Efficacy and safety of immunosuppressive therapy in myelin oligodendrocyte glycoprotein antibody–associated disease: a systematic review and meta-analysis

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Abstract

Background: A considerable number of patients with myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) will experience a relapse, but the effect of maintenance therapies on re-attack rates is currently unknown.

Objective: To investigate the efficacy and safety of immunosuppressive therapy for preventing disease relapses in patients with MOGAD, including rituximab (RTX), mycophenolate mofetil (MMF), and azathioprine (AZA).

Methods: English-language studies published prior to August 31, 2020, were searched in the NCBI (PubMed), ISI Web of Science, and the Cochrane Library databases. Patient characteristics, treatment regimens, outcome measures, and adverse effects were retrieved.

Results: We enrolled 11 studies in the final meta-analysis, including 346 patients with MOGAD. RTX therapy was demonstrated to result in reduced mean annualized relapse rate (ARR) by 1.35 (95% confidence interval (CI): 0.85–1.85) and reduced mean Expanded Disability Status Scale score by 0.80 (95% CI: 0.53–1.08) in patients with MOGAD. MMF therapy was associated with the mean ARR decreasing by 0.83 (95% CI: 0.31–1.35), and AZA was related to the mean ARR decreasing by 1.71 (95% CI: 0.83–2.58). The reported discontinuation rates of RTX, MMF, and AZA therapy due to adverse effects were 3/197 (1.52%), 3/39 (7.69%), and 4/37 (10.81%), respectively.

Conclusion: The study provided evidence to support the efficacy of RTX, MMF, and AZA on the preventive treatment in patients with MOGAD. However, large randomized controlled trials are still needed in the future.

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Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a transmembrane protein uniquely expressed on the surface of oligodendrocytes and the outermost surface of myelin sheath, making up less than 0.05% of the total central nervous system (CNS) myelin protein.[1] MOG was first identified 40 years ago as a target of demyelinating antibodies in guinea pigs.[2] Antibodies to MOG were originally thought to be involved in multiple sclerosis (MS), based on results from enzyme-linked immunosorbent assays employing linearized or denatured MOG peptides as antigen. Over the past few years, with the development of new-generation cell-based assays against full-length, conformationally intact human MOG, the role of antibodies to MOG in patients with inflammatory CNS demyelination has been revisited.[3]

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) is increasingly recognized as a distinct clinical entity, with

varying characteristics of phenotypes, disease courses, and response to treatment.[4,5] Recent studies with a long period of follow-up showed that a considerable proportion of patients with MOGAD tended to relapse.[6–8] Although the long-term outcome of motor and visual disability seemed better in MOGAD than that in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD) and MS, disability was accumulated from relapses, suggesting attack prevention may be necessary in MOGAD.[9,10]

According to the result of an international questionnaire investigation from 86 invited neurologists, the most favorable first-choice maintenance therapies in MOGAD were azathioprine (AZA), mycophenolate mofetil (MMF), and rituximab (RTX).[11] Up until now, there have been were no randomized controlled clinical trials in the maintenance treatment of MOGAD. Evidence-based guideline or consensus on management is urgently needed. In this study, we aimed to perform a systematic review and meta-analysis to investigate the efficacy and safety of RTX, MMF, and AZA in patients with MOGAD based on some observational studies.

Materials and methods

Study selection

We followed the PRISMA Statement guidelines[12] and Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE)[13] for conducting a systematic review. The authors (QLL and YXZ) independently searched relevant articles in NCBI (PubMed), ISI Web of Science, and the Cochrane Library databases for the period prior to August 31, 2020. The search was limited to English-language studies of humans. The search terms included "myelin oligodendrocyte glycoprotein", "MOG", "myelin oligodendrocyte glycoprotein antibody associated encephalomyelitis", "myelin oligodendrocyte glycoprotein antibody-associated disorders/disease", and "therapy", "treatment" "immunosuppressant", "mycophenolate mofetil", "azathioprine", and "rituximab". We retrieved all the articles and searched their reference lists to identify as many studies as possible.

Eligibility criteria

As no randomized clinical trials were identified, only observational studies were included in the

meta-analysis. The studies were read in their entirety to assess the appropriateness for their inclusion in the analysis. Studies were included if they met the following criteria: (1) original data from clinical studies; (2) MOG antibody testing was performed by a cell-based assay; (3) the exposure to MMF, AZA, or RTX; (4) the efficacy of medication was assessed by annualized relapse rate (ARR) and/or Expanded Disability Status Scale (EDSS), reporting the mean with standard deviation (SD), median with range or interquartile range. Single-case reports and studies concerning a single patient were excluded from the meta-analysis. All analyses were based on previously published studies, thus no ethical approval and patient consents are required.

Data extraction and quality assessment

All the studies were evaluated and examined carefully by two authors (QLL and YXZ). Discrepancies were discussed and resolved by verification from a third reviewer (CHS). The following characteristics were retrieved for each study: authors, publication year, study design, region, sample, age, gender ratio, treatment regimens, ARRs, and EDSS scores before and after treatment, adverse effects, and follow-up duration. The quality of included studies was assessed by an 11-item checklist which was proposed by the Agency for Healthcare Research and Quality (AHRQ) and recommended to estimate the quality of cross-sectional/prevalence studies.[14] Article quality was identified as follows: low quality=0–3; moderate quality=4–7; high quality=8–11.

