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REVIEW

Therapeutic plasma exchange vs conventional treatment with intravenous high dose steroid for neuromyelitis optica spectrum disorders (NMOSD): a systematic review and meta-analysis

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Abstract

Background Therapeutic plasma exchanges (TPE) has been recommended for neuromyelitis optica spectrum disorders (NMOSD) as a rescue therapy after nonresponding from the high-dose steroid and as an early therapy in severe attacks. We performed a systematic review to evaluate whether therapeutic plasma exchange (TPE) is better than conventional intravenous methylprednisolone (IVMP) in neuromyelitis optica spectrum disorders (NMOSD) patients.

Methods Systematic search was conducted in five databases: PubMed, Embase, Scopus, Web of Science, and CENTRAL for randomized controlled trials and observational studies of TPE compared to intravenous steroid in NMOSD patients with neurological or visual outcomes in English without publication date restriction. Quality assessment was performed using ROB2 and ROBINS-I. The meta-analysis was done using a random-effects model. Pooled risk ratio (RR) or mean difference with a 95% CIs of efficacy outcomes included the Expanded Disability Status Scale (EDSS), visual acuity, and LogMAR were measured.

Results Of 3439 potential studies, seven were included in the systematic review (1211 attacks; 433 patients) and three studies were included in the meta-analysis. Compared to high dose steroid alone, the add-on TPE increases a chance for the returning of EDSS to baseline at discharge (RR 3.02, 95% CI 1.34–6.81) and last follow-up (RR 1.68, 95% CI 1.01–2.79) as well as improves visual acuity at last follow-up.

Conclusion TPE as an add-on therapy to high-dose steroid injection during an acute attack in NMOSD patients is associated with returning to baseline EDSS at discharge and last follow-up, and a trend to have a lower disability at 6–12 months.

Keywords Neuromyelitis optica · NMOSD · Optic neuritis · Plasma exchange · Steroid · Meta-analysis

Abbreviations

AQP4	Aquaporin-4
AQP4-Ab	Aquaporin-4 autoantibody
ASFA	American Society of Apheresis
CNS	Central nervous system
EDSS	Expanded Disability Status Scale
GEE	Generalized estimating equation
HD-S	High dose steroid
IA	Immunoadsorption
IVMP	Intravenous methylprednisolone
LETM	Longitudinally extensive transverse myelitis
LogMAR	Logarithm of the minimum angle of resolution

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MS	Multiple sclerosis
MY	Myelitis
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorders
ON	Optic neuritis
OR	Odds ratio
PLEX	Plasma exchange
ROBINS-I	Risk of Bias In Non-randomized Studies of Interventions
RR	Risk ratio
SD	Standard deviation
TM	Transverse myelitis
TPE	Therapeutic plasma exchange
VA	Visual acuity

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune conditions in which pathogenic aquaporin-4 autoantibody (AQP4-Ab) binds to AQP4 at the foot processes of the astrocytes in the central nervous system [1]. The orchestra between AQP4-Ab and AQP4 antigen initiates complementary pathways and then later induce other cytokines and chemokines, results in primary astrocytes damage and then secondary demyelination [2, 3].

Treatment for an acute NMOSD attack must be immediately performed when the attack is identified to alleviate the accumulated inflammatory damage that leads to disability as neuromyelitis optica (NMO) is rarely progressive [4, 5]. Successful treatment of attacks determines good long-term outcomes and reduced disability. NMOSD attacks should be treated 'hard' and 'early' and escalation of therapy is recommended [6].

Therapeutic plasma exchange (TPE) was proven to be an effective treatment for the central nervous system (CNS) demyelinating diseases including NMOSD with an acute attack in a randomized sham-controlled study [7]. Several other studies had confirmed the benefit of TPE in pure NMOSD patients with an acute attack [8–15]. According to the American Society of Apheresis (ASFA), TPE is in Category II as a recommended treatment for NMO with an acute attack and in category III for maintenance in NMOSD [16]. TPE is anticipated to wash out AQP4-Ab, complement, and pathogenic cytokines as well as other proinflammatory factors from the blood circulation [17]. Nowadays, TPE is recommended as a second or rescue therapy for patients who do not respond to the treatment with high-dose steroid [18]. Early TPE in the severe acute attack has been considered but the inclusion criteria, amount of plasma volume exchange, outcome measurement are different across studies. In this review, we performed a meta-analysis to evaluate whether TPE is better than conventional intravenous methylprednisolone (IVMP) in NMOSD patients.

Methods

This study was conducted following the recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement. We registered the systematic review with PROSPERO International Prospective Register of Ongoing Systematic Reviews (registration number: CRD42020173632).

Search strategy

PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Clinical Trials were used to search for articles published in the English language up to 4 December 2019. The search strategy is presented in detail in the Supplement. Besides, the reference lists of included articles were searched, as well as related citations from other journals via Google Scholar.

Study selection

For this systematic review and meta-analysis, we worked with an information specialist to design an appropriate search strategy to identify original peer-reviewed articles of randomized controlled trials and observational studies evaluating the neurological or visual outcomes, or both of TPE, plasmapheresis, immunoadsorption, or other therapeutic apheresis; alone or in combination with other treatments compared to standard intravenous steroid treatment; alone or in combination with other treatments in patients with a diagnosis of NMOSD or a limited form of NMOSD based on 1999, 2006, and 2015 diagnostic criteria [7, 19, 20] Article screening was done by two independent reviewers (TN and SS) for eligible studies. Discrepancies between the two reviewers were resolved by consensus.

