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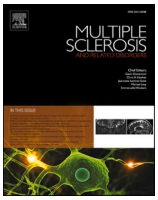

# Treatment of MOG-IgG associated disease in paediatric patients: A systematic review

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ABSTRACT

*Aim* to perform a systematic review of the literature on treatment of paediatric patients with MOG-IgG associated disease (MOGAD).

*Method* We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The search was conducted in Pubmed (MEDLINE) seeking articles of treatment of MOGAD in patients ≤ 18 years published between January 2012 and April 25th, 2020.

*Results* We found 72 non-controlled studies (observational studies, case reports and expert recommendations). There were no randomized controlled trials (RCTs). The most commonly reported acute phase treatment was intravenous methylprednisolone in 88% followed by oral steroids in 67%, intravenous human immunoglobulin (IVIG) in 66% and plasma exchange in 33% of the studies. Long-term maintenance treatment was described by 53 studies mainly in relapsing disease course. The most frequently reported treatments were prolonged oral corticosteroids in 53% of the studies followed by azathioprine (51%), mycophenolate mofetil (45%), rituximab (41%) and periodic intravenous immunoglobulin (26%).

*Interpretation* long-term treatment was reported mainly in relapsing MOGAD paediatric patients. However, the most frequently used medications are not those that have shown higher reduction in the annualised relapse rate in observational studies. RCTs with standardized outcomes are needed to confirm the safety and efficacy of current and new treatments.

## 1. Introduction

The myelin oligodendrocyte glycoprotein (MOG) is a neuronal protein expressed in the outermost surface of the myelin sheath of the central nervous system (CNS). Its localization makes it an accessible target for autoantibodies in inflammatory demyelinating disease.Peschl et al. (2017) Over the last years, antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been consistently associated to optic neuritis (ON), encephalitis – includes acute disseminated encephalomyelitis (ADEM)-like and cortical presentations, and/or myelitis (MONEM).Dos Passos et al. (2018) Each MOG-IgG+ patient may have any combination of clinical features described in the MONEM spectrum. Therefore, a single clinical diagnosis such as ADEM or ON may not cover the entire clinical picture neither at onset, nor over time, seen in these patients with MOG-IgG associated disease (MOGAD).

Recently, several groups have published case reports and observational studies reporting treatments regimes used in the clinical practice. Given the recent recognition of this condition, there is a lack of consensus on the therapeutic management of paediatric MOGAD patients. We performed a systematic review of the literature on the treatment of paediatric MOGAD patients.

## 2. Objective

To conduct a systematic review to investigate the pharmacological interventions in the acute phase, as well as the long-term maintenance therapy used in paediatric patients with MOGAD. We included all prospective and retrospective interventional and observational studies, as well as case series and case reports that contained information from at least one treatment used by those patients.

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## 3. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Liberati et al., 2009; Moher et al., 2015) reporting guidelines were followed.

### 3.1. Search strategy

The data were collected in Pubmed (MEDLINE) using the following search terms: 'myelin oligodendrocyte glycoprotein treatment pediatric' OR 'MOG treatment pediatric' OR 'myelin oligodendrocyte paediatric treatment' OR 'MOG paediatric treatment' OR 'myelin oligodendrocyte glycoprotein children adolescents treatment' OR 'MOG children adolescents treatment'. No restrictions were applied.

### 3.2. Study selection

We initially selected articles in humans, referring to treatment of paediatric patients (0–18 years) with MOGAD published between 2012 and July 1st, 2019. The studies were screened by their titles and abstracts for the basic eligibility criteria (e.g. articles in humans, language and presence of paediatric cases) by two researchers (BKC and DKS). Full articles of the selected studies were then evaluated in detail and searched for additional references. Before the analysis of the selected articles, we performed a new search using the same terms to include new articles published between July 2nd, 2019 and April 25th, 2020. Finally, additional published studies known by the authors and not returned by the original search terms were included at the end of the study selection to ensure maximum study coverage.

### 3.3. Eligibility criteria

We selected all interventional studies, case reports and case series that reported any treatment for paediatric patients with MOGAD. Review articles were evaluated for expert recommendations and case reports. Expert recommendations were considered in the discussion but not in the quantitative analysis. We included data from complete articles in English and abstracts in English from complete articles in other languages when the minimum information required by this study was available in the abstract. Studies that reported treatment of both adults and children were considered for inclusion if the data of paediatric patients were specified in the article or in the supplementary material. The same approach was adopted in neuromyelitis optica spectrum disorders (NMOSD) when MOG-IgG positive cases were described separately from anti-aquaporin-4 positive and double seronegative cases.

