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Original article

Effectiveness of treatments in Neuromyelitis optica to modify the course of disease in adult patients. Systematic review of literature.

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ABSTRACT

Background: : Neuromyelitis Optica spectrum disorder (NMOSD) is an inflammatory disease, which manifests mostly as recurrent episodes of optic neuritis or myelitis that cause important disability. Early diagnosis and prompt initiation of immunosuppressive therapy are crucial in reducing relapses, disability, and mortality. Even though, there are few prospective randomized controlled trials, several drugs have proved to be both effective and safe. Azathioprine and Rituximab represent the standard of care and are used as first-line treatment agents worldwide. However, recent studies have unveiled new therapies, such as monoclonal antibodies. To make treatment recommendations and management guidelines, it is imperative to define an appropriate standard of care.

Methods: : A systematic literature review was performed in MEDLINE, EMBASE, and LILACS databases using the following terms: "(NMO OR Devic OR Neuromyelitis Optica) AND (Azathioprine OR Prednisone OR Rituximab OR Tocilizumab OR Bortezomib OR Inebilizumab OR Eculizumab OR Satralizumab)" including both, randomized clinical trials and observational studies published between January 2006 and January 2021. The inclusion criteria comprised patients aged 18 or older, NMOSD diagnosis following the Wingerchuck criteria, two or more therapies been compared, and the evaluation of both efficacy and safety outcomes. All studies comparing treatment only with placebo were excluded. Quality was assessed according with the design of the study, and results were synthesized through comparative tables for each outcome evaluated, differentiating the results of randomized and non-randomized studies.

Results: : Thirteen studies with 1447 patients were included. Twelve studies evaluated the expanded disability status scale (EDSS) before and after treatment; in five of seven evaluating rituximab, it outperformed its comparators in improving the disability degree. Eleven studies assessed the annual relapse rate (ARR). Again, in six of seven evaluating rituximab, it was superior to other therapies. Time to relapse (TTR) was reported in five studies. The three studies that included Rituximab revealed a longer time to relapse in this arm of treatment. Finding were consistent in randomized and non-randomized studies. The new molecules Satralizumab, Eculizumab and Tocilizumab were evaluated in one study each, proving to be highly effective and safe. The safety profile analysis showed a higher number of adverse events for Azathioprine.

Discussion: : This systematic review demonstrates a superiority tendency of Rituximab upon the other treatments strengthening the available evidence about NMOSD management. Superiority in EDSS outcomes, annual relapse rate, time to first relapse and relapses during treatment time was evidenced in the Rituximab group compared to other medications, with lower rates of adverse events. New molecules Tocilizumab, Eculizumab and Satralizumab also showed superiority in the evaluated results, especially in the relapses during treatment time outcome, although with subtle differences in EDSS and ARR outcomes.

Conclusion: : Our results suggest that monoclonal antibodies are highly effective and safe for the treatment of NMOSD; Rituximab showed better performance on multiple outcomes and has more evidence available. New

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molecules: Eculizumab, Tocilizumab, Satralizumab are good options for treatment. Drugs like Azathioprine and Mycophenolate are effective, but with a worse risk-benefit ratio, therefore, they are useful alternatives in places that do not have access to monoclonal antibodies.

1. Introduction

Neuromyelitis Optica spectrum disorder (NMOSD) is an inflammatory, immune-mediated and demyelinating disorders of the central nervous system (CNS). The principal clinical characteristic are episodes of optic neuritis frequently bilateral and/or longitudinally extensive myelitis (Kim et al., 2017). The recurrent episodes of optic neuritis and transverse myelitis cause cumulative disability with a high risk of blindness and paraplegia (Pittock et al., 2014). The clinical course of NMOSD is typically relapsing, patients often do not experience a full functional recovery following each recurrence, and permanent disabilities may occur. Management is based on early diagnosis, acute phase treating, long-term maintenance therapy (Bruscolini et al., 2019; Trebst et al., 2014). The goal of long-term treatment in NMOSD is to avoid relapses, disability and mortality (Trebst et al., 2014). Early initiation of effective immunosuppressive therapy is crucial to avoid further recurrence because a single relapse generates devastating consequences. Several immunosuppressive treatments have been proved to be effective; however, not all patients respond to every treatment.

Conventional immunosuppressive and B-cell depletion therapies are the standard treatment of NMOSD (Bruscolini et al., 2019). Based on retrospective, open-label studies, Azathioprine has been recommended as a first-line treatment, reducing the relapse rate and disability. Nevertheless, many patients relapse and have side effects with prolonged use. Furthermore, since Azathioprine is often used in combination with corticosteroids, its efficacy as a monotherapy remains unclear (C Zhang et al., 2020). Other immunosuppressive drugs, such as Mycophenolate Mofetil, are recommended as second-line treatment (Trebst et al., 2014). Several case series and retrospective open-labeled studies have reported off-label use of Rituximab (Ip et al., 2013; Tahara et al., 2020); therefore, the Neuromyelitis Optica Study Group proposed Rituximab as first-line maintenance treatment for NMO in 2014 (Trebst et al., 2014; Tahara et al., 2020). In previous report, Tocilizumab reduces the frequency of relapses and disability in patients with NMOSD, including patients who have not responded to other treatment such as immunosuppressants or Rituximab (C Zhang et al., 2020; Ayzenberg et al., 2013); thus, it is recommended as a third-line therapy (Trebst et al., 2014).

In 2019 and 2020, various phase 3, randomized, double-blind, controlled, clinical trials were published evaluating the efficacy and safety of new treatments. *The PREVENT* (Prevention of Relapses in Neuromyelitis Optica) evaluated Eculizumab vs. placebo in patients with AQP4-IgG– positive NMOSD (Pittock et al., 2019). By contrast the *N-Momentum*, evaluated the Inebilizumab as monotherapy vs placebo in reducing the risk of attacks and disability in NMOSD (Cree et al., 2019), *SAkura-sky*, Satralizumab add-on vs. placebo (Yamamura et al., 2019) and *the SAkuraStar*, evaluated the efficacy and safety of Satralizumab as monotherapy vs. placebo in patients with NMOSD (Traboulsee et al., 2020). These trials showed the efficacy in reducing relapsing and safety profile.

Currently, Azathioprine and rituximab remain as the most frequently used first-line drugs worldwide (Trebst et al., 2014; C Zhang et al., 2020). However, the low prevalence and its severe course, hampers the possibility of prospective, randomized controlled trials. Thus, the lack of treatment recommendations are based on case reports, retrospective series and a few prospective studies. Because of this lack of evidence, it is imperative to compare the currently used treatments for NMOSD with an adequate standard to be compare to it. this research compares the changes on functional scales, relapse rates, time to first relapse, and the rate of adverse events of the current NMOSD medications, based on a systematic review including randomized and non-randomized studies.

