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E.U. paediatric MOG consortium consensus: Part 5 – Treatment of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders

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ABSTRACT

In recent years, the understanding about the different clinical phenotypes, diagnostic and prognostic factors of myelin oligodendrocyte glycoprotein-antibody-associated disorders (MOGAD) has significantly increased. However, there is still lack of evidence-based treatment protocols for acute attacks and children with a relapsing course of the disease. Currently used acute and maintenance treatment regimens are derived from other demyelinating central nervous system diseases and are mostly centre-specific. Therefore, this part of the Paediatric European Collaborative Consensus attempts to provide recommendations for acute and maintenance therapy based on clinical experience and evidence available from mainly retrospective studies. In the acute attack, intravenous methylprednisolone (IVMP) leads to a favourable outcome in the majority of patients and can be followed by tapering of oral steroids up to a maximum of three months to maintain the benefit of acute treatment by suppressing disease activity. Intravenous immunoglobulins (IVIG) and plasmapheresis constitute second-line therapies in case of

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IVIG
Corticosteroids

insufficient response to IVMP. After a first relapse, maintenance treatment should be started in order to prevent further relapses and the possibility of permanent sequelae. Four first-line therapies consisting of rituximab (RTX), azathioprine, mycophenolate mofetil or monthly IVIG have been identified by the consensus group. In case of further relapses despite maintenance treatment, the consensus group recommends treatment escalation with RTX or IVIG, followed by combining those two, and ultimately adding maintenance oral steroids. Many open questions remain which need to be addressed in further international prospective evaluation of MOGAD treatment. This international collaboration is essential to expand the state of current knowledge.

Contents

Abbreviations

AQP4-ab	aquaporin-4 antibody
AZA	azathioprine
DMT	disease modifying therapy
IVIG	intravenous immunoglobulins
IVMP	intravenous methylprednisolone
MMF	mycophenolate mofetil
MOG-ab	myelin oligodendrocyte glycoprotein antibody
MOGAD	MOG-ab-associated disorders
NMOSD	neuromyelitis optica spectrum disorders
ON	optic neuritis
PLEX	plasma exchange
RTX	rituximab
SCIG	subcutaneous immunoglobulins
TM	transverse myelitis

1. Introduction

Myelin oligodendrocyte glycoprotein antibodies (MOG-abs) have consistently been identified in a variety of demyelinating syndromes predominantly in children. MOG-ab-associated disorders (MOGAD) encompass optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), and relapsing forms, such as multiphasic disseminated encephalomyelitis, ADEM followed by one or more ON episode(s) (ADEM-ON), and relapsing ON [1–7]. More recently, the disease spectrum has been expanded with phenotypes such as autoimmune encephalitis and leukodystrophy-like presentations [8,9,10]. Initially, MOGAD was thought to be associated with a favourable outcome and monophasic disease course [11,12]. Subsequently, reports of MOG-ab-positive children with frequent relapses and sequelae in long-term outcome emerged, raising the demand for effective maintenance therapy in this subgroup of patients [2,6,13]. Prior to the detection of MOG-abs, patients with relapsing MOGAD were included under the umbrella of other acquired demyelinating syndromes (ADS) such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) with treatment strategies derived from these diseases. However, the wide disease spectrum of MOGAD with important clinical and biological differences compared to MS and NMOSD indicates that it is a separate disease entity, which should be treated differently [8]. To date, there is no formal consensus guideline for treatment in paediatric MOGAD and current strategies are largely centre-specific. Moreover, in a recent

international survey of adult and paediatric neurologists with expertise in MOGAD, the current treatment of MOGAD was identified to be highly variable, indicating a need for consensus-based treatment guidelines, while awaiting definitive clinical trials [14]. This review provides an overview of the current literature regarding acute and maintenance treatment in MOGAD and concludes with the Paediatric European Collaborative Expert Consensus recommendation for acute and maintenance treatment in paediatric MOGAD.

2. Acute treatment: efficacy and side effects

Although the acute treatment appears to have no effect on the following disease course in MOGAD [9,15], efficient treatment in the acute phase is mandatory in order to prevent residual symptoms in the long-term [3,9,16, 17]. In recent cohort studies regarding children with ADS and MOG-abs, acute treatment protocols included intravenous methylprednisolone (IVMP), with or without oral prednisone taper, intravenous immunoglobulins (IVIG) and plasma exchange (PLEX) [1,3,9,15,18].

2.1. Intravenous methylprednisolone (IVMP)

The vast majority of paediatric MOGAD patients were treated with IVMP at acute presentation (first episode or relapse), with dosages between 20 and 30 mg/kg/day over 3–5 days [1,3,9,15,18]. Short-term high-dose steroids are associated with mainly mild side effects, including hyperglycemia, electrolyte abnormalities, hypertension or neuropsychological alterations [19]. Besides, pulsed high-dose steroids during a short period of time have lower rates of serious side effects than long-term daily oral use of corticosteroids [20,21].

The treatment response of the acute phase has been analysed in a large retrospective cohort with primarily adult NMOSD patients with MOG-abs: in 50% of patients, IVMP treatment was followed by complete or almost complete recovery measured by visual acuity (VA) and Expanded Disability Status Scale (EDSS), and in 44% by partial recovery [22]. Similar effects were observed in paediatric MOGAD [3,9]. However, only temporary improvement with following relapse (defined by the consensus group as a new clinical episode accompanied by radiological evidence depending on the subtype of MOGAD, appearing at least one month subsequently to the last acute attack) or “flare-up” (defined by the consensus group as re-occurrence of symptoms within one month after start of acute treatment and not meeting definition of a relapse) were also reported [3,22]. In a multicentre retrospective cohort with relapsing MOGAD patients in half of all children a high risk of relapse was observed (1) at oral prednisone doses <0.5 mg/kg/day (2), within the first two months after IVMP pulse or (3) in cases with rapid oral prednisone taper (mean 1.5 months in relapsing vs. 5 months in monophasic patients) [23]. Reduction of relapse risk with slow steroid tapering, up to six months, was also reported in a further study which prospectively analysed 42 MOG-ab-positive patients (13 children and 29 adults; 24/42 relapsing disease course) [24]. However, these findings should be interpreted with caution and probably only in regard to the short-term risk of relapse, as the majority of patients included in these studies had a relapsing disease course, and therefore these findings may not account for the overall long-term risk of relapse. Due to limited data regarding oral steroid tapering with studies describing heterogeneous prednisone doses and duration [23,24], the effectiveness in relapse prevention remains uncertain.

Interestingly, IVMP seems to have no or only partial effect in selected patients, in whom treatment escalation via IVIG or PLEX was necessary [3,9,18,22,25]. However, timing issues, differences in MOG-abs titres, the dosage of IVMP given, and previous or concomitant treatments might play a role [22]. Therefore, in case of insufficient response to IVMP, treatment should be escalated to IVIG or PLEX, as treatment failure can lead to rapid accumulation of disability [3,9,18,22,23].

