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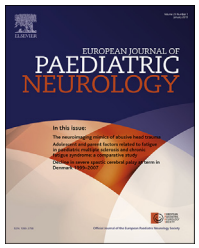

Review article

Mycophenolate mofetil, azathioprine and methotrexate usage in paediatric anti-NMDAR encephalitis: A systematic literature review

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ABSTRACT

Background: Available data on mycophenolate mofetil (MMF), azathioprine (AZA) and methotrexate (MTX) for paediatric-onset anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is limited.

Methods: Systematic literature review on patients treated with MMF/AZA/MTX for paediatric-onset anti-NMDARE, with focus on modes of use, efficacy and safety.

Results: 87 patients were included (age at onset median 11 years, range 0.8–18 years; 69% females). 46% had a relapsing course. 52% received MMF, 27% AZA, 15% MTX, and 6% a combination of MMF/AZA/MTX (7 patients received intrathecal MTX). Before MMF/AZA/MTX, 100% patients received steroids, 83% intravenous immunoglobulin and 45% plasma exchange, and 50% received second-line treatments (rituximab/cyclophosphamide). MMF/AZA/MTX were administered >6 months from onset in 51%, and only after relapse in 40%.

Worst mRS before MMF/AZA/MTX was median 4.5 (range 3–5). At last follow-up (median 2 years, range 0.2–8.6), median mRS was 1 (range 0–6). Median annualised relapse rate was 0.4 (range 0–6.7) pre-MMF/AZA/MTX (excluding first events), and 0 on MMF/AZA/MTX (mean 0.03, range 0–0.8).

7% patients relapsed on MMF/AZA/MTX. These relapsing patients had low rate of second-line treatments before MMF/AZA/MTX (25%), long median time between onset and MMF/AZA/MTX usage (18 months), and frequently they were started on MMF/AZA/MTX only after relapse (75%).

Relapse rate was lower among patients who received first immune therapy ≤30 days (25%) than later (64%), who received second-line treatments at first event (14%) rather than

Abbreviations: ARR, annualised relapse rate; AZA, azathioprine; CTCAE, common terminology criteria for adverse events; CMV, cytomegalovirus; CYC, cyclophosphamide; d.a., data available; F, female; IVIG, intravenous immunoglobulin; M, male; MMF, mycophenolate mofetil; MOG, myelin oligodendrocyte glycoprotein; mRS, modified Rankin scale; MTX, methotrexate; NMDAR, N-methyl-D-aspartate receptor; OP, oral prednisone; PE, plasma exchange; RTX, rituximab.

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not (64%), who were started on MMF/AZA/MTX after the first (12%) rather than subsequent events (17%), and who were started on MMF/AZA/MTX ≤3 months from onset (33%) rather than later (53%).

Adverse reactions to MMF/AZA/MTX occurred in 2 cases (cytomegalovirus colitis and respiratory infection), of grade 3 Common Terminology Criteria for Adverse Events v4.0.

Discussion: Our literature review disclosed heterogeneity in the use of MMF/AZA/MTX in paediatric-onset anti-NMDARE. MMF/AZA/MTX usage is mostly restricted to retrospective cohort descriptions. These agents may reduce risk of relapse, and have a reasonable safety profile, however data on larger cohorts are required to definitively determine effect.

Contents

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune syndrome characterised by a constellation of symptoms with multistage progression (psychiatric changes, speech dysfunction, movement disorder, epileptic seizures, consciousness and vigilance disturbances, sleep–wake cycle disruption, dysautonomias), and the presence of neuronal surface antibodies in the cerebrospinal fluid and serum targeting the NMDAR.[1–3] Despite the absence of definite treatment guidelines, in recent years a number of expert recommendations have been published on immune therapy for anti-NMDAR encephalitis.[4–10] First-line treatments usually include intravenous methylprednisolone, intravenous immunoglobulin[11–13] and plasma exchange.[14] In case of unsatisfactory response or in relapsing disease, second-line therapies are advised, such as rituximab and/or

cyclophosphamide. This approach is generally becoming more and more uniform, although major differences between centers and physicians do exist, especially in the use of second-line treatments.[15,16] When it comes to long-term immune-suppression, expert recommendations are less definite and physicians' approaches vary widely as regards the use of long-term therapy or not, the type of agent, and the duration of treatment.[15,16] Mycophenolate mofetil, azathioprine and methotrexate, generally referred to as steroid sparers, are widely used for prevention of transplant rejection and in a large array of autoimmune diseases, including rheumatologic, dermatologic, gastrointestinal and neurologic conditions.[17] The utility and safety of these agents in paediatric autoimmune encephalitis have not been thoroughly explored yet. In this context, we carried out a systematic literature review with the aim of collecting available data on the use of mycophenolate mofetil, azathioprine and methotrexate in paediatric anti-NMDAR encephalitis, with focus on the most frequent modes of use, safety and efficacy.