Data extraction

Data extraction was done by two independent reviewers (TN and SS) for published summary estimate data. Discrepancies between the two reviewers were resolved by consensus. We extracted the following data: (1) study characteristics (authors, year of publication, study type, journal name, contact information, country, and funding), (2) patients characteristics (sample size, age at onset, age at the attack, gender, comorbidities, concomitant with immunosuppressant use, location of the attacks, AQP4-Ab status, disease duration, number of the attacks, severity of the attack stratified by location of the attack), (3) intervention (type, duration of

treatment, the interval from attack onset to the first day of the intervention, intervention compliance), (4) comparators (type, duration of treatment, the interval from attack onset to the first day of the comparators), (5) outcomes (complete list of the names of all measured outcomes, unit of measurement, follow-up time point, missing data) as well as any other relevant information. All relevant text, tables, and figures were examined for data extraction. We contacted the authors of the study with incompletely reported data. If the trial authors did not respond within 14 days, we conducted analyses using the available data.

Quality assessment

The authors worked independently to assess the risk of bias in the included trials using the Cochrane Risk of Bias tool 2.0 for a randomized control trial study [21]. We assessed the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, selection of the reported result. We assigned each domain as a low risk of bias, some concerns, and a high risk of bias. For non-randomized trials, observational studies, and uncontrolled before-after studies; we used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) to investigate the confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result [22]. We assigned each domain as a low, moderate, serious, critical risk of bias, and no information. As mentioned above, we contacted the authors if there was not enough information to assess. If the trial authors did not respond within 14 days, we conducted the assessment using available data. We resolved the disagreement through discussion. We presented our risk of bias assessment in Fig. 2.

Statistical analysis

The primary outcome was Expanded Disability Status Scale (EDSS) which disability improvement was defined as a decrease of at least one point above the pre-treatment score if baseline score is less than 5.5, and of at least a half-point if baseline score is more than 5.5, of the Kurtzke EDSS [23]. The outcomes measured were the mean difference in the EDSS between before and after treatment with associated 95% confidence interval (CI) and relative risk (RR) for a patient who had EDSS returned to baseline after treatment with associated 95% CI, when reported. Visual outcome including visual acuity (VA) and the logarithm of the minimum angle of resolution (LogMAR) were also retrieved with adverse events when reported. The results of the studies were included in the meta-analysis and presented in a forest plot, which also showed statistical powers, confidence intervals, and heterogeneity.

We assessed clinical and methodological heterogeneity by examining participant characteristics, intervention regimen, duration of intervention, follow-up period, outcomes, and study design. We then assessed statistical heterogeneity using the I^2 and χ^2 statistics. We regarded level of heterogeneity for I^2 statistic as defined in chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions: 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75–100% considerable heterogeneity. The random-effects meta-analysis by DerSimonian and Laird method was used as clinical, methodological, and statistical heterogeneity encountered. The meta-analysis was performed using Revman 5.3 (Cochrane Collaboration, Oxford, UK).

Results

Study selection

The database search identified 3439 potential records. After removing duplicates, 1790 titles passed the initial screen and 271 theme-related abstracts were selected for further full-text articles assessed for eligibility (Fig. 1). A total of 264 articles were excluded as the following; 137 non-peer-reviewed, 26 case series, 21 non-English, 16 case reports, 14 review articles, ten letters to the editor, seven wrong population, six commentaries, six protocols, five duplicates, five wrong outcomes, five wrong intervention, three wrong comparators, three wrong settings. Only seven studies were eligible for the qualitative analysis and three studies [9, 14, 24] for EDSS lowering (final EDSS—acute EDSS) and delta EDSS (final EDSS—baseline EDSS) were recruited in the meta-analysis.

Study characteristics

The seven included studies were published between 2009 and 2019 (Tables 1, 2). There were four retrospective cohort studies, two ambispective nonrandomized studies, and one randomized control study. The number of patients per study ranged from 11 to 185, with a total of 1211 attacks in 433 patients (383 of them were females, 88.5%). The disease duration varied from 83.2 to 110.4 months. NMO patients with positive AQP4-Ab were documented between 26 and 100%. Diagnosis of NMO/SD was made according to the 1999 [9, 13], 2006 [11, 13, 24], and 2015 [14, 25, 26] criteria. One study also included idiopathic longitudinally extensive transverse myelitis (LETM) [9]. The mean age of onset varied from 34.0 to 40.3 years. The location of attack also varied with one study allowed only transverse myelitis