2.2. Intravenous immunoglobulins (IVIG)

The immunomodulatory and anti-inflammatory effects of high dose IVIG explain the widespread use of IVIG in diverse inflammatory disorders [26–28]. Overall, IVIG has a favourable side effect profile and is generally well tolerated, also in paediatric patients [29], although patients can experience e.g. headache, nausea, arthralgia and/or myalgia [30].

Application of IVIG in the acute phase after or in addition to IVMP has been described and associated with good recovery in MOGAD [1,3,9,22]. IVIG is usually administered over a course of 1–5 days with total dosage of 1–2 g/kg (not exceeding 1 g/kg/day). Evidence from other autoimmune diseases pleads for prolonged IVIG treatment (2 vs. 5 days), thereby reducing the risk of “flare-ups”, e.g. in paediatric Guillain-Barre syndrome patients [31]. Efficiency of IVIG in comparison to IVMP or PLEX in the acute phase of MOGAD has not been analysed in detail yet, however, IVIG has fewer side effects compared to PLEX.

2.3. Plasma exchange (PLEX)

The therapeutic objective of PLEX is to reduce the circulating levels of pathological molecules to stop the disease process [32]. Side-effects include disturbances of coagulation, vasovagal episodes, fluid overload or under-replacement, allergic or anaphylactic reactions due to plasma infusion, and catheter-associated infections [33]. The average number of PLEX cycles in patients with autoimmune encephalitis was 6.3 [34], which is in line with the five cycles in a retrospective multicentre study of MOG-ab-positive patients with TM and/or ON [22]. In adults with MOGAD, 3–5 cycles of PLEX are recommended [35].

PLEX constitutes an established treatment escalation during the acute phase in adult but also in paediatric MOGAD patients. Most often, PLEX is administered subsequently or in addition to IVMP [3,9,23]. In a retrospective multicentre study with 50 MOG-ab-positive, primarily adult patients with TM and/or ON, PLEX has also been described as stand-alone treatment in the acute phase [22]. In this study, treatment with PLEX (as stand-alone therapy or following IVMP) resulted in (almost) complete recovery in 40% of patients with a median number of five PLEX cycles. Full recovery was achieved even in patients with treatment failure to IVMP. In nearly 60% partial recovery was achieved with only two non-responders to PLEX [22]. In another single-centre retrospective study with 65 paediatric ADS patients with no or poor improvement to IVMP (31% MOG-ab positive), 72% of patients showed moderate to full functional recovery after PLEX (median six cycles), especially in patients with ON and TM. PLEX was started between 3 and 186 days after the acute attack (median 23 days). Interestingly, the time interval to PLEX initiation had no significant association with treatment benefit [36]. However, the variability in response to PLEX may be linked to differences in duration of PLEX treatment, as detectable MOG-abs after several plasma exchanges raise the question if PLEX treatment might be terminated too early in these cases. Apheresis with immunoadsorption is reported only in a few MOGAD patients [22], but data are limited in paediatric patients and more experience is needed.

Table 1
Overview of observational studies reporting efficacy of maintenance treatment (>6 m use).

Publication	Type of study	Cohort	Ages (y)	Med FU (y)	AZA	MMF	IVIG	RTX	Corticosteroids
Hacohen et al.; 2018 [3]	Prospective data collection; retrospective inclusion; E.U.	Relapsing MOG-ab+ (n = 102)	Paediatric (<18)	5.5	n = 20 ARR*: 1.84 > 1.0 (0.84; p < .001) EDSS^{S}: 2.5 > 2.6 (ns) Relapse: 50%	n = 15 ARR*: 1.79 > 0.52 (1.27; p = .003) EDSS^{S}: 1.7 > 1.9 (ns) Relapse: 54%	n = 16 (+RTX n = 2) ARR*: 2.16 > 0.51 (1.71; p < .001) EDSS^{S}: 2.2 > 1.2 (p = .01) Relapse: 33%	n = 9 (+IVIG n = 2) ARR*: 2.12 > 0.67 (1.61; p < .001) EDSS^{S}: 2.4 > 3.2 (ns) Relapse: 67% (86% despite depleted B cells; 0% if + IVIG)	n = 8 ARR: na EDSS: na Relapse: 63% relapse (60% while tapering; 20% after stop)
Wong et al.; 2018 [7]	Prospective data collection; retrospective inclusion; E.U.	ADEM-ON (n = 17; 94% MOG-ab+)	Paediatric (<18)	5.3	na	na	na	na	n = 10 No relapse on >10 mg/d
Zhou et al.; 2019 [45]	Retrospective; China	MOG-ab+ (n = 23)	Paediatric (≤14)	2.3	n = 3 ARR*: 1.85 > 0 (1.85)	n = 3 ARR*: 1.82 > 0.44 (1.38)	na	n = 8 ARR*: 1.78 > 0.87 (0.91)	n = 2 ARR*: 2.67 > 0 (2.67)
Armangue et al.; 2020 [9]	Prospective; Spain	MOG-ab+ (n = 116; 100 prospective since onset)	Paediatric (<18)	3.5	na	na	na	n = 14 ARR: na EDSS: na Relapse: 7% (med. FU after RTX initiation: 18 m)	na
Albassam et al.; 2020 [65]	Prospective; Canada	Relapsing MOG-ab+ (n = 12)	Paediatric (<18)	2	na	na	na	n = 12 ARR: 12 m on-treatment: 0.0 EDSS^{S}: 1.5 > 1.0 Relapse: 50% (33% despite depleted B cells) Treatment failure$^{\#}$: 8%	na
Jurynczyk et al.; 2017 [17]	3 cohorts; 1 prospective; UK	MOG-ab+ (n = 371)	Mixed	1.3 −2.3	na	na	na	na	n = 45 (+other IT n = 7) Relapse: ↓if treated >3 m vs < 3 m (p = .005)
Ramanathan et al.; 2018 [23]	Retrospective; Australasia	Relapsing MOG-ab+ (n = 59)	Mixed (56% < 18)	3.8	n = 4 ARR*: na Relapse: na Treatment failure$^{\#}$: 50%	n = 16 (+steroids n = 16; +other IT n = 5) ARR*: med 1.83 > 0.16 (p = .074) Relapse: 50% Treatment failure$^{\#}$: 44%	n = 7 (+steroids n = 6; +other IT n = 2) ARR*: med 2 > 0 (ns) Relapse: 71% (67% while weaning/ increasing dose interval) Treatment failure$^{\#}$: 43%	n = 6 (+steroids n = 6) ARR*: med 1.65 > 0 (ns) Relapse: 67% (25% despite depleted B cells) Treatment failure$^{\#}$: 17%	n = 20 (+other IT all) ARR*: med 2 > 0 (p < .001) Relapse: na Treatment failure$^{\#}$: 5%
Li et al.; 2020 [54]	Prospective; China	MOG-ab + MMF+/- (n = 79)	Mixed (37% < 18)	1.1	na	n = 54 (+steroids n = 47) Relapse: 7% Relapse risk MMF + vs -: HR 0.11 (p = .001)	na	na	n = 25 Relapse: 44%