Data analysis

Two primary efficacy outcome measures were assessed, namely, differences in mean ARR and EDSS score before and after treatment, separately of RTX, MMF, and AZA. The secondary outcomes were discontinuation of treatment and manifestations of adverse effects. If ARR or EDSS was provided in the form of median with range or interquartile range, it would be converted into mean with SD as described by Wan *et al.*[15] If ARR or EDSS was presented by individual data, it would be calculated into mean with SD. The data of interest were analyzed by mean difference (MD) as effect measures. Statistical heterogeneity was assessed using I^2 statistical; $p < 0.10$ or $I^2 > 0.50$ was considered significant. If substantial heterogeneity was detected, the analysis would be

performed on random-effect model with DerSimonian and Laird method. Otherwise, fixed-effect model would be used.

Sensitivity analysis was conducted by excluding each study individually and recalculating the combined estimates for the remaining studies to assess the influence of an individual result on the pooled estimates. Begg's tests were performed to evaluate publication bias, $p < 0.05$ was considered as existence of significant publication bias. All the data analyses were performed using STATA SE12.0 (Stata, TX, College Station, USA).

Data availability
Data were available upon request. Interested researchers may contact the corresponding author.

Results

Study characteristics
Eleven studies[16–26] were included in the final meta-analysis, as seen in Figure 1. All the studies collectively included 346 patients diagnosed with MOGAD, who were receiving RTX ($n = 231$), MMF ($n = 59$), or AZA therapy ($n = 56$). The median age of patients ranged from 5.4 to 37.9 years, and the female to male ratio ranged from 1:1 to 3:1. The median disease duration before RTX, MMF, or AZA therapy ranged from 0.41 to 22.3 years. The median follow-up duration ranged from 0.92 to 7.8 years. Two of these studies[23,26] were prospective observational studies, while the remaining nine being retrospective studies.[16–22,24,25] Three of these studies[18,24,26] focused on adults, three studies[19,20,23] on children, and the remaining five studies[16,17,21,22,25] on both adults and children. The quality score of each study were assessed by AHRQ checklist, indicating all included studies were identified as being high quality as shown in Table 1.

The clinical characteristics of each study were also presented in Table 1, including pre-ARR, clinical phenotype, immunotherapies prior, concomitant maintenance corticosteroids and immunosuppressants. In 4 of 11 included studies,[18,21,22,26] a varied proportion of patients had received other immunotherapies prior to RTX, MMF, or AZA, while patients received RTX, MMF, and AZA as first immunosuppressants to prevent relapses in the
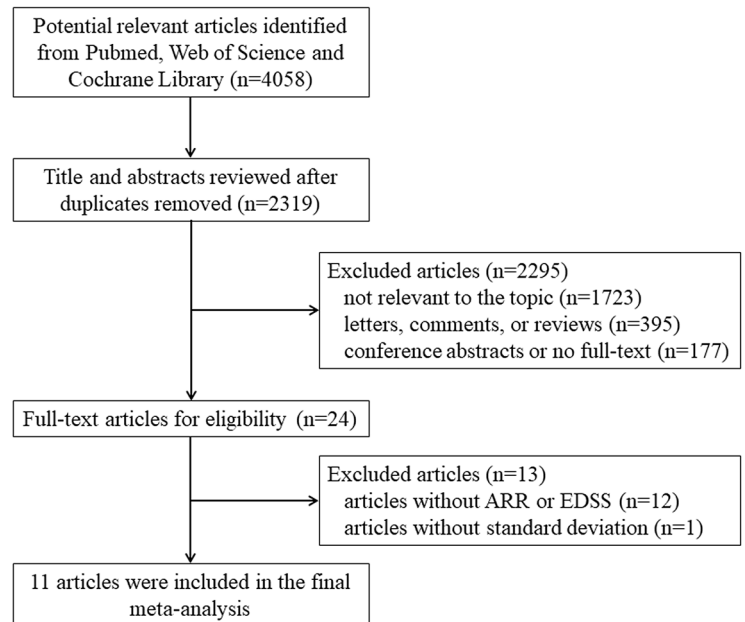
other studies.[16,17,19,20,23,24,25] With regard to concomitant maintenance corticosteroids, some patients received concomitant corticosteroids in two studies,[17,21] meanwhile, patients in seven studies[18–20,22–25] did not, and data were not available in the remaining two studies.[16,26] A certain proportion of patients received concomitant intravenous immune globulins or plasma exchange in three studies,[17,19,21] while patients in other studies[16,18,20,22–26] did not. Details of the RTX regimen were available for 180/231 (77.9%) patients[18,19,21,23,26] and varied among studies: 137 (60.9%) patients[21,26] received two fortnightly 1000-mg infusions, followed by 1000-mg infusion every 6 months or when memory B-cells re-emerged, 26 (11.6%) patients[18] received 1000-mg infusions every 6 months, 12 (5.3%) patients[23] were treated with 500 mg/m² (maximum 1000 mg) infusion every 2 weeks for two times, followed by 500 mg/m² (maximum 1000 mg) infusion when CD19 + memory B-cells re-emerged, and 5 (2.2%) patients[19] received two fortnightly 750 mg/m² infusions. Details of the MMF regimen was available for 32/59 (54.2%) patients:[16–18] 16 (27.1%) patients[16,18] were treated with 2000 mg daily and other 16 (27.1%) patients[17] were treated with 1000–2000 mg daily. Details of the AZA regimen was available for 11/56 (19.6%) patients:[18] all of them received 150 mg daily, as shown in Table 1.