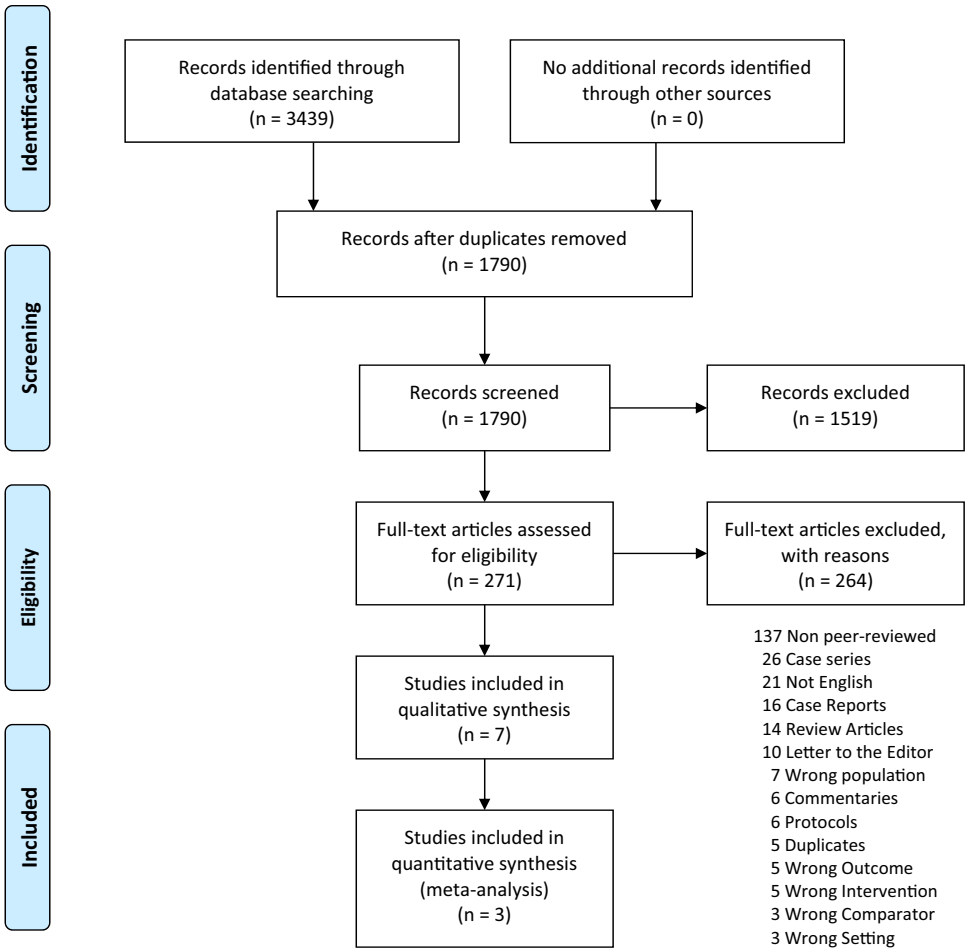

Fig. 1 Flow chart diagram presenting the study selection with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines

(TM) attack [9] and two studies [13, 25] included only optic neuritis (ON) attack. The follow-up period ranged from 6 to 12 months.

In five studies, the comparator was the arm that was treated with IVMP or high dose steroid (HD-S) 1–2 g/day for consecutive 3–7 days. While the intervention arm were the patients who received IVMP with subsequent treatment with 1.0–1.5 plasma volume plasma exchange (PLEX) or TPE for five sessions [9, 13, 14, 24, 25, 27]. Another study had 4 treatment regimens with HD-S, PLEX, immunoadsorption (IA) and others [11]. For the randomized control study, the comparator was IVMP added on with PLEX and the intervention was simultaneous treatment with IVMP and PLEX [26].

Quality assessment

For the risk of bias assessment, the randomized controlled trial [26] included in this study had some concerns risk of bias from deviation from intended intervention, missing outcome, measurement of outcome, and selection of reported results. For the six observational studies, [9, 11, 13, 14, 24, 25] there were high risks of bias due to confounding along with measurement and reporting of outcomes. A summary of the percentages of observational studies which were at low, moderate, and serious risk for each risk of bias domain (Fig. 2). Detailed risk-of-bias assessment for both randomized controlled trial and observational studies are provided in the appendix.

Qualitative analysis

Two ambispective, non-randomized studies, included ON related to NMO/SD, reported only visual outcome [13, 25]. Both declared that PLEX added on to NMO/SD patients with an optic neuritis attack who did not respond to IVMP alone would get more benefit with a better visual outcome at the last follow-up visit. Merle study also demonstrated that PLEX treatment was the only independent factor related to a VA outcome of better than 20/200 with the odds ratio (OR) of 6.80 (95% CI 1.2–37.4; $P = 0.02$) [13]. Unfortunately, only the Song study reported SD in association with mean LogMAR and, therefore, the meta-analysis could not be conducted for the visual outcome [25].