2. Methods

We conducted a systematic review of literature of randomized and non-randomized studies. The randomized clinical trials were included, following the Cochrane Manual for Systematic Reviews of Interventions recommendation and the non-randomized (case-controls, cohorts) according with specific recommendations for these type of studies (Muñoz Velandia and Ruiz, 2018; Higgins et al., 2013). The study protocol was published on the PROSPERO registry CRD42020214396. The consulted databases were MEDLINE, EMBASE, and LILACS, including studies published from January 2006, since on this date the antibodies against aquaporin 4 were identified, until January 2021. The search terms used were "(NMO OR Devic OR Neuromyelitis optica) AND (Azathioprine OR Prednisone OR Rituximab OR Tocilizumab OR Bortezomib OR Inebilizumab OR Eculizumab OR Satralizumab)". Additional searches were conducted using cross-references from articles and reviews. There were no language restrictions. Duplicate references were removed using the Mendeley tool.

Inclusion criteria were patients over 18 years old, with a diagnosis of Neuromyelitis optica established according to Wingerchuk criteria, either with the criteria published in 2006 (Wingerchuk et al., 2006) or the updated version of 2015 (Wingerchuk et al., 2015). Both randomized and non-randomized studies had to compare at least two of the following interventions (Rituximab, Azathioprine, Mycophenolate Mofetil, Tocilizumab, Bortezomib), regardless of the doses used. For the new molecules (Inebilizumab, Eculizumab, Satralizumab) we include a comparison between basal immunosuppressive therapy alone versus associated with these new therapies. The studies had to report at least one efficacy outcome such as annual relapse rate, impact on disability progression as measured by the Expanded Disability Status Scale (EDSS), time to fist relapse, proportion of patients with relapses during treatment or mortality; and at least one safety outcome such as serious adverse events (leukopenia, thrombocytopenia, infection, liver toxicity, electrolyte disorders, or heart failure), minor adverse events (nausea, vomiting, diarrhea, headache, epistaxis, myalgia), and medication discontinuation. All studies compared with placebo only, clinical case studies or case series studies, before and after studies, and all studies in which patients had other comorbid conditions in addition to NMO were excluded.

Two researchers (MV, EGC) selected the articles by title and abstract independently. All discrepancies were identified and resolved by consensus or with a third investigator (OM).

Once the initial selection was made, two reviewers independently carried out the quality assessment of the non-randomized clinical studies using the ROBINS I tool (MV, LAZ) (Sterne et al., 2016). This tool allows the classification of the risk of global bias for each study and each outcome, defining it as "low", "moderate", "serious" or "critical", according to three study temporality domains "before the intervention", "at the time of the intervention" and "after the intervention", with special emphasis on identifying possible selection biases (Muñoz Velandia and Ruiz, 2018). For randomized clinical trials, the quality evaluation was carried out using the SIGN tool (Network, 2012). This tool assesses whether the generation of the sequence was randomized, whether the assignment was masked, whether there was blinding of the staff participants, and in the analysis of the results, whether there was a loss to follow-up, selective reporting, or other types of bias. Each potential source of bias was rated as "low risk," "high risk," or "uncertain risk. If any of the domains had been classified as "high risk of bias," the study

was classified as "high risk of bias" (Network, 2012).

The extraction of the relevant data from each study was paired. The following data were extracted: year of publication, type of study, author, number of participants, age, gender, race, follow-up time, active treatment and comparator with their respective doses, concomitant use of steroids and doses, evaluation of the outcomes, and measure used both for effectiveness (time to first relapse, proportion of patients with relapses during treatment, EDSS scale and/or pre- and post-intervention relapse rate) and for safety. The discrepancies identified were resolved by consensus or with a third investigator (LAZ).

A meta-analysis of the information was planned if the clinical heterogeneity in terms of population, interventions used, or outcomes measured was low, using the RevMan software (Review Manager), recommended by the Cochrane collaboration. Otherwise, it was planned to synthesize the information through comparative tables for each outcome evaluated, differentiating the results of randomized and non-randomized studies.

3. Results

3.1. Descriptive results

A total of 1333 articles were identified, of which 13 were included in the final analysis (Zhang et al., 2020; Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Nikoo et al., 2017; Yang et al., 2018; Shi et al., 2020). The selection process is presented in the PRISMA diagram (Fig. 1). The thirteen included studies were published between 2014 and 2021, with a total of 1447 participants. Nine studies were non-randomized clinical trials (Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020), and four were randomized clinical trials (C Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019; Nikoo et al., 2017). The characteristics of the included studies are presented in (Table 1). The average age of the participants was similar for all the studies, ranging from 31.6 (Xu et al., 2016) to 48.1 years (Zhang et al., 2020).The majority of the population included was female (79,5%). The positivity of the AQP4 antibodies was variable among the studies participants, with a positive result of the participants between 6.6% (Mukherjee et al., 2020) and 100% (Jeong et al., 2015). The average time of evolution was between 0.8 (Yang et al., 2018) and 6.23 years (Nikoo et al., 2017).

Groups with Rituximab ($n = 205$), Azathioprine ($n = 559$), Mycophenolate ($n = 398$), Tocilizumab ($n = 59$), Satralizumab ($n = 41$) and Eculizumab ($n = 96$) were included. Rituximab was evaluated in seven studies (Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017; Yang et al., 2018), with a variable monthly accumulated dose between 400 mg (Yang et al., 2018) and 2550 mg (Jeong et al., 2015); Azathioprine was included in eleven studies (Zhang et al., 2020; Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Nikoo et al., 2017; Yang et al., 2018; Shi et al., 2020), with a similar daily dose between 1.75–3 mg/kg/day; Mycophenolate, was included in eight studies (Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020), evidencing variable doses between 1000 and 2000 mg/day. Tocilizumab, Satralizumab and Eculizumab were included only in one study each one (C Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019) with doses of 8 mg/kg/day every 4 weeks, 120 mg/ wk 0,2, 4/then every 4wk, 900 mg - 1200 mg, respectively. The concomitant use of Prednisolone was reported with Azathioprine in 65% of the cases, for