Publication	Type of study	Cohort	Ages (y)	Med FU (y)	AZA	MMF	IVIG	RTX	Corticosteroids
Whittam et al.; 2020 [66]	Retrospective; E.U.	MOG-ab + RTX+ (n = 121)	Mixed	1	Na	na	na	n = 101 (previously relapsing; +steroids n = 32; +other IT n = 20) ARR: med 1.82 > 0 (1.09; p < .001) Reduction relapse rate: 37% (63% if 1st line, 26% if 2nd/3rd line) Relapse: 47.5% (79% despite depleted B cells)	na
		Paediatric (n = 30)	Paediatric (<18)	1	Na	na	na	n = 30 (previously relapsing) ARR: med 1.64 > 0.37 (0.75; p < .001)	na

Table 1 (*continued*)

Publication	Type of study	Cohort	Ages (y)	Med FU (y)	AZA	MMF	IVIG	RTX	Corticosteroids
								Reduction relapse rate: 42%	
		Adult (n = 91)	Adult	1	na	na	na	n = 71 (previously relapsing) ARR: med 1.84 > 0 (1.13; p < .001) Reduction relapse rate: 29%	na
Chen et al.; 2020 [46]	Retrospective; USA	MOG-ab+ (n = 70)	Mixed	4.5	n = 22 (+steroids n = 10)	n = 19 (+steroids n = 2)	n = 10 (+steroids n = 2)	n = 37 (+steroids n = 5)	na
		Paediatric (n = 23)	Paediatric (<18)	6.3	n = 8 ARR*: med 0.9 > 0 Relapse: 50%	n = 4 ARR*: med 2.1 > 1.5 Relapse: 75%	n = 5 ARR*: med 4.4 > 0 Relapse: 20%	n = 7 ARR*: med 0.8 > 0.86 Relapse: 57%	na
		Adult (n = 47)	Adult	3.2	n = 14 ARR*: med 1.4 > 0.43 Relapse: 64%	n = 15 ARR*: med 0.9 > 0 Relapse: 73%	n = 5 ARR*: med 1.0 > 0.1 Relapse: 20%	n = 30 ARR*: med 2.4 > 0.59 Relapse: 62%	na
Jarius et al.; 2016 [22]	Retrospective; Germany	MOG-ab+ (n = 50)	Adults (>18)	Mean 6.3	n = 18 ARR: na Relapse: 85% (32% <3 m, 9% >3-<6 m after initiation; 83% without co-treatment steroids)	na	n = 1 ARR: na EDSS: clinical improvement Relapse: 0%	n = 9 ARR: na Relapse: 78% (often shortly after RTX influsion and 2 end of dose)	na
Cobo-Calvo et al; 2019 [47]	Retrospective; France/Spain	Relapsing MOG-ab+ (n = 125)	Adults (>18)	4.5	n = 19 ARR*: 1.05 > 0.43 (0.62; p = .041) EDSS^{S}: 1.86 > 1.68 (ns) Relapse: 45% Treatment failure$^{\#}$: 47%	n = 12 ARR*: 1.20 > 0.23 (0.97; p = .033) EDSS^{S}: 2.72 > 2.64 (ns) Relapse: 27% Treatment failure$^{\#}$: 58%	na	n = 30 ARR*: 1.08 > 0.43 (0.65; p = .012) EDSS^{S}: 3.11 > 2.58 (ns, but EDSS progression in 12%) Relapse: 27% Treatment failure$^{\#}$: 10%	na
Durozard et al.; 2020 [67]	Prospective; France	RTX+; MOG-ab+ (n = 16) AQP4-ab+ (n = 20)	Adults (>18)	1.6	na	na	na	n = 16 ARR: na EDSS^{S}: med 2 > 1.75 (p < .008) Relapse: 38% (80% despite depleted B cells)	na

ARR = annualized relapse rate, AZA = azathioprine, EDSS = expanded disability status scale, FU = follow-up, MMF = mycophenolate mofetil; MOG-ab+ = myelin oligodendrocyte-glycoprotein antibody positive, IT = immune therapy, IVIG = intravenous immunoglobulins; RTX = rituximab, ns: not significant; na = not assessed; med = median, m = months, y = years.

* ARR shown as mean ARR pre-treatment > mean ARR on-treatment (mean reduction; p-value). ARR pre-treatment: Number of relapses per year before treatment; excluding index event [3,7,23,47]. ARR on-treatment: Number of relapses per year on minimum of six months treatment [3,23,47].

^{S} EDSS sown as mean EDSS pre-treatment > mean EDSS on-treatment (p-value).

$^{\#}$ Treatment failure not further specified [23,47].

3. Maintenance treatment: efficacy and side effects

Currently used maintenance therapies for relapse prevention in MOGAD include a wide range of immunosuppressive treatments, which are mainly based on therapy regimens applied in adult aquaporin-4 antibody (AQP4-ab)-positive NMOSD. Clinical treatment trials in MOGAD are still lacking for various reasons. Sparse evidence comes from observational and mainly retrospective studies. Although these studies do not allow for a proper comparison between different treatment modalities, some conclusions can be made. Available data regarding different therapies are discussed in detail below and illustrated in Table 1.

3.1. Azathioprine (AZA)

AZA is commonly used as a first-line steroid-sparing immunosuppressive treatment due to its antiproliferative effect by inhibition of lymphocyte differentiation. A typical dose is 2–3 mg/kg/day, and treatment takes up to 3–6 months before being fully effective. Therefore, concomitant oral steroid treatment is recommended during this period [37]. The main side effect is bone marrow suppression, with increased risk of infections. In order to determine the risk of myelotoxicity, thiopurine methyltransferase (TPMT) genotypes or TPMT activity can be performed [38-41]. Moreover, patients should be monitored for hepatotoxicity. Rare but important, with long-term use of AZA, patients are at risk for malignancies, mainly skin cancer and lymphoma.

Effectiveness of AZA in reducing relapse risk in adult NMOSD has been shown by several prospective studies [42,43] and a randomised controlled trial [44], mainly including AQP4-ab-positive patients. In MOGAD, only retrospective studies are available, which showed a reduction of annualized relapse rate (ARR) after initiation of AZA, with stable EDSS scores in paediatric [3,7,45], mixed [23,46], and adult cohorts [47] with (mainly) relapsing MOG-ab-positive patients. Relapses were still observed in around 50% of patients [3,23,46,47]. In adult MOGAD patients treated both from

initial as well as relapsing attack, even higher percentages of relapses were observed in patients treated with AZA [22]. Importantly, a significant proportion of the relapses in this last study occurred within the first 3–6 months after start of AZA (32% before 3 months and 9% between 3 and 6 months). In 86% of these relapses, patients were not co-treated with oral prednisone, highlighting again the importance of co-treatment with oral steroid treatment in this latency period of AZA.