### 3.4. Data collection

We collected data about number of patients, median age, sex, ethnicity, follow-up, clinical phenotype, recurrence, acute and long-term treatments used in paediatric MOGAD. When available, we quantified the number of individual patients treated with each drug and dosing.

## 4. Results

We found 129 articles in the initial search. After revision of titles and abstracts, 54 articles were selected for further revision. The full text and supplemental data and appendices of the 54 selected articles were reviewed in detail for the eligibility criteria. Thirty articles met the study criteria and were included in the systematic review, while other 24 articles were excluded. Six articles did not distinguish MOGAD from other CNS inflammatory conditions and seven described data of paediatric and adult patients altogether. Two articles did not provide enough information for the objectives of this systematic review. Seven were review articles and did not contain expert recommendations and two had language exclusion criteria (see Table 1).

The references of all 54 initially screened articles were searched for additional manuscripts through title and/or abstract and/or full text evaluation. Twenty-one additional manuscripts fulfilled the study criteria and were included. Additional 13 published articles known by the authors were included at the end of the study selection (Fig. 1).

The second search performed at the end of the study, returned 28 new articles of which 21 were selected by revision of titles and abstracts. Of those, 8 were included. Four articles were excluded due to language limitations, 2 did not have enough information, 2 did not discriminate MOGAD from other conditions, 3 did not contain information of paediatric patients and 2 were review articles without expert recommendations.

In total, 72 studies were eligible. Of those, 4 were review articles containing expert opinion used for the discussion and 68 articles provided information for the quantitative analysis. We identified the paediatric cases from two articles (Jarius et al., 2016) originated from the same database and included them as a single one, resulting in a total of 67 studies.

### 4.1. Characteristics of the studies

All 67 studies included in the quantitative analysis were observational, case series or case reports. We did not find any RCT on acute phase and/or long-term maintenance treatments. All studies but one[e32] identified MOG-IgG through cell-based assays. We decided to include this, even though enzyme linked immunoassay (ELISA) was used, because the authors reported only one phenotype (ADEM-ON) that is highly associated with MOGAD. This systematic review comprises the treatments reported in a total of 658 paediatric patients. (Supplemental Table 1) The median sample size of the selected studies was 4 subjects (1–116). The reported age of the patients ranged between 1 and 18 years. Only 23 studies described the ethnicity of the patients. The most commonly reported ethnicities were Asian (12 studies) and Caucasian (11 studies).

Sixty-four studies reported sex distribution in 513 patients. Overall, 52% (269/513) were female and 48% (244/513) patients were male. The reported clinical syndromes were ON (recurrent and isolated), ADEM and multiphasic ADEM (MDEM), ADEM/MDEM combined with ON, transverse myelitis (TM), ON combined with TM, encephalitis, cerebral syndromes, brainstem syndromes and seizures. Sixty-six studies reported the disease course of 635 patients, 56 articles reported 387 patients with relapsing MOGAD and 37 reported 248 patients with a single attack. Twenty-four patients received the diagnosis of MS in 10 studies. Three studies reported 10 patients with an overlapping of N-methyl-D-aspartate (NMDAR) antibodies and MOG-IgG.

Since the reported outcomes of treatments were highly

**Table 1**
Study inclusion and exclusion criteria.

| |
|---|
| **Inclusion criteria** |
| - Studies with clinical data of paediatric patients with CNS inflammatory disorders associated with seropositivity to MOG-IgG |
| - Clinical data on acute or long-term treatments |
| - Complete manuscripts in English or abstracts in English when enough information was available on the abstract |
| **Exclusion criteria** |
| - Studies in animals |
| - Cases with MOG-IgG positivity restricted to the cerebrospinal fluid |
| - Absence of differentiation of adult from paediatric patients when reporting treatment approaches |
| - MOG-IgG associated disease reported together with other CNS inflammatory disease (e.g. NMOSD, autoimmune encephalitis associated to other antibodies) |
| - Review articles without expert recommendations |

MOG-IgG, antibodies against myelin oligodendrocyte glycoprotein; CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorders.

