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Safety outcomes of disease-modifying therapies for relapsing–remitting multiple sclerosis: A network meta-analysis

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ABSTRACT

Background: Randomised clinical trials (RCTs) and observational studies have reported adverse events that preclude the use of disease-modifying therapies (DMTs) in relapsing–remitting multiple sclerosis (RRMS) in the long term or in specific populations, however, little is known about the relationship between the use of DMTs and frequency of undesirable events. We aimed to conduct a systematic review and network meta-analyses (NMAs) of RCTs and observational studies to synthesise the evidence on the safety of all available DMTs for patients with RRMS.

Methods: PubMed, Scopus and a manual search were performed. Bayesian NMAs of safety outcomes reported in RCTs and observational studies assessing DMTs as monotherapies were conducted.

Results: Forty-seven studies were included in the systematic review. Considering all studies, 368 and 149 different safety outcomes were reported for at least one study and two studies, respectively. Considering clinical trials, 22 NMAs were conducted for 16 outcomes. Regarding geometry metrics, the median number of studies, DMTs, common comparator, strong edge, and patients were 5 (IQR 5–9), 5 (IQR 4–8), 44%, 33%, and 3998 (IQR 3380–6761). In summary, most comparisons showed similar risk of safety events for DMTs and placebo for all outcomes. Considering cohort studies, only three meta-analyses were conducted.

Conclusion: Safety outcomes are poorly reported in primary studies of DMTs in RRMS, precluding the conduction of robust meta-analyses. Therefore, the current available data on safety of these drugs is not contributing to regulatory and clinical decision making, with adverse event reports underbalanced compared to efficacy outcomes.

1. Introduction

The treatment of relapsing–remitting multiple sclerosis (RRMS) aims to reduce the frequency and severity of disease relapse, delay disease progression, decrease the number of lesions in the central nervous system, and maintain or improve patients' quality of life (Lublin et al., 2014). Therefore, it is expected that disease-modifying therapies (DMTs) such as alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferons, natalizumab, ocrelizumab, peginterferon or teriflunomide maintain quality of life in a safe manner.

The evidence-based efficacy of all internationally approved DMTs is well described in previous published network meta-analyses (NMAs), which shows the superiority of alemtuzumab, natalizumab and ocrelizumab for annualised relapse rate compared to the other DMTs (Hamidi et al., 2018; Lucchetta et al., 2018; Siddiqui et al., 2018). Even though randomised clinical trials (RCTs) have reported adverse events that preclude the use of DMTs in the long term or in specific populations, observational studies have also reported adverse events, which in some cases has led to drug withdrawal from the market (Clerico et al., 2017; Coles et al., 2017; Croteau et al., 2018; DTB, 2018; Faissner and Gold, 2018; Hellwig , 2011; ; Cohen, 2017), with safety being poorly reported in the RRMS NMAs. Additionally, little is known about the relationship between the use of DMTs and frequency of undesirable events, such as infections, cancer or hepatic disorders, as identified in some clinical studies (Lebrun and Rocher, 2018; Wijnands et al., 2018).

Thus, we aimed to conduct a systematic review and NMA of RCTs and observational studies to synthesise the evidence on the safety of all available DMTs for patients with RRMS.

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2. Methods

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analyses (PRISMA NMA) (Hutton et al., 2015) and Cochrane Collaboration recommendations (Higgins and Green, 2011), and is registered in the International Prospective Register of Systematic Reviews (PROSPERO), under the number CRD42018110830.

2.1. Search strategy and selection criteria

Electronic searches were conducted in the PubMed and Scopus databases without any time limit or language restriction (until April 2018). Trial registration databases (ClinicalTrials) and the reference lists of reviews and included studies were also searched. The complete search strategies are provided in the Online Resource, page 3.

We considered studies that fulfilled the following inclusion criteria: population – adults with RRMS; intervention and control – DMTs used as monotherapy (head-to-head or against placebo); alemtuzumab, 12 mg per day for five days (first course) and for three days (second course), with a one-year interval between each course (ALE12) intravenous (IV); cladribine cumulative dose of 3.5 per kg (CLA3.5) per oral (PO); dimethyl fumarate 240 mg twice a day (BG240BID) PO; fingolimod 0.5 mg per day (FING0.5QD) PO; glatiramer acetate 20 mg per day and 40 mg three times a week (GA20QD and GA40TIW) subcutaneous (SC); interferon beta 1a 30 mg each week (IFNA30QW) intramuscular (IM); interferon beta 1a 44 μg three times a week (IFNA44TIW) SC; interferon beta 1b 250 μg, every other day (IFNB250EOD) SC; pegylated interferon 125 μg every two weeks (PIFN125Q2W) SC; natalizumab 300 mg every four weeks (NAT300Q4W) IV; ocrelizumab 600 mg every six months (OCRE600Q6M), IV; and teriflunomide 7 and 14 mg per day (TERI7QD and TERI14QD), PO; outcomes – safety outcome; type of studies – case-control or cohort, prospective or retrospective, or randomised, phase II or later controlled trials (including post hoc analysis). For inclusion in this systematic review, dosages approved in drug labelling or recommended in international guidelines have been defined. Studies with a follow-up of less than 12 weeks, more than 162 weeks (long-term) or evaluating RRMS with other forms of MS or with less than 50 patients were excluded.