3.2. Mycophenolate mofetil (MMF)

Comparable with AZA, MMF is used as first-line steroid-sparing immunosuppressive treatment as well, as it has a selective antiproliferative effect on B and T lymphocytes via inhibition of de novo guanosine nucleotide syntheses. However, MMF is also only fully effective 3–6 months after initiation and thus additional oral steroids are required in this period. The dosages given differ between studies, ranging from 750 to 3000 mg/day [48] (in paediatric patients usually 650 mg/m2/day). Side effects include bone marrow depression, causing leukocytopenia among others, with risk of infections. Furthermore, patients often experience gastrointestinal symptoms, e.g. nausea and diarrhoea. If MMF is used long-term, the malignancy risk needs to be considered [49]. As MMF is teratogenic [50], young females should be counselled on contraceptive use.

MMF has been shown to reduce relapse rate in adult NMOSD patients, who were AQP4-ab-positive in the majority of cases [51,52]. One observational study from France also reported a beneficial effect of MMF in five MOG-ab-positive patients among 67 NMOSD patients [53]. Furthermore, a recent prospective observational study from China analysed the effect of MMF in paediatric and adult MOGAD, by a not-randomised comparison of 54 patients treated with MMF and 25 patients not treated with MMF [54]. Despite a short median follow-up time of one year, this study showed that patients treated with MMF had significantly lower relapse rates (7% vs. 44%), which remained significant even after adjusting for factors such as disease course. Importantly, 90% of MMF treated patients also received oral prednisone in addition to MMF (81% for six months or longer, dose not mentioned). Although this was not different from patients not treated with MMF, prednisone could have caused a synergetic effect on MMF, resulting in a lower relapse frequency than observed in previous retrospective studies with longer follow-up durations [3,23,45–47]. These studies all showed a reduction in ARR after initiation of MMF in paediatric [3,45], mixed [23,46], and adult cohorts [47] with mainly relapsing MOG-ab-positive patients. Additionally, studies reporting EDSS showed a stable EDSS under MMF [3,47]. Nevertheless, relapses were still observed in 27–75% of patients, often during tapering of steroids [23].

3.3. Immunoglobulins (IG)

Due to the diverse immunomodulatory and anti-inflammatory effects of high dose IVIG (1–2 g/kg in 1–5 days with a maximum of 1 g/kg/d), it is used on a monthly basis in a number of autoimmune and inflammatory disorders [26,27]. The side effect profile is favourable (mentioned above), however, due to the increasing demand for IVIG, high costs and supply shortages, treatment with IVIG might become a concern in the near future.

Compared to AQP4-ab-positive NMOSD [55], IVIG is more commonly used in MOGAD as acute treatment modality, but also more often as maintenance treatment for relapse prevention. A few retrospective observational studies described the efficiency of IVIG as maintenance treatment in MOGAD. Both in paediatric [3] and two mixed paediatric and adult cohorts [23,46] of mainly relapsing MOG-ab-positive patients, a reduction in ARR was observed with monthly IVIG treatment. In paediatric patients, IVIG treatment was associated with the lowest ARR [3] or the greatest reduction in relapse rate [46], compared to the other used immunosuppressive therapies. Additionally, IVIG was even associated with an improvement in EDSS, reported in the paediatric cohort [3]. Although these results seem promising, these effects have only been observed in a limited number of patients, including 29 MOG-ab-positive patients, of which two were co-treated with RTX and two with maintenance oral prednisone. Moreover, still 20–71% of these IVIG treated patients experienced relapses [3,23,46], although half of these occurred while weaning IVIG doses or increasing dosing interval [23].

In general, treatment with subcutaneous IG (SCIG) seems to have the same efficacy as IVIG and improves patients' quality of life due to the ability to administer treatment at home. Furthermore, costs may be reduced by SCIG as a result of fewer hospital admissions representing potentially an alternative to IVIG [30]. However, until now, studies analysing the efficiency of SCIG specifically in MOGAD are not available.

3.4. Rituximab (RTX)

The partially humanised monoclonal antibody RTX is directed against the human CD20 molecule expressed by B cells. RTX is administered intravenously, but dosing regimens vary between centres. In paediatric patients, treatment protocols include induction therapy of 375 mg/m^2 body surface once weekly for 2–4 weeks, or alternatively 375, 500 or 750 mg/m^2 twice with a two-week interval [56-60]. This induction therapy is followed by repeated infusions of 375 mg/m^2 once or twice with a two-week interval, or alternatively 500 or 750 mg/m^2 once. Immediately after infusion, RTX causes a rapid depletion of all circulating CD20-positive B cells. While some clinicians use a fixed dosage regimen with retreatment every six months, retreatment can also be based on repopulation of B cells with monitoring of CD19+/CD20+ B cells and/or CD27$^+$ memory B cells [58]. Side effects mainly comprise infusion-related adverse events, including pruritus, headache, rash or fever. However, pre-medication with analgesic, antihistamine and (intravenous) prednisolone is recommended to reduce the risk of these side effects. Other possible serious side effects include (severe) infectious complications, persistent leukopenia or hypogammaglobulinemia, also described in paediatric patients [59,61,62]. Recently, a protocol for the application of RTX in paediatric patients was published, with suggestions for dosing and monitoring in clinical practice [60]. This protocol was developed for paediatric MS in particular, although the authors conclude it could also be applied to other ADS.

Although the autoantibody-producing plasma cells, not expressing CD20, are not eliminated by RTX, their precursor memory B cells are. In AQP4-ab-positive NMOSD, RTX is found to be effective in reducing relapse rate [63,64]. Several observational studies also described the effect of RTX in MOGAD and reported a reduction in ARR in paediatric [3,9,45,65], mixed [23,46,66] and adult [22,47,67] cohorts with MOG-ab-positive patients, almost all of them having a relapsing disease course. Furthermore, some studies showed stabilising [3,65] or even improving [67] EDSS, although one adult study also reported further EDSS progression in 12% of patients treated with RTX [47]. Despite these observed effects of RTX in MOGAD, all studies reported relapses in up to 67% of patients [3,22,23,45-47,66,67]. Strikingly, and in contrast to AQP4-ab-positive NMOSD, relapses also occurred despite adequate B-cell depletion (in 25–86% of relapses) [3,23,65-67], or shortly after RTX infusion [22], suggesting relapse in MOGAD is independent of depleted memory B cells [66,67]. Interestingly, but comparable with the observation in AQP4-ab-positive NMOSD, is that the

majority of MOGAD patients treated with RTX remained MOG-ab-positive for 12 months or more after therapy commencement observed in children [65], or after a mean of six infusions during a mean period of 30 months observed in adults [67], both in prospective observational studies. These findings suggest RTX may not have impact on long-lived plasma cells and the production of MOG-abs. Nevertheless, this needs further investigation in prospective studies with predefined follow-up measurements of MOG-abs titres. In conclusion, although RTX efficacy in adult MOGAD seems to be limited compared to AQP4-ab-positive NMOSD [67], several studies showed a reduction in ARR in adult as well as paediatric MOG-ab-positive patients [3].