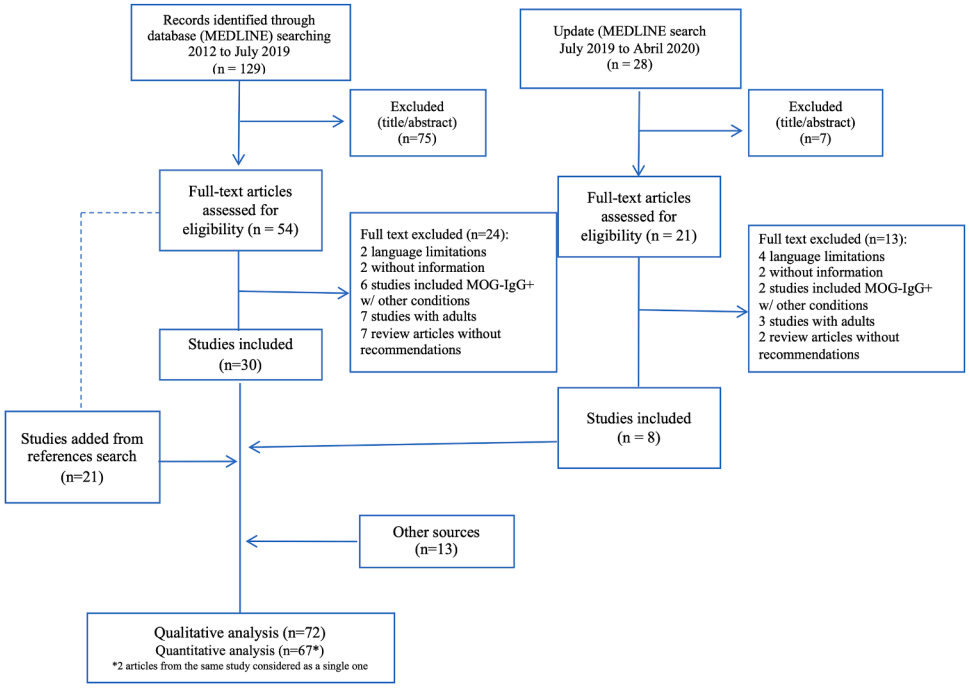


**Fig. 1.** Systematic review study flow diagram. Figure legend: The PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened, and the full texts retrieved. Abbreviation: MOG, myelin oligodendrocyte glycoprotein.

heterogeneous between studies, we were unable to compare them to estimate treatment efficacy through a meta-analysis. Nevertheless, we described comprehensively the treatment strategies that have been used in paediatric patients with MOGAD around the world.

### 4.2. Acute phase treatments

Sixty-one out of 67 studies with data from 621 patients reported acute phase treatments. All but one of them described the use of corticosteroids (Yılmaz et al., 2019). Intravenous methylprednisolone (IVMP) was reported in 88% of the studies (54/61), oral steroids in 67% (41/61), dexamethasone in 8% (5/61) and the use of steroids without specification (type/administration) was reported in 23% (14/61) of the studies. Twenty-eight studies reported the use of corticosteroids for a duration longer than 4 weeks and will be discussed in the long-term treatments section. among studies that provided information about the number of patients treated in the acute phase, 40% (250/621) of the patients were treated with IVMP, with a dose range from 10 to 30 mg/kg/day for 3–5 days up to a maximum of 1 g/day and 27% (165/621) patients received oral corticosteroids usually within a dose range of 1–2 mg/kg/day and only 0.8% (5/621) patients received dexamethasone.

Besides steroids, intravenous human immunoglobulin (IVIG) was reported in the acute phase in 66% (40/61) of the studies. IVIG was used to treat acute relapses in at least 21% (128/621) of the patients in the following doses/regimens: 1–2 g/kg in 2–5 days or 400 mg/kg/day in 5 days. A single study (Takano et al., 2019) reported the use of IVIG160 mg/kg in a single dose (2.5 g). Thirty-three percent (20/61) of the studies described the use of plasma exchange (PLEX), 3 to 7 cycles, in 4% (26/621) of the patients. (Fig. 2, Supplemental Table 2). IVIG was used alone or after intravenous or oral corticosteroids. PLEX was employed after steroids when patients presented incomplete responses. A single study (Baumann et al., 2016) reported the use of PLEX followed by IVIG to treat a clinical attack without preceding corticosteroids.