2. Methods

2.1. Literature search

We conducted a systematic literature review on the use of steroid sparing agents (mycophenolate mofetil, azathioprine and methotrexate) for paediatric-onset anti-NMDAR encephalitis. The search was carried out in Pubmed, up to date to 10.09.2018, with the search terms "anti–N-methyl-D-aspartate receptor encephalitis" OR "N-methyl-D-aspartate antibody encephalitis" OR "anti-NMDAR encephalitis" OR "NMDA receptor encephalitis". The available articles were filtered manually for patients in paediatric age (≤18 years), and searched for "mycophenolate", "azathioprine", and "methotrexate".

2.2. Inclusion criteria

Articles reporting patients who received mycophenolate mofetil, azathioprine and/or methotrexate for paediatric-onset anti-NMDAR encephalitis were included. Articles reporting mixed populations of children and adults with pooled data, in which the age of the patients treated with steroid sparing agents was not clear, were excluded.

2.3. Data collection

Articles were searched for data on demographics, disease severity and course, treatment, efficacy and safety of mycophenolate mofetil, azathioprine and methotrexate. Other therapies received beside steroid sparers were categorised into first-line (corticosteroids, intravenous immunoglobulin, plasma exchange), second-line (cyclophosphamide, rituximab) and other. Data collection was subject to data availability, therefore in the results section of this work denominators may differ.

2.4. Efficacy

Effectiveness of mycophenolate mofetil, azathioprine and methotrexate was evaluated on several parameters[18]: change in modified Rankin Scale (mRS)[19] between the acute phase pre-steroid sparers and at last follow-up (as reported in the original article or independently scored by two of the main authors (MN, SS), when not available in the text; discordances were resolved by discussion); percentage of patients free of relapse on mycophenolate mofetil, azathioprine and methotrexate; and pre- and post-treatment change in the annualised relapse rate (ARR). The ARR was calculated as number of disease events multiplied by 12 (months), divided by the number of months during which the events occurred (calculated only for time intervals ≥6 months).[20] ARR was calculated before (excluding first events), during and after treatment with steroid sparing agents.

2.5. Safety

Adverse reactions to mycophenolate mofetil, azathioprine and methotrexate were classified using the Common Terminology Criteria for Adverse Events (CTCAE v4.0), into grade 1 (mild), 2 (moderate), 3 (severe or medically significant but not immediately life-threatening), 4 (life-threatening consequences) and 5 (death).[21]

3. Results

3.1. Demographics, clinical data and disease course

41 articles reporting a total of 87 patients treated with mycophenolate mofetil, azathioprine and/or methotrexate for paediatric-onset anti-NMDAR encephalitis were included in the literature review (Supplementary Table 1).[22–62] Only 6 of the 41 articles were focused on treatment, whereas the remaining had other variable focus; none of the articles was focused on treatment safety. 9 of the articles described only 1 case of paediatric anti-NMDAR encephalitis, 8 described 2 or 3 cases, whereas the remaining 24 articles were case series reporting between 4 and 46 paediatric patients with anti-NMDAR encephalitis. According to our systematic literature review, steroid sparers were used in about 23.6% of the total cohorts described in the relative articles (87/369) (Supplementary Table 1). Most of the articles were published between 2014 and 2018 (31/41, 76%). Data relative to the whole cohort of patients with paediatric-onset anti-NMDAR encephalitis treated with mycophenolate mofetil, azathioprine and/or methotrexate are detailed in Table 1. Median age at onset was 11 years (mean 10, range 0.8–18; data available in 76/87), and 69% (53/77) of the patients were females. Tumour was reported in 3 patients.[35,51,59] 46% of the patients had a relapsing disease course (31/68). In these relapsing patients, the median number of total events per patient (including disease onset) was 2.5 (mean 3.3, range 2–11; data available in 28/31).

3.2. Overall treatment

Immune therapy was started within 30 days from disease onset in 57% of patients (20/35). Before steroid sparing agents, all children received steroids (76/76, 100%), 83% intravenous immunoglobulin (63/76), and 45% underwent plasma exchange (34/76). Second-line treatments were used in 50% (38/

Table 1 – Disease course and outcome in the whole cohort and according to type of steroid sparing agent (mycophenolate mofetil/azathioprine/methotrexate) in the literature cohort of patients with paediatric-onset anti-NMDAR encephalitis treated with mycophenolate mofetil, azathioprine and/or methotrexate. Denominators vary according to data availability.