Two researchers (RCL and LPL) independently screened the titles and abstracts of retrieved studies to identify irrelevant records. In a second stage, full-text articles were also independently evaluated by the same two researchers according to the aforementioned inclusion and exclusion criteria. Discrepancies were reconciled in consensus meetings, using a third researcher as a referee (AW).

2.2. Data analysis

The following data were independently extracted by two researchers (RCL and LPL): (i) study characteristics (authors' names, year of publication, country, trial design, sample size, evaluated DMTs, mean follow-up), (ii) baseline data (patients' gender and age, disease duration, time from onset of symptoms); (iii) safety outcome and results (Online Resource). Specific safety outcomes were classified considering Common Terminology Criteria for Adverse Events (CTCAE) when possible. In case of identification of non-classified outcomes by CTCAE (e.g., death, relapse, discontinuation due to adverse events), they were reported as the original description.

The critical evaluation of risk of bias of the included studies was conducted by two independent reviewers (RCL and LPL), using the Cochrane Collaboration revised Risk of Bias (RoB 2.0) assessment tool (Higgins et al., 2016) for clinical trials and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016) for observational studies. In the absence of consensus, points of disagreement were resolved by the opinion of a third researcher (AW).

Statistical analyses were performed using software R v. 3.4.1/R studio 1.0.153 (Team), packages READR (Wickham et al., 2017), META (Schwarzer, 2007), METAFOR (Conducting meta-analyses in R with the metafor package, 2010), GeMTC (Valkenhoef and Kuiper, 2016), RJAGS (Plummer, 2016) and CODA (Plummer et al., 2006). Transitivity analyses were performed by comparing population, interventions and control, and outcome definitions among the included studies in the meta-analyses. Transitivity means that there are no systematic differences between the groups other than the treatments being compared (Rouse et al., 2017).

NMAs were conducted for the five most reported safety events, considering RCTs and observational studies of 96 weeks (i.e. discontinuation due to adverse events, headache, serious adverse events, any adverse events and influenza-like illness). Additionally, NMAs for adverse events associated with the pharmacological action or high frequency of report were also conducted when possible (i.e. any hepatic dysfunction, increase of alanine transferase >3 upper limit of normal (ULN), increase of ALT >5 ULN, any infection, upper respiratory tract infection, urinary tract infection, any thyroid dysfunction, hyperthyroidism, hypothyroidism, lymphocytopenia, neoplasia, depression, hypertension and rash). NMAs using a Bayesian framework for each outcome based on the Markov Chain Monte Carlo (MCMC) simulation method were performed. Arm-level entry data were used. A common heterogeneity parameter was assumed for all comparisons instead of comparison-specific, as this is the recommended approach when there is a small number of studies per direct comparison (Lu and Ades, 2004; Rouse et al., 2017). We opted for a conservative analysis of non-informative priors, to reflect a position of prior ignorance and avoid any subjectivity on prior distributions (Higgins and Green, 2011; Turner et al., 2012). All chains were run with 5000 burn-in iterations (number of iterations of the MCMC simulation that are discarded before the inference phase), followed by 20,000 iterations (number of iterations of the MCMC simulation that are used to draw inferences on the posterior distributions) with a thinning of 10 (to reduce auto-correlation and computation cost). Effect size measures were expressed as relative risk with a 95% credibility interval. Both fixed and random-effect models were tested, and the one with the lowest deviance information criteria was selected. Convergence was attained based on visual inspection of Brooks–Gelman–Rubin plots and potential scale reduction factor (PSRF) ($1 < \text{PSRF} \leq 1.05$). To estimate the robustness of the network, inconsistency – the difference between the pooled direct and indirect evidence for a comparison – was assessed using node-splitting analysis (Dias et al., 2013).

Network plots are represented followed by description of geometry. This description is useful to allow a more in-depth graph analysis. The parameters assessed were: (a) number of studies and patients for each comparison; (b) number of nodes (total number of comparators); (c) number of edges (total number of direct comparisons); (d) density, that shows the intensity of graph connectedness, and is calculated as the number of connections divided by the number of possible connections (values close to 1 represent a dense graph and close to 0 represent a sparse graph); (e) median thickness, that is the median number of studies per edge; (f) percentage of common comparators, the higher the percentage of common comparators, more connected the network is; and (g) percentage of strong edges, i.e., percentage of edges with more than one study, the higher the number, more robust the evidence is (Tonin et al., 2019).

2.3. Role of funding source

This study was funded by the Institutional Development Support Programme of the National Health System (Proadi-SUS) and Hospital Alemão Oswaldo Cruz (n. 01/2017). The funders had no role in any of the phases of the study (i.e. study design, data collection, data analysis, interpretation, writing of the report and responsibility for submission).

