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Review Article

Efficacy and tolerability of mitoxantrone for neuromyelitis optica spectrum disorder: A systematic review

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ABSTRACT

The review assessed the efficacy and tolerability of mitoxantrone in patients with neuromyelitis optica spectrum disorder (NMOSD). Eight articles were reviewed with a total of 117 patients. Annualized relapse rate and progression of disability dramatically decreased post-treatment in most studies. Mitoxantrone was generally tolerated. Only one patient developed acute myeloid leukemia, which lead to septicemia and death. No serious cardiotoxicity was reported.

Mitoxantrone may be effective in reducing the frequency of relapse and slowing down the progression of disability in patients with NMOSD. The risk of cardiotoxicity and leukemia detains it as a second-line agent for NMOSD.

1. Introduction

1.1. Description of the condition

Neuromyelitis optica (NMO), also known as Devic's disease, and neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system causing demyelination of the optic nerves and spinal cord. The pathogenesis of the disease involves the humoral immune system, with the identification of aquaporin-4 antibody. This was found to be disease-specific for NMO. Studies showed that titers correlate with the length of the longitudinally extensive spinal cord lesions and with disease activity. Levels drop after immunosuppressive therapy and during remission (Mandler et al., 1993; Lennon et al., 2004; Takahashi et al., 2007).

NMO and NMOSD are rare, with a prevalence of 0.5–1.0/100,000. Incidence is 10 times higher in women. Age of onset is between the 32 to 41 years old. As the pathogenesis of the disease unfolded throughout years, the diagnostic criteria for similarly changed— initially requiring the simultaneous clinical spinal and ophthalmologic presentation to the present diagnostic criteria that includes of neuroimaging and laboratory criteria (Wingerchuk, 2009; Wingerchuk et al., 2015).

1.2. Description of the intervention

Acute attacks are initially treated with high-dose intravenous methylprednisolone. If unresponsive and with severe symptoms, plasmapheresis can be done. Long-term immunosuppression is initiated as soon as a diagnosis of NMOSD is made, for prevention of relapse. The most common studied agents used in NMOSD are azathioprine, mycophenolate mofetil, rituximab, methotrexate and mitoxantrone. Immunosuppression is continued for at least five years in seropositive patients, and those presenting with a single attack (Carroll and Fujihara, 2010; Collongues and de Seze, 2011; Kleiter et al., 2016).

1.3. How the intervention might work

Mitoxantrone (MTX) is an anthracenedione exerting its cytotoxic effect by intercalating with the DNA and inhibiting topoisomerase II enzyme activity needed for DNA repair. Immunosuppression is achieved by reducing the number of B cells, inhibiting T helper cell function, and augmenting the T cell suppressor activity. Its suppression of the humoral immunity highlights its role in the treatment of NMOSD. MTX has been approved for use in breast cancer, leukemia, non-Hodgkin lymphoma and multiple sclerosis (MS).

The most common reported adverse effect is cardiac insufficiency, seen in higher cumulative doses, followed by persistent neutropenia and thrombocytopenia (Faulds et al., 1991; Martinelli Boneschi et al., 2013).

1.4. Why is it important to do a review?

The low prevalence of the disease limits the availability of

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controlled trials. The currently recommended first-line immunotherapy for NMOSD includes azathioprine and rituximab, with the latter becoming more accepted because of its long-term efficacy and acceptable safety profile. MTX is only recommended as a second-line treatment because of its associated cardiotoxicity and leukemia reported in the treatment for MS (Burton and Costello, 2018; Trebst et al., 2014; Sellner et al., 2010). However, compared to rituximab and azathioprine, studies on MTX for NMOSD are only limited to observational studies. MTX is also likely to be cost-effective for secondary progressive or progressive relapsing MS. But presently, there are no published cost-effectiveness analysis study done for NMOSD. Hence, this systematic review is warranted to investigate the effectiveness and tolerability of MTX for its potential use in clinical practice on patients with NMOSD (Touchette et al., 2003).

1.5. Objectives

The objective of the review was to determine the efficacy and tolerability of MTX as an immunosuppressive therapy in patients with NMOSD, in terms of:

1. Reducing the relapse rate
2. Reducing the progression of the disability
3. Acceptable safety profile

2. Methods

2.1. Criteria for considering studies for review

2.1.1. Types of studies

Case reports, case series, prospective/retrospective cohort, case control, cross-sectional trials and randomized controlled trials were all considered in this systematic review.