Disease course and outcome in the whole cohort and according to type of steroid sparing agent (MMF/AZA/MTX)								
	All patients ($n = 87$)[a]		MMF ($n = 48$)[c]		AZA ($n = 27$)[d]		MTX ($n = 17$)[e]	
Overall disease severity and course								
Worst mRS in the acute phase	Median 4.5, mean 4.3, range 3–5 (d.a. in 76/87)		Median 4, mean 4.3, range 3–5 (d.a. in 45/48)		Median 4, mean 4.3, range 3–5 (d.a. in 19/27)		Median 5, mean 4.6, range 3–5 (d.a. in 16/17)	
mRS 3	12/76 (15.8%)		9/45 (20%)		3/19 (15.8%)		1/16 (6.2%)	
mRS 4–5	64/76 (84.2%)		36/45 (80%)		16/19 (84.2%)		15/16 (93.7%)	
Overall relapsing disease course	31/68 (46%)		23/47 (48.9%)		7/17 (41.2%)		3/9 (33%)	
Treatment								
Onset to first therapy ≤30 days	20/35 (57.1%)		12/16 (75%)		7/15 (46.7%)		4/7 (40%)	
Immune therapies other than MMF/AZA/MTX	Before steroid sparers	At any time during disease	Before steroid sparers	At any time during disease	Before steroid sparers	At any time during disease	Before steroid sparers	At any time during disease
Steroids	76/76 (100%)	76/76 (100%)	46/46 (100%)	46/46 (100%)	19/19 (100%)	19/19 (100%)	15/15 (100%)	15/15 (100%)
IVIG	63/76 (83%)	63/76 (83%)	39/46 (85%)	39/46 (85%)	17/19 (89.5%)	17/19 (89.5%)	11/15 (73%)	11/15 (73%)
PE	34/76 (45%)	35/76 (45%)	21/46 (46%)	22/46 (48%)	10/19 (52.6%)	10/19 (52.6%)	5/15 (33%)	5/15 (33%)
Any second-line immune therapy (RTX and/or CYC)	38/76 (50%)	44/76 (58%)	18/46 (39%)	23/46 (50%)	11/19 (57.9%)	11/19 (57.9%)	11/15 (73%)	12/15 (%)
RTX	28/75 (37%)	34/73 (46%)	12/45 (27%)	17/43 (39%)	8/19 (42.1%)	8/18 (44.4%)	10/15 (67%)	11/15 (73%)
CYC	23/76 (30%)	24/74 (32%)	13/45 (29%)	14/43 (32%)	8/20 (40%)	8/19 (42.1%)	3/15 (20%)	3/15 (20%)
Other[b]	2/77 (3%)	3/76 (4%)	2/46 (4%)	2/46 (4%)	0/19 (0%)	1/19 (5.3%)	1/15 (7%)	1/15 (7%)
Age at MMF/AZA/MTX administration (years)	Median 13, mean 11.4, range 2.2–26 (d.a. in 38/87)		Median 9.5, mean 10.5, range 2.2–26 (d.a. in 24/48)		Median 16.4, mean 13.9, range 3.5–18.5 (d.a. in 9/27)		Median 13.5, mean 1.3, range 6–17.1 (d.a. in 8/15)	
Disease course before treatment with MMF/AZA/MTX								
Time from onset to commencement of MMF/AZA/MTX (months)	Median 8.2, mean 14.6, range 1–60 (d.a. in 34/87)		Median 9.5, mean 17.9, range 1–60 (d.a. in 22/48)		Median 8.5, mean 10.3, range 1.5–31 (d.a. in 10/22)		Median 5, mean 11.2, range 1–45 (d.a. in 6/17)	
≤6 months	19/39 (49%)		9/25 (36%)		5/10 (50%)		6/8 (75%)	
Number of events before MMF/AZA/MTX (including 1st events)	Median 1, mean 1.9, range 1–11 (d.a. in 58/87)		Median 1, mean 2.1, range 1–11 (d.a. in 39/48)		Median 1, mean 1.4, range 1–4 (d.a. in 15/27)		Median 1, mean 1.9, range 1–5 (d.a. in 8/17)	
≥2 events	23/58 (40%)		18/39 (46%)		4/10 (40%)		3/8 (37%)	
ARR before MMF/AZA/MTX (excluding 1st events)[f]	Median 0.4, mean 0.87, range 0–6.67 (d.a. in 22/87)		Median 0.4, median 0.9, range 0–6.7 (d.a. in 15/48)		Median 0.5, mean 0.8, range 0–2 (d.a. in 8/22)		Median 0.5, mean 0.5, range 0–1.1 (d.a. in 2/17)	
Disease course during treatment with MMF/AZA/MTX								
Time on MMF/AZA/MTX (months)	Median 12, mean 12.2, range 1–48 (d.a. in 38/87)		Median 12, mean 14.2, range 1–48 (d.a. in 20/48)		Median 2, mean 13.3, range 1–36 (d.a. in 7/29)		Median 12, mean 8, range 1–12 (d.a. in 13/17)	
Proportion of patients relapsing whilst on MMF/AZA/MTX	4/62 (6.5%)		3/37 (8%)		1/14 (7.1%)		0/14 (0%)	
ARR whilst on MMF/AZA/MTX	Median 0, mean 0.03, range 0–0.8 (d.a. in 29/87)		Median 0, mean 0, range 0–0 (d.a. in 17/48)		Median 0, mean 0.2, range 0–1 (d.a. in 4/27)		Median 0, mean 0, range 0–0 (d.a. in 10/17)	
Disease course after MMF/AZA/MTX discontinuation (if applicable)								
Proportion of patients who discontinued MMF/AZA/MTX	14/30 (47%)		5/17 (29%)		4/7 (57.1%)		6/7 (86%)	
Time from MMF/AZA/MTX discontinuation to follow-up (months)	Median 11, mean 10.7, range 1–25 (d.a. in 11/14)		Median 6, mean 11.3, range 6–22 (d.a. in 3/5)		Median 6, mean 8.3, range 1–18 (d.a. in 3/4)		Mean 11.5, median 12.5, range 2–25 (d.a. in 6/6)	