Figure 1. Study selection flow diagram.

The flow diagram contains the following boxes:

- Potential relevant articles identified from Pubmed, Web of Science and Cochrane Library (n=4058)
- Title and abstracts reviewed after duplicates removed (n=2319)
- Excluded articles (n=2295)
  not relevant to the topic (n=1723)
  letters, comments, or reviews (n=395)
  conference abstracts or no full-text (n=177)
- Full-text articles for eligibility (n=24)
- Excluded articles (n=13)
  articles without ARR or EDSS (n=12)
  articles without standard deviation (n=1)
- 11 articles were included in the final meta-analysis

Table 1. Characteristics of the studies included in the final meta-analysis.

Study (authors, year)	Study design	Region	Groups	No. of cases	Median or mean age	Female:male ratio	Clinical phenotype	Pre-treatment ARR, median (range)	Disease duration before treatment, years (median)
Montcuquet et al.[16]	Retrospective	France	Adults and children	5	37.9	2.9:1	NMO: 60% TM: 40%	1 (1–1)	NA
Ramanathan et al.[17]	Retrospective	Australia	Adults and children	22	12	2.11:1	ADEM: 20% ON: 54% Others: 26%	MMF 1.83 [0.47–6] RTX 1.65 [0.67–2]	MMF 0.67 RTX 1.25
Zhou et al.[20]	Retrospective	China	Children	14	5.4	1.3:1	NMOSD: 47.8% ADEM: 21.7% Others: 30.4%	1.17 [0.25–7.67]	RTX 1.05 MMF 1.5 AZA 2.91
Pedapati et al.[25]	Retrospective	India	Adults and children	18	30.5	3:1	ON: 75% TM: 15% NMO: 5% Others: 5%	AZA 3.24 ± 3.13[a] MMF 0 ± 0[a]	NA
Tzartos et al.[24]	Retrospective	Greece	Adults	7	34	1.33:1	ON: 57.1% NMO: 14.3% Others: 28.6%	0.33 [0–5]	AZA 17 MMF 22.3
Mao et al.[19]	Retrospective	China	Children	5	6.6	1.08:1	NMOSD: 60% ADEM: 40%	2.4 (0.67–8)	0.92
Cobo-Calvo et al.[18]	Retrospective	France and Spain	Adults	48	34.1	1.23:1	ON: 65.6% TM: 20% NMO: 7.2% Others: 7.2%	0.79 ± 0.91[a]	AZA 2.4 MMF 1.7 RTX 3.3
Albassam et al.[23]	Prospective	Canada	Children	12	10	2:1	NMOSD: 33.3% ON: 16.7% ADEM: 50%	NA	0.41
Durozard et al.[26]	Prospective	France	Adults	16	33.5	1:1	NA	2 (1–10)	0.65
Chen et al.[22]	Retrospective	America	Adults and children	70	29	1.38:1	ON: 47% TM: 11% NMO: 10% ADEM: 31%	1.6 [0–9.7]	NA
Whittam et al.[21]	Retrospective	Multicenter	Adults and children	121	23.2	1.42:1	ON: 29% TM: 12.4% NMO: 28.1% ADEM: 12.4% Others: 18.2%	1.82 [0.74–3.4][b]	1.59

Study (authors and year)	Other immunotherapies prior to MMF, AZA, and RTX	Concomitant CS	Concomitant IVIG/PE	Immunosuppressant (no. of cases) and dosage	Available index	Median follow-up duration, years	Quality score
Montcuquet et al.[16]	None	NA	None	MMF (5): 2000 mg daily	ARR, EDSS	3.58	9
Ramanathan et al.[17]	None	MMF: 16/16 RTX: 6/6	RTX: IVIG 1/6, PE 1/6 MMF: None	MMF (16): 1000–2000mg daily; RTX (6): NA	ARR	MMF 1.25; RTX 1.04	10

(Continued)

Table 1. (Continued)