Kleiter study concluded that TPE with PLEX or IA were superior to high dose steroid as the first-line therapy

Table 1 Characteristics of the included studies

	Country	Study design	Interventions	Sample size (no. attack)	AQP4-Ab positive; *n* (%)	Female; *n* (%)	Age at onset/attack (year); mean (range) unless indicated	Disease duration (month); mean (range) unless indicated
Bonnan et al. [9]	France	Retrospective cohort	(1) IVMP 1 g/day × 3–10 days (started day 1) (2) IVMP + 1 PV-TPE × 5 (ASAP 2 days after attack)	43 (96)	6 of 23 tested (26.0%)	40 (93.0%)	Onset: 34 (14–82)	NR
Merle et al. [13]	France	Ambispective, nonrandomized	(1) IVMP 2 g/day × 2–5 days (2) IVMP added on 1 PV-PLEX × 5 (when available)	52	19 (36.5%)	47 (90.0%)	Onset: 35.6 (13–61; 33.2 vs 40.5)	110.4 (129.6 vs 69.6)
Abboud et al. [24]	USA	Retrospective cohort	(1) IVMP 1 g/day × 5 days (started day 1) (2) IVMP + 1–1.5 PV-PLEX × 5 days of on 2nd week of attack (for steroid-resistant)	59 (83)	51 (86.4%)	55 (93.2%)	Attack: 41.6 (33.9 vs 43.8)	NR (24 vs 72)
Kleiter et al. [11]	Germany	Retrospective cohort	(1) HD-S; IVMP 1 or 2 g/day × 3–5 days (810) (2) PE × 3–7 (192) (3) IA × 3–7 (38) (4) Others (80) vs unknown (33)	185 (871)	156 (84.0%)	152 (82.0%)	Onset: 40.3 Attack: 42.9 (HD-S) vs 43.3 (PE)	NR (34.8 for HD-S vs 39.6 for PE)
Srisupa-Olan et al. [14]	Thailand	Retrospective cohort	(1) IVMP 1 g/day × 5 days—> OPN 2 weeks (2) IVMP added on 1 PV-PLEX × 5 (for non-responder)	52 (67)	48 (92.3%)	50 (96.2%)	Attack: 43.7	83.2 (0–229)
Song et al. [25]	China	Ambispective, nonrandomized	(1) IVMP 3–5 days (2) IVMP add-on PLEX 2–3 times a week (when VA had no/poor improvement after IVMP)	31	28 (90.3%)	28 (90.3%)	Onset: 36.1 (12–67)	NR

Table 1 (continued)

	Country	Study design	Interventions	Sample size (no. attack)	AQP4-Ab positive; *n* (%)	Female; *n* (%)	Age at onset/attack (year); mean (range) unless indicated	Disease duration (month); mean (range) unless indicated
Songthamawat et al. [26]	Thailand	Randomized control trial	(1) IVMP 1 g/day × 7 days added on IPV-PLEX × 5 (non-responders) (2) simultaneous IVMP + PLEX (started on day 1)	11	11 (100.0%)	11 (100.0%)	Onset: 37.4 vs 40.4 Attack: 45.4 vs 48.6	NR (median 79 vs 77)

AQP4-Ab aquaporin-4 antibody, *ASAP* as soon as possible, *EDSS* Expanded Disability Status Scale, *HD-S* high dose steroid, *IA* immunoadsorption, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *NMO* neuromyelitis optica, *NMOSD* neuromyelitis optica spectrum disorders, *NR* not reported, *OPN* oral prednisolone, *PE* plasma exchange, *PLEX* plasma exchange, *PV* plasma volume, *TPE* therapeutic plasma exchange, *VA* visual acuity

especially for isolated myelitis regardless of remission ($P = 0.04$) rate and change in EDSS ($P = 0.03$) [11]. In addition, multivariate generalized estimating equation (GEE) analysis in this study showed the predictive factors of complete remission included age (OR 0.97; $P = 0.01$), presence of myelitis (OR 0.38; $P = 0.002$), having complete remission from previous attack (OR 6.85; $P < 0.001$), and having first-line therapy with PLEX or IA rather than the other treatments (OR 4.38; $P = 0.006$).

Only Songthammawat study was a randomized control trial comparing IVMP treatment with subsequent PLEX; which is a common practice, and simultaneous IVMP and PLEX [26]. It demonstrated that both treatment regimens showed benefit over IVMP alone. However, the significant difference between the two therapies could not be demonstrated, perhaps due to small sample size. Nevertheless, simultaneous IVMP and PLEX treatment tended to have a more favourable visual outcome and a trend of a faster and better improvement assessed by EDSS at 6 months follow-up, although not significantly. Three studies [9, 14, 26] reported adverse events. No major adverse event related to PLEX treatment was reported.

Quantitative analysis

Only three studies, [9, 14, 24] which reported EDSS lowering and/or delta EDSS, were recruited in meta-analysis. Bonnan and Srisupa-Olan studies showed a favourable outcome with EDSS lowering of an acute attack with NMO/SD treated with PLEX added on, [9, 14] whereas Abboud study showed an EDSS improvement with the treatment with IVMP alone [24]. Although IVMP with an add-on PLEX showed a trend to lower EDSS at the last follow-up, it was not significantly (mean difference − 0.68, 95% CI − 2.07–0.72) (Fig. 3).

Only Bonnan study showed a significant benefit in favour of the treatment with IVMP added on to PLEX [9]. While meta-analysis of the three studies showed a trend of the benefit in favour the treatment with IVMP subsequent followed by PLEX over IVMP alone; mean difference was − 0.47 (95% CI − 1.50–0.56) (Fig. 4).

The benefit of treatment with IVMP added on to PLEX for steroid-resistant patients had a risk ratio (RR) for the returning of EDSS to baseline at the discharge of 3.02 (95% CI 1.34–6.81) in two studies [14, 24] and at the last follow-up of 1.68 (95% CI 1.01–2.79) in three studies [9, 14, 24] (Figs. 5, 6).