Proportion of patients relapsing after MMF/AZA/MTX discontinuation	0/13 (0%)	0/5 (0%)	0/3 (0%)	0/6 (0%)
ARR after MMF/AZA/MTX discontinuation	0 (d.a. in 9/14)	Median 0, mean 0, range 0–0 (d.a. in 3/5)	Median 0, mean 0, range 0–0 (d.a. in 2/4)	Mean 0, median 0, range 0-0 (d.a. in 5/6)
Outcome				
Length of follow-up from disease onset (years)	Median 2, mean 2.5, range 0.2–8.6 (d.a. in 59/87)	Median 1.9, mean 2.5, range 0.2–8.6 (d.a. in 38/48)	Median 3, median 2.7, range 0.7–5.2 (d.a. in 18/27)	Mean 2, median 2.1, range 1–5.2 (d.a. in 7/17)
mRS at last follow-up				
mRS 0–1	42/69 (60.9%)	28/45 (62.2%)	10/19 (52.6%)	6/9 (67.7%)
mRS 2–3	25/69 (36.2%)	17/45 (37.8%)	8/19 (42.1%)	2/9 (22.2%)
mRS 4–6	2/69 (2.9%)	0/45 (0%)	1/19 (5.3%)	1/9 (11.1%)

anti-NMDAR: anti-N-methyl-D-aspartate receptor; AZA: azathioprine; CYC: cyclophosphamide; d.a.: data available; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; mRS: modified Rankin scale; MTX: methotrexate; PE: plasma exchange; RTX: rituximab.

[a] 7/87 patients had associated demyelinating episodes[32,33,62]; 1/87 patients also had NMOSD.[32] 3 patients had tumour: 1 15-year-old girl had an ovarian teratoma,[51] 1 12-year-old girl had mediastinal teratoma[59] and 1 16-year-old boy had a mediastinal teratoma[33] (all 3 patients had a monophasic disease).

[b] Other treatments before mycophenolate, azathioprine, methotrexate: 2/77 patients received interferon and alemtuzumab prior to steroid sparers (1/77 each); during the whole disease course, 3/77 other treatments: interferon, alemtuzumab and tacrolimus in 1/77 patients each.

[c] 1/48 of these patients also received AZA, and 2/48 also received MTX.

[d] 2/27 of these patients also received MTX, and 1/27 also received MMF.

[e] 2/17 of these patients also received AZA, and 2/17 also received MMF.

[f] In the 82/87 patients who received monotherapy with mycophenolate mofetil, azathioprine or methotrexate, the median ARR before steroid sparers (excluding the first episode) was 0.2 (mean 0.9, range 0–6.67; data available in 19/82) and on steroid sparers was 0 (mean 0.03, range 0–0.8; data available in 23/82). In the 9/82 patients with monotherapy and availability of both ARR pre and during steroid sparing agents, ARR before treatment (excluding first events) was median 0.5 (mean 1.2, range 0–6.67), and ARR during/after treatment was median 0 (mean 0, range 0–0).