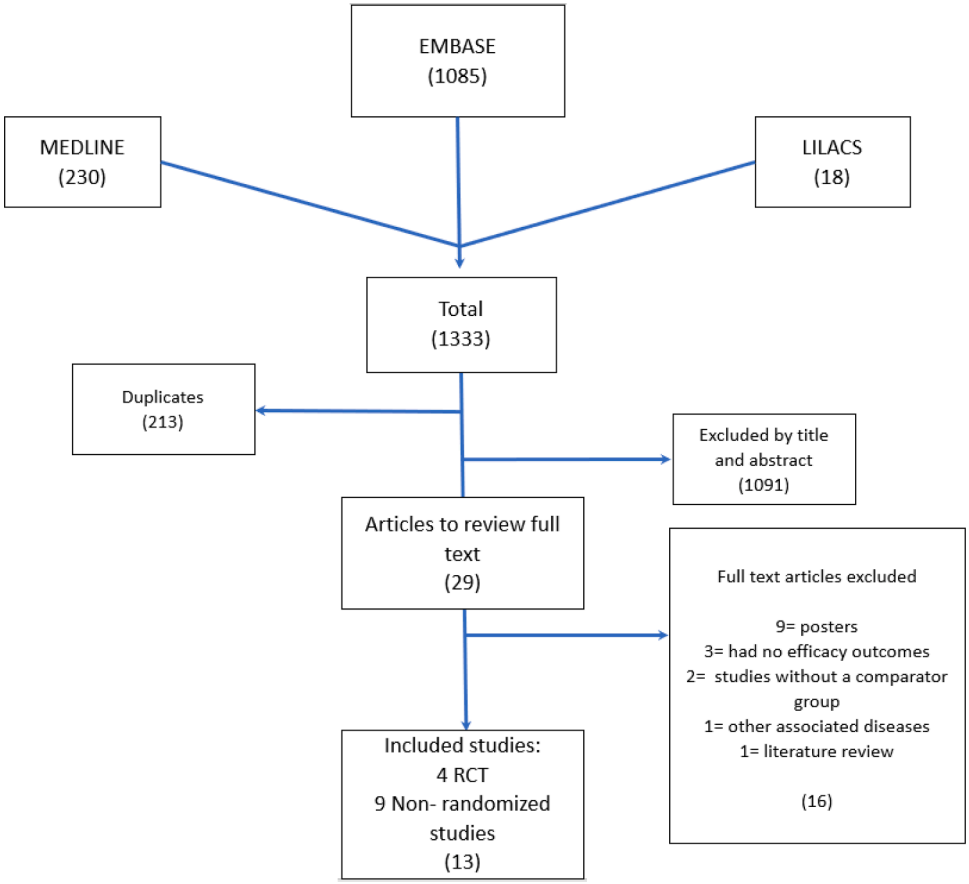

Fig. 1. Selection process of the articles included: PRISMA graphic.

Table 1
Characteristics of the included studies.

	Study design	Dx criteria	Treatment	Patients, n	Follow-up time in months, mean ± SD, [median] (Range)	Age in years, mean ± SD, [median] (Range)	Women, n (%)	Aquaporin 4 positive, n (%)	Evolution time in Years, mean ± SD, [median] (Range)	Concomitant use of prednisolone, n (%)	EDSS pre, mean ± SD, [median] (Range)	ARR pre, mean ± SD, [median] (Range)	Dose
	Non-randomized studies												
Mealy 2014	Retrospective observational	Wingerchuck 2006	**Rituximab**	30	[20] (5–83)	[44,9] (13–79)	25 (83)	15 (50)	–	–	N/A	2,89	1000 mg/wk x 2wk
			Azathioprine	32	[6] (0–122)	[39,5] (3–70)	29 (91)	16 (50)	–	32 (100)	N/A	2,26	2–3 mg/kg/d
			Mycophenolate	28	[26] (6–86)	[36,1] (19–74)	26 (93)	17 (60,7)	–	13 (46,4)	N/A	2,61	1000–2000 mg/d
Jeong 2015	Retrospective observational	Wingerchuck 2006	**Rituximab**	55	[64,7] (6,2–99,8)	[42] (15–68)	50 (90,9)	52 (94,5)	[3,5] (0,2–19,3)	1 (1,8)	[4,5] (0–8,5)	1,66	375 mg/m^2/wk
			Azathioprine	49	[15,1] (0,3–141,5)	[41] (17–65)	40 (81,6)	45 (91,8)	[3,1] (0,03–28,9)	34 (69,4)	[3] (0–7,5)	1,26	1,75–2,5 mg/kg/d
			Mycophenolate	34	[26,1] (5,5–68,6)	[39] (14–63)	29 (85,3)	32 (94,1)	[1,3] (0,1–16,1)	9 (26,5)	[3] (0–7)	1,54	2000 mg
Torres 2015	Retrospective observational	Wingerchuck 2006	**Rituximab**	32	[22] (14–39)	38 (12–71)	11 (14)	2 (3)	[1,46] (0,41–5,8)	–	[7] (5,5–7,25)	[1,17] (0,77–3,66)	1000 mg/wk x 2wk
			Azathioprine	22	[21] (12–46)	39 (13–68)	3 (9)	0	[1,33] (0,41–9)	–	[7] (5–7,5)	[0,92] (0–1,5)	–
			Mycophenolate	11	[23] (13–60)	37 (18–68)	4 (18)	1 (4)	[2,33] (1,83–5,9)	–	[4] (3–6,5)	[1,06] (0,84–2,31)	–
Xu 2016	Prospective cohort	Wingerchuck 2015	**Rituximab**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Azathioprine	119	[16,3] (0,2–53,2)	39,7 ± 13,9	110 (92,4)	110 (92,4)	[1,91] (0,05–18,3)	119 (100%)	[2] (0–9)	[0,8] (0–8)	100 mg/d
			Mycophenolate	38	[15,2] (6,6–26,4)	31,6 ± 14	32 (84,2)	33 (86,8)	[1,19] (0,15–23)	–	[2] (0–9)	[0,8] (0–3,8)	1500 mg/d
Chen 2016	Prospective observational	Wingerchuck 2006	**Rituximab**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Azathioprine	105	[36] (6–78)	41,6 ± 11,9	99 (94,3)	91 (86,7)	[2,7] (0,1–17,1)	89 (84,8)	[3] (0,5–9)	[1,4] (0,2-14,6)	2 mg/kg
			Mycophenolate	105	[16,8] (6–78)	44 ± 12,1	97 (92,4)	89 (84,8)	[1,9] (0,2–21,4)	49 (46,7)	[3] (0,5–8)	[1,2] (0,1–7)	20 mg/kg
Zhang 2017	Retrospective cohort	Wingerchuck 2015	**Rituximab**	31	27,45 ± 11,68	42,16 ± 16,86	23 (74,2)	25 (80,65)	4,05 ± 2,11	0	5,62 ± 1,35	1,39 ± 0,42	100 mg/wk/3wk/3ts
			Azathioprine	34	31,32 ± 11,32	32,35 ± 16,74	24 (70,6)	28 (82,35)	4,08 ± 2,03	34 (100)	5,63 ± 1,29	1,28 ± 0,34	2 mg/kg/d
			Mycophenolate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yang 2018	Prospective cohort	Wingerchuck 2015	**Rituximab**	20	[29] (18–40)	40,7 ± 11,4	19 (95)	10 (50)	[0,9] (0,02–20)	4 (20)	[3,5] (2–9)	[0,9] (0–5,2)	100 mg/wk x 4wk
			Azathioprine	22	[26] (18–36)	39,6 ± 12	20 (90,9)	8 (36,4)	[0,8] (0,02–15)	19 (86,4)	[3] (2–8,5)	[0,8] (0–4,5)	2 mg/kg/d
			Mycophenolate	30	[28,5] (19–42)	42,6 ± 11,7	26 (86,7)	13 (43,3)	[0,8] (0,03–16,7)	28 (93,3)	[3,5] (2–8,5)	[0,9] (0–5)	1000 mg/d
Shi 2020	Prospective cohort	Wingerchuck 2015	**Rituximab**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			Azathioprine	58	[2,3] (1–7,4)	41 ± 13	52 (90)	51 (88)	[1,8] (0,1–21,5)	–	[3] (1–8,5)	[1,2] (0,2–3)	100–150 mg/d
			Mycophenolate	150	[2,4] (1–6,9)	44 ± 12	34 (89)	129 (87)	[1,7] (0,1–24,3)	–	[3] (10–9)	[1] (0,1–3,7)	1000- 1500 mg/d
Mukherjee 2020	Prospective cohort	Wingerchuck 2015	**Rituximab**	4	23	26,6 (12–55)[a]	26 (86,6) [a]	2 (6,6)	–	–	[8,25] (8–9)	[0,37]	–
			Azathioprine	24	23			0	–	–	[7] (5,5–9)	[2,63]	–
			Mycophenolate	2	23			0	–	–	[6,5] (6–7)	[1,79]	–
	Randomized clinical trials												