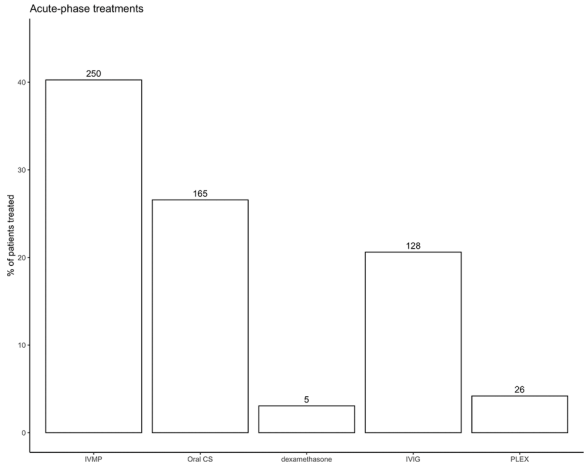


**Fig. 2.** Acute-phase treatments reported. Number of patients treated with each acute-phase medication over the total number of patients in studies that reported acute-phase treatments. Abbreviation: IVMP, intravenous methylprednisolone; Oral CS, oral corticosteroids; DEX/CS, dexamethasone or unspecified corticosteroids; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

### 4.3. Long-term treatments

Few articles described the clinical rationale for the use of long-term maintenance treatments in paediatric MOGAD. From those studies with this information, the main reason was relapses, although concurrence with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, MS diagnosis and the persistence of MOG-IgG seropositivity and radiological evidence of new inflammatory CNS lesions were also reported.

Overall, 79% (53/67) of the studies reported the use of long-term maintenance treatment in at least 537 paediatric patients with MOGAD. Among these, 53% (28/53) of the studies reported the use of oral corticosteroids for $>$ 4 weeks, 51% (27/53) described the use of azathioprine in 69 patients, 45% (24/53) reported 60 patients treated

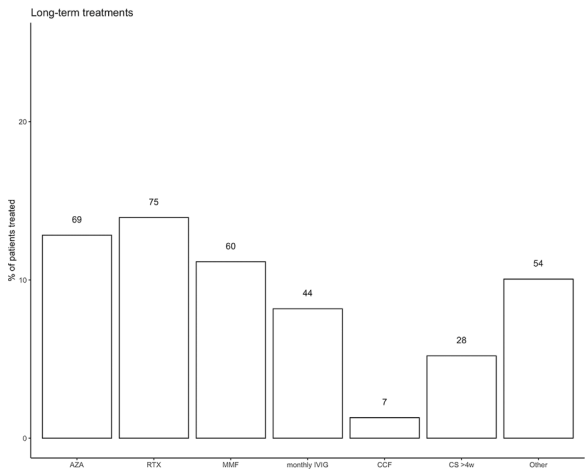


**Fig. 3.** Long-term treatments reported. Number of patients treated with long-term immunotherapies over the total number of patients in studies that reported long-term treatments. Abbreviation: IVIG, intravenous immunoglobulin; AZA, azathioprine; RTX, rituximab; MMF, mycophenolate mofetil; CCF, cyclophosphamide; CS>4w, corticosteroids for longer than 4 weeks.

with mycophenolate mofetil, 41% (22/53) used rituximab in 75 patients, 26% (14/53) reported 44 patients with monthly infusions of IVIG in and 7% (4/53) used cyclophosphamide in 7 patients. (Fig. 2, Supplemental Table 3). Sixteen studies described the use of first-line injectable disease modifying treatments (DMTs) for MS such as interferon beta formulations and glatiramer acetate in 39 patients. Two studies reported 2 patients who received teriflunomide, 2 studies described 2 patients treated with fingolimod, 5 studies reported 7 patients treated with natalizumab, and one study described a single patient treated with ofatumumab (anti-CD20). We also found two studies reporting 2 patients treated with tocilizumab (anti-IL6 receptor), and one study reported one patient treated with anakinra (anti-IL1b). Unfortunately, most studies did not report the long-term outcomes of paediatric patients with MOGAD treated with DMTs for MS and/or other monoclonal antibodies.

When analysing the 10 studies that reported only patients with a single attack, 40% (4/10) reported the use of chronic long-term treatment after the first demyelinating episode (4 reported treatment with oral steroids for more than 4 weeks and one study reported the use of azathioprine). Twenty-nine studies described only patients with relapsing disease courses. Of these, 93% (27/29) described the use of long-term maintenance treatments (16 studies with azathioprine, 17 studies with oral steroids for > 4 weeks, 14 studies with rituximab, 12 studies with mycophenolate mofetil, 10 studies with monthly IVIG, and 2 study with cyclophosphamide).