76) before mycophenolate mofetil, azathioprine and methotrexate: rituximab in 37% (28/75), and cyclophosphamide in 30% (23/76). As per inclusion criteria, all patients received steroid sparing agents (87/87, 100%): 52% received mycophenolate mofetil (45/87), 27% azathioprine (24/87) and 15% methotrexate (13/87); an additional 6% of patients received a combination of these treatments (5/87: 2/87 azathioprine and methotrexate, 2/87 mycophenolate mofetil and methotrexate, 1/87 mycophenolate mofetil and azathioprine).

3.3. *Modes of use of mycophenolate mofetil, azathioprine and methotrexate*

Age at commencement of steroid sparing agents was median 13 years, mean 11.4, range 2.2–26 (data available in 38/87) (≤12 years in 30/66, 45%). Timing of initiation of maintenance immune therapy with mycophenolate mofetil, azathioprine and/or methotrexate was median 8.2 months from disease onset (mean 14.6; range 1–60) (data available in 34/87) (≤6 months in 19/39, 49%). In 40% (23/58) of the patients, steroid sparers were started only after relapses had occurred. Treatment duration with steroid sparers was median 12 months, mean 12.2, with a wide range (1–48 months; data available in 38/87). Route of administration was oral in all cases but in only 9 of the 17 patients who received methotrexate, the remainder receiving methotrexate intravenously in 2 cases,[42,57] and intrathecally in 7.[37,49,57,61] With the limitations imposed by data availability, dose ranged between 200 mg twice a day to 750 mg twice a day for mycophenolate mofetil (data available in 5/48 patients treated with mycophenolate mofetil; dose 600 mg/m^2/day in one of these), and between 50 mg and 150 mg a day for azathioprine (data available in 6/27 patients treated with azathioprine). As regards methotrexate, dose was 10 mg/m^2/week for oral methotrexate,[30,40] and 10 mg weekly for 4 weeks in 2 patients treated intrathecally (data available in 9/17 patients treated with methotrexate). Further data on use of methotrexate is detailed in Supplementary Table 2. Methotrexate was used for relapse prevention in 6 cases, and as a second-line treatment in case of unsatisfactory response to previous treatments in 8 (data available in 14/17 patients treated with methotrexate). In these latter cases, methotrexate was administered intrathecally in 7 of the 8 patients, and only after using rituximab or cyclophosphamide in 6 of the 8 cases.

3.4. *Efficacy*

3.4.1. *mRS*

Worst mRS before steroid sparers was median 4.5 (mean 4.3, range 3–5; data available in 76/87). At last follow-up at median 2 years (mean 2.5, range 0.2–8.6; data available in 59/87), median mRS was 1 (mean 1.2, range 0–6; data available in 69/87; mRS 0–1 in 42/69). One patient with multiple medical complications did not respond to treatment with plasma exchange, steroids, intravenous immunoglobulin, rituximab, cyclophosphamide, intrathecal methotrexate and bilateral oophorectomy, and died after ventilator support was withdrawn 12 months after onset.[57] The proportion of patients with good outcome (mRS 0–1) at last follow-up was similar in patients who received mycophenolate mofetil (28/45, 62.2%), azathioprine (10/19, 52.6%), and methotrexate (6/9, 67.7%).

3.4.2. *Proportion of patients free of relapses*

93.5% (58/62) patients were free of relapses whilst on mycophenolate mofetil, azathioprine or methotrexate. The proportion of patients who relapsed whilst on steroid sparers was slightly higher in patients on mycophenolate mofetil (3/37, 8%) and azathioprine (1/14, 7%) than in patients on methotrexate (0/14, 0%).

3.4.3. ARR

Median ARR prior to receiving steroid sparers (excluding first events) was 0.4 (mean 0.87, range 0–6.67; data available in 22/87), and 0 whilst on mycophenolate mofetil, azathioprine and/or methotrexate (mean 0.03, range 0–0.8, data available in 29/87). In 11/87 patients with availability of ARR both before and during steroid sparing agents, pre-treatment ARR (excluding first events) was median 0.5 (mean 1.1, range 0–6.67), and ARR during treatment was median 0 (mean 0.07, range 0–0.8).

3.5. *Study of relapses*

3.5.1. *Data on patients who relapsed whilst on mycophenolate mofetil, azathioprine and methotrexate*

Patients who relapsed on mycophenolate mofetil, azathioprine and methotrexate (4 patients, total 5 relapses) had low rates of use of second-line immune therapies before steroids sparers (1/4, 25%), long median time between onset and steroid sparers (median 18 months, mean 17, range 2–31; data available in 3/4), and frequently they were started on steroid sparers only after relapse (3/4, 75%) (Table 2). In 3 of the 4 relapses with available data, the event occurred at 1, 4 and 5 months from mycophenolate mofetil commencement respectively, and only in 2 of the 5 relapses another immune therapy was administered at the same time as steroid sparers.