(*continued on next page*)

Table 1 (*continued*)

	Study design	Dx criteria	Treatment	Patients, n	Follow-up time in months, mean ± SD, [median] (Range)	Age in years, mean ± SD, [median] (Range)	Women, n (%)	Aquaporin 4 positive, n (%)	Evolution time in Years, mean ± SD, [median] (Range)	Concomitant use of prednisolone, n (%)	EDSS pre, mean ± SD, [median] (Range)	ARR pre, mean ± SD, [median] (Range)	Dose
Nikoo 2017	Randomized clinical trial	Wingerchuck 2015	**Rituximab**	33	12	35,33 ± 8,98	29 (87,9)	13 (39,4)	6,23 ± 4,29	–	3,55 ± 1,95	1,3 ± 0,65	1000 mg/wk x 2wk
			Azathioprine	35	12	32,35 ± 9,56	28 (80)	20 (57,1)	6,12 ± 5,54	35 (100)	2,4 ± 1,24	1 ± 0,38	2–3 mg/kg/d
			Mycophenolate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yamamura 2019	Randomized clinical trial	Wingerchuck 2015	**Satralizumab+TB**	41	26.85 (0.5–56)	40.8 ± 16.1	37 (90)	27(66)	N/A	17(41)	3.83 ± 1.57	1.5 ± 0.5	120 mg/wk 0,2,4/then every 4wk
			Usual care*	42	8.12 (0 - 45)	43.4 ± 12.0	40(95)	28(67)	N/A	20(48)	3.63 ± 1.32	1.4 ± 0.5	Continued basline treatment*
Pittock 2019	Randomized clinical trial	Wingerchuck 2015	**Eculizumab+TB**	96	N/A	43.9 ± 13.32	88 (92)	96(100)	N/A	16(17)	4.0 (1.0–7.0)	1.94 ± 0.9	900 mg/wk x 4wk then 1200 mg every 2wk
			Usual care**	47	N/A	45.0 ± 13.29	42(89)	47(100)	N/A	11(23)	4.0 (1.0–6.5)	2.07 ± 1.04	Continued basline treatment
Zhang 2020	Randomized clinical trial	Wingerchuck 2015	**Azathioprine**	59	14	45,3 ± 14,5	53 (90)	53 (90)	6,2 ± 3,1	–	[4,5] (4–6)	1,68 ± 0,68	2–3 mg/kg/d
			Tocilizumab	59	14	48,1 ± 13,4	55 (93)	50 (85)	6 ± 2,9	–	[4,5] (4–5,5)	1,71 ± 0,60	8 mg/kg/d/ every 4wk

(TB) Treatment at baseline. **(-)** No data. **(N/A)** Not applicable / not evaluated. **(EDSS)** Expanded disability status scale. **(ARR)** Annual relapse rate. **([a])** No data on the characteristics of the populations of each treatment arm. **(*)** Usual care included Azathioprine (maximum, 3 mg X kg / day), mycophenolate mofetil (maximum, 3000 mg /day) and oral glucocorticoids (maximum, 15 mg of prednisolone equivalent/ day). **(**)** Usual care, included glucocorticoids alone, Azathioprine with or without glucocorticoids, Mycophenolate mofetil with or without glucocorticoids, Other drug with or without glucocorticoids as cyclosporine, cyclophosphamide, methotrexate, mizoribine, and tacrolimus.

Mycophenolate in 24.9%, and for Rituximab in 2.4%

The pre-treatment EDSS scale was measured in 12 of the studies with mean values ranging from 2 (Xu et al., 2016) to 8.25 (Torres et al., 2015). The pre-treatment annual relapse rate ranged between 0.8 (Xu et al., 2016) and 2.89 (Mealy et al., 2014). The pharmaceutical industry was not mentioned as a source of funding in any of the studies.

3.2. Quality evaluation

3.2.1. Non-randomized clinical trials

Regarding the confounding factors associated with the intervention, in all studies, prednisolone doses were administered concomitantly, especially in the Azathioprine branch. Three studies (Mealy et al., 2014; Jeong et al., 2015; Chen et al., 2017) reported prior treatment with other immunosuppressants (serious risk of confusion). In two studies (Jeong et al., 2015; Yang et al., 2018), the basal disability score (EDSS) was worse for the Rituximab group compared to the other interventions; an overview of the risk of bias of the individual studies is provided in (Fig. 2a).

3.2.2. Randomized clinical trials

In the Nikoo et al. A method to generate the random sequence was reported in the 2017 study (Nikoo et al., 2017) but did not use a blinding strategy, and the groups had significantly different baseline EDSS and ARR, thus this study was considered to be at high risk of bias. Likewise, the study by (Zhang et al., 2020) was not blinded for investigators and patients. For the study by Pittock et al., (2019) loss to follow-up was greater than 20%. An overview of risk of bias for individual studies is provided in (Fig. 2b).

3.3. Clinical outcomes

3.3.1. Change in EDSS

Eight non-randomized studies (Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020) and four randomized studies (Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019; Nikoo et al., 2017) reported the degree of disability through EDSS before and after implementing the pharmacological intervention (Table 2a). In five of the seven studies in which Rituximab was included (Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017; Yang et al., 2018), it outperformed its comparators in improving the degree of disability measured by EDSS, a finding that was consistent across both randomized and non-randomized studies. Only one non-randomized study (Mukherjee 2020) (Mukherjee et al., 2020) was changeless in the Rituximab group; however, patients assigned to such management had a significantly higher degree of basal disability (Median EDSS pre-treatment 8.25 vs. 7).

Seven non-randomized studies (Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020) compared Azathioprine with Mycophenolate, with no evident significant differences in the change in disability level between these medications (Table 2a).

Only one randomized study (Zhang et al., 2020) compared Tocilizumab with Azathioprine, showing a greater change in EDSS values with tocilizumab treatment. One randomized study (Yamamura et al., 2019) compared Satralizumab plus baseline immunosuppressant therapy vs baseline immunosuppressant therapy alone, evidencing a smaller change in EDSS values in the group treated with Satralizumab.(Pittock et al., 2019), compared Eculizumab added or not to baseline immunosuppressant therapy, evidencing a greater change in EDSS values in patients treated with Eculizumab. Considering the high heterogeneity in terms of the baseline severity of the patients, the doses of drugs used, and the measures of central tendency reported in the studies (mean or median), it was decided not to meta-analyze the information.