2.1.2. Types of participants

Studies included patients, male or female, with a diagnosis of NMOSD based on the NMOSD diagnostic criteria published in 1999, 2006 and 2015 or limited form of NMOSD (Wingerchuk et al., 2015; Wingerchuk et al., 2006). No restrictions were done in terms of ethnicity, age at onset, duration of illness, number of relapses prior to treatment, previous treatment, baseline EDSS. Studies on patients with MS alone were not included.

2.1.3. Type of intervention

All studies describing the use of MTX, independent of dosage, frequency and duration, were included. It was not restricted on the use of MTX monotherapy alone.

2.1.4. Types of outcomes measures

The main outcomes considered for this review were:

1. Annualized relapse rate (ARR)- A relapse is defined as neurologic symptoms lasting for > 24 h, which occur at least 30 days after the onset of a preceding event. ARR is computed as a function of the number of relapse over the number of days (years) in observation. Post-treatment ARR was compared to pre-treatment ARR (Lavery et al., 2014).
2. Expanded disability status scale (EDSS)- Disability progression was defined as an increase of at least 1 point above the pre-treatment score if baseline score < 5.5, and of at least a half point if baseline score > 5.5, of the Kurtzke EDSS. Outcome measured was the mean change in the EDSS from before and after treatment (Kurtzke, 1983).
3. Relapse-free rate- the absence of relapse during the observation period of the study reported as percentage per study.
4. Frequency of major and minor side effects during the follow-up period

2.2. Search methods for identification of studies

2.2.1. Electronic searches

Four online databases were searched for relevant articles. These are: The Cochrane Central Register for Controlled Trials (CENTRAL) by The Cochrane Library, MEDLINE by PubMed, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), and HERDIN (Health Research and Development Information Network) websites. The most recent search was done last September 20, 2018.

2.2.2. Other sources

Reference lists from eligible articles and reviews of NMOSD treatment were searched. Clinical trials register database (Clinicaltrials and Clinical Register Trials, www.clinicaltrials.gov) was also searched to find ongoing studies.

2.3. Data collection and analysis

2.3.1. Selection of studies

The titles and abstracts yielded by the strategic search strategy were screened using the criteria mentioned. The full-text articles were retrieved if the abstract was insufficient for screening. Relevant articles fulfilling the screening criteria were retrieved in full-text articles and were reviewed for eligibility. Eligible studies fulfilling the inclusion and exclusion criteria below, were included in this review.

2.3.2. Inclusion criteria

All primary research, and available full-text article were included in this review. English abstracts of foreign language articles, if with sufficient data were also considered. All studies reporting use of MTX in patients clinically diagnosed with NMOSD were included in this review.

2.3.3. Exclusion criteria

Articles including reviews reporting secondary data, and those with no full-text report accessible were not included. Duplicate reports with the same data were discarded.

2.3.4. Selection of studies

Two review authors (CAGE and AIE) independently assessed and selected full text articles and resolved any disagreement on the eligibility of the included studies through discussion, achieving a final consensus. A senior reader (PMDP) resolved any disagreement through discussion, if warranted.

2.3.5. Data extraction and management

Data gathering was done using a data collection form. The following information were collected on each article: methods or study design, the population with the inclusion and exclusion criteria, the treatment protocol (dose and duration of MTX treatment/ other interventions given). Treatment outcomes included were ARR pre and post treatment, EDSS pre and post treatment as well as relapse-free rate. Tolerability was assessed using the number of events reported per adverse reactions (i.e. leukopenia, cardiotoxicity, death).

Both dichotomous and continuous data were extracted from included studies. The continuous data (i.e. ARR, EDSS) were reported as means with standard deviation. Dichotomous data (i.e. events of adverse reactions) were reported as percentages (the number of events divided by the total sample size).

2.3.6. Quality assessment for nonrandomized studies

The Newcastle-Ottawa Quality Assessment Form was used to assess the quality of eligible nonrandomized study (Luchini et al., 2017).

2.3.7. Measures of treatment effect

Treatment effect was measured as mean differences. Significance was reported as p value $< .05$.

Table 1
Search strategies.