### 4.4. Review of expert consensus

Some review articles have addressed the issues related to the treatment of paediatric patients with MOGAD. In earlier literature, DMTs approved for MS were suggested for relapsing MOGAD, as both have demyelinating episodes. However, more recently, the use of DMTs approved for MS has been strongly discouraged due to lack of efficacy or even the risk of worsening in MOGAD patients. Hacohen et al. (2018); Hennes et al. (2018) and Armangue et al. (2020) Many patients with MOGAD may have a relapsing disease requiring long-term therapies to reduce the risk of further attacks. Subsequent review articles advocated for immunosuppressive therapies, such as mycophenolate mofetil, azathioprine, and anti-CD20 B-cell depleting therapies. Dale et al. (2012) Konuskan and Anlar (2019) recommended mycophenolate mofetil or azathioprine as first line medications associated with low dose steroids or monthly IVIG until full efficacy and RTX or cyclophosphamide for severe or refractory cases. Hennes et al. (2018) suggested that RTX and IVIG should be the initial choices. Chitnis (2019) advocate for mycophenolate mofetil or rituximab, suggesting azathioprine for the MOG-IgG patients diagnosed as AQP4-IgG seronegative NMOSD. Hacohen and Banwell (2019) suggested the use of mycophenolate mofetil, azathioprine or rituximab. For refractory relapsing patients they recommended monthly IVIG. If treatment response is satisfactory, re-evaluation is recommended after 2 years. Hacohen and Banwell (2019) Even though expert recommendations include similar drugs used as off-label indication, an international treatment guideline is yet to be defined.

## 5. Discussion

Our research identified 67 studies with detailed data about treatment of paediatric patients with neurological syndromes related to MOGAD. Since this is a rare and newly recognized condition, we found a high number of case reports and case series. Some articles described only initial symptoms and others reported the clinical evolution over years of follow-up. A few articles described patients diagnosed with MS and others with NMO/NMOSD possibly guided by former diagnostic criteria. It is uncertain if the same patients would fulfil diagnostic criteria for these conditions nowadays. The evaluation of treatment response and outcomes in paediatric patients with MOGAD were also heterogeneous. For example, most studies did not report the same outcomes. This precluded the comparison of treatment efficacy between the different therapeutic approaches.

Regarding acute relapse treatments, IVMP was used as first line treatment in most of the studies. The treatments like IVIG and PLEX were commonly used for severe, life threatening attacks, or for patients with poor response to corticosteroids. We observed that most studies reported the use of IVIG over PLEX, but this might be due to the lack of availability of PLEX in several centres. One controversial topic is the oral corticosteroids tapering, as some experts suggest that the oral steroid tapering could prevent early relapses (Hennes et al., 2018; Konuskan and Anlar 2019) and others have concerns about a possible iatrogenic effect of steroid taper increasing the number of relapses by adrenal suppression especially in young children. Hacohen and Banwell (2019)

There is no consensus regarding the use and type of the long-term maintenance treatment. Most authors indicate the use of long-term maintenance treatment in relapsing disease. However, some studies reported the use of prolonged courses of oral corticosteroids and even azathioprine in MOG-IgG+ patients after the first demyelinating episode. The indication of prolonged treatment after a severe first event or when the initial phenotype is more associated with a high risk of recurrences (e.g., ON) still remain to be defined.

he most commonly reported long-term maintenance treatments were azathioprine, mycophenolate mofetil, rituximab, IVIG and cyclophosphamide in decreasing order. None of the studies reported the use of methotrexate. Meanwhile, a recent cohort study (Hacohen et al., 2018) of paediatric patients with relapsing MOGAD showed efficacy of IVIG in reducing the annualized relapse rate (ARR) when compared to immunosuppressants. Rituximab, mycophenolate mofetil and azathioprine also reduced ARR in a decreasing order of magnitude.Hacohen et al. (2018) The most frequently reported treatments in this review are not the ones that showed higher reduction in ARR in a multicentric retrospective study designed to evaluate outcomes (Hacohen et al., 2018). Further studies with standardized endpoints are needed to define the best treatment strategy to paediatric patients with MOGAD.

More recently, the Paediatric European Collaborative Expert Consensus provided recommendations on treatment of MOGAD patients. Bruijstens et al. (2020) They also recommended the use of maintenance therapy only to relapsing patients and individualized evaluation of specific phenotypes more associated to relapses (persistence of MOG-IgG seropositivity, older ages at presentation and ON). They suggested treating the first demyelinating episode with IVMP. IVIG

is indicated if no/partial improvement. PLEX is suggested as an alternative for more severe cases. In relapsing patients, azathioprine or mycophenolate mofetil (combined with oral steroids during the first 3–6 months of treatment) were suggested as initial maintenance therapy switching to IVIG or rituximab if relapses were observed. If further relapses occur, combination therapy (IVIG plus rituximab) with or without oral steroids are recommended.