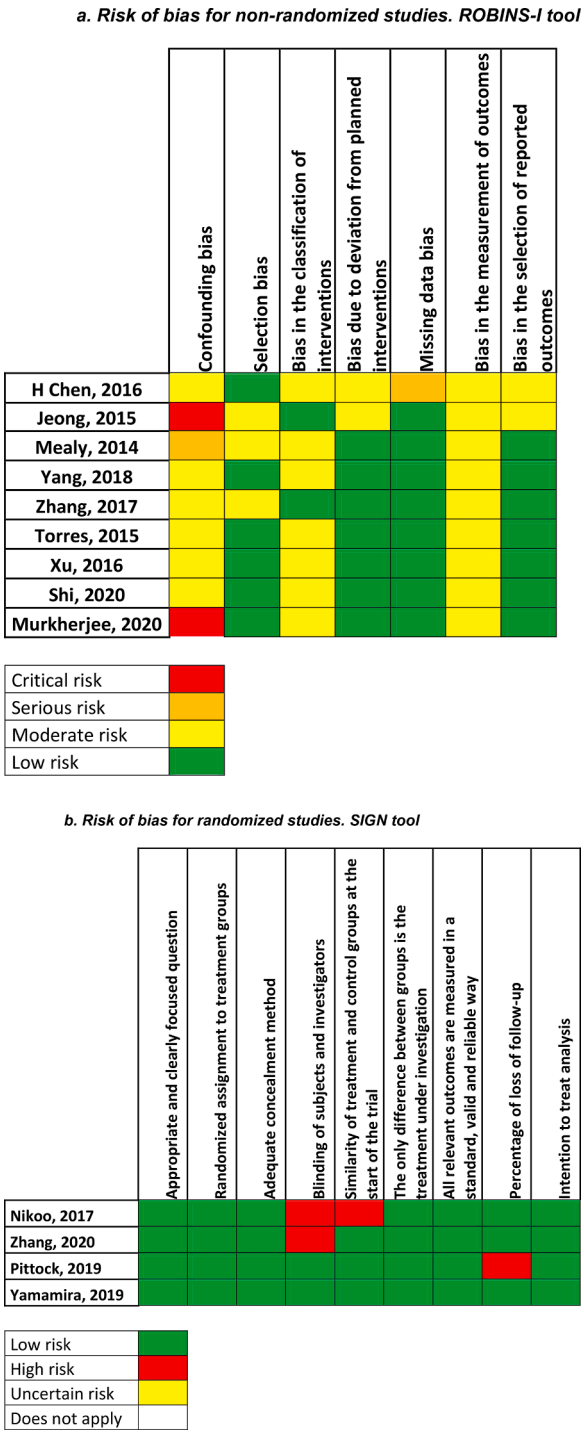

Fig. 2a. (a) Risk of bias for non-randomized studies. ROBINS-I tool. (b) Risk of bias for randomized studies. SIGN tool.

3.3.2. Change in annual relapse rate

The annual relapse rate (ARR) was measured in the nine non-randomized studies (Mealy et al., 2014; Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020) and three randomized clinical experiments (Pittock et al., 2019; Yamamura et al., 2019; Nikoo et al., 2017) (Table 2b). In six of the seven studies in which Rituximab was included (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017; Yang et al., 2018), it outperformed its comparators in reducing annual relapse rates, a finding that was consistent in both the randomized and non-randomized studies. Only

Table 2a
Change in disability measures (measured by EDSS), before and after treatment.

Study	Intervention / Dose	Participants	Outcome measure	Pre EDSS	Post EDSS	Change in EDSS
	Non-randomized studies					
Jeong 2015	Rituximab 375 mg/m^2/wk x 4wk	55	Median (Range)	4,5 (0–8,5)	3 (0–8)	1,5
	Azathioprine 1,75–2,5 mg/kg/d	49		3 (0–7,5)	3 (0–7,5)	0
	Mycophenolate 2000 mg	34		3 (0–7)	2 (0–7)	1
Torres 2015	Rituximab 1000 mg/wk x 2wk	32	Median (Range)	7 (5,5–7,25)	5	2
	Azathioprine no specific dose	22		7 (5–7,5)	6	1
	Mycophenolate no specific dose	11		4 (3–6,5)	5	−1
Xu 2016	Azathioprine 100 mg/d	119	Median (Range)	2 (0–9)	2 (0–9)	0
	Mycophenolate 1500 mg/d	38		2 (0–9)	2 (0–8,5)	0
Chen 2016	Azathioprine 2 mg/kg	150	Median (Range)	3 (0,5–9)	1 (0–8,5)	2
	Mycophenolate 20 mg/kg	150		3 (0,5–8)	2 (0,5–7,5)	1
Zhang 2017	Rituximab 100 mg/wk x 3wk x 3ts	31	Mean (SD)	5,62 (1,35)	4,48 (0,78)	1,14
	Azathioprine 2 mg/kg/d	34		5,63 (1,29)	5,05 (1)	0,58
Yang 2018	Rituximab 100 mg/wk x 4wk	20	Median (Range)	3,5 (2–9)	2 (0,5–7,5)	1,5
	Azathioprine 2 mg/kg/d	22		3 (2–8,5)	2 (1–7,5)	1
	Mycophenolate 1000 mg/d	30		3,5 (2–8,5)	2 (0,5–7)	1,5
Shi 2020	Azathioprine 100–150 mg/d	58	Median (Range)	3 (1–8,5)	1 (0–4)	2
	Mycophenolate 1000- 1500 mg/d	150		3 (0–9)	1 (0–3)	2
Mukherjee 2020	Rituximab no specific dose	4	Median (Range)	8,25 (8–9)	4,5 (4,5–4,5)	3,75
	Azathioprine no specific dose	24		7 (5,5–9)	3 (1,5–6)	4
	Mycophenolate no specific dose	2		6,5 (6–7)	2,5	4
	Randomized clinical study					
Nikoo 2017	Rituximab 1000 mg/wk x 2wk	33	Mean (SD)	3,55 (1,95)	2,56 (1,99)	0,99
	Azathioprine 2–3 mg/kg/d	35		2,4 (1,24)	1,95 (1,13)	0,45
Yamamura 2019	Satralizumab 120 mg+TB	41	Mean (SD)	3.83 (1.57)	3.73	0,1
	Usual care	42		3.63 (1.32)	3.42	0,21
Pittock 2019	Eculizumab 900mg-1200mg+TB	96	Median (Range)	4.0 (1–7)	3.82	0,18
	Usual care	47		4.0 (1–6,5)	4.12	−0,12
Zhang 2020	Azathioprine 2–3 mg/kg/d	59	Median (Range)	4,5 (4–6)	4,37	0,13
	Tocilizumab 8 mg/kg/d every 4wk	59		4,5 (4–5,5)	4,18	0,32

(TB) Treatment at baseline. **(EDSS)** Expanded disability status scale.

one non-randomized study (Mukherjee 2020) (Mukherjee et al., 2020) showed a smaller change in the Rituximab group, since, in that group the annual pretreatment relapse rate was lower (0.37).

Seven non-randomized studies (Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020) compared Azathioprine with Mycophenolate in terms of change in annual relapse rates with conflicting results: two studies showed superiority of Azathioprine, two studies evidenced superiority of Mycophenolate, and three showed no differences between both groups (Table 2a). No studies evaluated relapse rates with tocilizumab. One randomized study (Yamamura et al., 2019) comparing Satralizumab added or not to baseline immunosuppressant therapy, evidenced a greater change in ARR when Satralizumab was administered. One randomized study (Pittock et al., 2019) comparing Eculizumab added or not to baseline immunosuppressant therapy, evidenced greater change in ARR when Eculizumab was administered. Due to heterogeneity in pre-treatment relapse rates, central tendency measures used, and drug doses, it was decided not to meta-analyze the data.