	Search terms	Items found
Cochrane Central Register of Controlled Trials (CENTRAL) by the Cochrane Library)		
#1	Search mitoxantrone or mitoxantrone acetate or mitoxantrone hydrochloride	1215
#2	Search neuromyeltis optica spectrum disorder or NMO spectrum disorder or devic neuromyelitis optica or Devic's neuromyelitis optica or neuromyelitis optica	118
#3	Search #1 and #2	17
MEDLINE by PubMed		
#1	Search ((mitoxantrone) or mitoxantrone acetate) or mitoxantrone hydrochloride	5825
#2	Search ((((neuromyeltis optica spectrum disorder) or NMO spectrum disorder) or Devic neuromyelitis optica) or Devic's neuromyelitis optica) or neuromyelitis optica	3056
#3	Search ((((mitoxantrone) or mitoxantrone acetate) or mitoxantrone hydrochloride)) and (((((neuromyeltis optica spectrum disorder) or NMO spectrum disorder) or devic neuromyelitis optica) or Devic's neuromyelitis optica) or neuromyelitis optica)	23
Clinicaltrials.gov		
#1	Search ((((mitoxantrone) or mitoxantrone acetate) or mitoxantrone hydrochloride)) and (((((neuromyeltis optica spectrum disorder) or NMO spectrum disorder) or Devic neuromyelitis optica) or Devic's neuromyelitis optica) or neuromyelitis optica)	2
LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde)		
#1	Search ((((mitoxantrone) or mitoxantrone acetate) or mitoxantrone hydrochloride)) and (((((neuromyeltis optica spectrum disorder) or NMO spectrum disorder) or Devic neuromyelitis optica) or Devic's neuromyelitis optica) or neuromyelitis optica)	1
HERDIN (Health Research and Development Information Network) website		
#1	Search ((((mitoxantrone) or mitoxantrone acetate) or mitoxantrone hydrochloride)) and (((((neuromyeltis optica spectrum disorder) or NMO spectrum disorder) or Devic neuromyelitis optica) or Devic's neuromyelitis optica) or neuromyelitis optica)	3

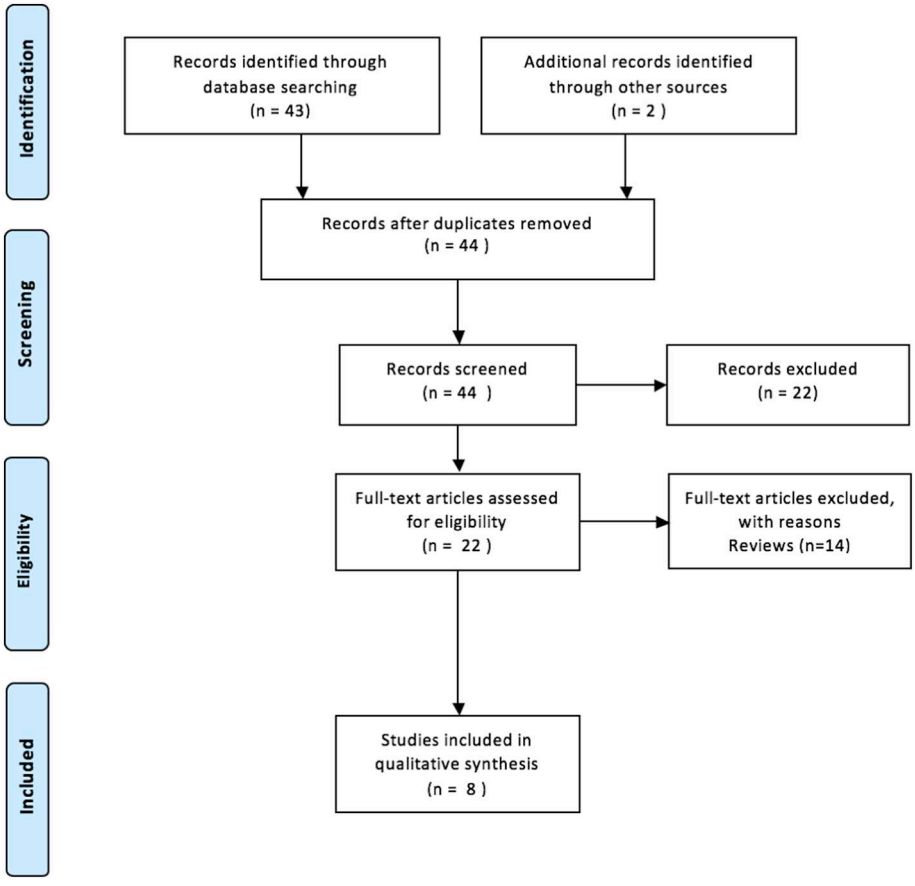

Fig. 1. PRISMA 2009 study flow diagram.

2.3.8. Unit of analysis

The individual participant was the unit of analysis.