3.5.2. *Treatment-related factors influencing relapse risk*

The proportion of patients who relapsed was lower among patients who received the first immune therapy within 30 days from onset compared to those treated later (5/20, 25%; versus 7/11, 64%), and in patients who received second-line immune therapy at first event than in those who did not (3/21, 14%; versus 27/42, 64%) (Table 3). As regards steroid sparing agents, fewer patients started on mycophenolate mofetil, azathioprine and methotrexate after the first event rather than subsequent events had further relapses (4/34, 12%; versus 4/23, 17%), and the proportion of patients with relapsing disease was lower in the subgroup started on steroid sparers within 3 months from onset than later (2/6, 33%; versus 15/28, 53%).

3.6. *Safety*

Adverse reactions were reported only for mycophenolate mofetil in 2 cases, with grade 3 severity according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (severe or medically significant, but not immediately life-threatening).[51] One of these patients was a 13-year-old girl

Table 2 – Study of relapses occurred whilst on mycophenolate mofetil, azathioprine or methotrexate.

Study of 5 relapses occurred in 4 patients whilst on MMF/AZA/MTX

Gender, age at onset	Event number (including 1st event) of the events occurred whilst on MMF/AZA/MTX	MMF/AZA/MTX (dose if available)	Time from MMF/AZA/MTX commencement to the event	Other immune therapy at the event	Medication weaning (or medication discontinuation ≤2 months prior to the event)	Second-line immune therapy (RTX and/or CYC) before the event
M, 13.4 years[24]	3	MMF	1 month	IVIG	IVIG 1 g/kg spaced from every week to every 2 weeks	No
F, 14 years[34]	2	MMF	4 months	No	No	No
	3	MMF	5 months	OP 80 mg/day	No	No
F, 13 years[29]	4	MMF	Not available	No	No	No
F, 11 years[37]	5	AZA (100 mg/day)	14 months	No	No	Yes (RTX 14 months before the relapse)

AZA: azathioprine; CYC: cyclophosphamide; F: female; IVIG: intravenous immunoglobulin; M: male; MMF: mycophenolate mofetil; MTX: methotrexate; OP: oral prednisone; RTX: rituximab.

who received intravenous steroids in the acute phase, and chronic treatment with oral steroid taper for 4 months and mycophenolate mofetil for 1 year; she was admitted for cytomegalovirus colitis and mycophenolate mofetil was discontinued. The other patient was a 17-year-old girl treated with intravenous steroids, intravenous immunoglobulin, rituximab and cyclophosphamide in the acute phase, and with mycophenolate mofetil for 1.5 years; she required hospitalization for a respiratory infection. Both patients had no tumour, and had a monophasic disease course; mycophenolate mofetil was dosed twice daily at a dose of 750 mg for body surface area of 1.25–1.5 m^2 and 1 g for body surface area > 1.5 m^2 (timing of the adverse reaction and concomitant medications not available).

4. Discussion

To our knowledge, this is the first systematic literature review focused on the use of mycophenolate mofetil, azathioprine and methotrexate in paediatric-onset anti-NMDAR encephalitis.

4.1. *Modes of use of steroid sparing agents*

While our study was not designed to assess the frequency of use of mycophenolate mofetil, azathioprine and methotrexate in paediatric-onset anti-NMDAR encephalitis, it appears these agents are used in a minority of cases (23.6% of the total cohorts described in the relative articles, 87/369), especially as regard azathioprine and methotrexate. Our results disclosed a great heterogeneity in the use of steroid sparing agents in paediatric-onset anti-NMDAR encephalitis. Firstly, while all patients in our literature cohort received first-line immune therapy before steroid sparers, preceding second-line treatments (rituximab and/or cyclophosphamide) were administered only in 50% (38/76). Secondly, there was a huge variability in the timing of initiation of mycophenolate mofetil, azathioprine and methotrexate, with only 49% (19/39) of the patients started on one of these agents within 6 months from onset. Similarly, only in 60% were these treatments started after the first event (35/58), whereas for the remaining part they were introduced only after one or more relapses had occurred. In this regard, the high relapse rate in our literature cohort (31/68, 46%), as compared to that of the largest series available so far (12%),[63] confirms that steroid sparers are often used only after relapses have occurred. The duration of maintenance treatment with steroid sparing agents was also highly variable in our literature cohort (range 1–48 months), reflecting the lack of recommendations.[10] Indeed, it is unclear how long the inflammatory component of disease lasts for. In this respect, the correlation between anti-NMDAR antibodies and clinical course is unclear,[64] while there is some correlation of CXCL13 and disease severity and relapse[65–67] that may be useful in guiding treatment. Data on doses in our literature review was limited; commonly used doses of steroid sparers in paediatric neurology are 600 mg/m^2 twice a day (maximum 1000 mg twice a day) for mycophenolate mofetil, 2–3 mg/kg/day for azathioprine,[68] and 10 mg/m^2/week for oral methotrexate.[30]

Table 3 – Treatment-related factors influencing risk of relapse. Denominators vary according to data availability.