3.3.3. *Time to first relapse*

Four non-randomized studies (Jeong et al., 2015; Zhang et al., 2017; Yang et al., 2018; Shi et al., 2020) and one randomized study (Zhang et al., 2020) evaluated the time measured in months to first relapse (Table 2c). In the three non-randomized studies in which Rituximab was evaluated (Jeong et al., 2015; Zhang et al., 2017; Yang et al., 2018), the time to first relapse was longer in this treatment arm. In the randomized study of (Zhang et al., 2020), the time to first relapse was measured in patients treated with Azathioprine and Tocilizumab and was longer in the latter (13.4 vs. 18.41 respectively).

3.3.4. *Patients with relapses during treatment*

Seven non-randomized studies (Zhang et al., 2020; Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Chen et al., 2017; Yang et al., 2018), and four randomized studies (Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019; Nikoo et al., 2017) evaluated the percentage of patients that suffered relapses during the treatment with each specific drug as shown in (Table 2d). For most of these studies, the shortest treatment duration was in the group of Azathioprine with periods of treatment as short as 6 weeks (Mealy et al., 2014), except for Zhang et al. that carried a 31.3 week treatment (Zhang et al., 2020). In all of the studies that included Rituximab (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017; Yang et al., 2018) this group showed the lowest rates of relapses, oscillating between 16.1% (Zhang et al., 2017) and 53% (Torres et al., 2015)in the non randomized studies and 7% in the randomized study (Nikoo et al., 2017), despite the fact that in most studies this treatment had the longest follow-up time. Azathioprine and Mycophenolate where compared in 6 studies (Zhang et al., 2020; Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Chen et al., 2017; Yang et al., 2018), four of them (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Chen et al., 2017) showed less relapses in the Mycophenolate group and two (Yang et al., 2018; Shi et al., 2020) showed less relapses in the Azathioprine group.

The evaluation of relapses for the new molecules Satralizumab, Eculizumab and Tocilizumab were performed in three randomized studies (C Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019). All of them showed a lower percentage of patients with relapses compared to baseline immunosuppressant therapy for Satralizumab and Eculizumab (Pittock et al., 2019; Yamamura et al., 2019) and compared to Azathioprine for Tocilizumab (Zhang et al., 2020). Due to heterogeneity in follow up time, and definition of relapse in the studies, it was decided not to meta-analyze the data.

3.3.5. *Adverse events*

Nine studies reported safety outcomes (Pittock et al., 2019; Yamamura et al., 2019; Jeong et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Nikoo et al., 2017; Yang et al., 2018; Zhang et al., 2020) for the interventions; in the Rituximab group, adverse events were

Table 2b
Change in annual, pre- and post-treatment relapse rates.

Study	Intervention / Dose	Participants	Outcome measure	pre ARR	post ARR	Change in ARR
	Non-randomized studies					
Mealy 2014	Rituximab 1000 mg/wk x 2wk	30	Mean	2,89 *	0,33 *	2,56
	Azathioprine 2–3 mg/kg/d	32		2,26 *	0,63 *	1,63
	Mycophenolate 1000–2000 mg/d	28		2,61 *	0,33 *	2,28
Jeong 2015	Rituximab 375 mg/m^2/wk x 4wk	55	Mean	1,66 *	0,09 *	1,57
	Azathioprine 1,75–2,5 mg/kg/d	49		1,26 *	0,37 *	0,86
	Mycophenolate 2000 mg	34		1,54 *	0,18 *	1,36
Torres 2015	Rituximab 1000 mg/wk x 2wk	32	Median (Range)	1,17 (0,77–3,66)	0,25 *	0,92
	Azathioprine no specific dose	22		0,92 (0–1,5)	0,56 *	0,36
	Mycophenolate no specific dose	11		1,06 (0,84–2,31)	0,39 *	0,67
Xu 2016	Azathioprine 100 mg/d	119	Median (Range)	0,8 (0–8)	0 (0–7,1)	0,8
	Mycophenolate 1500 mg/d	38		0,8 (0–3,8)	0 (0–1,4)	0,8
Chen 2016	Azathioprine 2 mg/kg	105	Median (Range)	1,4 (0,2- 14,6)	0 (0–2,1)	1,4
	Mycophenolate 20 mg/kg	105		1,2 (0,1–7)	0 (0–2)	1,2
Zhang 2017	Rituximab 100 mg/wk x 3wk x 3ts	31	Mean (SD)	1,39 (0,42)	0,05 (0,13)	1,34
	Azathioprine 2 mg/kg/d	34		1,28 (0,34)	0,49 (0,21)	0,79
Yang 2018	Rituximab 100 mg/wk x 4wk	20	Median (Range)	0,9 (0–5,2)	0 (0–3)	0,9
	Azathioprine 2 mg/kg/d	22		0,8 (0–4,5)	0 (0–3)	0,8
	Mycophenolate 1000 mg/d	30		0,9 (0–5)	0 (0–2,4)	0,9
Shi 2020	Azathioprine 100–150 mg/d	58	Median (Range)	1,2 (0,2–3)	0 (0–0,8)	1,2
	Mycophenolate 1000- 1500 mg/d	150		1 (0,1–3,7)	0 (0–0,4)	1
Mukherjee 2020	Rituximab no specific dose	4	Median	0,37 *	0 *	0,37
	Azathioprine no specific dose	24		2,63 *	0,26 *	2,37
	Mycophenolate no specific dose	2		1,79 *	0,74 *	1,05
	Randomized clinical study					
Nikoo 2017	Rituximab 1000 mg/wk x 2wk	33	Mean (SD)	1,3 (0,65)	0,21 (0,42)	1,09
	Azathioprine 2–3 mg/kg/d	35		1 (0,38)	0,51 (0,55)	0,49
Yamamura 2019	Satralizumab 120 mg+TB	41	Mean (SD)	1.5 (0.5)	0.11 *	1.39
	Usual care	42		1.4 (0.5)	0.32 *	1.08
Pittock 2019	Eculizumab 900mg-1200mg+TB	96	Mean (SD)	1,94 (0,90)	0,02 [a]	1,92
	Usual care	47		2,07 (1,04)	0,35 [a]	1,72

(TB) Treatment at baseline. **(ARR)** Annual relapse rate. **(*)** Measure of dispersion not reported. **([a])** Adjudicated relapse: relapse adjudication committee (RAC) for adjudication of all on-trial relapses, was introduced to strengthen the robustness of the analysis of the primary end point by mitigating against intersite variability observed in the identification of relapses during the trial.

reported in 4.4% of the patients, mostly related to allergic reactions. 22% of the patients treated with Azathioprine presented adverse events, 56.4% corresponded to an elevation of hepatic enzymes, 35.4% hematological alterations, 10.4% hair loss, 2.4% menstrual alterations, 10.5% gastrointestinal intolerance, 1.6% avascular necrosis associated with the concomitant use of Prednisolone. In the study conducted by Chen et al. 2016 (Chen et al., 2017), it was necessary to exclude 10 patients from the Azathioprine treatment group due to serious adverse events related to paraclinical abnormalities and discomfort for the participants that were not specified.

