Efficacy and Safety of Mycophenolate Mofetil Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: Neuromyelitis optica spectrum disorders (NMOSD) is an autoimmune demyelinating disease of the central nervous system characterized by severe attacks of optic nerve and spinal cord. Mycophenolate mofetil (MMF) is an immunosuppressive agent (IS) which is widely prescribed for NMOSD patients. This systematic review and meta-analysis aims to assess the efficacy and safety of MMF in controlling relapse and disease severity.

Methods: Studies were obtained from the EMBASE and Ovid MEDLINE databases. Eligible studies were the studies of NMOSD patients treated with MMF which reported treatment outcomes as Annualized Relapse Rate (ARR) or Expanded Disability Status Scale (EDSS) before and after treatment. Case reports, case series less than 3 patients, and reviews were excluded.

Results: Fifteen studies included 1047 patients, of whom 915 (87.4%) were aquaporin-4 immunoglobulin seropositive. The total number of patients that received MMF was 799. Meta-analysis on ARR and EDSS were conducted in 4 studies with a total of 200 patients and 3 studies with a total of 158 patients, respectively. The result showed a significant improvement with a mean reduction of 1.13 (95% confidence interval (CI), 0.60 to 1.65) in ARR and a mean reduction of 0.85 (95% CI, 0.36 to 1.34) in EDSS after MMF therapy. Adverse drug reactions occurred in 106 (17.8%) of 594 patients that were documented having side effects during MMF therapy.

Conclusion: This systematic review and meta-analysis showed that using MMF as a preventive therapy in NMOSD patients can significantly reduce relapse rate and improve disease severity with an acceptable tolerability.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an immune-mediated inflammatory disease of the central nervous system with aquaporin-4 immunoglobulin G (AQP-4 IgG) as a pathogenic autoantibody. The original notion of monophasic attack of optic neuritis (ON) and transverse myelitis (TM) had been replaced by the recurrent course in the majority of cases. [1, 2] Unlike multiple sclerosis (MS), the disability in NMOSD patients correlates with the number of recurrent attacks rather than the stage of disease progression. Therefore, most treatments aim to prevent relapses. [3] Prior to the new efficacy-proven medications for NMOSD such as eculizumab, satralizumab, and inebilizumab, several immunosuppressive agents (IS) were used. These include corticosteroids, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate, cyclophosphamide (CYP), mitoxantrone, and rituximab (RTX). [4–6]

MMF is a prodrug of mycophenolic acid (MPA), a reversible, non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH). MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation. Therefore, treatment with MMF suppress both cell-mediated immune responses and antibody formation.

Application of MMF has extended from post organ transplantation to many autoimmune diseases, including NMOSD. [7] The first case series that suggested using MMF as a preventive treatment for relapses in NMOSD patients was published in 2009. [8] Subsequent studies have also corroborated the same benefit of MMF as a preventive therapy in NMOSD as well as its ability to reduce neurological impairment.

Randomized controlled trials of MMF in NMOSD patients are not available, as there are only case series, mostly with a retrospective study design. Therefore, we conducted a systemic review to evaluate the efficacy as well as adverse drug reactions (ADRs) of MMF in NMOSD patients.

Materials And Methods

Study Selection

Two investigators (S.S. and P.K.) independently searched for eligible published peer-reviewed studies indexed in Ovid MEDLINE and EMBASE databases from inception to April 2020. The search terms “neuromyelitis optica spectrum disorder” and “mycophenolate mofetil” were used (supplementary data), and was limited to English-language human studies. Eligible studies could be either randomized-controlled trials or cohort studies/case series that investigated the efficacy of MMF in NMOSD patients. Changes in either the annualized relapse rate (ARR) ratio or Expanded Disability Status Scale (EDSS) score before and after treatment must be reported. To avoid non-representativeness of cases, case series that included fewer than 3 patients were excluded. The studies were reviewed in full-length to assess the appropriateness for their inclusion in the systematic review. Any differences in the determination of study eligibility between the two aforementioned investigators were re-evaluated, and the disagreement was resolved by discussion with other investigators (J.J. and P.U.).

Data Extraction

The extracted data included year and country of publication, study design, diagnostic criteria of NMO/NMOSD, demographic data of patients (patient population, female sex ratio, age of onset, follow-up duration, mean disease duration, ARR, EDSS score before and after MMF treatment, and AQP4-IgG serostatus), MMF treatment protocols (dose and duration of MMF treatment, and previous or concurrent therapy) and outcome measures.

Efficacy And Safety Measures

For the primary outcome on efficacy, differences in ARR and the mean and median EDSS scores before and after MMF treatment were assessed. Safety outcomes included the proportion of deaths, drug withdrawals due to toxic effects and the ADRs. Relapse-free rate and the changes in EDSS were also obtained if available.