Table 2 Interventions and outcomes of the included studies

	Number of patients/attacks of each intervention	Specific population/location of attack	Diagnostic criteria used	Baseline/Nadir/final EDSS or VA; median unless indicated	Time to IVMP from attack (mean) (days)	Time to PLEX from attack (mean) (days)	Time to PLEX from day 1 of IVMP (days)	Outcome	F/U period (months)
Bonnan et al. [9]	Patient = 25 vs 18 Attack = 67 vs 29	All were TM	NMO 1999 (79%) + idiopathic LETM (21%)	baseline EDSS 4.0 vs 5.0 nadir EDSS 8.0 vs 8.0 final EDSS 6.5 vs 5.5	Day 1 admission	9.4 ± 10.1 5.4 ± 3.1 (excluded delayed in 5 attacks)	2 days after admission	PE may be employed early in severe spinal attacks in the NMOSD to maximize improvement rate EDSS lowering – 0.5 vs − 2.0; $P < 0.01$ ΔEDSS: 2.0 vs 0.5; $p < 0.01$ A low basal impairment is associated with a better outcome PE efficiency is independent of NMO-IgG positivity	> 6
Merle et al. [13]	Patient = 36 vs 16	All were ON related NMO/SD	NMO/SD (1999 and 2006)	mean EDSS at assessment = 4.8 mean baseline VA 20/400 vs 20/400 mean final VA 20/400 vs 20/50	ASAP after admission	NR	Since 2006, PE was added on when available	Gain in VA was 20/200 vs 20/30 ($P = 0.01$) Final VA > 20/200 and ≤ 20/40 = 56% vs 13%; $P = 0.01$ PLEX treatment was the only independent factor related to a final VA > 20/200 (OR 6.8, 95% CI 1.2–37.4; $P = 0.02$)	6
Abboud et al. [24]	Patient = 43 vs 16 Attack = 65 vs 18	TM 54.2%, ON 36.1%, Brain/brainstem 14.4%, > 1 locations 13.2%	NMO 2006	baseline EDSS 2.5 vs 5.75 nadir EDSS 4.5 vs 7.75 final EDSS 4 vs 6.5	Day 1 admission	2nd week of attack	NR	Improvement to ≤ baseline EDSS at D/C 16.6% vs 51% (OR 5.17, 95% CI 1.36–19.68; $P = 0.02$) at F/U 35% vs 65% (OR 3.36, 95% CI 1.07–10.60, $P = 0.04$)	12

Table 2 (continued)

	Number of patients/attacks of each intervention	Specific population/location of attack	Diagnostic criteria used	Baseline/Nadir/final EDSS or VA; median unless indicated	Time to IVMP from attack (mean) (days)	Time to PLEX from attack (mean) (days)	Time to PLEX from day 1 of IVMP (days)	Outcome	F/U period (months)
Kleiter et al. [11]	Attack = 810 (1) vs 192 (2) vs 38 (3) vs 80 (4) vs 33 (unknown)	Isolated MY 59.4%, Isolated ON 28.4%, MY + ON 10.2%, Others 1.5% Unknown 0.5%	NMO 2006 or AQP4-pos NMOSD	baseline EDSS 4.0 vs 6.0	NR	NR	NR (varying intervals from 1st to 2nd to 5th course), latest 3 mo after the onset of attack	Particularly MY and bilateral ON have poor remission rates Escalation of attack therapy improves outcome PE/IA were superior to HD-S as 1st Rx course in isolated MY regarding remission rate ($P = 0.04$) and change in EDSS ($P = 0.03$) Predictors of CR in multivariate GEE analysis were age (OR 50.97; $P = 0.01$) presence of MY (OR 50·38, $P = 0.002$) CR from previous attack (OR 56.85; $P < .001$), and 1st-line PE/IA vs HD-S (OR 54.38; $P = 0.006$)	NR

Table 2 (continued)

	Number of patients/attacks of each intervention	Specific population/location of attack	Diagnostic criteria used	Baseline/Nadir/final EDSS or VA; median unless indicated	Time to IVMP from attack (mean) (days)	Time to PLEX from attack (mean) (days)	Time to PLEX from day 1 of IVMP (days)	Outcome	F/U period (months)
Srisupa-Olan et al. [14]	Attack = 39 vs 28	TM 56·7%, ON 19·4%, Brain/brainstem 5%	NMOSD 2015	For IVMP responder vs IVMP responder/no PLEX vs IVMP non-responder/PLEX responder vs IVMP/PLEX non-responder; baseline EDSS 2 vs 1.5 vs 2 vs 5 nadir EDSS 6.5 vs 5.75 vs 8 vs 7.75 final EDSS 5 vs 5.25 vs 5.25 vs 6.25 ΔEDSS-baseline EDSS 0.5 vs 2 vs 0.75 vs 1.25	Median; 6 vs 10.5 vs 6 vs 5	Median NR vs NR vs 13 vs 12	NR	IVMP non-responders/PLEX responders showed continuous and maximum improvement at 6 months (ΔEDSS from nadir: 1 for IVMP-responders vs 0.5 for IVMP non-responders without PLEX vs 2.75 IVMP non-responders/PLEX-responders vs 0.5 IVMP/PLEX non-responders; $P = 0.49$) and had comparable outcomes to the IVMP-responders (nadir EDSS 8.0–5.25 (ΔEDSS = 2.75) vs nadir EDSS 6.5 to 5.0; (ΔEDSS = 1.5)	≥ 6
Song et al. [25]	Patient = 31 vs 15	All were ON related NMOSD	NMOSD 2015	mean baseline VA (LogMAR) 1.94 ± 0.83 mean final VA (LogMAR) 1.78 ± 0.83 vs 1.26 ± 0.66	NR	NR	1·6	All ON attacks improved after PLEX add-on Rx for VA ($P < 0.001$)	6