In the case of Mycophenolate, adverse events were reported in 3% of patients; 30% associated with hair loss, 30% elevation of hepatic enzymes, 10% infection of the upper respiratory tract, and 12.5% gastrointestinal intolerance. In the Tocilizumab treatment arm adverse events were reported in 61% of patients; associated mostly to hepatotoxicity, upper respiratory tract infection, urinary tract infection, anemia and fatigue. Serious adverse events were reported in 9 patients.

The study assessing Eculizumab (Pittock et al., 2019) showed adverse events in 92% of the patients, including higher rates of upper respiratory tract infection and headache. With 16% of them accounting for severe adverse events, including one death secondary to pulmonary empyema. In the controlled group, receiving basal immunosuppressive therapy alone, 91% of the patients showed adverse events, of which 15% were severe (Pittock et al., 2019). Yamamura et al., (2019) showed that 90% of patients receiving Satralizumab plus basal immunosuppressive treatment had adverse reaction in contrast with 95% of patients with basal treatment, most of them comprising infections and injection related reactions. 17% of the Satralizumab group and 21% of the control group accounted for severe adverse reactions. No deaths were reported.

61 patients required discontinuation of medication associated with adverse events, of which 58 were in the Azathioprine group, one in the

Table 2c
Time to first relapse.

Study	Intervention / Dose	Participants	Outcome measure	Time to first relapse in months
	Non-randomized studies			
Jeong 2015	Rituximab 375 mg/m^2/wk x 4wk	55	Median (Range)	48,1 (0,2–98,4)
	Azathioprine 1,75–2,5 mg/kg/d	49		13 (0,3–103,4)
	Mycophenolate 2000 mg	34		18,5 (0,6–67,7)
Zhang 2017	Rituximab 100 mg/wk x 3wk x 3ts	31	Mean (SD)	16,6 (6,91)
	Azathioprine 2 mg/kg/d	34		15,11 (8,62)
Yang 2018	Rituximab 100 mg/wk x 4wk	20	Median (Range)	24 (8–27)
	Azathioprine 2 mg/kg/d	22		20 (9–30)
	Mycophenolate 1000 mg/d	30		20,5 (8–28)
Shi 2020	Azathioprine 100–150 mg/d	58	Median (Range)	42 (26–57)
	Mycophenolate 1000- 1500 mg/d	150		52 (NA)
	Randomized clinical study			
Zhang 2020	Azathioprine 2–3 mg/kg/d	59	Median (Range)	13,4 (7,67–19)
	Tocilizumab 8 mg/kg/d every 4wk	59		18,41 (13,6–21,1)

Table 2d
Relapses during treatment time.

Study	Intervention / Dose	Participants	Treatment duration in weeks, median (range), [mean] ± SD	Patients with relapses during treatment, No. (%)	Relapse definition
	Non-randomized studies				
Mealy 2014	Rituximab 1000 mg/wk x 2wk	30	20 (5–83)	10 (33)	New CNS symptoms and signs that lasted longer than 24 h, with or without an associated new lesion on gadolinium enhancing magnetic resonance imaging
	Azathioprine 2–3 mg/kg/d	32	6 (0–122)	7 (53)	
	Mycophenolate 1000–2000 mg/d	28	26 (6–86)	10 (36)	
Jeong 2015	Rituximab 375 mg/m^2/wk x 4wk	55	65	15 (27,3)	New worsening of neurological function that increased a patient's EDSS score by ≥ 0.5 points, or if there was an increase of ≥ 1 point in two functional systems, or an increase of ≥ 2 points in one functional system that lasted for at least 24 h
	Azathioprine 1,75–2,5 mg/kg/d	49	15	23 (46,9)	
	Mycophenolate 2000 mg	34	26	12 (35,3)	
Torres 2015	Rituximab 1000 mg/wk x 2wk	32	22 (14–39)	17 (53)	Any new neurological symptoms
	Azathioprine no specific dose	22	21 (12–46)	15 (68)	
	Mycophenolate no specific dose	11	23 (13–60)	8 (73)	
Chen 2016	Azathioprine 2 mg/kg	105	36 (6–78)	50 (47,6)	Any acute attack, but do not specify criteria for these attacks
	Mycophenolate 20 mg/kg	105	16,8 (6–78)	46 (43,8)	
Zhang 2017	Rituximab 100 mg/wk x 3wk x 3ts	31	[27,4] ± 11,68	5 (16,1)	New neurological symptom that occurred 1 month after a previous relapse, and the EDSS score increased by at least 1 point or 1 point of the two functional scores
	Azathioprine 2 mg/kg/d	34	[31,3] ± 11,32	28 (82,35)	
Yang 2018	Rituximab 100 mg/wk x 4wk	20	29 (18–40)	7 (35)	New CNS symptoms and signs that lasted longer than 24 h and increased the overall EDSS score by at least half a point, with or without an associated new lesion on gadolinium-enhancing magnetic resonance
	Azathioprine 2 mg/kg/d	22	26 (18–36)	10 (45,5)	
	Mycophenolate 1000 mg/d	30	28,5 (19–42)	12 (40)	
Shi 2020	Azathioprine 100–150 mg/d	58	27,6 (12–88,8)	24 (41)	New worsening neurological function lasting more than 24 h in the absence of other identifiable causes and occurring more than 30 days after a previous attack
	Mycophenolate 1000-1500 mg/d	150	28,8 (12–82,8)	49 (33)	
	Randomized clinical study				
Nikoo 2017	Rituximab 1000 mg/wk x 2wk	33	12	7 (21,2)	Occurrence of new neurological symptoms or acute increased EDSS
	Azathioprine 2–3 mg/kg/d	35	12	16 (45,7)	
Yamamura 2019	Satralizumab 120 mg+TB	41	107,4 (2–224)	8 (20)	New or worsening neurological symptoms, lasting > 24 h, attributable to NMOSD, that met protocol-defined criteria for increase in EDSS and/or functional system scores from baseline
	Usual care	42	32,5 (0–180)*	18 (43)	
Pittock 2019	Eculizumab 900mg-1200mg+TB	96	91	3 (3)	New or worsening neurological symptoms with objective exam change, lasting > 24 h, attributable to NMOSD, onset after ≥ 30 days of clinical stability
	Usual care	47	43	20 (43)	
Zhang 2020	Azathioprine 2–3 mg/kg/d	59	90	28 (47)	New onset of neurological symptoms or worsening of existing neurological symptoms with an objective change on neurological examination that persisted for more than 24 h and preceded by at least 30 days of clinical stability
	Tocilizumab 8 mg/kg/d every 4wk	59	90	8 (14)	

(TB) Treatment at baseline. **(EDSS)** Expanded disability status scale. **(*)** 143,1 week extension.

Rituximab group, two in the Mycophenolate group, two in the Tocilizumab group and three in Eculizumab and Satralizumab groups.