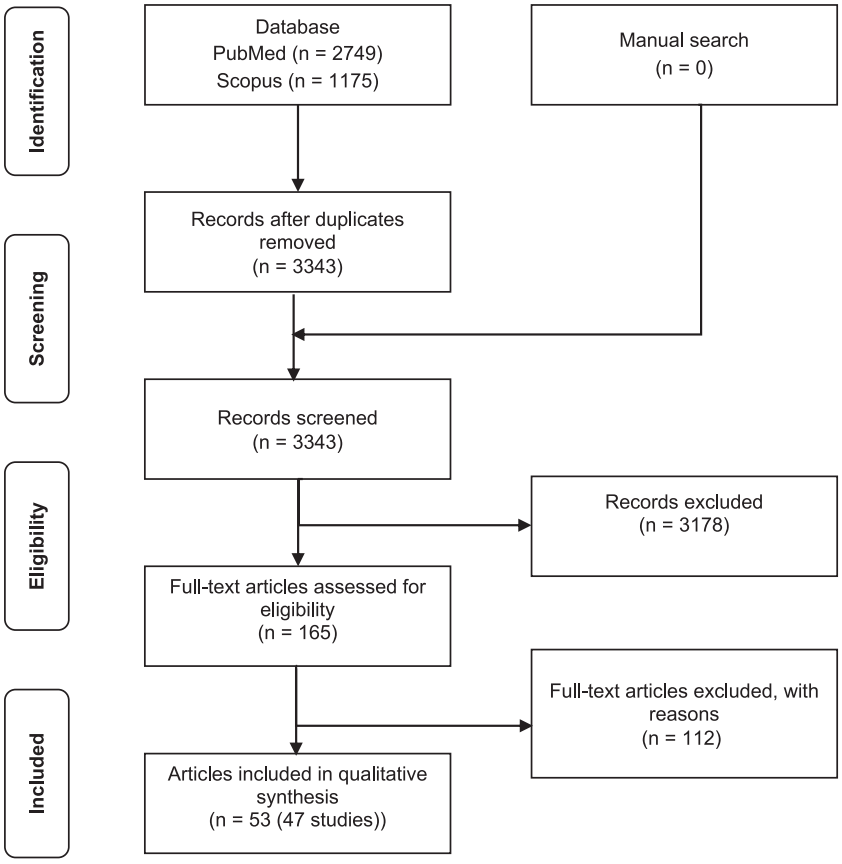


Fig. 1. Study selection.

3. Results

Our systematic review identified 3343 records after duplicates were removed; 3178 were considered irrelevant during the screening and 112 were excluded in the full-text appraisal (Fig. 1 and Online Resource, page 4). The remaining 53 records represent 33 RCTs and 14 cohort studies included in the qualitative synthesis. The articles were published between 1995 and 2018. Most of the studies were multicentric, conducted in more than one country (n = 28). In total, 26,892 participants (median of 215; interquartile range: 96–410) were included, of which 61% were female (eight studies did not report this information). Five studies included only treatment-naïve participants, and five studies assessed only treatment-experienced patients; 18 studies did not report this information. Altogether, 13 approved dosages of DMTs were identified, with 28 studies comparing active therapies (head-to-head), and the remaining evaluating the active treatment against a placebo. No study evaluating teriflunomide 14 mg per day fulfilled the inclusion criteria. Most of the studies had a follow-up of 96 weeks (median 96; interquartile range: 48–96). The main characteristics of the included studies are presented in Table 1 (supplemental characteristics are presented in the Online Resource, page 10).

The methodological quality assessed by RoB 2.0 is presented in the Online Resource, pages 12–13. The domain most associated with a 'high risk of bias' was measurement of the outcome; the domain most associated with 'some concerns' was deviations from intended interventions, and the domain most associated with 'low risk of bias' was selection of the reported result. Regarding overall risk of bias, most studies presented a 'low risk of bias' (n = 19), followed by 'some concerns' (n = 11) and a 'high risk of bias' (n = 4). The methodological quality assessed by ROBINS-I is presented in the Online Resource, page 14. The domain most associated with 'critical risk of bias' and 'serious risk of bias' was confounding, 'moderate risk of bias' was classification of interventions, 'no information' was deviations from intended interventions and all the other domains presented a 'low risk of bias' (e.g., selection of participants into the study, missing data, measurement of outcomes and selections of the reported result).

Considering all studies, 368 and 149 different safety outcomes were reported in at least one study and two studies, respectively (Online Resource, pages 15–19). Regarding CTCAE, most studies reported general disorders and administration site conditions (n = 34 studies, 40 adverse events), followed by nervous system disorders (n = 29 studies, 19 adverse events). However, non-specific adverse events such as discontinuation due to adverse events were more often reported (n = 42) (Table 2).

After assuring the transitivity of comparisons, i.e., assuring that the groups of different studies were similar enough to be compared in one sole analysis, the network meta-analyses were performed. The network characteristics of the most reported outcomes in clinical trials are presented in Fig. 2, and the other outcomes are shown in the Online Resource, pages 20–25. TERI7QD, IFNA44TIW, IFNA30QD, FING0.5QD, ALE12, OCRE600Q6M and GA20QD could not integrate the main network for some outcomes, resulting in multiple NMAs for any adverse event, serious adverse event, any infection, neoplasm, upper respiratory tract infection and urinary tract infection.

Considering clinical trials, 22 meta-analyses were conducted for 16 outcomes. Regarding geometry metrics, the median number of studies per direct comparison, number of nodes, edges, density, thickness, percentage of common comparator, percentage of strong edge, and number of patients were 5 (IQR 5–9), 5 (IQR 4–8), 5 (IQR 3–8), 0.40 (IQR 0.30–0.50), 1.25 (IQR 1.00–1.59), 44%, 33%, and 3998 (IQR 3380–6761). The networks withthe highest number of studies, patients and DMTs were those built for the outcomes discontinuation due to adverse events, headache, serious adverse event, and any adverse events (Fig. 2). In only ten of the 22 NMAs, differences between DMTs

Table 1
Characteristics of the included studies in the systematic review.