Table 2 (continued)

	Number of patients/attacks of each intervention	Specific population/location of attack	Diagnostic criteria used	Baseline/Nadir/final EDSS or VA; median unless indicated	Time to IVMP from attack (mean) (days)	Time to PLEX from attack (mean) (days)	Time to PLEX from day 1 of IVMP (days)	Outcome	F/U period (months)
Songthamawat et al. [26]	Patient = 5 vs 5	TM 57.1% ON 42.9%	NMOSD 2015	baseline EDSS 1 (0–8) vs 2.5 (0–8) nadir EDSS 8 (mean 6.7) vs 8 (mean 7.2) ΔEDSS − 1.2 vs − 1.8	Median 8 vs 5	Median 10.5 vs 5	NR	Both had benefit but no differences in mean EDSS changes at any time point of F/U visits IVMP + PLEX group tended to have a more favorable visual outcome at 6 months F/U and have a trend of a faster and better improvement assessed by EDSS, although not significantly	≥ 6

AQP4 aquaporin-4, *ASAP* as soon as possible, *CR* complete remission, *D/C* discharge, *EDSS* Expanded Disability Status Scale, *EDSS lowering* final EDSS—nadir EDSS, *ΔEDSS* delta Expanded Disability Status Scale (final EDSS—baseline EDSS), *F/U* follow-up, *GEE* generalized estimating equation, *IPND* International Panel for NMO Diagnosis, *HD-S* high dose steroid, *IA* immunoadsorption, *IVCS* intravenous corticosteroid (methylprednisolone or dexamethasone), *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *LETM* longitudinally extensive transverse myelitis, *LogMAR* logarithm of the minimum angle of resolution, *MOG* myelin oligodendrocyte glycoprotein, *MY* myelitis, *NMO* neuromyelitis optica, *NMOSD* neuromyelitis optica spectrum disorders, *NR* not reported, *ON* optic neuritis, *PE* plasma exchange, *PLEX* plasma exchange, *TM* transverse myelitis, *TPE* therapeutic plasma exchange, *VA* visual acuity

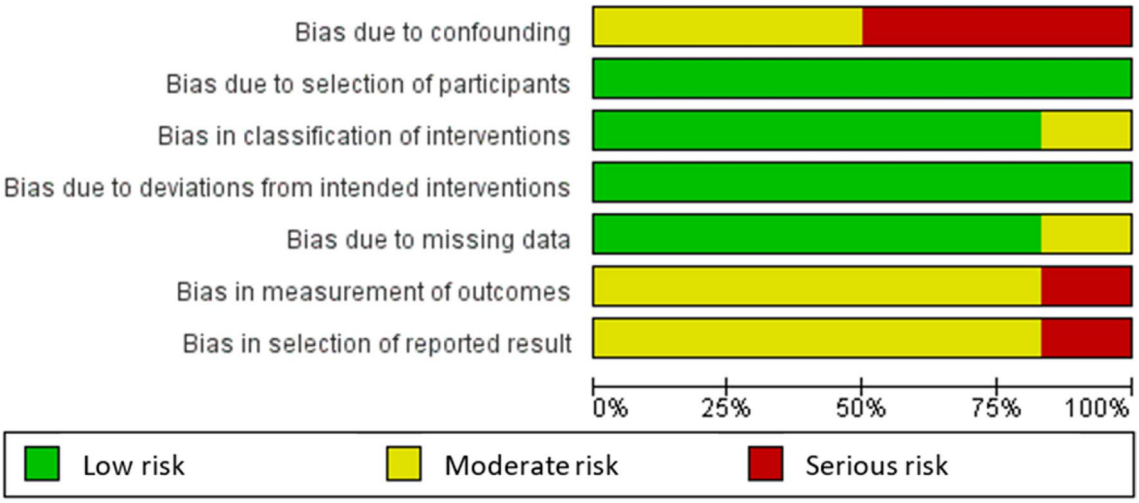

Fig. 2 Review authors' assessment about the risk of bias of included observational studies. Bars show percentages across all included observational studies