Over the last years several autoimmune conditions have been treated with human immunoglobulins. In inflammatory CNS conditions, IVIG is an alternative to treat attacks unresponsive to steroids and it has been used to avoid relapses in periodic intravenous infusions. Some of its advantages are the high tolerability and reduced risks of infections. However, as the use of IVIG expands, the global demands for plasma fractionation in order to obtain human immunoglobulins also increase surpassing its availability. Burnouf and Seghatchian (2014) The use of IVIG might be limited by health insurances due to costs. Moreover, lower income countries have lower purchase power and might have technologic difficulties for performing domestic fractionation (plasma freezing problems, limited storage capacity, sophistication of the techniques for purification and viral-reduction). Burnouf and Seghatchian (2014) To increase the availability of IVIG in developing countries, collaborative initiatives and governmental support are needed. Also, the development of recombinant immunoglobulins might be an alternative for the future.

Collaborative large-scale studies in countries with variable access to medications are needed to evaluate the efficacy and safety from each therapeutic intervention. Furthermore, since many MOGAD paediatric patients may experience a single attack without relapses after years of follow-up, it would be interesting to investigate whether this subgroup of patients have a transitory immune dysregulation or if acute treatment approaches used in clinical practice have any impact in the risk of further relapses.

Designing a clinical study to evaluate efficacy of treatments in MOGAD in paediatric patients has several challenges. First, paediatric MOGAD cases may not have a relapsing course, so long-term maintenance treatment after the acute phase is probably unnecessary for most of them. Second, if only relapsing MOGAD patients were selected it would be difficult to recruit a large number of patients to evaluate treatment efficacy in a phase 3 randomized controlled trial. This scenario is especially complicated considering the ethical issues involving placebo-controlled studies in paediatric population and studies using active comparator would probably require a higher number of patients for each treatment arm.

Another issue is defining specific study outcomes designed for MOGAD patients. In our systematic review, we found studies that measured ARR to estimate efficacy. However, only few groups evaluated long-term functional outcomes in MOGAD paediatric patients independently of clinical relapses. It would be interesting to evaluate the effects of each treatment on attack-related and non-related long-term disability and quality-of-life parameters.

Currently, there is no consensus on the value of monitoring MOG-IgG titres and its utility in the therapeutic decision in clinical practice. While some authors suggested that the persistence of MOG-IgG seropositivity may indicate higher risk of recurrences (Hacohen et al., 2018), patients can relapse despite converting to seronegative. Waters et al. (2020) Specifically, a study by Waters and Fadda et al. found that 40% of paediatric patients that became MOG-IgG negative after a first attack had relapses; on the other hand, 72% of those patients that remained MOG-IgG positive did not presented further relapses over a median of 4 years of follow-up. Waters et al. (2020) Therefore, it is still controversial to initiate long-term maintenance treatment in MOG-IgG+ patients with a single demyelinating episode without any further relapse based solely on the persistent MOG-IgG seropositivity after several months/years.

Our study has several limitations. First, we did not find any RCT to provide high-class of evidence data related to treatments in paediatric patients with MOGAD. Second, most of the articles used different clinical outcomes after treatments and the long-term therapeutic response from each individual was not reported in the majority of the studies. Third, many studies were retrospective case series or case reports that includes risk of missing information and lacks standardized data required for a meta-analysis with measures of consistency. At last, the total number of paediatric patients with MOGAD per treatment is probably higher than reported by this review given that some studies provided only the treatment strategy without the number of patients treated.

## 6. Conclusions

In the last years, we have advanced in describing the clinical phenotypes associated with MOGAD. Of note, a significant proportion of the paediatric patients may not have relapses, so long-term maintenance treatment initiated after the first demyelinating episode may not benefit these patients. Moreover, this approach may expose them to the risk of opportunistic infections.

In the absence of comparative RCTs, the drug availability and cost have been guiding treatment decisions in several centres. We need standardized outcome measures in observational studies in order to compare treatment efficacy between groups around the world. Along with better understanding of the pathobiology of MOGAD disease, this might help in the design of future clinical trials with current or newly developed medications.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103216.

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