3. Results

3.1. Results of the search

Five major databases were searched for relevant articles. First search yielded 45 results (CENTRAL 17; PubMed 22; LILACS 1; HERDIN 3; ClinicalTrials.gov 2) using the search strategies described in Table 1. One duplicate article was discarded. Using the screening criteria, 22 records were removed. Most were studies on MS and trials using other immunotherapies alone. There were 22 articles reviewed for eligibility. Using the inclusion and exclusion criteria, only 8 articles were considered for this systematic review. The flow diagram for this systematic review is summarized in Fig. 1.

Table 2
Study characteristics.

Studies included	Population			Intervention				Outcomes measured			
Authors/year published/design	Country/ sample	Inclusion criteria	Exclusion criteria	MTX dose	Duration and frequency of MTX treatment	Cumulative dose	Other interventions	Relapse	Disability	Adverse events	Others
Weinstock-Guttman et al., 2006 Case series	USA 5	Recurrent LETM (> / 3 segments of spinal cord involvement on MR images) With or without recurrent ON (unilateral or bilateral) Normal brain MRI Cerebrospinal fluid required no intrathecal IgG synthesis or oligoclonal bands EDSS score of 7 or less	Cardiac risk factors (eg, history of congestive heart failure and LVEF 50%) Systemic diseases such as systemic lupus erythematosus, Sjogren syndrome, antiphospholipid antibody syndrome, sarcoidosis, rheumatoid arthritis, or vitamin B12 deficiency Previous treatment with mitoxantrone or anthracyclines.	12 mg/m2 not exceeding 20 mg/m2	Monthly for 3–6 months then quarterly up to 2 years	100 mg/m2	1000 mg IV methylprednisolone succinate	ARR	EDSS	Leukopenia infection cardiac dysfunction	None
Jarius et al., 2008 Case series	Austria 3	NMO–IgG-positive patients Isolated longitudinally extensive transverse myelitis With or without optic neuritis	NR	NR	NR	NR	NR	ARR	NR	NR	None
Singhal et al., 2009 Case series	India 2	NMO 2006 criteria	NR	12 mg/m2	Quarterly	140 mg/m2	1000 mg IV methylprednisolone on relapse	ARR	EDSS	NR	None
Kim et al., 2011 Case series	Korea 20	NMO 2006 Criteria at least 2 relapses during the 12 months preceding the start of mitoxantrone therapy	Cardiac dysfunction Hepatic or renal disease Abnormal baseline white blood cell or platelet counts Pregnant or lactating women, and those of reproductive age who were not willing to use contraception were excluded from mitoxantrone therapy	12 mg/m2	Monthly for 3–6 months then quarterly up to 2 years	100 mg/m2	NR	ARR	EDSS	Leukopenia transaminasemia cardiac dysfunction	CD19+ CD27+ memory B cells
Nakano et al., 2011 Case report	Japan 1	NA	NA	7 mg/m2	NR	38 mg/m^2	11 mg prednisolone	NR	NR	VZV infection	None
Cabre et al., 2013 Case series	French Carribean and Guyana 51	NMO 2006 criteria limited form of NMO Each patient had to have presented at least one episode of ON and/or LEM in the year prior to the inclusion EDSS score ≤ 7.0	Monophasic IgG-NMO-LEM IgG-NMO-patients with a single episode of ON suggestive of NMO	12 mg/m2	Monthly induction for 3 months then quarterly for 9 months	72 mg/m^2	1000 mg IV methylprednisolone	ARR	EDSS	Cardiac dysfunction	None
Frau et al. 2014 Case report	Italy 1	NA	NA	10 mg/m2	NR	52 mg/m^2	Rituximab 375 mg/mq was administered every week for four infusions	NR	NR	Leukopenia	CD19 count
	Germany 34				90 days	NR	Intrathecal steroids		NR	NR	NR

(*continued on next page*)

Table 2 (*continued*)

Studies included	Population			Intervention			Outcomes measured			
Authors/year published/design	Country/ sample	Inclusion criteria	Exclusion criteria	MTX dose	Duration and frequency of MTX treatment	Cumulative dose	Other interventions	Relapse	Disability	Adverse events	Others
Stellmann et al., 2017 Retrospective Cohort		NMO 2006 Criteria OR with AQP4-ab-positive NMO spectrum disorder (NMOSD)	Treatments with uncertain treatment start or stop Overlapping treatments	10–12 mg/m^2				HR compared to Interferon Beta			

ARR-annualized relapse rate. EDSS-estimated disability status scale. LETM-longitudinally extensive transverse myelitis. LVEF-left ventricular ejection fraction. HR- hazard ratio. NA-not applicable. NMO-neuromyelitis optica. NR-not reported. ON-optic neuritis.