Study	Year	Follow-up	Evaluated alternatives	# Participants (# Women)	Age, mean in years (SD)	Baseline EDSS, mean (SD)	Disease duration, mean in years (SD)	Symptom onset, mean in years (SD)	Previous DMT
Randomised clinical trials									
ADVANCE[f]	2014	96	PLA	500 (358)	36.3 (9.7)	2.4 (1.2)	3.5 (4.6)	6.3 (6.3)	17%
ADVANCE[f]	2014	96	PIFN125Q2W	512 (361)	36.9 (9.8)	2.5 (1.3)	4.0 (5.1)	6.9 (6.6)	17%
AFFIRM	2006	96	NAT300Q4W	627 (449)	35.6 (8.5)	2.3 (1.2)	5.0 (0.0; 34.0)[b]	NR	NR
AFFIRM	2006	96	PLA	315 (211)	36.7 (7.8)	2.3 (1.2)	6.0 (0.0; 33.0)[b]	NR	NR
BEYOND[f]	2009	96	GA20QD	448 (306)	35.0 (27.0; 43.0)[a]	2.0 (1.5; 3.0)[a]	5.1 (3.0)	NR	0%
BEYOND[f]	2009	96	IFNB250EOD	897 (627)	35.0 (28.0; 43.0)[a]	2.0 (1.5; 3.0)[a]	5.4 (3.0)	NR	0%
Boiko	2018	48	PLA	28 (NR)	NR	NR	NR	4.0 (2.0; 7.5)[a]	NR
Boiko	2018	48	GA20QD[d]	61 (NR)	NR	NR	NR	3.0 (2.0; 8.0)[a]	NR
BRAVO[f]	2014	96	PLA	450 (321)	37.5 (30.3; 45.4)[a]	2.5 (1.5; 3.5)[a]	1.2 (0.3; 4.0)[a]	4.7 (2.0; 9.7)[a]	6%
BRAVO[f]	2014	96	IFNA30QW	447 (307)	38.5 (30.3; 45.9)[a]	2.5 (1.5; 3.5)[a]	1.4 (0.3; 4.7)[a]	5.3 (2.4; 10.3)[a]	9%
CAMMS223[f]	2008	144	ALE12	112 (72)	31.9 (8.0)	1.9 (0.7)	NR	1.3 (0.1; 3.5)[b]	0%
CAMMS223[f]	2008	144	IFNA44TIW	111 (71)	32.8 (8.8)	1.9 (0.8)	NR	1.4 (0.2; 6.3)[b]	0%
CARE-MS I	2012	96	IFNA44TIW	187 (122)	33.2 (8.5)	2.0 (0.8)	NR	2.0 (1.3)	0%
CARE-MS I	2012	96	ALE12	376 (243)	33.0 (8.0)	2.0 (0.8)	NR	2.1 (1.4)	0%
CARE-MS II[f]	2012	96	ALE12	426 (281)	34.8 (8.4)	2.7 (1.3)	NR	4.5 (2.7)	100%
CARE-MS II[f]	2012	96	IFNA44TIW	202 (131)	35.8 (8.8)	2.7 (1.2)	NR	4.7 (2.9)	100%
CLARITY[f]	2010	96	PLA	437 (288)	38.7 (9.9)	2.9 (1.3)	8.9 (7.4)	NR	33%
CLARITY[f]	2010	96	CLA3.5	433 (298)	37.9 (10.3)	2.8 (1.2)	7.9 (7.2)	NR	26%
CMSSG	1995	96	GA20QD	125 (88)	34.6 (6.0)	2.8 (1.2)	7.3 (4.9)	NR	NR
CMSSG	1995	96	PLA	126 (96)	34.3 (6.5)	2.4 (1.3)	6.6 (5.1)	NR	NR
CombiRx	2013	144	IFNA30QW	250 (173)	37.6 (10.2)	2.0 (1.2)	1.4 (4.0)	NR	NR
CombiRx	2013	144	GA20QD	259 (185)	39.0 (9.5)	1.9 (1.2)	1.0 (2.9)	NR	NR
CONFIRM[f]	2012	96	GA20QD	350 (247)	36.7 (9.1)	2.6 (1.2)	4.4 (4.7)	NR	29%
CONFIRM[f]	2012	96	PLA	363 (251)	36.9 (9.2)	2.6 (1.2)	4.8 (5.0)	NR	31%
CONFIRM[f]	2012	96	BG240BID	359 (245)	37.8 (9.4)	2.6 (1.2)	4.9 (5.1)	NR	28%
DEFINE[f]	2012	96	PLA	408 (306)	38.5 (9.1)	2.5 (1.2)	5.8 (5.8)	NR	42%
DEFINE[f]	2012	96	BG240BID	410 (296)	38.1 (9.1)	2.4 (1.3)	5.6 (5.4)	NR	40%
ECGA	2001	36	PLA	120 (NR)	34.4 (7.4)	2.4 (1.2)	8.3 (5.6)	NR	NR
ECGA	2001	36	GA20QD	190 (NR)	34.0 (7.6)	2.3 (1.1)	8.0 (5.6)	NR	NR
EVIDENCE	2007	48 and 64	IFNA44TIW	339 (254)	38.3 (18.0; 55.0)[c]	2.3 (NR)	6.5 (NR)	NR	0%