Quality assessment and statistical analysis

Quality assessment for included observational studies was performed using the Newcastle-Ottawa quality assessment scale which consists of 3 domains: (a) selection of the participants; (b) comparability between the groups; (c) ascertainment of the outcome in cohort studies. [9] Differences in assessment were discussed and resolved with consensus among investigators.

Continuous and dichotomous data were both included in this study. Continuous data (ARR and EDSS) were reported as a median with range or mean with standard deviation (SD) depending on available data in original articles. Dichotomous data (i.e. number of ADRs, number of AQP4-IgG seropositive patients) were presented by a number with percentage.

Meta-analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Mean pre- and post-treatment ARR, as well as mean pre- and post-treatment EDSS along with their SD were extracted from each study, and the mean difference (MD) was calculated. If the study reported 95% confidence interval (95% CI) instead of SD, the SD would be calculated from an upper limit of the 95% CI. Statistical heterogeneity was evaluated using Cochrane's Q test, which was complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I^2 value from 0%-25% represents insignificant heterogeneity, 26%-50% represents low heterogeneity, 51%-75% represents moderate heterogeneity, and > 75% represents high heterogeneity. [10] A result is considered to be statistically significant if 95% CI of MD did not include null value; zero, for continuous data.

Results

Study identification and selection

There were 1167 articles identified through database searching from Ovid MEDLINE and EMBASE. After excluding 170 duplicates, a total of 997 studies were screened by titles and abstracts. Forty-two studies were analyzed for eligibility assessment. Of these 42 studies, 27 studies were excluded (2 studies were reviews, 5 studies were case reports or case series with fewer than three patients, 7 studies had no reported ARR or EDSS pre- and post- treatment, 4 studies were duplicates, 8 studies had no full-text available, and 1 study had no English article available). As a result, 15 studies (10 retrospective and 5 prospective) published from 2009–2020 met our study criteria and were included in the systemic analysis. (Fig. 1) None were randomized controlled trials, 14 were cohort studies, and 1 was a case series

Assessment of risk of bias

Demographic and clinical characteristics

The characteristics and demographic data for the 15 studies are described in Table 1 and the supplementary table. There were a total of 1047 patients (799 of them were treated with MMF). The total number of female patients was 915 (overall 87.4%) with the female proportion varying from 73.8–93.3% for each individual study. The AQP4-IgG serostatus was reported for all patients, of whom 886 patients (84.6%) were AQP4-IgG seropositive. Diagnosis of NMO/NMOSD was given according to the 2006 [2], 2007 [11], or 2015 [1] criteria.

Table 1
Baseline characteristics of 15 studies in neuromyelitis optica spectrum disorders treated with mycophenolate mofetil

Author	Study design	Diagnosis of NMO/ NMOSD	Number with positive AQP4 antibody/Total number (%)	Number of females/Total number (%)	Number of patients treated with MMF	Age of onset, years old	Dose of MMF	Other immune-suppressive (IS) therapy prior to MMF; number of patients (%)	Concurrent use of corticosteroid; number of patients (%)
Jacob et al. 2009 [8]	Retrospective case series	The 2006 NMO criteria OR The 2007 NMOSD criteria	23/24 (95.8%)	19/24 (79.2%)	24	Median 56 (range 34–77)	Median 2000 mg/day (range 750–3000)	17 (70.8%)	9 (37.5%)
Huh et al. 2014 [24]	Retrospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	52/58 (89.7%)	50/58 (86.2%)	58	Median 34 (range 10–53)	1000–2000 mg/day	22 (37.9%)	1 (1.72%)
Mealy et al. 2014 [26]	Retrospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	17/28 (60.7%)	26/28 (92.9%)	28	Median 36 (range 19–74)	1000–2000 mg/day	8 (28.6%)	13 (46.4%)
Torres et al. 2015 [20]	Retrospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	4/11 (36.4%)	10/11 (90.9%)	11	Median 37 (range 18–68)	NR	7 (63.6%)	NR
Chen et al. 2016 [13]	Prospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	52/62 (83.9%)	58/62 (93.5%)	62	Mean 38.7 (SD 12.0)	20 mg/kg	7 (11.3%)	24 (38.7%)

Abbreviations: AQP4: Aquaporin4; AZA: azathioprine; CYP: cyclophosphamide; IS: immunosuppressive; kg: kilogram; mg: milligram; MMF: mycophenolate mo
neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorders; NR: not reported; ON: optic neuritis; SD: standard deviation; IPND: International Panel
Neuromyelitis optica Diagnosis