Study (authors and year)	Other immunotherapies prior to MMF, AZA, and RTX	Concomitant CS	Concomitant IVIG/PE	Immunosuppressant (no. of cases) and dosage	Available index	Median follow-up duration, years	Quality score
Zhou et al.[20]	None	None	None	RTX [8]: NA; MMF [3]: NA; AZA [3]: NA	ARR	0.92	9
Pedapati et al.[25]	None	None	None	AZA [15]: NA; MMF [3]: NA	ARR	AZA 1.0; MMF 3.25	8
Tzartos et al.[24]	None	None	None	AZA [5]: NA; MMF [2]: NA	ARR	7.8	8
Mao et al.[19]	None	None	IVIG: 5/5 PE: None	RTX [5]: 2×750mg/m², Days 1 and 15	ARR	1.25	8
Cobo-Calvo et al.[18]	Prior to AZA: 21.1% Prior to MMF: 50% Prior to RTX: 36.7%	None	None	AZA [11]: 150 mg daily; MMF [11]: 2000 mg daily; RTX [26]: 1000 mg infused every 6 months	ARR, EDSS	AZA 2.1; MMF 1.7; RTX 1.7	8
Albassam et al.[23]	None	None	None	RTX [12]: Two doses of 500 mg/m²(max 1 g) given 10–14 days apart. Subsequently, one dose of 500 mg/m² (max 1 g) was administered when CD19 cell counts >0	EDSS	2.0	10
Durozard et al.[26]	Prior to RTX: 31.2%[c]	NA	None	RTX [16]: Induction: 1000 mg infused twice at a 2-week interval. Maintenance: a single infusion of 1000 mg at 6 months or CD27-positive B-cells reached 0.05%	ARR, EDSS	1.59	9
Chen et al.[22]	Prior to MMF: 53% Prior to AZA: 23% Prior to RTX: 32%	MMF: 2/19 AZA: 10/22 RTX: 5/37	None	MMF [19]: NA; AZA [22]: NA; RTX [37]: NA	ARR	MMF 1.1; AZA 1.7; RTX 1.2	9
Whittam et al.[21]	Prior to RTX: 45.6%[d]	32/121	IVIG: 7/121 PE: None	RTX [121]: Initial 1000 mg on Day 0 and 15 or 375 mg/m² weekly for 4 weeks. Interval between subsequent treatment was either fixed at 6-months or determined by periodic testing of circulating CD19 + B-cell or CD19 + CD27 + memory B-cell levels	ARR, EDSS	1.0	8

ADEM, acute disseminated encephalomyelitis; ARR, annualized relapse rate; AZA, azathioprine; CS, corticosteroids; EDSS, Expanded Disability Status Scale; IVIG, intravenous immune globulins; MMF, mycophenolate mofetil; NA, not available; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; PE, plasma exchange; RTX, rituximab; TM, transverse myelitis.
[a]Represents mean ± SD.
[b]Represents median (interquartile range).
[c]Previous treatments included mycophenolate mofetil for two and natalizumab, fingolimod, and teriflunomide for the remaining three patients.
[d]Previous treatments included azathioprine [27], mycophenolate mofetil [20], intravenous immune globulins [7], maintenance plasma exchange [2], cyclophosphamide [6], mitoxantrone [3], methotrexate [2], tacrolimus [1], ciclosporin [1], and multiple sclerosis—disease-modifying therapies [11].
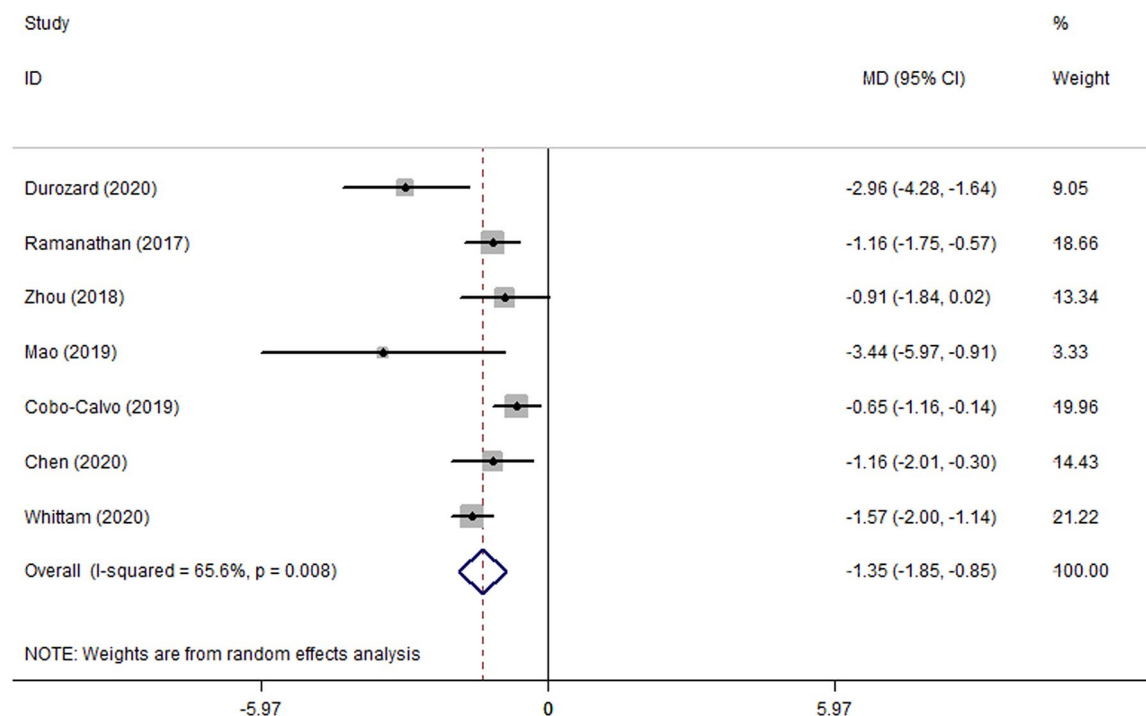
Figure 2. Forest plot of the mean difference in annualized relapse rate associated with the rituximab therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.