3.5. Corticosteroids

Continuous corticosteroids have an immunosuppressive and anti-inflammatory effect by a multitude of functions, e.g. reducing cytokine levels and enhancing synthesis of anti-inflammatory proteins [26]. Treatment with corticosteroids can be of extra benefit in central nervous system inflammatory diseases, because corticosteroids improve blood-brain barrier integrity and control oedema [68]. However, beside these properties, long-term use of corticosteroids may also lead to several (possibly permanent) side effects, like weight gain, growth retardation, decreased bone density, hypertension, and increased risk of (serious) infections, which can be worrisome especially in paediatric patients [69].

The overall good response to corticosteroids (IVMP/oral prednisone taper) in acute MOGAD attacks has already been mentioned. In some MOGAD patients, corticosteroids were also used as maintenance monotherapy or in combination with other immunomodulatory treatments. It can comprise oral prednisone at low dose daily or every alternate-day, or IVMP pulses monthly. The comparison of treatment efficacy of maintenance steroids between previous studies is interfered by the possible co-use of other immune therapies, and additionally by the varying use of daily doses of oral prednisone. However, as already mentioned above, oral prednisone appears to be effective in reducing relapses [3,7,23,45]. Nevertheless, the risk of (permanent) side effects limits its use as maintenance treatment, in particular when given daily.

Interestingly, in the largest study analysing treatment efficacy in relapsing MOG-ab-positive patients so far, a very low failure rate of oral prednisone (5%) was observed [23]. However, almost all these patients received concurrent treatment with other immune therapies like AZA, MMF, IVIG or RTX, suggesting a synergetic effect of these combined therapies. This has also been observed in MMF treated patients co-treated with oral prednisone [54]. In that study, monotherapy with oral prednisone was not associated with significant reduction of relapse risk (44%), but with oral prednisone and MMF combined relapses occurred only in 7% of patients.

3.6. MS disease modifying treatments (DMTs)

As MOG-abs were previously thought to be linked to MS, MOG-ab-positive patients were treated with MS DMTs in the past. However, multiple studies have now shown that baseline DMTs including interferon-beta, glatiramer acetate and even natalizumab, are not effective in preventing relapses in MOGAD. ARR and EDSS were both not reduced in paediatric [3,25,46], and adult [22,46,47] cohorts with MOG-ab-positive patients by these treatments. Some patients even showed progression in EDSS [47] or severe relapses [22]. Although the effect of baseline DMTs may be less harmful compared to (AQP4-ab-positive) NMOSD [70-72], baseline DMTs are not beneficial in MOGAD.

3.7. Other immune therapies

Few studies described a limited number of patients treated with cyclophosphamide, cyclosporin, mitoxantrone or methotrexate [3,22,23,46,47]. Most of these studies reported no changes in ARR, nor EDSS, and high percentages of treatment failure (50–100%) [3,23,46,47], while there was risk of cumulative dose toxicity in some [23]. Only one retrospective study reported lower ARR in 5/6 patients treated with methotrexate, compared to the cumulative ARR among all patients with a relapsing disease [22].

3.8. Switch and combination of immune therapies

One study described the efficacy of switched maintenance immune treatment in seven patients, because of treatment failure of initial agent in five (71%) of these patients (AZA n = 1, MMF n = 2 and MTX n = 2) [23]. After this switch, two patients had further relapses, which resulted in treatment failure in only one (14%). The relapse rate in this small group of patients was significantly reduced after the switch of maintenance therapy, which suggests that switch of maintenance treatment is important if the initial therapy fails.

In case of treatment failure, also a combination with oral prednisone should be considered, as synergetic effects of oral prednisone are suggested in combination with AZA, MMF, IVIG or RTX [23,54]. Synergetic effect was also observed in other combinations: although only observed in a limited number of patients, efficacy of RTX may increase if combined with IVIG treatment [3]. Some cases may continue to relapse despite the use of different immune therapies as monotherapy, resembling treatment-refractory patients. In these patients, a combination of immune therapies might be essential.

4. Paediatric European Collaborative Expert Consensus treatment recommendation paediatric MOGAD

4.1. Recommendation acute treatment

Our Paediatric European Collaborative Expert Consensus recommendation on acute treatment in paediatric MOGAD is shown in Fig. 1. If a patient presents with symptoms highly suggestive of MOGAD, at onset or with a clinical relapse, we recommend administration of 20–30 mg/kg/day IVMP (max. 1 g/day) for 3–5 days.

Following the administration of IVMP, the group of experts was divided with regards to the use, dose and duration of an oral steroid taper to maintain the benefit of acute treatment by suppressing disease activity. *If* administered, there was consensus of a rapid tapering of steroids in the first weeks, and application of tapering period not extending beyond a total of three months. Here, a starting dose of oral prednisone of 1–2 mg/kg/day with a maximum of 60 mg/day for 1–4 weeks was chosen, followed by a taper to 0.5 mg/kg/day or less, to avoid side effects. Additionally, an alternate-day steroid strategy may be employed as in other autoimmune diseases, such as rheumatic diseases or Hashimoto's thyroiditis with oral prednisone doses ranging from 5 to 10 mg depending of the child's weight [73,74]. Close monitoring is important with prednisone doses <0.5 mg/kg/day and after cessation, as frequent relapses have been described in this period [23].

If the patient shows no treatment response after three days of IVMP, or the patient has insufficient improvement with residual symptoms after five days, treatment should be escalated with IVIG with a total dose of 1–2 g/kg in 1–5 days (not exceeding 1 g/kg/d), with most experts recommending 5 days. As an alternative, especially in patients with severe disease burden (i.e. paraplegia in TM,