Author	Study design	Diagnosis of NMO/ NMOSD	Number with positive AQP4 antibody/Total number (%)	Number of females/Total number (%)	Number of patients treated with MMF	Age of onset, years old	Dose of MMF	Other immune-suppressive (IS) therapy prior to MMF; number of patients (%)	Concurrent use of corticosteroid; number of patients (%)
Jeong et al. 2016 [15]	Retrospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	32/34 (94.1%)	29/34 (85.3%)	34	Median 35 (range 10–53)	1500–2000 mg/day	None (0%)	9 (26.4%)
Xu et al. 2016 [16]	Prospective cohort	The 2015 IPND	33/38 (86.8%)	32/38 (84.2%)	38	Mean 28.7 (SD 13.0)	1500 mg/day	None (0%)	All (100%)
Chen et al. 2017 [14]	Prospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	89/105 (84.8%)	97/105 (92.4%)	105	Mean 44.0 (SD 12.1)	20 mg/kg/d	None (0%)	49 (46.6%)
Montcuquet,et al. 2017 [17]	Retrospective Cohort	The 2015 IPND	45/67 (67.2%)	50/67 (74.6%)	67	Median 37.9 (range 6–67)	2000 mg/day	None (0%)	16 (23.9%)
Huang et al. 2018 [22]	Prospective cohort	The 2006 NMO criteria OR The 2015 IPND	90/90 (100%)	84/90 (93.3%)	90	Median 36 (range 10–65)	1000 mg/day	20 (22.2%)	All (100%)
Jiao et al. 2018 [12]	Retrospective cohort	The 2006 NMO criteria OR The 2007 NMOSD criteria	74/86 (86.0%)	77/86 (89.5%)	86	Median 43 (range 6–68)	High dose (1750–2000 mg) Moderate dose (1250–1500 mg) Low dose (≤ 1000 mg)	56 (65.1%)	65 (76%)

Abbreviations: AQP4: Aquaporin4; AZA: azathioprine; CYP: cyclophosphamide; IS: immunosuppressive; kg: kilogram; mg: milligram; MMF: mycophenolate mo
neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorders; NR: not reported; ON: optic neuritis; SD: standard deviation; IPND: International Panel
Neuromyelitis optica Diagnosis

Author	Study design	Diagnosis of NMO/ NMOSD	Number with positive AQP4 antibody/Total number (%)	Number of females/Total number (%)	Number of patients treated with MMF	Age of onset, years old	Dose of MMF	Other immune-suppressive (IS) therapy prior to MMF; number of patients (%)	Concurrent use of corticosteroid; number of patients (%)
Mealy et al. 2018 [21]	Retrospective cohort	The 2015 IPND	208/245 (84.9%)	216/245 (88.2%)	103	Median 37 (range 7–79)	1500–2000 mg/day	Some had glatiramer acetate	None (0%)
Yang et al. 2018 [18]	Prospective cohort	The 2015 IPND	13/30 (43.3%)	26/30 (86.7%)	30	Mean 42.6 (SD 11.7)	1000 mg/day	None (0%)	28 (93.3%)
Zhou et al. 2019 [23]	Retrospective cohort	The 2006 NMO criteria OR The 2015 IPND	Pediatric group: 23/31 (74.2%)	Pediatric group: 25/31 (80.6%)	4	Pediatric group: Median 14 (range 10–17)	1000 mg/day	Some had AZA or CYP	All (100%)
			Adult group: 96/96 (100%)	Adult group: 85/96 (88.8%)	17	Adult group: Median 35 (range 18–96)	1000 mg/day		All (100%)
Poupart et al. 2020 [19]	Retrospective cohort	The 2015 IPND	35/42 (83.3%)	31/42 (73.8%)	42	Mean 41.4 (SD 17.6)	1000–2000 mg/day	None (0%)	8 (19.1%)

Abbreviations: AQP4: Aquaporin4; AZA: azathioprine; CYP: cyclophosphamide; IS: immunosuppressive; kg: kilogram; mg: milligram; MMF: mycophenolate mo neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorders; NR: not reported; ON: optic neuritis; SD: standard deviation; IPND: International Panel Neuromyelitis optica Diagnosis

Treatment regimens

MMF was administered 1000–2000 mg/day in most of the studies. One study by Jiao et al., reported categorized dosages (1000 mg/day or less, 1250–1500 mg/day, 1750–2000 mg/day as low, moderate and high dose respectively). [12] Studies by Chen et al. prescribed 20 mg/kg dosage. [13, 14] Of the 799 patients treated with MMF, MMF was used as a first-line therapy in 6 studies [15, 16, 14, 17–19] with a total of 316 patients (39.5%). The other 9 studies included patients who had suboptimal treatment from prior IS including AZA, CYP, mitoxantrone, fingolimod. hydroxychloroquine sulfate, beta-interferons, and glatiramer acetate, however contained no detailed information of the proportionate use. Data on concomitant corticosteroids were available in all but one study [20]. The proportion of steroid use ranged from 0% [21] to 100% [16, 22, 23]. In four studies [16, 22, 23, 18], 177 patients (22.2%) had been taking oral corticosteroid at the time of MMF treatment. Two studies [21, 24] were conducted with 160 patients (20.0%) who did not receive corticosteroid during MMF treatment. The remaining 10 studies contained both groups of patients.