Efficacy of RTX on the ARR and EDSS score

ARRs before and after RTX therapy were reported in seven studies,[17–22,26] including 199 patients with MOGAD. A forest plot of the MD in the ARR was shown in Figure 2. This finding suggested that the MD reduction of ARR after RTX therapy was 1.35 (95% CI: 0.85–1.85; p_heterogeneity = 0.008, I^2 = 65.6%) using the random-effect model. Subgroup analyses by age (adults *vs* children) and study design (retrospective *vs* prospective) were performed. Similar MDs were observed in the subgroup of adults (−1.67, 95% CI, −2.63 to −0.72; p_heterogeneity = 0.001, I^2 = 81.9%) and children (−1.06, 95% CI, −1.99 to −0.13; p_heterogeneity = 0.071, I^2 = 57.2%; Table 2). After excluding one prospective study,[27] the MD of ARR among the remaining six retrospective studies[17–22] was −1.17 (95% CI: −1.60 to −0.75; p_heterogeneity = 0.057, I^2 = 53.3%). Sensitivity analyses were performed successively by removing each study in turn and re-analyzed. No studies were found to significantly affect the MD and heterogeneity (MD ranged from −1.17, 95% CI: −1.60 to −0.75 to −1.50, 95% CI: −2.00 to −1.00). No obvious publication bias was suggested from the results of Begg's test for ARR (*p* = 0.548), as shown in Supplemental eFigure 1.

EDSS scores were described in four studies with RTX therapy,[18,21,23,26] including 175 patients. A forest plot of the MD in the EDSS before and after RTX therapy was shown in Figure 3. The result revealed that the MD of EDSS after RTX therapy was −0.80 (95% CI: −1.08 to −0.53; p_heterogeneity = 0.955, I^2 = 0.0%) on the fixed-effect model. No obvious publication bias was found from the results of Begg's test for EDSS (*p* = 0.308), as shown in Supplemental eFigure 2.

Efficacy of MMF on the ARR and EDSS score

ARRs before and after MMF therapy were reported in seven studies[16–18,20,22,24,25] including 59 patients for the meta-analysis. As seen in Figure 4, a forest plot indicated the MD of ARR after MMF therapy on random-effect model was −0.83 (95% CI: −1.35 to −0.31; p_heterogeneity = 0.005, I^2 = 67.8%). When conducting the subgroup analysis by age, the MD of ARR after MMF therapy was −1.12 (95% CI: −1.77 to −0.47; p_heterogeneity = 0.697, I^2 = 0.0%) in adults and −1.40 (95% CI: −2.40 to −0.40; p_heterogeneity = 0.843, I^2 = 0.0%) in children, showing the heterogeneity was well eliminated (Table 2). No obvious publication bias was suggested from the

Table 2. The results of meta-analysis and subgroup analysis in myelin oligodendrocyte glycoprotein antibody–associated disease.

Subgroup	Studies no.	Patients no.	MD (95% CI) fixed model	MD (95% CI) random model	Heterogeneity test	
					I^2 (95%)	P
RTX on ARR	7	199	−1.25 (−1.50, −0.99)	−1.35 (−1.85, −0.85)	65.6%	0.008
Adults	4	143	−1.30 (−1.67, −0.93)	−1.67 (−2.63, −0.72)	81.9%	0.001
Children	4	50	−1.09 (−1.60, −0.58)	−1.06 (−1.99, −0.13)	57.2%	0.071
RTX on EDSS	4	175	−0.80 (−1.08, −0.53)	−0.80 (−1.08, −0.53)	0.0%	0.955
MMF on ARR	7	59	−1.00 (−1.00, −1.00)	−0.83 (−1.35, −0.31)	67.8%	0.005
Adults	3	28	−1.12 (−1.77, −0.47)	−1.12 (−1.77, −0.47)	0.0%	0.697
Children	2	7	−1.40 (−2.40, −0.40)	−1.40 (−2.40, −0.40)	0.0%	0.843
MMF on EDSS	2	16	−0.23 (−1.50, 1.04)	−0.23 (−1.50, 1.04)	0.0%	0.666
AZA on ARR	5	56	−1.49 (−2.04, −0.95)	−1.71 (−2.58, −0.83)	55.7%	0.061
Adults	3	30	−0.97 (−1.60, −0.34)	−0.97 (−1.60, −0.34)	0.0%	0.482
Children	2	11	−2.01 (−3.42, −0.61)	−2.01 (−3.42, −0.61)	0.0%	0.753