EVIDENCE	2007	48 and 64	IFNA30QW	338 (252)	37.4 (18.0; 55.0)[c]	2.3 (NR)	6.7 (NR)	NR	0%
FREEDOMS[f]	2010	96	FING0.5QD	425 (296)	36.6 (8.8)	2.3 (1.3)	NR	8.0 (6.6)	43%
FREEDOMS[f]	2010	96	PLA	418 (298)	37.2 (8.6)	2.5 (1.3)	NR	8.1 (6.4)	59%
FREEDOMS II[f]	2014	96	FING0.5QD	358 (275)	40.6 (8.4)	2.4 (1.3)	NR	10.4 (8.0)	74%
FREEDOMS II[f]	2014	96	PLA	355 (288)	40.1 (8.4)	2.4 (1.3)	NR	10.6 (7.9)	73%
GALA	2013	48	PLA	461 (313)	38.1 (9.2)	2.7 (1.2)	NR	7.6 (6.4)	14%
GALA	2013	48	GA40TIW	943 (641)	37.4 (9.4)	2.8 (1.2)	NR	7.7 (6.7)	14%
GATE	2015	36	PLA	84 (57)	32.6 (8.7)	2.7 (1.2)	NR	5.7 (6.0)	NR
GATE	2015	36	GA20QD[d]	357 (238)	33.8 (9.0)	2.7 (1.2)	NR	6.4 (6.0)	NR
GIMN	2017	24	FING0.5QD	230 (162)	35.4 (2.3)	3.1 (0.2)	6.0 (0.4)	NR	100%
GIMN	2017	24	IFNA44TIW	28 (NR)	NR	NR	NR	NR	100%
GIMN	2017	24	GA20QD	40 (NR)	NR	NR	NR	NR	100%
GLACIER	2015	16	GA20QD	101 (83)	50.4 (9.3)	2.4 (1.4)	12.1 (10.0)	16.2 (11.0)	NR
GLACIER	2015	16	GA40TIW	108 (89)	50.9 (11.0)	2.5 (1.4)	10.8 (8.6)	15.7 (11.1)	NR
IMPROVE	2012	16	PLA	60 (NR)	NR	NR	NR	NR	NR
IMPROVE	2012	16	IFNA44TIW	120 (NR)	NR	NR	NR	NR	NR
INCOMIN	2002	96	IFNA30QW	92 (57)	34.9 (7.9)	2.0 (0.7)	6.7 (5.4)	NR	NR
INCOMIN	2002	96	IFNB250EOD	96 (66)	38.8 (7.1)	2.0 (0.7)	5.9 (4.2)	NR	NR
Kappos[f]	2011	24	IFNA44TIW	54 (38)	38.1 (9.3)	NR	3.3 (0.1; 20.2)[b]	5.3 (0.8; 35.2)[b]	31%
Kappos[f]	2011	24	OCRE600Q6M	55 (35)	35.6 (8.5)	NR	3.6 (0.1; 16.5)[b]	6.5 (0.5; 20.5)[b]	53%
Kappos[f]	2011	24	PLA	54 (36)	38.0 (8.8)	NR	2.7 (0.1; 19.2)[b]	4.8 (0.6; 26.2)[b]	30%
MSCRG	1996	96	PLA	143 (103)	36.9 (0.6)	2.3 (0.1)	6.4 (0.5)	NR	0%
MSCRG	1996	96	IFNA30QW	158 (118)	36.7 (0.6)	2.4 (0.1)	6.6 (0.5)	NR	0%
OPERA I	2017	96	IFNA44TIW	411 (272)	36.9 (9.3)	2.9 (1.2)	3.7 (4.6)	6.3 (6.0)	29%
OPERA I	2017	96	OCRE600Q6M	410 (270)	37.1 (9.3)	2.8 (1.3)	3.8 (4.8)	6.7 (6.4)	26%
OPERA II	2017	96	IFNA44TIW	418 (280)	37.4 (9.0)	2.8 (1.3)	4.1 (5.1)	6.7 (6.1)	25%
OPERA II	2017	96	OCRE600Q6M	417 (271)	37.2 (9.1)	2.8 (1.4)	4.2 (5.0)	6.7 (6.1)	27%
OWIMS[f]	1999	48	IFNA44TIW	98 (70)	35.5 (7.4)	2.6 (1.4)	6.7 (5.3)	NR	NR
OWIMS[f]	1999	48	PLA	100 (74)	34.9 (7.8)	2.6 (1.3)	6.3 (4.7)	NR	NR
PRISMS[f]	1998	96	PLA	187 (75)	34.6 (28.8; 40.4)[a]	2.4 (1.2)	4.3 (2.4; 8.4)[a]	NR	NR
PRISMS[f]	1998	96	IFNA44TIW	184 (66)	35.6 (28.4; 41.0)[a]	2.5 (1.3)	6.4 (2.9; 10.3)[a]	NR	NR
REGARD	2008	96	IFNA44TIW	386 (267)	36.7 (9.8)	2.4 (1.3)	NR	5.9 (6.3)	NR
REGARD	2008	96	GA20QD	378 (272)	36.8 (9.5)	3.2 (1.3)	NR	6.6 (7.1)	NR
Saida	2017	24	PLA	47 (32)	35.1 (8.2)	2.1 (1.5)	5.1 (4.9)	6.8 (5.5)	85%