Treatment-related factors influencing risk of relapse	Proportion of patients who relapsed
Timing of initiation of first immune therapy after onset (d.a. in 35/87)	
≤30 days (20/35)	5/20 (25%)
>30 days (15/35)	7/11 (64%)
Use of second-line immune therapy at first event (RTX/CYC) (d.a. in 64/87)	
Yes (21/64)	3/21 (14%)
No (43/64)	27/42 (64%)
Use of steroid sparing agents (MMF/AZA/MTX) at first event (d.a. in 58/87)	
Yes (35/58)	4/34 (12%)
No (23/58)	4/23 (17%)[a]
Timing of initiation of steroid sparing agents (MMF/AZA/MTX) after onset (d.a. in 39/87)	
≤3 months (6/34)	2/6 (33%)
>3 months (28/34)	15/28 (53%)

AZA: azathioprine; CYC: cyclophosphamide; d.a.: data available; MMF: mycophenolate mofetil; MTX: methotrexate.

[a] In the 23 patients in whom mycophenolate mofetil, azathioprine or methotrexate were administered only after the second or more event had occurred, the proportion of patients with further relapses was considered.

4.2. *Efficacy and study of relapses*

While there is literature to support the efficacy of steroid sparing agents in other autoimmune or immune-mediated conditions such as neuromyelitis optica[70,71] and MOG-associated disease,[18,20,72] the role of long-term immunosuppression with oral agents is still unclear as regards autoimmune encephalitis.[10] In our cohort, 93.5% (58/62) patients were free of relapses whilst on mycophenolate mofetil, azathioprine or methotrexate, and the median ARR dropped from 0.4 before steroid sparers, to 0 afterwards. In the subset of patients who were started on steroid sparers after the first event, the rate of further relapses (4/34, 12%) appeared to be slightly lower than that reported in some of the main literature series, where this figure mostly ranges between 12%[63] and 22.7%.[10,41,73] While these results are encouraging, it should be taken into account that figures based on relapse rate in anti-NMDAR encephalitis may not be accurate due to the low tendency to relapse in this condition, and that our data is limited by the very small number of cases.

In the attempt to identify treatment-related factors affecting the risk of relapse on mycophenolate, azathioprine or methotrexate, we observed that the 4 patients who relapsed on steroid sparing agents had low rates of use of second-line immune therapies before steroids sparers (1/4, 25%), long median time between onset and steroid sparers (median 18 months), and frequently they were started on steroid sparers only after relapse (3/4, 75%). We also observed that in 3 of the 4 relapses occurred on steroid sparers with available data, the event occurred at 1–5 months from initiation of mycophenolate mofetil, suggesting possible suboptimal treatment duration with incomplete efficacy, and that in only 2 of the 5 relapses there was overlap of steroid sparers with another immune therapy. Indeed, the initiation of a chronic treatment such as mycophenolate mofetil or azathioprine may have a slow onset of efficacy, and there should be initially overlap with other immune therapies for a few months.[6] Although, these observations should be interpreted with extreme caution given the limited number of cases.

In our literature cohort, there was a higher relapse rate among patients who did not receive rituximab or cyclophosphamide prior to steroid sparers (27/42, 64%) than in those who did (3/21, 14%), and in those with late start of first immune therapy (>30 days after onset) (7/11, 64%) than in patients who were treated early (5/20, 25%). Similarly, a late start of mycophenolate mofetil, azathioprine or methotrexate (after 3 months from onset) seemed to associate with a slightly higher proportion of patients who relapsed (15/28, 53%), as compared to those treated early (2/6, 33%). These results are consistent with previous data in the literature, supporting early and aggressive commencement of immune therapy.[11]

Differently to mycophenolate mofetil and azathioprine, methotrexate was used not only for relapse prevention, but also as a second-line treatment (mostly intrathecally) in case of unsatisfactory response to previous therapies. Treatment escalation in the 7 children who received intrathecal methotrexate for lack of response to previous therapies occurred in 2 cases after first-line treatments only, and in the remaining 5 after first-line followed by rituximab or cyclophosphamide (Supplementary Table 2). Direct administration of immune therapies in the cerebrospinal fluid aims to target the central population of plasmocytes producing anti-NMDAR antibodies and decrease intrathecal production[37,69]; although, efficacy and safety of intrathecal treatments for paediatric anti-NMDAR encephalitis remains to be evaluated.[69] Similarly, the efficacy of intrathecal methotrexate as a second-line agent as compared to rituximab or cyclophosphamide has not been studied yet.