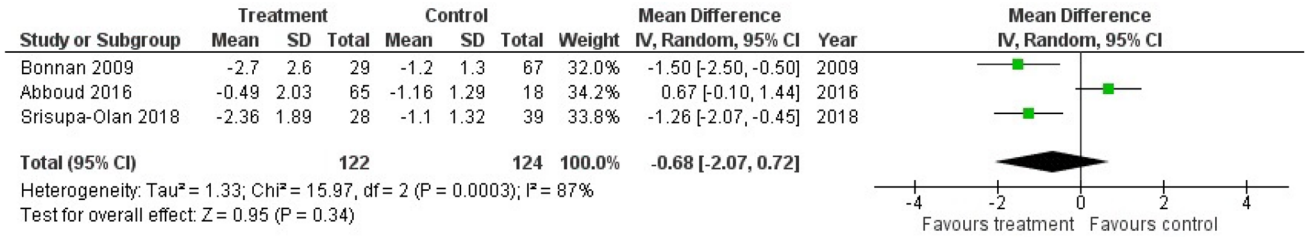

Fig. 3 Forest plot showing the effect of therapeutic plasma exchange versus high dose intravenous steroid on EDSS lowering (final EDSS—acute EDSS) at last follo-up. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

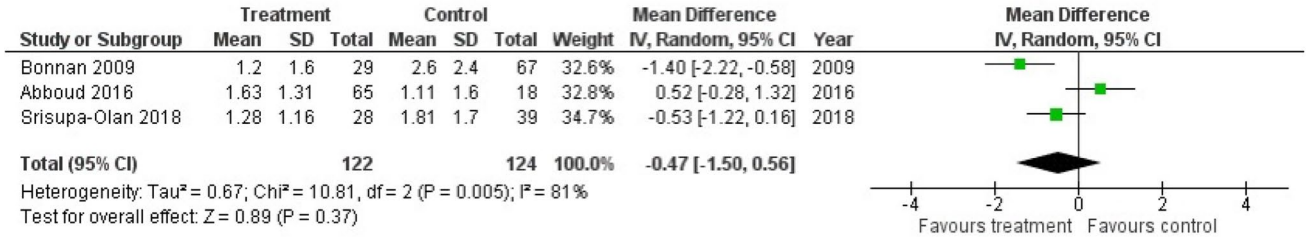

Fig. 4 Forest plot showing the effect of therapeutic plasma exchange versus high dose intravenous steroid on delta EDSS (final EDSS—baseline EDSS) at last follow-up. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

Discussion

Our meta-analysis suggests that the treatment with PLEX as an added on therapy to IVMP were 3.02 times and 1.68 times more likely to have EDSS returning to baseline at discharge and 6-to-12 months after the treatment, respectively than IVMP alone in NMOSD patients with an acute attack. Although not significantly, treatment with IVMP subsequently followed by PLEX also gave a better result in decreasing of EDSS from attack by 0.68 points and changing EDSS by 0.47 points at the last follow-up visit comparing to IVMP alone.

It is hard to conclude from the trials because of the heterogeneity of the population targets, treatment regimens, interval time to treatment from the onset of the attack, location of the attack and outcome measurements. Nonetheless, the findings suggested the benefit of an add-on PLEX over

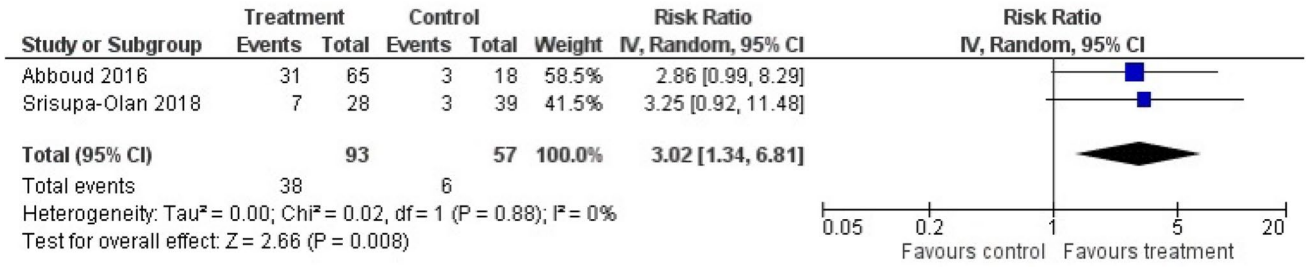

Fig. 5 Forest plot showing the effect of therapeutic plasma exchange versus high dose intravenous steroid on EDSS return to baseline at discharge. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

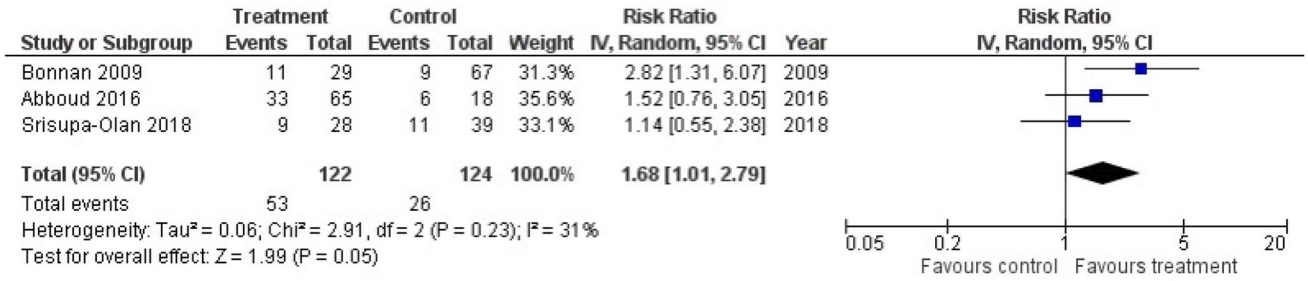

Fig. 6 Forest plot showing the effect of therapeutic plasma exchange versus high dose intravenous steroid on EDSS return to baseline at last follow-up. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

standard IVMP treatment for NMOSD with an acute attack; however, they needed more robustness to provide a high level of evidence.