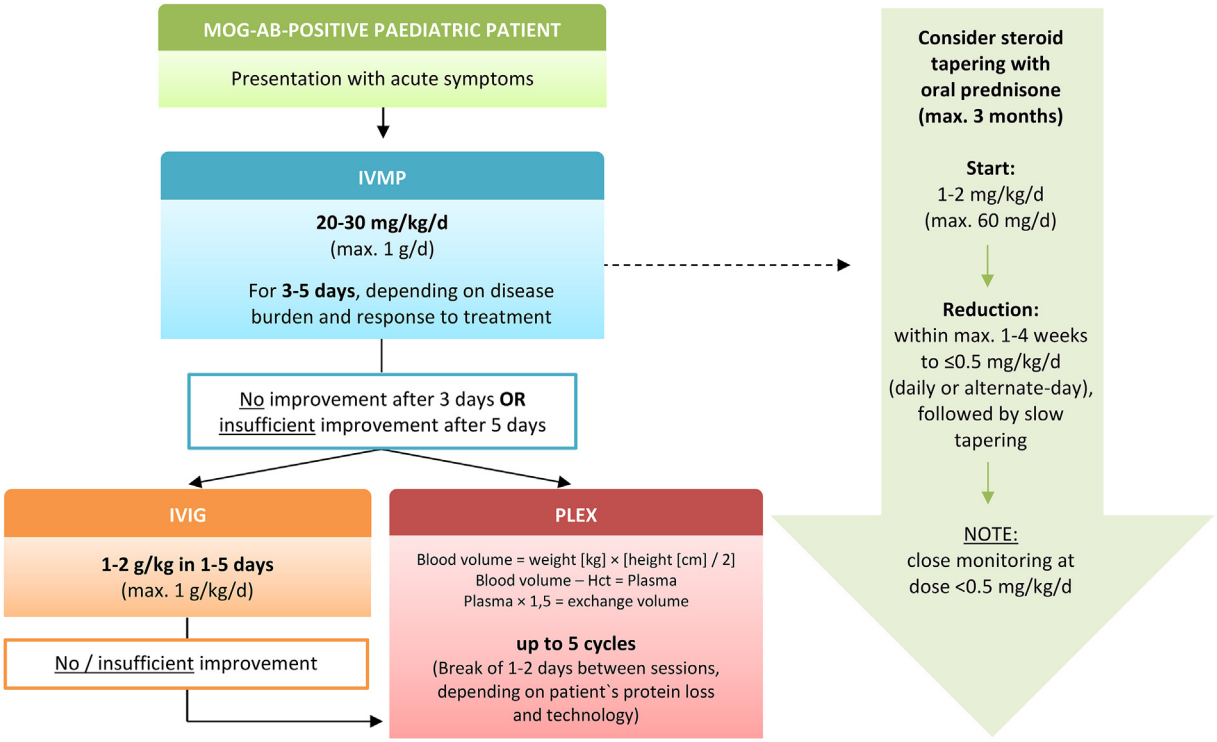


Fig. 1. Paediatric European Collaborative Expert Consensus recommendation for acute treatment in paediatric MOGAD. d = day, g = gram, IVIG = intravenous immunoglobulins, IVMP = intravenous methylprednisolone, kg = kilogram, mg = milligram, MOG-ab = myelin oligodendrocyte glycoprotein antibody, PLEX = plasma exchange, TM = transverse myelitis.

blindness in ON), we recommend application of PLEX for up to five cycles. There are no data comparing treatment response of IVIG and PLEX in the acute phase. However, IVIG has fewer side effects and administration is easier compared to PLEX, which is why IVMP is mostly followed by IVIG. On the other hand, if PLEX is considered after administration of IVIG, treatment response to IVIG should be reliably absent, because otherwise PLEX may abrogate IVIG treatment. The advantage of PLEX before IVIG treatment is that IVIG can be administered without latency after PLEX in case of insufficient treatment response.

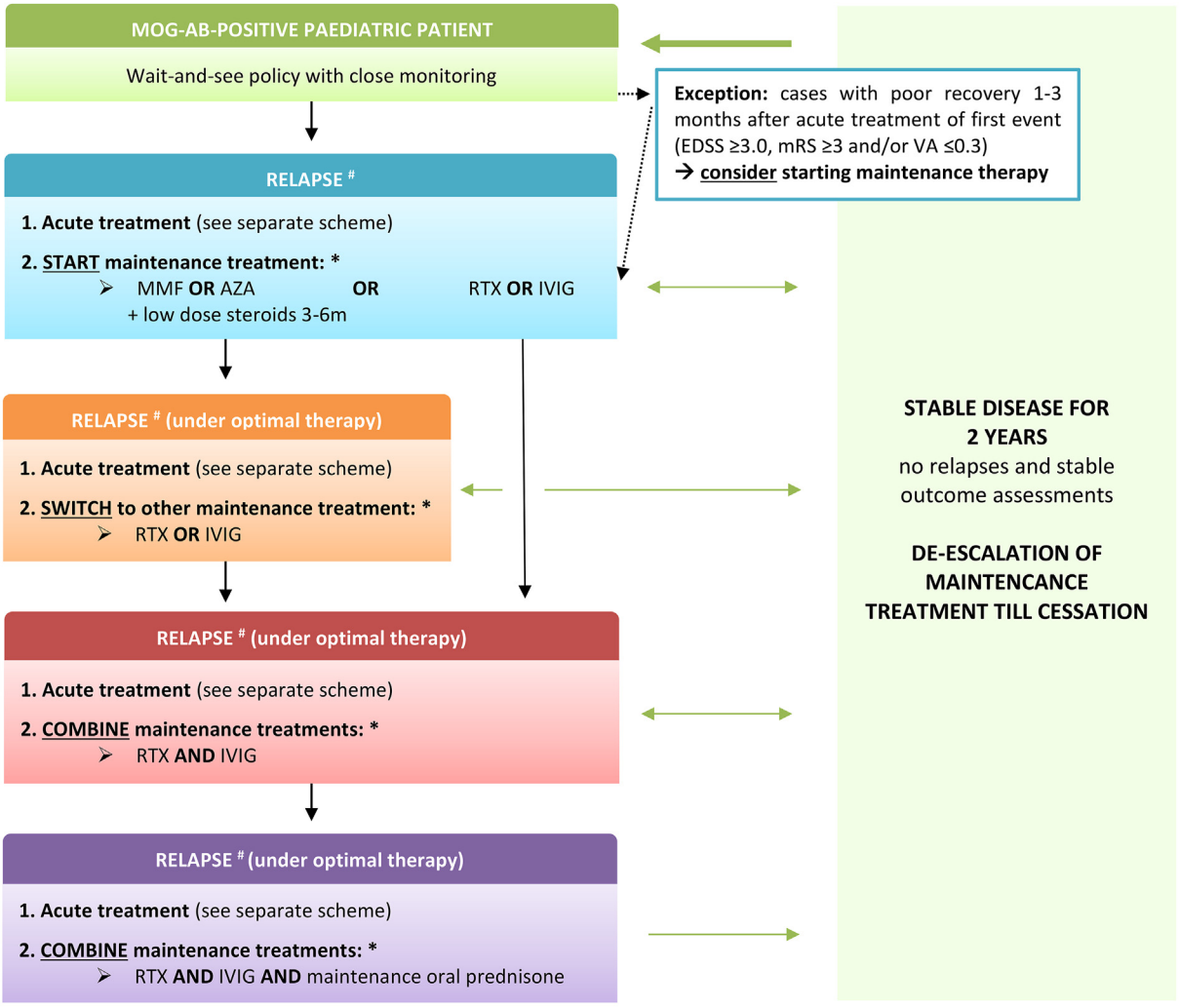
4.2. Recommendation maintenance treatment

Fig. 2 includes our Paediatric European Collaborative Expert Consensus recommendation for maintenance treatment of paediatric MOGAD. This is a stepwise consensus treatment protocol, with different levels of escalation in case of relapses and de-escalation in case of a stable disease. The recommendations are discussed below in detail.