ARR, annualized relapse rate; AZA, azathioprine; CI, confidence interval; EDSS, Expanded Disability Status Scale; MD, mean difference; MMF, mycophenolate mofetil; RTX, rituximab.
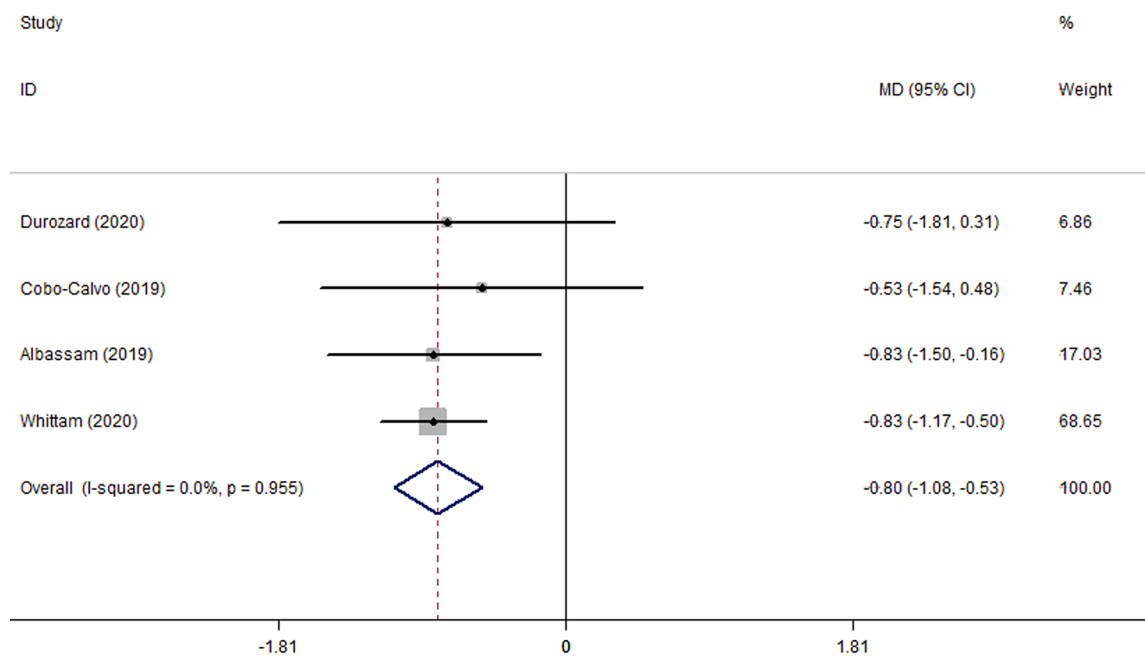
Figure 3. Forest plot of the mean difference in Expanded Disability Status Scale score associated with the rituximab therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.
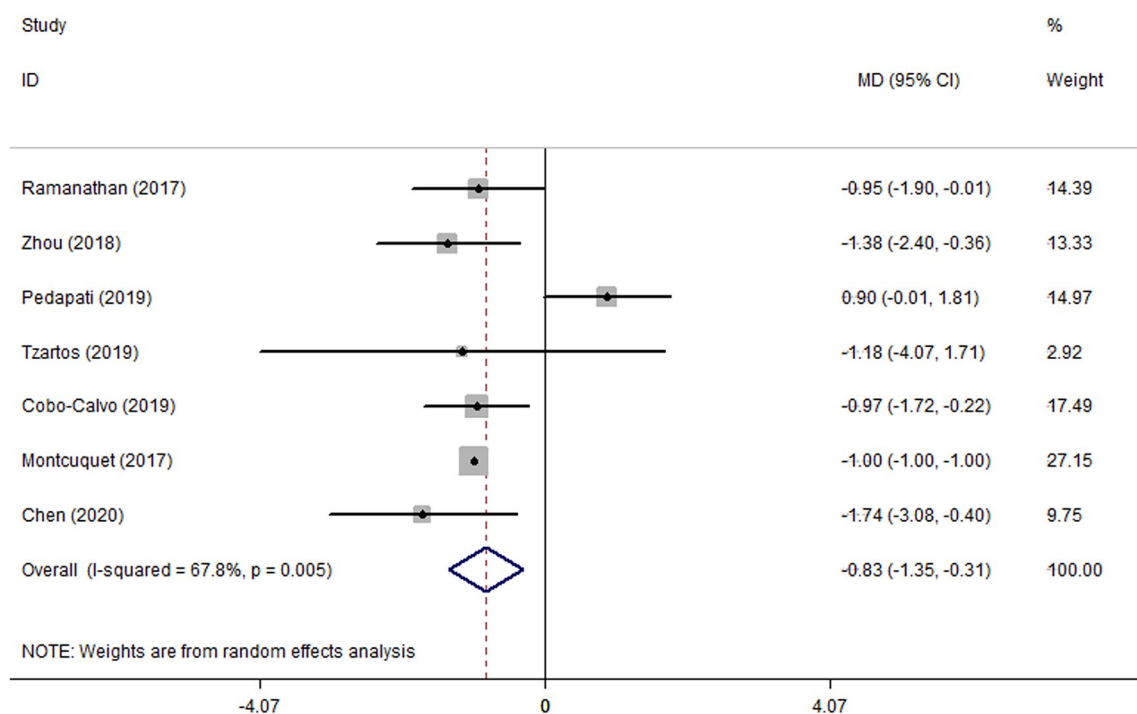
Figure 4. Forest plot of the mean difference in annualized relapse rate associated with the mycophenolate mofetil therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.

results of Begg's test for ARR ($p = 0.368$), as shown in Supplemental eFigure 3.

EDSS scores were reported in two studies with MMF therapy,[16,18] including 16 patients for the analysis. A forest plot suggested that the MD of EDSS after MMF therapy was −0.23 (95% CI: −1.50 to 1.04; p_heterogeneity = 0.666, $I^2 = 0.0\%$, Figure 5). No obvious publication bias was observed by the Begg's test for EDSS ($p = 1.000$), as shown in Supplemental eFigure 4.