4.3. *Safety*

Steroid sparing agents were administered also in young ages in our literature cohort, especially as regards mycophenolate mofetil and azathioprine. Adverse reactions were reported only for mycophenolate mofetil in 2 cases (cytomegalovirus colitis and respiratory infection).[51] Although, extreme caution should be used in interpreting safety data derived from our results, since side effects were probably under-reported and lacking in details in our review, as none of the articles included were focused on drug tolerability (Supplementary Table 1).

In general, some adverse reactions are common to mycophenolate mofetil, azathioprine and methotrexate, and include gastrointestinal symptoms (abdominal pain, diarrhoea, vomiting), myelosuppression with increased risk of infections, and hepatotoxicity with elevation of liver enzymes.[68,74,75] Steroid sparing agents should be used very cautiously in women of childbearing age.[74,75] Mycophenolate mofetil and azathioprine carry an increased risk of malignancies, particularly lymphoproliferative disorders and non-melanoma skin cancers for azathioprine.[75]

Other rare adverse reactions, more likely in case of concomitant administration of other immunosuppressants, include progressive multifocal leukoencephalopathy for mycophenolate mofetil,[74,75] pancreatitis for azathioprine and interstitial pneumonitis for methotrexate.[75] Intravenous or intrathecal administration of methotrexate has been associated with neurologic toxicity in oncology studies,[37,69] although it was not reported in our literature cohort.

Recent data on adult neuromyelitis optica suggest significantly better tolerability for mycophenolate than azathioprine,[71] but definite data in paediatric-onset anti-NMDAR encephalitis are lacking.

Adequate drug monitoring and accurate review of concomitant medications should be carried out in order to minimise adverse reactions to steroid sparers.

4.4. *Limitations*

Our literature review is limited by several factors. The retrospective nature of data collection unavoidably impacts on data accuracy and completeness. Several pieces of information, such as drug doses and monitoring, could not be retrieved in the great majority of papers. Severity of disease was estimated via the mRS score, although this scale was not designed to detect and render the vast array of disturbances that characterise anti-NMDAR encephalitis, especially as regards movement disorder, autonomic disturbances, psychiatric symptoms and neuropsychological changes.[76] ARR (Table 1) was calculated in order to provide data on the tendency to relapse before, during and after treatment with mycophenolate mofetil, azathioprine, or methotrexate; although, the utility of ARR in this setting is strongly limited by the consideration that, although recurrences are possible, anti-NMDAR encephalitis is typically not a chronic relapsing disease. The analysis of the results of our literature review is also limited by the restricted number of patients, especially when subdivided according to treatment type; therefore, a comparison between efficacy of mycophenolate mofetil, azathioprine and methotrexate could not be carried out. In view of the inclusion criteria, also a direct comparison between disease course in the patients who did and did not receive one of these agents could not be performed; this would be of great clinical interest and warrants further studies. Similarly, the efficacy of steroid sparers for sustained remission and relapse prevention should be explored further in comparison to other approaches proposed in the literature, such as monthly rituximab, intravenous immunoglobulin or plasma exchange, or sustained use of oral corticosteroids.[9,10]

4.5. *Conclusions*

Despite these important limitations, our literature review is the first work exploring most frequent current treatment modes, efficacy and tolerability of mycophenolate mofetil, azathioprine, and methotrexate in paediatric-onset anti-NMDAR encephalitis. Our results disclosed a huge heterogeneity in the use of these agents in paediatric-onset anti-NMDAR encephalitis, especially as regards the overall associated immune therapies, the timing and the duration of treatment.

Our review highlights the need for improved data in larger cohorts.

In conclusion, while paediatric anti-NMDAR encephalitis is usually characterised by a relatively good outcome, relapses are possible. Although there is general consensus that rituximab should be used in severe acute disease, steroid sparing agents (mycophenolate mofetil, azathioprine, and methotrexate) may have a role, either in patients with refractory acute disease (methotrexate), or for relapse prevention. As highlighted in this review, some clinicians use steroid sparing agents early in disease course, and without relapse, presumably to potentially reduce the steroid burden. However, the 'risk versus benefit' of this practice, as this review demonstrates, is unclear.

Conflicts of interest

There are no conflicts of interest to declare.

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