3.2. Included studies

The characteristics of the included studies are summarized in Table 2. A total of eight articles were included in this systematic review. There were five case series studies: The studies of Weinstock-Guttman, Kim and Cabre focused on the efficacy and tolerability of MTX alone, on patients with NMOSD (Weinstock-Guttman et al., 2006; Kim et al., 2011; Cabre et al., 2013). Singhal also studied the efficacy and tolerability of MTX, but the population of his study mostly included patients with MS (Singhal et al., 2009). Jarius studied the correlation of Anti-AQP4 positivity to long term follow-up of patients, looking into its levels during relapse, remission and in response to immunotherapies (Jarius et al., 2008). No comparator intervention was used in these studies. Two case reports, Nakano and Frau, were included to describe the management of adverse events during and after MTX infusion (Nakano et al., 2011). The article by Stellmann is a retrospective cohort study, that analyzed the predictors for relapses and number of attacks of different immunotherapies in comparison to interferon-beta. Results were reported as hazard ratio (Stellmann et al., 2017).

The main outcomes measured in most of the studies are the ARR and the expanded disability severity scale (EDSS) before and after treatment. Some studies reported the relapse-free rate among samples. Other outcomes include adverse events reported and death.

3.3. Quality assessment of nonrandomized studies

Only one retrospective cohort study was included in this systematic review. Using the Newcastle-Ottawa Quality Assessment Form, the study by Stellmann is deemed to be of good quality, with a total of 8 out of 9 stars.

3.4. Population of the studies included

In summary, a total of 117 patients from 8 different articles were analyzed (See Table 3). The population of studies mostly included patients within the 3rd to 4th decade of life. Most patients were female. The duration of illness for all studies reported is < 10 years. NMO-IgG seropositivity was only included in the diagnostic criteria after the publication of the 2006 criteria. Because of this, this was noted in Weinstock-Guttman's case series published on the same year. This was also not reported in the abstract of the Nakano's case report.

3.5. Effects of the intervention

The effects of the intervention are summarized in Table 4.

3.5.1. Annualized relapse rate (ARR)

Five studies reported the ARR before and after treatment. Studies by Weinstock-Guttman, Singhal, Kim and Cabre showed a dramatic decrease in the ARR within the observation period of as early as 6 months to 5 years. It should be considered that Cabre's case series (n = 51) had a low ARR at baseline. The results from the article by Jarius showed an increase in the mean ARR. Out of the three subjects in his series, only one had a decreased ARR post-treatment.

The retrospective cohort study by Stellmann reported the risk of relapse as hazard ratio (with interferon-beta as reference). HR was 0.9, 95%CI 0.5–1.6. This concludes that MTX did not decrease the risk of attack as compared to interferon-beta.

3.5.2. Expanded disability status scale (EDSS)

Four articles (Weinstock-Guttman, Singhal, Kim, Cabre) looked into the effect of MTX on the EDSS. All reported a significant decrease in the EDSS post-treatment within the observation period of 1 to 5 years. Singhal's study had the most substantial change in the EDSS from a mean EDSS of 7.5 to 1.

Table 3
Population of the studies included.

Study	n	Present age, years (Mean ± SD)	Age at onset, years (Mean ± SD)	Sex (%F)	Duration of illness, years (Mean ± SD)	Relapses since disease onset, number (Mean ± SD)	NMO-IgG (% positive)
Weinstock-Guttman et al., 2006	5	36.4 ± 13.9	29 ± 13.2	60%	7.4 ± 10.21	4 ± 1.22	NR
Jarius et al., 2008	3	NR	NR	NR	NR	NR	100%
Singhal et al., 2009	2	36.5 ± 10.61	23.5 ± 14.9	100%	13 ± 4.25	NR	100%
Kim et al., 2011	20	33.25 ± 10.76	NR	100%	5.925 ± 4.19	4.05 ± 1.43	100%%
Nakano et al., 2011	1	36	NR	100.00%	NR	NR	NR
Cabre et al., 2013	51	41.7 ± 12.2	NR	90.20%	4 ± 5.4	3.9	50%
Frau et al. 2014	1	47	NR	100.00%	7 years	8	100.00%
Stellmann et al., 2017	34	46.8 ± 13.4	NR	76.50%	5.4 (5.9)	NR	88.20%

NR- not reported.