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Follow-up	Evaluated alternatives	# Participants (# Women)	Age, mean in years (SD)	Baseline EDSS, mean (SD)	Disease duration, mean in years (SD)	Symptom onset, mean in years (SD)	Previous DMT
Randomised clinical trials									
Saida	2017	24	NAT300Q4W	47 (34)	37.7 (8.6)	2.5 (1.6)	5.9 (5.0)	8.7 (5.7)	91%
TENERE	2014	48	IFNA44TIW[e]	104 (71)	37.0 (10.6)	2.0 (1.2)	NR	7.7 (7.6)	24%
TENERE	2014	48	TERI7QD[e]	109 (70)	35.2 (9.2)	2.0 (1.2)	NR	7.0 (6.9)	21%
TRANSFORMS[f]	2010	96	FING0.5QD	431 (282)	36.7 (8.8)	2.2 (1.3)	NR	7.5 (6.2)	55%
TRANSFORMS[f]	2010	96	IFNA30QW	435 (295)	36.0 (8.3)	2.2 (1.3)	NR	7.4 (6.3)	56%
Observational studies									
Barak 2002	2002	48	IFNB250EOD	23 (NR)	47.4 (12.8)	NR	14.5 (7.6)	NR	NR
Barak 2002	2002	48	PLA	23 (NR)	40.1 (8.8)	NR	9.6 (6.1)	NR	NR
Baroncini	2016	96	FING0.5QD	102 (77)	38.1 (9.2)	2.0 (1.5; 3.0)[a]	11.2 (7.8)	NR	100%
Baroncini	2016	96	NAT300Q4W	102 (73)	37.7 (9.3)	2.0 (1.5; 2.5)[a]	10.3 (6.2)	NR	100%
Carruthers	2014	96	FING0.5QD	36 (22)	39.6 (9.7)	1.8 (0.0; 8.0)[b]	7.9 (7.0)	NR	81%
Carruthers	2014	96	NAT300Q4W	69 (50)	38.4 (10.1)	1.5 (0.0; 6.0)[b]	8.4 (6.6)	NR	87%
D'Amico	2018	96	FING0.5QD	49 (32)	29.4 (9.9)	2.8 (1.5)	13.8 (9.5)	NR	100%
D'Amico	2018	96	IFNA44TIW	43 (32)	30.1 (11.5)	1.7 (1.2)	12.6 (6.8)	NR	100%
Flechter 2002[f]	2002	96	GA20QD	20 (13)	NR	NR	NR	NR	NR
Flechter 2002[f]	2002	96	IFNB250EOD	20 (15)	NR	NR	NR	NR	NR
Gajofatto	2014	92	FING0.5QD	30 (21)	39.0 (7.8)	2.5 (0.0; 5.5)[b]	11.1 (1.1; 30.2)[b]	NR	97%
Gajofatto	2014	92	NAT300Q4W	57 (43)	38.0 (9.3)	3.0 (2.0; 8.0)[b]	8.4 (0.5; 35.1)[b]	NR	91%
Guger	2017	48	FING0.5QD	332 (226)	39.3 (9.8)	2.7 (1.5)	9.9 (7.2)	NR	90%
Guger	2017	48	NAT300Q4W	246 (174)	34.1 (10.3)	2.5 (1.6)	6.6 (5.7)	NR	86%
Hersh	2017	96	BG240BID	293 (NR)	NR	NR	NR	NR	NR
Hersh	2017	96	FING0.5QD	215 (NR)	NR	NR	NR	NR	NR
Koch-Henriksen	2016	96	FING0.5QD	464 (327)	38.7 (10.1)	3.2 (1.6)	7.8 (6.2)	NR	94%
Koch-Henriksen	2016	96	NAT300Q4W	464 (327)	39.3 (10.1)	3.1 (1.5)	7.7 (6.3)	NR	94%
Milanese	2003	48 and 84	IFNB250EOD	834 (NR)	NR	2.4 (NR)	NR	NR	85%
Milanese	2003	48 and 84	IFNA30QW	647 (NR)	NR	2.2 (NR)	NR	NR	73%
PROOF	2008	24	IFNA30QW	69 (59)	38.0 (8.3)	1.8 (1.1)	0.3 (0.0; 13.0)[b]	NR	NR
PROOF	2008	24	IFNA44TIW	67 (51)	37.1 (8.6)	2.2 (1.3)	0.4 (0.0; 9.0)[b]	NR	NR
Puz 2016	2016	73	FING0.5QD	30 (NR)	NR	NR	NR	NR	100%
Puz 2016	2016	73	NAT300Q4W	14 (NR)	NR	NR	NR	NR	100%
QUASIMS[f]	2017	96	IFNA30QW	1442 (NR)	36.2 (9.2)	2.6 (1.3)	4.4 (5.1)	NR	NR
QUASIMS[f]	2017	96	IFNB250EOD	1393 (NR)	37.7 (10.1)	3.0 (1.6)	4.3 (5.4)	NR	NR
QUASIMS[f]	2017	96	IFNA44TIW	249 (NR)	35.5 (9.6)	2.8 (1.5)	4.0 (5.0)	NR	NR
Trojano[f]	2003	12	IFNA30QW	217 (153)	32.4 (8.1)	2.4 (0.9)	7.1 (5.4)	NR	NR
Trojano[f]	2003	12	IFNB250EOD	234 (157)	31.4 (7.6)	2.5 (1.0)	7.1 (5.4)	NR	NR

