of relapses and a worse functional recovery [13,16] as well as a shorter median time to second attack, supporting the use of long-term relapse prevention treatments in adult patients with MOG-IgG-positive ON and/or TM. However, this continues to be a matter of debate as other large studies could not confirm this observation. Considering that adults MOGAD patients can have a monophasic or relapsing course and MOG-IgG may transiently be positive during an initial relapse but negative during follow-up, therapeutic decision-making is difficult in clinical practice. Although a concern of unnecessary long-term immunosuppression for potentially monophasic disease exist, long-term preventive treatment for adult patients with a relapsing course or with significant disability from a prior relapse is typically recommended to prevent further disease activity, in line with our standard clinical practice.

Decision to start a preventive longer-lasting immunosuppressive treatment should be made according to individual cases, considering: 1) severity and recovery from the acute attack (particularly the first one), 2) Relapse recurrence, and 3) MOG-IgG titers and its persistency. Therefore, results on MOG-IgG status should include not only qualitative results (e.g. negative or positive), but also quantitative results measured as serum dilution or FACS binding ratio, when possible. Optimal duration of the initial immunosuppressant treatment after the first relapse also remains unclear. However, we recommend oral steroids for at least 6 months after the initial relapse, as the risk of relapse is higher during the first months of disease onset. If MOG-IgG become negative at 6 months, treatment could be tapered and discontinued. As persistent MOG-IgG over time was associated to relapse in adult MOGAD patients [13], if MOG-IgG persist positive at 6 months, oral steroids can be maintained for 12 months, when they should be retested. If MOG-IgG become negative at 12 months and there are no relapses, initial immunosuppressant treatment might be slowly discontinued. Conversely, either AZA or MMF can be used if new relapses (recurrent MOGAD) and/or MOG-IgG persist at 12-months, or adverse effects and/or intolerance to oral steroids are observed. Due to that full biologic effect of AZA and MMF are observed after at least 3–6 months of treatment, it is recommended to use steroids during this period (around 20 mg of prednisone daily) as a bridging therapy until the therapeutic effect of AZA and MMF is achieved [27]. Induction with IVIgG followed by IVIgG monthly is another option that proved to be effective. Of note, rituximab seems to be less effective in MOGAD than in AQP4-ab-positive NMOSD [23].

Further researches in well-defined cohorts of adults MOGAD patients including current use of off-label drugs as well as other emerging drugs such as inhibitors of the neonatal Fc receptor (e.g. rozalixizumab and efgartigimod), which can induce the clearance of pathogenic IgG autoantibodies, or Bruton's tyrosine kinase inhibitors, are needed in order to optimize short- and long-term therapeutic decision-making in patients with MOGAD.

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