3.5.3. Relapse-free rate

Only four studies reported the relapse-free rate after MTX therapy. The two NMO patients in Singhal's case series, had no relapse at least 2 years after the MTX therapy. On the other hand, the three patients reported by Jarius had relapses 11 months after MTX therapy. Weinstock-Guttman and Kim reported a relapse-free rate of 60% (3/5) and 50% (10/20), respectively.

3.5.4. Adverse events and death

Leukopenia is seen in most studies, with persistent neutropenia in 3 cases, causing delay in treatment. Neutropenia was transient and resolved without the need for granulocyte-colony stimulating factor. Leukopenia in the case reported by Frau lead to delayed and decreased doses of MTX. Because of the suboptimal dosing, the patient had relapse during therapy, and was shifted on Rituximab infusions leading to stabilization of the disease.

Infections reported include recurrent urinary tract infection and staphylococcal skin infection. The staphylococcal skin infection led to discontinuation of MTX therapy. The case reported by Nakano developed Herpes Zoster infection in the thigh followed by Varicella Zoster Virus Meningitis after five courses of MTX (7 mg/m2). This was managed with intravenous antivirals (Valaciclovir and Aciclovir).

One patient developed acute myeloid leukemia during treatment after presenting as fulminant NMO refractory to MTX, cyclophosphamide and rituximab infusions. The patient died of septicemia.

A total of five deaths were reported in the eight articles, including the patient who died from septicemia as a consequence of leukemia. The four deaths were attributed to complications of relapses. One was from the case series of Weinstock-Guttman, who died because of pulmonary embolism during relapse. The rest were from the case series of Cabre. Two patients died of acute respiratory failure that occurred 2 years and 4 years after starting MTX. One also died from pulmonary embolism during a severe spinal cord relapse just after completion of MTX treatment (Table 5).

4. Discussion

4.1. Summary of main results

4.1.1. Recommended dose and frequency of MTX for patients with NMOSD

Most of the studies used a dose of 12 mg/m^2 which was administered in the induction phase monthly (Table 1). The recommended duration of the induction phase is 3–6 months. However, patients who were started on 3-month induction phase had high rates of relapse hence, the induction phase was extended to 6 months for the succeeding patients included in the studies of Weinstock-Guttmann and Kim. The induction phase was followed by a maintenance phase, consisting of quarterly injections of MTX.

4.1.2. Recommended cumulative dose of MTX for patients with NMOSD

The maximum cumulative dose of MTX used for most patients in the studies reviewed was up to 135 mg/m^2 given over a period of two years. The maximum cumulative dose of MTX for MS is 140 mg/m^2 because of the increased risk of cardiotoxicity whether or not cardiac risk factors are present. With the recommended protocol for MTX in both MS and NMOSD, the maximum cumulative dose is already maximized within the period of two years.

4.1.3. MTX on reducing frequency of relapse

This systematic review suggests that MTX may be effective in decreasing the frequency of relapse in patients with NMOSD. This is true, regardless of the frequency of relapse at baseline. The retrospective cohort study by Stellmann compared the risk of attack of MTX with interferon-beta. This is difficult to interpret because interferon-beta is not the standard of care in NMOSD. In fact, it was proven to be unsafe in patients with NMOSD (Uzawa et al., 2010).

The reported reduction in the mean ARR in the studies reviewed is comparable to the recommended first-line agents. In a systematic review and meta-analysis of Rituximab for NMOSD including 438 patients from 46 studies, the mean reduction in ARR is 0.64 (SD 0.27) within a mean follow-up of 27.5 months. For Azathioprine, a study on 70 patients with > 12 months of follow-up showed median ARR post-treatment of 0.64 from pre-treatment median ARR of 2.18, $p < .001$. In a retrospective case series of NMOSD patients who were given Mycophenolate Mofetil including 19 patients with a median follow-up of 28 months, the post-treatment mean ARR is 0.09 from a pre-treatment mean ARR of 1.3, $p < .001$ (Damato et al., 2016; Costanzi et al., 2011; Jacob et al., 2009).

4.1.4. MTX on slowing down the progression of disability in patients with NMOSD

MTX is also effective in reducing the progression of disability in patients with NMOSD. This is also applicable for patients with a very severe disability at baseline. Although not as dramatic as the change in the frequency of attacks, MTX reduces the disability, in terms of EDSS post-treatment.