Efficacy of AZA on the ARR and EDSS score

ARRs before and after AZA therapy were reported in five studies,[18,20,22,24,25] including 56 patients for the meta-analysis. Our study demonstrated that the MD of ARR after AZA therapy on random-effect model was −1.71 (95% CI: −2.58 to −0.83; p_heterogeneity = 0.061, $I^2 = 55.7\%$, Figure 6). Given the underlying heterogeneity, subgroup analysis by age was performed. The MD of ARR after AZA therapy was −0.97 (95% CI: −1.60 to −0.34; p_heterogeneity = 0.482, $I^2 = 0.0\%$) in adults and −2.01 (95% CI: −3.42 to −0.61; p_heterogeneity = 0.753, $I^2 = 0.0\%$) in children on the fixed-effect model, revealing that the heterogeneity

was well subsided. No publication bias was indicated from the result of Begg's test for ARR ($p = 0.462$) and the Begg's funnel plot was symmetrical (Supplemental eFigure 5). EDSS scores before and after AZA therapy were only reported in one of the included studies[18] which was not sufficient to conduct a meta-analysis.

Safety and discontinuation of treatment

As seen in Table 3, drug discontinuation was recorded in nine studies.[16–21,23,25,26] In six studies[18–21,23,26] reporting the RTX discontinuation, 27/197 (13.71%) patients discontinued RTX therapy due to adverse effects (3/197, 1.52%), the others discontinued RTX because of physician or patient decision (6/197, 3.05%) and treatment failure (18/197, 9.14%). In five studies[16–18,20,25] with the details of MMF discontinuation, 13/39 (33.33%) patients discontinued MMF therapy due to adverse effects (3/39, 7.69%). In three studies[18,20,25] reporting AZA discontinuation, 9/37 (24.32%) patients discontinued AZA therapy due to adverse effects (4/37, 10.81%).

The detailed adverse effects were recorded in four of included studies.[21,23,25,26] Among the patients

Figure 5. Forest plot of the mean difference in Expanded Disability Status Scale score associated with the mycophenolate mofetil therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.

Figure 6. Forest plot of the mean difference in the annualized relapse rate associated with the azathioprine therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.

receiving RTX therapy with the records of adverse effects,[21,23,26] 7/149 (4.70%) patients experienced infusion related reactions, 8/149 (5.37%) patients developed leucopenia, 6/149 (4.02%) patients developed hypogammaglobulinemia, 2/149 (1.34%) patients developed infection. The information about adverse effects of MMF and AZA were recorded only in one of the studies,[25] in

Table 3. Discontinuation and adverse effects of immunosuppressive therapy in patients with myelin oligodendrocyte glycoprotein antibody–associated disease.

Immunosuppressant	Discontinuation of treatment	Manifestations of adverse effects
RTX[18–21,23,26]	27/197 (13.71%) discontinued 3/197 (1.52%) adverse effects 6/197 (3.05%) physician or patient decision 18/197 (9.14%) treatment failure	7/149 (4.70%) experienced infusion related reactions 8/149 (5.37%) developed leucopenia 6/149 (4.02%) developed hypogammaglobulinemia 2/149 (1.34%) developed infection
MMF[16–18,20,25]	13/39 (33.33%) discontinued 3/39 (7.69%) adverse effects 2/39 (5.13%) physician or patient decision 8/39 (20.51%) treatment failure	1/3 (33.3%) developed diarrhea
AZA[18,20,25]	9/37 (24.32%) discontinued 4/37 (10.81%) adverse effects 3/37 (8.11%) physician or patient decision 2/37 (5.41%) treatment failure	0/15 (0%) experienced adverse effects

AZA, azathioprine; MMF, mycophenolate mofetil; RTX, rituximab.

which 1/3 (33.3%) patient on MMF therapy developed diarrhea while 0/15 (0%) patient on AZA therapy experienced any adverse effects.

Discussion

Frequent attacks contributed to disability in patients with MOGAD. As previous studies suggested, 62.2% of patients remitted completely or almost completely after the initial attack, while the proportion became lower for subsequent attacks (40.6%) and dropped to 26.4% after the fifth relapse.[6] Some studies have suggested that long-term immunosuppressive therapy was potentially related to a reduced relapse rate, similar to that in patients with MS and NMOSD.[7,8,27,28] To the best of our knowledge, this is the first meta-analysis on the efficacy and safety of RTX, MMF, and AZA in disease prevention of MOGAD.