4. Discussion

In this systematic review of the literature, we compared the most frequently drugs used in the NMO treatment, evaluating the efficacy and safety. A trend of superiority in EDSS outcomes (Mukherjee et al., 2020; Jeong et al., 2015; Torres et al., 2015; Yang et al., 2018), annual relapse rate (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Xu et al., 2016; Zhang et al., 2017; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020), time to first relapse (Jeong et al., 2015; Zhang et al., 2017; Yang et al., 2018) and relapses during treatment time (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017; Yang et al., 2018) was evidenced for Rituximab compared to other medications, with lower rates of adverse events. The new molecules Tocilizumab, Eculizumab and Satralizumab also showed superiority, especially in the relapses during treatment time, although with subtle differences in EDSS and ARR outcomes. Evidence needs to be developed comparing rituximab with these new therapies.

When evaluating EDSS, we found that in most studies (Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Nikoo et al., 2017), patients with Rituximab had greater change, a finding consistent in randomized and non-randomized studies with low risk of bias. A similar finding was evident in ARR, with the greatest reduction in the Rituximab-treated groups. The study conducted by (Mukherjee et al., 2020) evidenced worse outcomes with Rituximab vs. Azathioprine and Mycophenolate; however, the baseline disability degree was the highest among all, in

each of the treated arms, conditioning worse prognosis, which limits its comparability with other studies (Sato et al., 2012).

It is noteworthy that in several studies the group of patients assigned to Rituximab presented greater pre-treatment EDSS (Mukherjee et al., 2020; Jeong et al., 2015; Nikoo et al., 2017) or higher pre-treatment relapse rates (Mealy et al., 2014; Jeong et al., 2015; Torres et al., 2015; Zhang et al., 2017; Chen et al., 2017; Nikoo et al., 2017). It should be noted that even in this scenario, these patients achieved low scores on the EDSS and relapse rates below 1, with greater changes than the other drugs. In the same way, it was evidenced that the time until the first relapse was longer in the patients who received Rituximab (Jeong et al., 2015; Zhang et al., 2017; Yang et al., 2018). Likewise, Rituximab proved to be safer, with a rate lower than 4.4% of adverse events, mostly minor allergic reactions.

In the comparison of Azathioprine and Mycophenolate, the results were contradictory, both drugs showed the same difference in EDSS (Mukherjee et al., 2020; Xu et al., 2016; Shi et al., 2020). In contrast some studies showed Azathioprine as superior (Torres et al., 2015; Chen et al., 2017) and mycophenolate in others (Jeong et al., 2015; Yang et al., 2018). It should be noted that Azathioprine showed clinically significant changes in the EDSS defined as changes >1, in 6/10 of the studies evaluated (Mukherjee et al., 2020; Torres et al., 2015; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020), compared to Mycophenolate in 5/7 (Mukherjee et al., 2020; Jeong et al., 2015; Chen et al., 2017; Yang et al., 2018; Shi et al., 2020). However, in the randomized clinical trials evaluated, none of the drugs exceeded the clinically significant change. The group of patients treated with Azathioprine presented a higher number of adverse events, most of them corresponding to the elevation of hepatic enzymes.

Our results are compatible with the reported by (Espiritu and Pasco, 2019), who found Azathioprine inferior to Rituximab in effectiveness. The addition of three new studies, two non-randomized and one randomized (Zhang et al., 2020; Mukherjee et al., 2020; Shi et al., 2020), increases confidence in our conclusions.

The new molecules had better performance than their comparators in EDSS for Eculizumab, Satralizumab and Tocilizumab, (Zhang et al., 2020; Pittock et al., 2019; Yamamura et al., 2019) specially in seropositive patients, however in the first two there were no statistically significant differences. Satralizumab and Eculizumab (Pittock et al., 2019; Yamamura et al., 2019) also showed better performance in ARR and adjudicated ARR outcome respectively. However, for both of these outcomes the new molecules had minor difference compared with the studies evaluating rituximab, taking into account that these are mostly non-randomized studies. In terms of relapses the three new molecules demonstrated to be highly effective in preventing NMOSD attacks, although this effect was primarily seen in AQP4-IgG-positive patients.

Is to highlight the difference between the non-Randomized and the randomized trials, much greater differences in EDSS and ARR were seen in those no-randomized, this effect maybe because of the methods and basal characteristics in the beginning of those studies. Randomized trials had the strongest evidence however the difference pre and post treatment were subtle.

Currently it is not easy to decide which is the optimal treatment of NMO. Other randomized clinical studies report excellent efficacy and safety results, such as Inebilizumab (N-MOMENTUM) (Cree et al., 2019), and SAkurastar trial comparing Satralizumab with placebo (Traboulsee et al., 2020). These studies were excluded from the analysis because they had placebo as the only comparator. Our study suggests that the treatments, Rituximab, Eculizumab, Satralizumab and Tocilizumab are highly effective and safe, however, Rituximab showed better performance in more outcomes and had more evidence available, therefore, should be the comparator for new therapies. Additionally, our data highlights the need to develop cost-effectiveness and head to head studies that compare new agents to Rituximab. This information will be vital to develop treatment algorithms and consensus.

There are several limitations to this study. First, the small amount of evidence from randomized studies, explained by the low frequency of the disease. Therefore, it is essential to consider evidence from non-randomized studies, recognizing the greater potential for bias in these studies as this review did. The evaluation of the risk of bias with new tools (ROBINS 1) allowed us to detect studies with a high risk of bias associated with systematic differences in the baseline characteristics of patients assigned to the different management arms and to take this information into account for the analysis of the data.

A second limitation was the heterogeneity in the severity of the patients included, in the doses of the medicines used, follow up time, difference in the definition of relapse and how the outcomes were reported, which made it impossible to meta-analyze the information collected, limiting the estimation of the size of the differences in the effect of the treatments evaluated. Despite this, the different studies showed consistent findings demonstrating the superiority of Rituximab over other treatments. A third limitation is given by the small number of studies evaluating the new molecules Satralizumab, Eculizumab and Tocilizumab.

5. Conclusions

Our results suggest that Rituximab and the new molecules Satralizumab, Eculizumab and Tocilizumab are highly effective and safe, however, Rituximab showed better performance in multiple outcomes and had more evidence available, therefore it should be the comparator for new therapies being developed for this disease. The new molecules Satralizumab, Eculizumab and Tocilizumab showed better effectiveness in NMO seropositive patients. Drugs such as Azathioprine and Mycophenolate also modify disability, annual relapse rates, time to first relapse and relapses in treatment time, but with a less favorable risk-benefit ratio. Therefore, they are useful alternatives in places where the monoclonal antibodies are not accessible. New randomized clinical trials are needed to increase the available evidence.

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CRediT authorship contribution statement

Mario Velasco: Project administration, Investigation, Validation, Visualization, Supervision, Writing – review & editing. **Luis Alfonso Zarco:** Validation, Supervision, Conceptualization, Writing – review & editing. **Mariana Agudelo-Arrieta:** Data curtion, Writing – review & editing. **Isabel Torres-Camacho:** Investigation, Writing – review & editing. **Elkin Garcia-Cifuentes:** Investigation, Writing – review & editing. **Oscar Muñoz:** Methodology, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

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