This is also comparable to the recommended first-line agents. In the systematic review and meta-analysis of Rituximab for NMOSD, there is a mean reduction in the EDSS of 0.64 (SD 0.27) post-treatment. For Azathioprine, the same study mentioned above showed improved EDSS in 29% of patients, and stable EDSS in 33% of patients. Overall, the mean EDSS pre- and post-treatment remained the same at 3.5. Also, in the same study for Mycophenolate Mofetil, the median EDSS score was 6 (range, 0–8)pre-treatment and 5.5 (range, 0–10) post-treatment. The EDSS scores was unchanged and improved in 91% of patients (Damato et al., 2016; Costanzi et al., 2011; Jacob et al., 2009).

Table 4
Effects of the intervention.

Study	n	Treatment		ARR			EDSS			Relapse-free		
		Cumulative dose (mg/m2)	Duration	Pretreatment (Mean ± SD)	Posttreatment (Mean ± SD)	Duration of observation	Pretreatment (Mean ± SD)	Posttreatment (Mean ± SD)	Duration of observation	Events	Percentage	Duration of observation
Weinstock-Guttman et al., 2006	5	96 to 104	24 months	2.4 ± 0.89	0.4 ± 0.55	2 years	4.40 ± 1.88	2.25 ± 0.65	2 years	3	60%	2 years
Jarius et al., 2008	3	NR	NR	1.99 ± 0.55	2.63 ± 1.56	NR	NR	NR	NR	0	0%	11 months
Singhal et al., 2009	2	NR	1–2 years	0.415 ± 0.40	0	2 years	7.5 ± 1.41	1 ± 0	2 years	2	100%	2 years
Kim et al., 2011	20	Mn ± SD 101.76 ± 12.22	Mn ± SD 16.55 ± 4.03	2.81 ± 1.06	0.65 ± 0.76	8–22 months	5.58 ± 2.06	4.33 ± 1.66	8–22 months	10	50%	8–22 months
Nakano et al., 2011	1	38	Four courses	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cabre et al., 2013	51	Mn ± SD 107 ± 28	1 year	1.82	0.55 0.37 0.43 0.53 0.47 0.41	0.5 yr 1 yr 2 yr 3 yr 4 yr 5 yr	5.8 ± 1.9	4.5 4.5 4.7 4.7 4.8	1 yr 2 yr 3 yr 4 yr 5 yr	NR	NR	NR
Frau et al. 2014	1	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stellmann et al., 2017	34	NR	90 days	HR 0.9, 95% CI (0.5–1.6) *in comparison to IFN-beta			NR	NR	NR	NR	NR	NR

ARR- annualized relapse rate. EDSS- estimated disability status scale. HR- hazard ratio. NR- not reported.

4.1.5. Tolerability of MTX therapy

MTX was tolerated in most of the patients, with only one death probably related to MTX. There were few major adverse events leading to delay or discontinuation of the therapy. The major safety concern is the occurrence of acute myeloid leukemia in one patient, which eventually lead to death. The rest of the deaths reported were all attributable to poorly controlled relapse. The leukopenia was transient and the infections were self-limiting or were easily managed with antibiotic or antiviral therapy. No serious cardiotoxicity was reported, but MTX should be used with caution in patients with baseline cardiac insufficiency. The more frequently reported minor adverse effects were amenorrhea, alopecia and bluish discoloration of the nails.

In a large real-life cohort study of 411 patients with relapsing and progressive MS who were given MTX (cumulative dose of 72 mg/m^2 to 120 mg/m^2) and followed-up for ten years, there were four cases of cardiomyopathies identified. One was considered to be related to the patient's diabetes mellitus. A total of 7 patients developed leukemia. Three of which were considered as chronic, while 4 were acute myeloid leukemias which developed 2–5 years after the last dose of MTX. There were also 25 other cases of malignancies reported (Chartier et al., 2018). In a larger case-series including 5472 MS patients who were given MTX, the mean dose is 74.2 mg/m^2, ranging from 12 to 120 mg/m^2. Therapy-related acute leukemia was diagnosed in 0.30% of cases. The onset of leukemia after cessation of MTX ranged from 4 to 60 months, with a median of 18.5 months. There is a strong relationship between the risk of developing leukemia and cumulative dose, with a relative risk of 1.44 in patients exposed to > 60 mg/m^2 (Ellis et al., 2015).

The lack of long-term follow-up studies in patients with NMOSD who received MTX limits the observation of adverse events in these patients.