SD: standard deviation; EDSS: Expanded Disability Status Score; DMT: disease-modifying therapies; NR: not reported. ALE12: alemtuzumab, 12 mg/ day per 5 days and 12 months later per 3 days; OCRE600Q6M: ocrelizumab 600 mg every 6-months; NAT300Q4W: natalizumab, 300 mg, every monthly; CLA3.5: cladribine, cumulative dose 3.5 mg/kg; BG240BID: dimethyl fumarate, 240 mg, twice-times daily; FING0.5QD: fingolimod, 0.5 mg daily; PIFN125Q2W: peginterferon, 125 μg, every 2-week; GA40TIW: glatiramer acetate, 40 mg three-times weekly; GA20QD: glatiramer acetate, 20 mg daily; IFNA44TIW: interferon 1a beta 44 μg three-times weekly; IFNB250EOD: interferon 1b beta, 250 μg, every other day; TERI7QD: teriflunomide 7 mg daily; IFNA30QW: interferon 1a beta, 30 μg weekly; PLA: placebo.

[a] Median (interquartile range).
[b] Median (range).
[c] Mean (range).
[d] Considered glatiramer acetate branded.
[e] Considered only arms of therapies that included only patients with RRMS.
[f] Excluded non-approved dose therapy.

were identified: discontinuation due to adverse event, serious adverse event, headache, depression, upper respiratory tract infection, urinary tract infection, hypertension, lymphocyte count decreased, neoplasm and ALT > 3ULN. In summary, most comparisons showed a similar risk of safety events for DMTs and placebo for all outcomes (Online Resource, pages 26–28).

The effect size measures for the outcomes discontinuation due to adverse events and number of serious adverse events are shown in Table 3. The meta-analyses results for other outcomes can be found in the Online Resource, pages 26–28. IFNA30 came out safer than placebo and CLA for serious adverse events (Table 3). For discontinuation due to adverse events, PIFN125Q2W stood out as the drug with more statistically significant differences. PIFN125Q2W showed a higher risk of discontinuation compared with placebo, BG240BID, FING0.5QD, IFNA30QW, IFNB250EOD, and NAT300Q4W (Table 3).

Considering cohort studies, three meta-analyses were conducted: any adverse event and influenza-like illness, with differences identified in both, and discontinuation due to adverse event, with no differences (Online Resource, page 29) Regarding network geometry metrics, the median number of studies per direct comparison, number of nodes, edges, density, thickness, percentage of common comparator, percentage of strong edge, and number of patients were 2 (IQR 2–4), 4 (IQR 4–4), 3 (IQR 3–4), 0.67 (IQR 0,59–0,67), 1,00 (IQR 0.75–1.00), 33%, and 0%, and 2375 (IQR 1485 – 2750)(Online Resource, page 25).

The analysis of inconsistency by the node-splitting technique was possible for only four outcomes (discontinuation due to adverse events, any adverse events, serious adverse events and headache at 96 weeks). The issue of multiple testing was considered when interpreting the p-values (i.e., using a Bonferroni correction based on the number of possible inconsistencies in the network). Thus, no substantial differences in the magnitude or direction between the results of the direct and indirect effects were identified in the NMAs, which suggests that the NMAs for which the inconsistency analysis was possible are coherent and robust (Online Resource, page 30).

4. Discussion

We investigated the safety of DMTs in RRMS through the

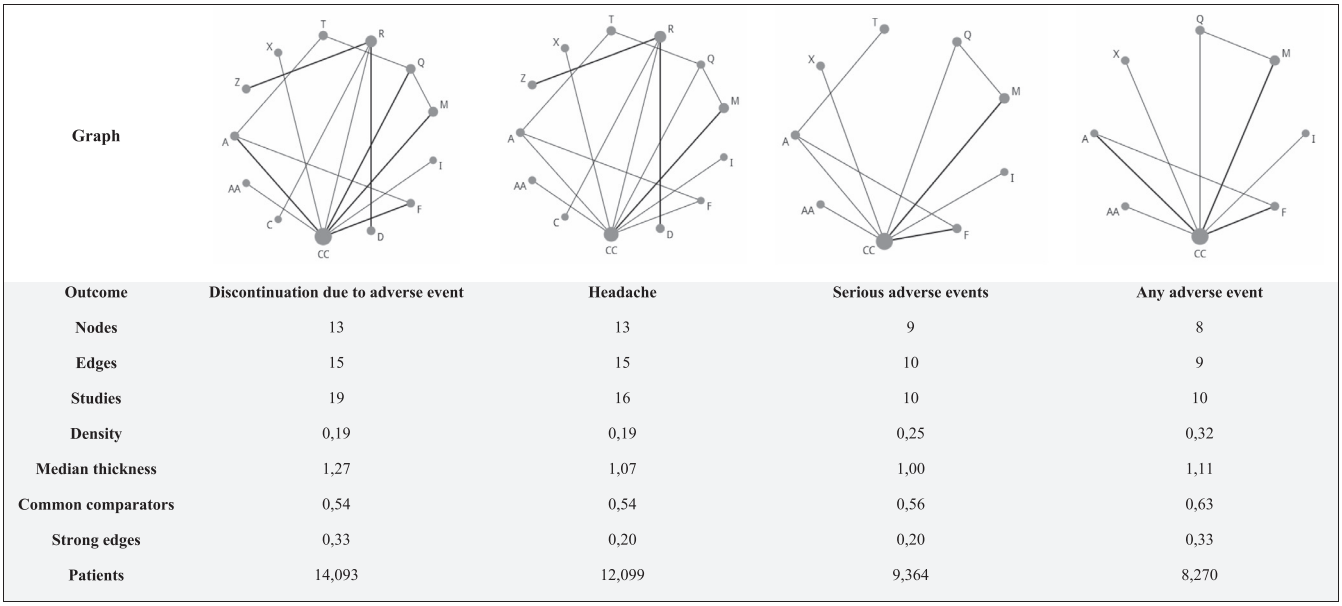
Table 2
Adverse drug events reported according type of study and follow-up time, considering Common Terminology Criteria for Adverse Events and other classification.