RTX is a human and mouse chimeric IgG1 monoclonal antibody that targets the B-cell CD20 antigen, which is involved in cell cycle progression. RTX was originally approved for the treatment of B-cell lymphoma, but it has been increasingly used in B-cell-related autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, autoimmune encephalitis, MS, and NMOSD.[29–34] In MOGAD, the pathogenic role of MOG antibody remains uncertain. Some studies suggested that MOG antibody might lead to MOGAD *via* two possible mechanisms: (1) MOG antibody–induced demyelination mediated by complements and (2) MOG-reactive T-cell-induced inflammation through antigen-presenting cells.[35]

In this study, we found that RTX treatment was robustly associated with reduced ARR and disability levels in patients with MOGAD, and it was still effective in adults and children when stratified by age. The MD reduction of ARR after RTX therapy in patients with MOGAD was 1.35 (95% CI: 0.85–1.85), which was close to that in those with NMOSD (1.56, 95% CI: 1.29–1.82) and MS (1.00, 95% CI: 0.83–1.17).[33,34] A multi-center observational study indicated that the relapse-free rate during RTX treatment was 92.9% (13/14), consistent with our result.[36] Concurrently, another study showed that the relapse-free rate during RTX therapy dropped to 22.2% (2/9), which might be affected by the prolonged follow-up duration (6.25 years), the small sample and other potential confounders.[6] A recent systematic review conducted by Lu *et al.*[37] also revealed that RTX could reduce the relapse rate in the patients with MOGAD, using a qualitative analysis based on the Oxford Center for Evidence-Based Medicine 2011 Levels. As for safety concerns, we identified that adverse events occurred infrequently and only a few patients discontinued RTX therapy due to adverse effects. Thus, it can be concluded that RTX is an effective and safe treatment in patients with MOGAD.

MMF is a prodrug of mycophenolic acid (MPA), which inhibits de novo guanosine nucleotide synthesis and selectively targets proliferation of T and B lymphocytes.[38,39] In the past few years, MMF has been used for the prevention of allograft rejection in organ transplantation and is increasingly used in the treatment of autoimmune diseases, such as NMOSD because of its potential efficacy and good tolerance.[40]

Our study demonstrated that MMF treatment is effective in reducing the ARR in patients with MOGAD. Li *et al.*'s[41] study conducted a prospective observational cohort study with 79 MOGAD patients, suggesting the relapse-free rate in the MMF group was 92.6% (50/54) with the median follow-up of 400 days, consistent with our result. However, with an extension of follow-up, the relapse-free rate probably drops. In a retrospective multicenter study, the relapse-free rate after MMF treatment was 46.7% (7/15) during a median follow-up of 5.5 years.[42] When subgroup analysis was performed by age, the heterogeneity subsided, suggesting that age may be a potential source of heterogeneity. A particular concern was the different clinical phenotypes in patients with MOGAD, which changed from acute disseminated encephalomyelitis (ADEM) like (ADEM, ADEM-optic neuritis, and multiphasic disseminated encephalomyelitis) in children to opticospinal (optic neuritis and myelitis) in adults.[43] Our study was not qualified enough to conclude on the association between MMF treatment and EDSS scores, mainly due to the limited number of studies. Therefore, further studies on disability levels after MMF treatment are required. Notably, reported MMF discontinuation rate due to adverse effects was 7.69%, which was not rare. Our result supported the notion that MMF was effective for the maintenance treatment in patients with MOGAD.

Similar to MMF, AZA is an immune-modulating drug, originally developed for the prevention of graft rejection in transplant surgery.[44] Considering widespread application, popular price, and reliable efficacy, AZA has gradually become one of the most commonly prescribed preventive treatment in immune-mediated neurological diseases, including myasthenia gravis, autoimmune encephalitis and NMOSD.[45–47] As a consequence, an international questionnaire investigation for neurologists found that AZA was the most popular first-choice maintenance therapy in MOGAD.[11]

Unsurprisingly, our study also identified AZA treatment effective in reducing the ARR in patients with MOGAD, which was in agreement with Lu *et al.*'s[37] qualitative review. In a retrospective multicenter study, the relapse-free rate after AZA treatment was 50.0% (10/20) and ARR was also lowered with a median follow-up of 5.5 years.[42] Subgroup analysis exhibited that AZA treatment is effective in both adults and children. In addition, there seemed to be a moderate tendency that AZA was more effective in children than in adults, probably due to different clinical phenotypes between them. This finding suggested that it would be better for future studies to be aware of the age stratification and different phenotypes. Reported discontinuation of AZA treatment due to adverse effects was 10.81%. To conclude, AZA is an effective therapy for preventing disease relapses in patients with MOGAD.

This study has several limitations. First, all the studies included in our meta-analysis were retrospective or prospective observational studies with heterogeneous designs, which may not control sufficiently all the related confounders. Second, potential heterogeneities were indeed observed among the pooled estimates of ARRs after RTX, MMF, or AZA therapy. We speculated that disease course, number of attacks before therapy, treatment protocols, delayed efficacy of drugs and combination of corticosteroids might contribute to the heterogeneities across the studies. Of note, a certain proportion of patients were on concomitant corticosteroids or combination therapy which might inflate the therapeutic effect of RTX, MMF, and AZA. Third, we converted non-normally distributed statistics (median with range or interquartile range, individual data) to normally distributed statistics (mean with SD), which may lead to bias. Fourth, the efficacy and safety of MMF and AZA needed to be explained with caution, due to the small sample, incomplete information on dosing regimens and adverse event data.

Conclusion

In summary, this systematic review and meta-analysis provided further evidence that RTX is associated with reduced relapse rates and disability levels in patients with MOGAD. MMF and AZA were also identified to be effective in preventing disease relapses. Our findings highlighted the necessity of large randomized clinical trials to

thoroughly evaluate the efficacy and safety of RTX, MMF, and AZA as maintenance therapy in patients with MOGAD.

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Supplemental material
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