Treatment outcome analysis

The efficacy of MMF treatment determined by changes in ARR and EDSS is shown in Table 2. The median follow-up duration ranged from 13.5 months [22] to 95 months [21], with less than 24 months in 8 studies and 24 months or more in 7 studies. (Table 1)

Table 2
Changes in Expanded Disabilities Status Score and annualized relapse rate after treatment with mycophenolate mofetil

Author	EDSS			Improved or stabilized EDSS (%)	ARR			Relapse free rate (%)
	Median Pre-treatment (Range)	Median Post-treatment (Range)	P-value		Median Pre-treatment (Range)	Median Post-treatment (Range)	P-value	
Jacob et al. 2009 [8]	6.0 (0.0–8.0)	5.5 (0.0–10)	0.17	91%	1.15 (0.23–11.78)	0.18 (0.00-1.50)	< 0.01	46%
Huh et al. 2014 [24]	3.0 (0.0–8.0) 3.2 (2.2)[a]	2.5 (0.0–7.0) 2.7 (1.9)[a]	0.01	91%	1.50 (0.30–11.80) 2.6 (2.7)[a]	0.00 (0.00-2.60) 0.5 (0.8)[a]	< 0.01	60%
Mealy et al. 2014 [26]	NR	NR	NR	NR	2.61 (NR)	0.33 (NR)	< 0.01	64%
Torres et al. 2015 [20]	4.0 (3.0-6.5)	5.0 (NR)	0.46	NR	1.06 (0.84–2.31)	0.39 (NR)	< 0.05	27%
Chen et al. 2016 [13]	4.0 (0.5-8.0) 4.1 (2)[a]	2.0 (0.5–7.5) 2.8 (2.1)[a]	< 0.01	95.2%	1.20 (0.20-7.00) 1.7 (1.2)[a]	0.00 (0.00-1.70) 0.4 (0.5)[a]	< 0.01	58.1%
Jeong et al. 2016 [15]	3.0 (0.0–7.0)	2.0 (0.0–7.0)	< 0.01	NR	1.54 (NR)	0.18 (NR)	< 0.01	64.7%
Xu et al. 2016 [16]	2.0 (0.0–9.0) 2.7 (2)[a]	2.0 (0.0-8.5) 2.0 (1.8)[a]	< 0.01	97.4%	0.80 (0.00–8.00) 1.0 (1.0)[a]	0.00 (0.00-1.40) 0.1 (0.3)[a]	0.05	NR
Chen et al. 2017 [14]	3.0 (0.5-8.0)	2.0 (0.5–7.5)	< 0.01	NR	1.20 (0.10-7.00)	0.00 (0.00–2.00)	< 0.01	56.2%
Montcuquet et al. 2017 [17]	4.0 (0.0-8.5)	3.8 (0.0–10.0)	< 0.05	NR	1.00 (0.10–3.20)	0.00 (0.00–3.00)	< 0.05	49.3
Huang et al. 2018 [22]	4.0 (0.0-8.5)	3.0 (0.0-8.5)	< 0.01	90%	1.02 (0.00-19.21)	0.00 (0.00-2.44)	< 0.01	73%
Jiao et al. 2018 [12]	3.0 (0.0-8.5)	2.5 (0.0-8.5)	0.01	87%	1.40 (0.10–11.00)	0.00 (0.00-2.80)	< 0.01	64%
Mealy et al. 2018 [21]	NR	NR	NR	NR	1.79	0.29	< 0.01	64.7%
Yang et al. 2018 [18]	3.5 (2.0-8.5)	2.0 (0.5-7.0)	< 0.01	100%	0.90 (0.00–5.00)	0.00 (0.00-2.40)	< 0.01	60%
Zhou et al. 2019 [23]	NR	NR	NR	NR	1.00 (0.23–3.43) in adult patients 0.98 (0.35–2.11) in pediatric patients	0.00 (0.00–0.71) in adult patients 0.28 (0-0.71) in pediatric patients	< 0.01	80% in adult patients 50% in pediatric patients
Poupart et al. 2020 [19]	NR	NR	NR	NR	0.71 (0.43–1.15)[b]	0.20 (0.11–0.35)[b]	NR	NR

[a]mean (SD) [b]mean (95% CI)

Abbreviations: EDSS, Expanded Disability Status Scale; ARR, Annual Relapse Rate; NR, not reported

Only 4 studies [24, 16, 13, 19] reporting ARR and 3 studies [24, 16, 13] reporting EDSS reported values by mean and SD, and therefore were included in the meta-analysis. (Table 2)

Qualitative analysis

All 15 studies reported median ARR before and after treatment. All but one [19] demonstrated significant ARR reduction after receiving MMF ($p < 0.05$). The relapse-free rate was 60% (ranged from 27–80%).

For the 11 studies reporting EDSS as a treatment outcome, 7 studies revealed stabilization or improvement of disability in patients receiving MMF treatment measured by EDSS with the proportion varying from 87–100%. 11 studies reported median EDSS before and after MMF treatment. Of those, 9 showed

significant post-treatment median EDSS changes ($p < 0.05$).