4.2.1. Start of maintenance treatment

Although subtypes of MOGAD with frequent relapses are described [2,3,6,7,25,75], there is a predominance of monophasic presentations with good response to initial treatment, particularly in paediatric cohorts [2,75]. Furthermore, although some prognostic factors for relapsing disease course have been established (persisting MOG-ab positivity [16,76], older age, ON phenotype and shorter time to first relapse [16]), at onset of disease these parameters cannot reliably predict further relapses. Hence, we recommend commencement of maintenance therapy only in patients with a relapsing disease course (Fig. 2). Because every relapse potentially has a cumulative effect resulting in increased disability at long-term follow-up [47], maintenance treatment should be initiated or at least considered with the first clinical relapse. Briefly, a clinical relapse constitutes of a new clinical episode accompanied by radiological evidence depending on the subtype of MOGAD, appearing at least one month subsequently to the last acute attack. Importantly, the clinical challenge is distinguishing a worsening of symptoms following an initial improvement after acute treatment, often termed as “flare-up”, from a clinical relapse. Notably, a “flare-up” is likely to need new acute treatment, but is no indication for start of maintenance therapy. As patients with an initial ADEM phenotype can have fluctuating clinical and/or radiological symptoms during the acute phase of three months [8], the possibility of a “flare-up” instead of new relapse needs to be considered within one month but up to three months after start of IVMP treatment at onset of disease. In addition to a clinical relapse, maintenance treatment should be considered in case of subclinical worsening of ON documented with optical coherence tomography (OCT; [16, 77]. Same applies to asymptomatic progression on magnetic resonance imaging (MRI), although this is very rare in MOGAD in contrast to MS, and therefore, other diseases such as MS should be reconsidered in this case.

The expert group noted that there are exceptions to the recommendation of starting maintenance treatment after the first relapse (Fig. 2): (1) In patients with a poor recovery from the initial event (mainly TM or ON patients); new disease activity can be devastating, possibly resulting in being wheelchair-bound or blind. Hence, in patients with a poor recovery 1–3 months after acute treatment of initial event (EDSS ≥3.0, modified rankin scale (mRS) ≥3, and/or VA ≤1/3 (0.3), timely initiation of maintenance treatment should be considered in an attempt to prevent a first relapse; (2) Patients who have a long interval between initial episode and first relapse (>18 months), in addition to good clinical recovery after acute treatment; in these patients, initiation of maintenance therapy should be discussed individually. Although the first relapse



Maintenance treatments	Dose	Frequency	Route	Monitoring
Azathioprine (AZA)	2-3 mg/kg/d	Daily	Oral	TPMT genotype / activity before start
Mycophenolate Mofetil (MMF)	600-1200 mg/m²/d (max. 2 g/d)	Daily	Oral	
Rituximab (RTX)	Induction: 2-4x 375 mg/m² with 1w interval **OR** 2x 375-500 mg/m² with 2w interval (max. 1 g/infusion) Reinfusion: 1x 375-500 mg/m² (max. 1 g/infusion)	Every 6m **OR** if CD19+ B cells ≥10x10⁶ cells/L <6 m	IV	CD19+ B cells at 3m, 4m and 5m
Immunoglobulins (IG)				
- IVIG	Induction: 1-2 g/kg in 1-5d (max. 1 g/kg/d) Reinfusion: 1 g/kg in 1-3d	Monthly	IV	
- SCIG	0.5-0.8 g/kg	Monthly	SC	
Prednisone				
- Add-on 3-6 m (AZA/MMF)	Oral: 0.5 mg/kg/d (min. 10 mg/d, max. 20 mg/d) **OR** IV: 20-30 mg/kg/d for 3-5d (max. 1 g/d)	Daily / alternate-day **OR** monthly pulses	Oral **OR** IV	Close monitoring if dose <0.5 mg/kg/d and after stop
- Maintenance	As low as possible			

Fig. 2. Paediatric European Collaborative Expert Consensus recommendation for maintenance treatment in paediatric MOGAD.
#Clinical relapse (new clinical episode accompanied by radiological evidence depending on the subtype of MOGAD, appearing at least one month subsequently to the last acute attack), but also consider for subclinical worsening (OCT) and asymptomatic progression (MRI).
Note 1: A "flare-up" with progression of symptoms or reoccurrence of same symptoms within one month after start of acute treatment is no indication to start or switch maintenance treatment, although new acute treatment application has to be considered.
Note 2: As patients with an initial ADEM phenotype can have fluctuating clinical symptoms and/or fluctuating radiological abnormalities during the acute phase of three months [8], the possibility of a "flare-up" instead of relapse in these patients needs to be considered up to three months after onset of disease.
* Consider to continue current policy in cases with a long latency to relapse (>18 months) in combination with good clinical recovery of initial event and relapse(s): continuation of wait-and-see policy in case of first relapse >18 months and continuation of current used maintenance treatment option in case of new relapse >18 months.
AZA = azathioprine, d = day(s), g = gram, IG = immunoglobulins, IV = intravenous, IVMP = intravenous methylprednisolone, kg = kilogram, max = maximum, mg = milligram,

mostly occurs within 12 months subsequently to the first episode [2,3,24], there are also reports of patients with relapsing MOGAD who have a long period of stable disease until the next relapse occurs, even without maintenance therapy [3,7]. In these patients the risk and benefits of maintenance treatment should be balanced.

Prophylactic immunosuppression after the first episode of ON was suggested previously [17,22], because a high risk of relapse was assumed, with short median time to second attack, and a risk of developing visual disability even after initial recovery. We agree that close monitoring of these patients is essential to be able to detect subclinical ON symptoms at an early stage. However, considering that a substantial proportion of ON patients has a monophasic presentation [5,78] together with the side-effects of immunosuppressive therapy, we recommend also in patients with an ON phenotype to only initiate maintenance therapy after a first relapse. Importantly, start of maintenance therapy solely on the basis of persisting or increasing high MOG-ab titres is not recommended, as they can remain positive for more than 12 months also in monophasic patients [76, 79].

4.2.2. Escalation of maintenance treatment

To prevent a further relapsing disease course with accumulation of disability in MOGAD, maintenance therapy must be adapted in case of treatment failure.

Escalation of maintenance immunotherapy in case of further relapses must be balanced individually for each patient, depending on age, phenotype, severity of symptoms, clinical course, treatment history and, importantly, compliance of the patient. We recommend escalation of maintenance therapy in case of a clinical relapse, if the use of currently used immunotherapy is not flawed by suboptimal dosing, insufficient B-cell depletion in case of RTX, or patient incompliance (Fig. 2). If it is, current immunotherapy should be optimised before escalation of therapy. In relapsing patients with high disease burden, MRI and OCT may be used additionally to direct management: if follow-up assessment shows concealed hints for a progressive or relapsing disease course without clinical symptoms, e.g. isolated new MRI lesions or worsening of OCT results, escalation of maintenance immunotherapy can be considered as well, taking into account the aspects mentioned above.