4.2. Overall completeness and applicability of evidence

The studies included were heterogeneous in terms of the population, the inclusion criteria and the treatment dosage and regimen. Some of the case series only had a few data on outcome and details on the intervention were not specified. Follow-up was only restricted to 2 years in most of the studies. Adverse effects more importantly AML, developed at least 2 years after the cessation of MTX in patients with relapsing and progressive MS. With this limited data and long-term follow-up on patients with NMOSD who received MTX, the overall review of the reported outcomes suggests that MTX may be an effective and safe treatment for NMOSD. The risk of cardiotoxicity and leukemia reported in studies on MS restricts its use as a second-line agent for NMOSD.

4.3. Quality of evidence

Meta-analysis of available data was the initial goal of the authors. However, the articles evaluated have high risk of bias for meta-analysis. There is a lack of a concurrent control group. As such, it is difficult to conclude effectiveness as it is difficult to establish any observed effect is a 'true' intervention effect as we cannot rule out the contribution of the natural course of NMOSD, placebo effect, or the effect of other concurrent treatment.

4.4. Potential biases in the review

A broad search was done to minimize bias. Other sources beyond the electronic database were explored. The eligibility of studies for inclusion was evaluated independently by the authors.

4.5. Agreements and disagreements with other studies or reviews

No systematic review about the use of MTX alone on NMOSD has

Table 5
Adverse events reported.

Studies	N	Adverse event	Number of events	Percentage	Effect on treatment	Notes
Weinstock-Guttman et al., 2006	5	Leukopenia	NR	NR		Transient within 10 days
		Infection	1	20%		Recurrent urinary tract infection
		Cardiac insufficiency	1	20%	Discontinued	LVEF from 60% at baseline to 44% at 86 mg/m2, recovered after discontinuation
		Death	1	20%		Pulmonary embolism
Jarius et al., 2008	3	NR	NR	NR	NR	NR
Singhal et al., 2009	2	NS	NS	NS	NS	NS
Kim et al., 2011	20	Neutropenia (< 500)	2	10%	Delayed	
		Cardiac insufficiency	1	5%	Discontinued	Asymptomatic from 64% to 54% after a cumulative dose of 72 mg/m^2
		Elevated SGPT/SGOT	4	20%		
		Hair loss	5	25%		
		Amenorrhea	5	25%		
Nakano et al., 2011	1	Infection	1	100%	Discontinued	Varicella Zoster Virus Meningitis after cumulative dose of 38 mg/m^2
Cabre et al., 2013	51	Cardiac insufficiency	1	1.96%		LVEF < 50%
		Emesis	4	7.80%		
		Alopecia	8	15.60%	Discontinued in 1 case	
		Bluish nail discoloration	5	9.80%		
		Amenorrhea	6	13.00%		
		Neutropenia (< 500)	1	1.96%		
		Infection	1	1.96%	Discontinued	*S. aureus* infection
		Leukemia	1	1.96%	Discontinued	Type 1 AML
		Death	4	1.96%%		Two from respiratory failure One from pulmonary embolism One from acute myeloid leukemia
Frau et al. 2014	1	Leukopenia	1	100%	Delayed and reduced dose	After cumulative dose of 52 mg/m^2
Stellmann et al., 2017	34	NR	NR	NR	NR	

AML- acute myeloid leukemia. LVEF- left ventricular ejection fraction. NR- not reported. NS- not specified.

been published. The published guidelines for NMOSD recommending MTX as a second-line immunosuppressant are based on observational studies and expert opinion. The guidelines mentioned that MTX is deemed effective in preventing relapse and slowing down progression of disability in NMOSD. However, it was also emphasized that the restriction on the use of MTX as second-line immunosuppressant is because of its potential toxicity and limited duration of therapy. This systematic review suggests that the cardiac insufficiency caused by MTX for patients with NMOSD doesn't lead to heart failure and is reversible upon discontinuation of MTX (Burton & Costello, n.d.; Trebst et al., 2014; Sellner et al., 2010).

5. Conclusions

5.1. Implications for practice

This systematic review found that MTX may be effective in reducing the frequency of relapse as well as slowing down the progression of disability in patients with NMOSD for at least two years. Adverse events are tolerable but use should be cautious in patients with baseline neutropenia and cardiac insufficiency.

5.2. Implications for research

Up to now, studies on MTX use in NMOSD is limited to small population and observational studies. There is a need for randomized controlled trials to confirm the beneficial effects and risks of MTX therapy but this is limited by the availability of less toxic immunomodulators (i.e. rituximab, ecrulizumab). Studies on determining the ideal treatment regimen are also encouraged.

Conflict of interest

The authors have no any conflict of interest.

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