Meta-analysis: Efficacy on the reduction of ARR

All the 4 studies [24, 16, 13, 19] including 200 NMOSD patients with the majority of patients being AQP4-positive (80–90%) showed a significant ARR reduction with the mean reduction of 1.13 (95% CI, 0.60 to 1.65) after MMF therapy with a dosage between 1000–2000 mg/day for 15.2–35 months, compared to the ARR at initiation of treatment. (Fig. 3a)

Meta-analysis: Efficacy on the EDSS

All the 3 studies [24, 16, 13, 19] with 158 NMOSD patients showed a significant EDSS lowering after MMF therapy with a mean reduction of 0.85 (95% CI, 0.36 to 1.34). Moreover, the Chen study [13] showed a large decrease in disability measured by EDSS from baseline of moderately severe (EDSS 4.1) to full independent (EDSS 2.1). (Fig. 3b)

Safety

ADRs are summarized in Table 3. For all 799 patients, data on safety of MMF therapy were recorded for 594 patients. 106 (17.8%) patients were reported to have developed ADRs. One of the most common ADRs were infections (33 patients; 5.6%)—including respiratory infection/pneumonia (12 patients; 2.0%), urinary tract infection (8 patients; 1.3%), herpes zoster infection (8 patients; 1.3%), herpes simplex infection (2 patients; 0.3%), and abnormal liver function tests (27 patients; 4.5%). The other common ADRs were hair loss (17 patients; 2.9%), gastrointestinal (GI) side effects (14 patients; 2.4%)—including nausea, diarrhea /abdominal pain, and constipation—bone marrow suppression (16 patients; 2.7%)—including anemia (6 patients; 1.0%), agranulocytosis (1 patient; 0.2%), leukopenia (8 patients; 1.3%), thrombocytopenia (1 patient; 0.2%), and amenorrhea in 3 patients (0.5%). Uncommon documented side effects were headaches, phlegm on normal CT chest, chronic dermopathy of the hand, rectal cancer, renal insufficiency, rash, hypotension, fatigue, easy bruising, anxiety, and sun sensitivity. The data on discontinuation of MMF were available for 687 patients, 27 (3.9%) of them discontinued MMF from ADRs such as rash, agranulocytosis, leukopenia, thrombocytopenia, arthromyalgia, GI side effects, and amenorrhea. All ADRs were reversible after discontinuation of MMF. One was discovered with high CERA. Three patients died during MMF treatment: one with EDSS 8.5 succumbed from complications of immobilization, another developed disseminated varicella zoster with acute respiratory distress syndrome, and the other had—according to death certificate documents —“cardiopulmonary failure; respiratory drive failure and Devic’s disease”. [17, 22, 8]

Table 3
Adverse events in 15 studies on mycophenolate mofetil in neuromyelitis optica spectrum disorders

Author	Total number of patients	Number of patients with adverse events (%)	Adverse events	Number of events (%)	Total number of discontinuation due to adverse effects (%)
Jacob et al. 2009 [8]	24	6 (25%)	Headache	1 (4.2%)	1 (4.2%) due to low white blood cell counts
			Constipation	1 (4.2%)	
			Easy bruising	1 (4.2%)	
			Anxiety	1 (4.2%)	
			Hair loss	1 (4.2%)	
			Diarrhea and abdominal pain	1 (4.2%)	
			Low white blood cell counts	1 (4.2%)	
Huh et al. 2014 [24]	58	14 (24.13%)	Rash	1 (1.7%)	1 (1.7%) due to rash
			Amenorrhea	2 (3.4%)	
			Herpes zoster	1 (1.7%)	
			Cystitis	3 (5.2%)	
			Pneumonia	1 (1.7%)	
			Hypotension	1 (1.7%)	
			Fatigue	1 (1.7%)	
			Mild hair loss	4 (6.9%)	
Mealy et al. 2014 [26]	28	NR	NR	NR	0 (0%)
Torres et al. 2015 [20]	11	4 (36%)	Sun sensitivity	NR	NR
			Recurrent infection	NR	
Chen et al. 2016 [13]	62	3 (4.8%)	Mild hair loss	2 (3.2%)	0 (0%)
			Mildly elevated liver enzyme (After reused, no elevated liver enzyme)	1 (1.6%)	
Jeong et al. 2016 [15]	34	NR	NR	NR	0 (0%)
Xu et al. 2016 [16]	38	2 (5.3%)	Agranulocytosis	1 (2.6%)	2 (5.3%) due to agranulocytosis, amenorrhea
			Amenorrhea	1 (2.6%)	
Chen et al. 2017 [14]	105	5 (4.8%)	Mild hair loss	3 (2.9%)	0 (0%)
			Mildly elevated liver enzyme	1 (1.0%)	
			Phlegm on normal CT chest	1 (1.0%)	
Montcuquet et al. 2017 [17]	67	9 (13.4%)	Gastrointestinal side effects	6 (9.0%)	9 (13.4%)
			Infection	3 (4.5%)	
Huang et al. 2018 [22]	90	39 (43%)	Diarrhea	2 (2.2%)	8 (9%)
			Deranged liver enzyme	18 (20%)	
			Hyperbilirubinemia	2 (2.2%)	
			Respiratory infection	11 (12.2%)	
			Urinary tract infection	5 (5.6%)	
			Varicella-zoster virus infection	5 (5.6%)	
			Anemia	6 (6.7%)	
			Leukopenia	4 (4.4%)	