Kleiter study showed that PLEX/IA treatment was superior to HD-S if used as the first-line treatment in NMO/SD with a myelitis attack and encourage to escalate the treatment to second-line therapy if the first-line treatment did not show benefit [11]. The preferable location for treatment with PLEX was a spinal attack as demonstrated in Bonnan study [9].

Bonnan study included only MY attack in NMOSD patients, and also included idiopathic LETM [9]. The majority of the patient were AQP4-negative patients. Moreover, the median baseline EDSS of the population was at moderately severe disability. The study was planned to start PLEX as an add-on therapy 2 days after IVMP initiation, not like other studies that waited until patients showed steroid non-responsive. These may imply the severe spinal cord attack regardless of the etiology may get a better outcome with a more EDSS lowering and changes in EDSS with an early added on PLEX treatment to IVMP.

Nevertheless, Abboud study demonstrated similar improvement of EDSS returning to baseline both at discharge and follow-up period in added on PLEX treatment, it was the only one in our meta-analysis showing a better outcome assessed with EDSS lowering and changes in EDSS in the group treated with IVMP alone [24]. These may be explained by the gap difference in baseline EDSS; 2.5 in IVMP arm vs 5.75 in PLEX added on arm. Also, the interval from the attack onset to PLEX treatment was 2 weeks which may decrease the maximum response from PLEX treatment (Lazarus effect) [28].

Srisupa-Olan and Songthamawat studies imitated the real-world practice and depicted problems in assessment treatment response in NMOSD patients with an acute attack [14, 26]. Up to date, there is no standard time to assess the outcome and no specific outcome measurement. However, the study determined the seventh day as the time to assess steroid non-responsive, defined the scales for treatment response and severity of the attack at each attack location.

Worsening of the clinical symptoms in patients with NMOSD attack who has been receiving high dose steroid is not uncommon. It may be caused by glucocorticoid resistance from GCS–receptor mutations, lower GR expression or lower DNA binding activity [29], or from other unclear explanations.

The therapeutic mechanism of PLEX is to eliminate pathologic AQP4-antibody, complements, and cytokines from blood circulation. Moreover, it causes pulsed induction of antibody redistribution, and subsequent immunomodulatory changes, shifting the cytokine balance and modification of Fc receptor activation. Furthermore, it may also alter the cellular immune response, which can involve modulation of macrophages, NK cells or APCs, relieving conduction

block and allowing for repairing of demyelinated lesions [17, 28]. Previous in vitro study illustrated that forming NMOSD lesion has a temporal course and approximately on day 7 it showed early axonal injury which will progress to neuronal death [30]. Bonnan study also suggested that the crucial time for the treatment of NMOSD attack should be commenced as early as possible from the attack onset, and perhaps should not be later than 2–3 weeks [27]. A lower level of AQP4 autoantibody titer after TPE [31, 32] and the consequence of antibody redistribution, and immunomodulatory changes may explain the reduction of disability in NMOSD patients after receiving the treatment [16, 17, 28, 31]. However, the long term outcome with maintenance intermittent TPE has never been evaluated.

There were several limitations in this meta-analysis. First, the difficulty to conclude the data from the heterogeneous characteristics of the patients, definition of treatment response, and timing of outcome assessment. Moreover, since NMOSD is not common, it is hard to get enough subjects in each arm to make a significant difference. Second, there is no specific outcome measurement for treatment response in NMOSD. The EDSS, which is adopted from MS, depends mainly on mobility and may not be adequate to measure other domain of disabilities. The outcome measurements i.e. specific score for NMOSD, cognition, visual outcome and biomarker are underway. A collaborative randomization study including more NMOSD patients with various types of attack and the same protocol for selecting treatment regimens is recommended to evaluate the efficacy of TPE as an added-on therapy to IVMP in steroid non-responsive. In addition, the benefit of simultaneous treatment with IVMP and PLEX over the conventional subsequent PLEX added on IVMP when indicated is still a matter of debate.

Conclusion

This systematic review and meta-analysis suggest that adding TPE to IVMP treatment during an acute attack in NMOSD patients is associated with the chance to get EDSS returning to baseline at discharge and the last follow-up, and a trend to have lower disability measured by EDSS lowering and the change in EDSS at 6–12 months, comparing to IVMP treatment alone. However, more robustness is still needed to provide a high level of evidence.

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Availability of data and material All data of this work (abstracts, reviewed articles, data entry spreadsheet, and statistical analysis) will be available to qualified investigators on request.

Compliance with ethical standards

Conflicts of interest S. Siritho serves as a speaker honoraria from Merck Serono, Pacific Healthcare (Thailand), Menarini (Thailand), Biogen Idec, UCB (Thailand), Eisai Inc, Sanofi-Aventis, Terumo BCT and Novartis. No other disclosures were reported. T. Nopsopon reports no disclosures. K. Pongpirul reports no disclosures.

Ethical approval The manuscript does not contain clinical studies or patient data.

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