There is one exception to our recommendation for escalation of maintenance treatment: if patients have a long latency to relapse (>18 months), combined with (1) good clinical recovery to acute treatment after the relapse; and (2) good tolerance and compliance of current immunotherapy, continuation or current maintenance treatment should be considered.

Close assessment of treatment response is important in order to recognise worsening of symptoms or a new MOGAD episode. Herein, recommendations for assessment of outcome, as summarised in this special issue Part 4 [16], are helpful. Primarily in patients with ON attacks, an unfavourable long-term outcome is supposed to result from unnoticed and therefore untreated attacks [80]. Hence, we highlight the follow-up examination and possible adaption of maintenance therapy for the long-term outcome of the patient, if necessary with consultation of an expert centre.

4.2.3. Cessation of maintenance treatment

There are no official recommendations for de-escalation and cessation of maintenance immunotherapy in MOGAD right now. The observation that some relapsing patients have a long period of stable disease without treatment, and have a new relapse only after years (sometimes even after more than 10–20 years) [3,7], demonstrates that patients would have been over-treated if they had received maintenance treatment for all those years.

In general, we recommend de-escalation of maintenance immunotherapy after two years of stable disease without relapses and stable assessments concerning visual, motor, autonomic and cognitive outcome as specified in this special issue Part 4 (Fig. 2) [16]. If the patient suffers from a new relapse after treatment cessation subsequently to a stable disease under maintenance immunosuppression, maintenance therapy should be restarted again. In addition, accordingly to treatment escalation, time for treatment cessation can be decided individually for each patient. Due to individual reasons, e.g. distinct side-effects of maintenance treatment, an earlier stop of maintenance treatment can be discussed. Furthermore, in case of a previous disease course with a high relapse frequency together with a poor outcome, continuation of the currently used maintenance treatment should be considered.

4.2.4. Maintenance treatment options

Data available from mainly retrospective studies with a limited number of patients show that AZA, MMF, IVIG, RTX and corticosteroids all reduce ARR and stabilise EDSS, although relapses occur among all these treatments. Studies show lowest ARR and failure rates with IVIG in paediatric patients [3,46], corticosteroids and RTX in a mixed paediatric and adult cohort [23], but a proper comparison between the different maintenance treatments is not possible due to the retrospective observational design of available studies and lack of randomised control studies. Nevertheless, the fact that relapse rates are reduced by these treatments and that relapses mainly occur in weaning phase of corticosteroids, IVIG and possibly RTX emphasise the effect of immune therapy in relapse prevention in MOGAD [21].

If maintenance treatment is started, treatment options include MMF, AZA, RTX or IVIG (Fig. 2). Treatment choice can be made based on side effect profile and preference of patient (oral or intravenous administration). In pubertal girls, AZA is preferred over MMF, due to the strong teratogenic effect of MMF [50]. In case of AZA, TPMT activity should be tested before the start of treatment, in order to identify patients at high risk of potentially fatal myelosuppression. In case of RTX, we recommend to treat every six months, or according to close monitoring of $CD19^{+}$ B cells (at three, four and five months) and shorten re-dosing regimen in case of earlier re-emergence of B cells ($\geq 10 \times 10^{6}$ cells/L) [67]. As mentioned previously, the use, dose and duration of a concomitant steroid administration was discussed controversially. However, we clearly recommend that if maintenance treatment with AZA or MMF is started, steroids should be used as add-on therapy for 3–6 months, to bridge the drug-latency period of both drugs [22]. Steroids can be given as oral prednisone administered daily or every alternate-day, or administered monthly as IVMP pulses.

We recommend to switch to another treatment option in case of relapse or further disease progression [23]. Therefore, if a relapse occurs under optimal treatment with AZA or MMF, treatment should be escalated to RTX or monthly IVIG. Although IVIG seems promising, it has only been observed in a limited number of patients and because there are currently no studies available comparing RTX and IVIG treatment, the consensus group agreed that superiority cannot be determined at the moment. If a relapse occurs under optimal treatment with RTX or IVIG monotherapy, further escalation is needed with a combination of RTX and IVIG. If all options discussed are still not effective in preventing relapses despite optimal treatment, a combination of RTX, IVIG and

min = minimum, m = month(s), MMF = mycophenolate mofetil, MOG-ab = myelin oligodendrocyte glycoprotein antibody, ON = optic neuritis, RTX = rituximab, SC = subcutaneous, TM = transverse myelitis.

maintenance oral prednisone is recommended. Importantly, after a stable disease without relapses and stable outcome assessments [16] for two years, treatment should be de-escalated.

5. Challenges and future directions

This consensus paper addresses the current evidence and approach in the treatment of children with monophasic and relapsing MOGAD. The paper further attempts to give guidance in the management of an acute episode and the available immunomodulatory options of children with a relapsing course of the disease acknowledging the fact that recommendations are mainly based on results from retrospective, observational studies including varying MOGAD clinical phenotypes, and expert opinions only. Therefore, we would like to emphasise that prospective studies of patients with MOGAD are needed in the future to support our recommendations. Research should focus on finding the optimal dosing and duration of steroid administration in the initial phase of the disease and treatment efficacy within the different clinical phenotypes, in order to find the best timing and most effective treatment regimen for each phenotype. Furthermore, studies assessing the value of serial testing of MOG-ab titres and disease course of relapsing patients are needed to determine whether a negative MOG-ab serostatus during follow-up can be used to guide de-escalation of treatment. Besides, assessing the value of new biomarkers such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in clinical practice is of utmost importance for prognosis and treatment response [76].

Interestingly, a recent international study with 121 MOG-ab-positive children and adults treated with RTX showed that RTX used as first-line therapy was associated with a higher reduction in relapses compared to RTX used as second or third-line therapy (63% vs. 26%, respectively) [66]. Ideally, this should be investigated in future prospective studies, analysing the potential of RTX in the treatment of MOGAD.

Finally, treatment trials, preferably randomised, are important to be able to determine superiority of treatments currently used in MOGAD. In these trials an accurate clinical classification is necessary to be able to determine the most effective treatment regime for each clearly defined phenotype (clinical classification proposed in this issue Part 1 [8]). As discussed in this special issue Part 3, IL-6 in cerebrospinal fluid may be an important future biomarker in MOGAD, as it is in NMOSD [76]. Therefore, the IL-6 inhibitor tocilizumab, which has been shown to be beneficial over AZA in AQP4-ab-positive NMOSD [81], might also be a potential treatment candidate in MOGAD. However, such trials are difficult to perform due to the rarity of this antibody-associated disease. International collaboration is essential to expand the state of current knowledge.

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