[a]Total number of patients = 109 (86 of them received MMF > 6 months and were included in efficacy assessment)

[b]The article did not report adverse events other than serious infection events

Abbreviation: NR, not reported

Author	Total number of patients	Number of patients with adverse events (%)	Adverse events	Number of events (%)	Total number of discontinuation due to adverse effects (%)
			Rectal cancer	1 (1.1%)	
			Renal insufficiency	1 (1.1%)	
			Hair loss	2 (2.2%)	
Jiao et al. 2018 [12]	109[a]	21 (19%)	Hair loss	5 (4.6%)	1 (0.9%)
			Mildly elevated liver enzyme	3 (2.8%)	
			Diarrhea and abdominal pain	2 (1.8%)	
			Constipation	1 (0.9%)	
			Leukopenia	3 (2.8%)	
			Thrombocytopenia	1 (0.9%)	
			Shingles	2 (1.8%)	
			Herpes simplex infection	2 (1.8%)	
			Headache	2 (1.8%)	
			Chronic dermopathy of hands and nail	1 (0.9%)	
Mealy et al. 2018 [21]	245	NR	NR	NR	NR
Yang et al. 2018 [18]	30	3 (10%)	Mildly elevated liver enzyme	2 (6.7%)	0 (0%)
			Nausea	1 (3.3%)	
Zhou et al., 2019 [23]	31	NR	NR	NR	NR
Poupart et al. 2020 [19]	42	5 (11.9%)[b]	Serious infection events	5 (11.9%)	5 (11.9%) due to thrombocytopenia, arthromyalgia, Gastrointestinal side effects

[a]Total number of patients = 109 (86 of them received MMF > 6 months and were included in efficacy assessment)

[b]The article did not report adverse events other than serious infection events

Abbreviation: NR, not reported

Discussion

Our meta-analysis demonstrated that treatment with MMF between 13–95 months has preventive efficacy in ARR reduction with the mean difference of 1.13 times a year and EDSS lowering by 0.85 points, compared to before initiation of the treatment in NMOSD patients. MMF has been anecdotally used in several autoimmune diseases, including NMOSD. Since there has never been a randomized controlled trial, we aimed to gather evidences to support the efficacy and safety of MMF treatment in NMOSD patients. Fifteen studies met our inclusion criteria, and all were observational studies. Diagnosis of NMO/NMOSD was done via either the 2006, 2007, or 2015 criteria. AQP4-IgG autoantibody was present in 84.6% of the total patients (range 36.4–100%). After excluding the pediatric NMOSD patients with a median age of onset of 14 years old [23], the median age of onset in the remaining patients varied from 28.7 to 56.0 years old. Since disability in NMOSD patients is related to attacks and accumulation of the incomplete recovery, therefore, reducing the number of the attacks should provide less neurological deficit. Our study showed approximately 90% of patients had stabilized or even improved EDSS scores as well as having significant reduction in relapses after treatment with MMF. Moreover, 46–80% of the patients were free from relapses. Nevertheless, our meta-analysis showed only 0.85 point change in EDSS lowering. The degree of disability measured by EDSS depends mainly on ambulation, and the change in EDSS at the higher level is not equal to the same amount of EDSS change at the lower level. The pre-treatment disability in 9 studies was moderately severe with the median EDSS between 3.0 to 4.0. One study even had severe pre-treatment disability with a median EDSS of 6.0. [8] Only one study reported mild to moderate disabilities with a baseline median EDSS of 2.0 before initiation of MMF. [16] Also, the 3 studies in meta-analysis had moderately severe disability before initiation of MMF treatment with the mean EDSS around 3.0–4.0. Therefore, reversibility of the permanent damages may not be obvious. Nevertheless, these findings suggested that MMF exerted positive effects in preventing future relapses and considerably decreasing disability measured by EDSS. The efficacy of MMF was comparable to that of AZA but with less ADRs [25, 14, 16, 15, 26, 18]. In addition, MMF has been substituted when treatment with AZA showed suboptimal responses or patients cannot tolerate the side effects of AZA. [24, 22] Huang et al. compared the efficacy and safety of MMF with RTX, AZA, CYP, and cyclosporine A (CyA) and found that MMF was superior to AZA and CYP but inferior to RTX and CyA. However, MMF had the highest tolerability among all IS in the study. [27] A larger proportion of the study population was from China or Korea than from USA or Europe, and hence, the ethnic difference was significant. There may be an effect of racial difference on the severity of attacks. However, race is not an independent predictor of long-term treatment outcome. Further studies on pharmacogenomics are needed to understand the effect of racial difference and response to IS. [28]

Previous study suggested that the efficacy of MMF with or without low dose steroids are not statistically different. [13] Adding supraphysiologic doses of steroids may increase the efficacy of MMF, but also increase the risk of infections. [29] Most of the studies in our analysis reported one- to two-thirds of patients had concomitant use of corticosteroids. Two studies reported concomitant use of MMF with corticosteroid in all patients. However, details regarding dose and duration of steroid treatment use in each study were not available. Future study on the benefit or risk of MMF with and without steroids is needed.

The present study demonstrated common ADRs were infections, abnormal liver function tests, hair loss, GI symptoms, and bone marrow suppression. ADRs reported from other studies were infections, bone marrow suppression, and malignancy. [30] Increased risk of malignancy has not been proven in another study. [31] ADRs from MMF was not severe nor life-threatening. There were only 27 patients (3.9%) who discontinued MMF due to ADRs and 3 cases with fatalities, one from infections and the other two seeming to be related to NMOSD. These findings are also consistent with other studies reporting tolerable side effects of MMF when compared to other IS, e.g. AZA, CYP, or RTX, which led to better drug compliance. [27]

Limitation

Our analysis has several limitations. Firstly, the studies included in this review were mostly observational cohort studies, which were subjected to certain bias. Secondly, the heterogeneity of the study populations—particularly racial differences, pre-treatment disability and frequency of relapse reflected severity of disease, variety of MMF dosage use, and concomitant corticosteroids use or prior use of other IS - could contribute to different treatment outcomes and ADRs. The efficacy of MMF in NMOSD patients should be cautiously interpreted and further studied; nevertheless, it seems to show reasonable effects for relapse prevention in NMOSD patients.

Conclusion

This systematic review and meta-analysis indicates that receiving MMF as a preventive therapy in NMOSD patients is associated with ARR reduction and EDSS lowering, compared to pre-treatment use. It also had acceptable ADRs and low rates of discontinuation.

Abbreviations

NMOSD: Neuromyelitis optica spectrum disorders; AQP-4 IgG: aquaporin-4 immunoglobulin G; ON: optic neuritis; TM: transverse myelitis; MS: multiple sclerosis; AZA: azathioprine; MMF: Mycophenolate mofetil; CYP: cyclophosphamide; MPA: mycophenolic acid; IMPDH: inosine-5'-monophosphate dehydrogenase; ADRs : adverse drug reactions; ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; SD: standard deviation; MD: mean difference; IS: immunosuppressive agents, GI: gastrointestinal; RTX: rituximab; CyA : cyclosporine A

Declarations

Ethical Approval and Consent to participate: Not applicable

Consent for publication: I, the corresponding author, give my consent for information about the manuscript number JNEU-D-20-00633 to be published in Journal of Neuroinflammation.

Availability of supporting data: All data generated or analysed during this study are included in this published article.

Competing interests

Dr. Songwisit S. declares that he has no competing interests.

Dr. Kosiyakul P. declares that she has no competing interests.

Dr. Jitprapaikulsan J. declares that she has no competing interests.

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Dr. Ungprasert P declares that he has no competing interests.

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Figures

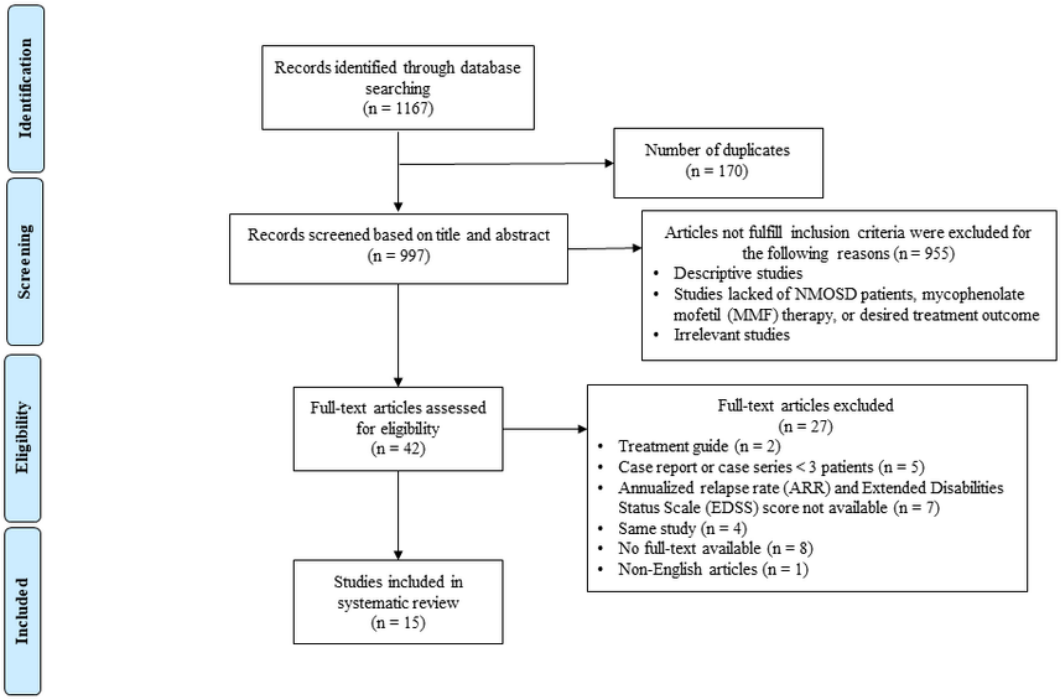


Figure 1: The PRISMA flow diagram of this systematic review

Figure 1

Figure 1

Study	Selection	Comparability	Outcome
Prospective cohort study			
Chen et al. 2016	★★★★	★★	★★
Xu et al. 2016	★★★★	★★	★★★
Chen et al. 2017	★★★★	★★	★★
Huang et al. 2018	★★★★	★★	★★★
Yang et al. 2018	★★★★	★★	★★★
Retrospective cohort study			
Huh et al. 2014	★★★★	★★	★★★
Mealy et al. 2014	★★★★	★★	★★
Torres et al. 2015	★★★★	★★	★★
Jeong et al. 2016	★★★★	★★	★★
Montcuquet et al. 2017	★★★★	★★	★★
Jiao et al. 2018	★★★★	★★	★★★
Mealy et al. 2018	★★★★	★★	★★★
Yifan et al. 2019	★★★★	★★	★★★
Poupart et al. 2020	★★★★	★★	★★★

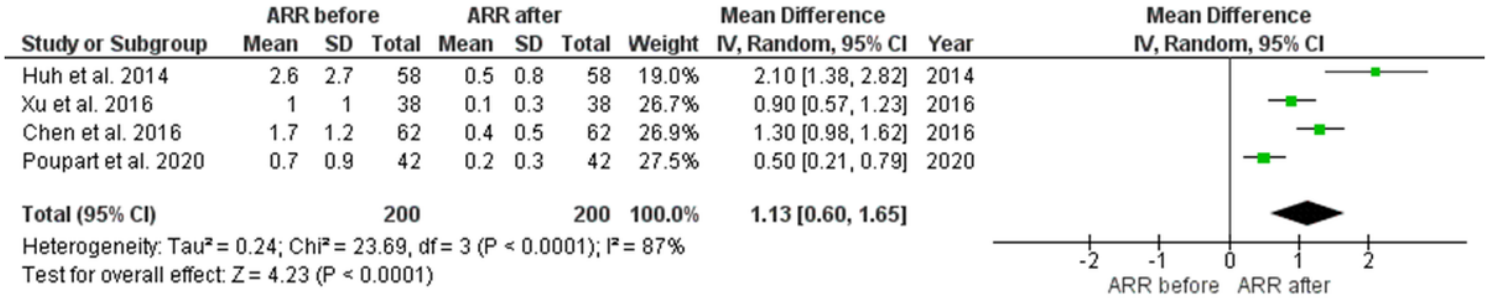
Figure 2: Quality assessment of 14 observational studies by using Newcastle-Ottawa Scale

Figure 2

Figure 2

Figure 3: Meta-analysis on efficacy of MMF in annual relapse reduction and EDSS lowering

A: Annual relapse reduction



B: EDSS lowering

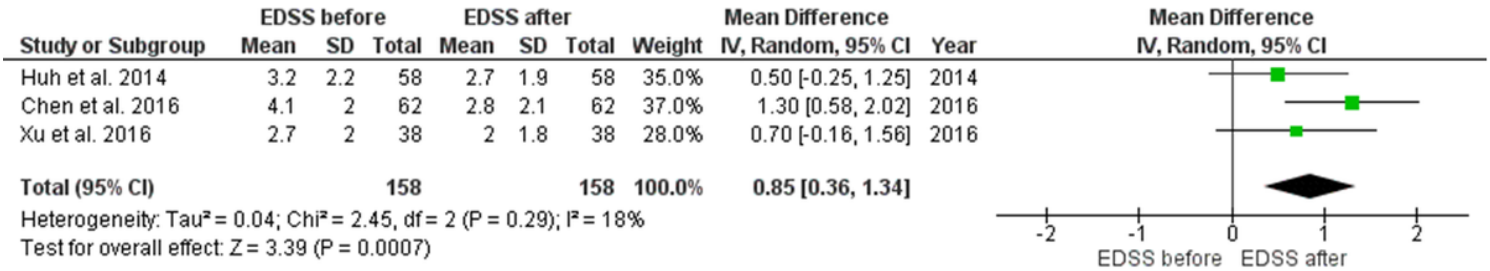


Figure 3

Figure 3

Supplementary Files

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