All studies CTCAE	RCT48 # studies	RCT96 # adverse events	RCTother # studies	ObS48 # adverse events	ObS96 # studies	ObSother # adverse events	# studies	# adverse events	# studies	# adverse events	# studies	# adverse events	# studies	# adverse events
General disorders and administration site conditions	34	40	4	14	17	30	8	14	0	0	3	4	2	5
Nervous system disorders	29	19	3	4	17	14	6	8	0	0	2	2	1	1
Musculoskeletal and connective tissue disorders	24	19	4	7	15	13	3	8	0	0	1	2	1	1
Infections and infestations	22	53	2	8	14	44	5	23	0	0	1	5	1	1
Psychiatric disorders	22	10	4	6	12	6	4	4	0	0	1	1	1	1
Investigations	21	47	2	21	13	38	3	5	0	0	2	3	1	1
Gastrointestinal disorders	20	22	1	8	14	16	4	12	0	0	1	2	0	0
Immune system disorders	15	10	1	1	9	9	3	3	0	0	1	1	1	1
Neoplasms benign, malignant and unspecified[a]	15	22	1	2	12	22	2	2	0	0	0	0	0	0
Vascular disorders	13	11	2	4	9	9	1	2	0	0	1	1	0	0
Cardiac disorders	13	18	2	4	8	16	2	2	0	0	1	1	0	0
Hepatobiliary disorders	13	7	3	4	7	4	3	2	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	13	11	3	5	5	7	4	3	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders	12	11	2	3	8	9	2	3	0	0	0	0	0	0
Blood and lymphatic system disorders	9	6	1	1	5	5	1	1	0	0	1	1	1	1
Renal and urinary disorders	7	9	0	0	6	7	1	2	0	0	0	0	0	0
Ear and labyrinth disorders	6	4	1	2	5	3	0	0	0	0	0	0	0	0
Endocrine disorders	6	7	0	0	3	6	2	5	0	0	0	0	1	1
Eye disorders	6	5	1	2	3	2	1	1	0	0	1	1	0	0
Reproductive system and breast disorders	6	4	1	1	2	3	2	2	0	0	0	0	1	1
Injury, poisoning and procedural complications	5	8	1	2	2	6	2	2	0	0	0	0	0	0
Pregnancy, puerperium and perinatal conditions	5	6	1	1	4	5	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders	1	1	0	0	1	1	0	0	0	0	0	0	0	0
Surgical and medical procedures	1	1	0	0	0	0	1	1	0	0	0	0	0	0
Other classification														
Discontinuation due to adverse events	42	NA	6	NA	19	NA	7	NA	3	NA	6	NA	1	NA
Serious adverse events	27	NA	5	NA	15	NA	6	NA	0	NA	1	NA	0	NA
Any adverse events	26	NA	4	NA	14	NA	5	NA	0	NA	2	NA	1	NA
Death	18	NA	2	NA	13	NA	3	NA	0	NA	0	NA	0	NA
Multiple sclerosis relapse	12	NA	0	NA	9	NA	2	NA	0	NA	0	NA	1	NA
Other[b]	9	9	1	2	6	9	1	1	0	NA	1	1	0	NA
Suspected or concerns PML	4	NA	0	NA	0	NA	1	NA	0	NA	2	NA	1	NA
Adverse events related to study treatment	3	NA	1	NA	1	NA	1	NA	0	NA	0	NA	0	NA
Incorrect dose administered	1	NA	0	NA	1	NA	0	NA	0	NA	0	NA	0	NA
Severe adverse event	1	NA	0	NA	0	NA	1	NA	0	NA	0	NA	0	NA

CTCAE: Common Terminology Criteria for Adverse Events; N: number; RCT48: randomized clinical trial of 48 weeks; RCT96: randomized clinical trial of 96 weeks; RCTother: randomised clinical trial of 16, 24, 36 or 144 weeks; ObS48: observational study of 48 weeks; ObS96: observational study of 96 weeks; ObSother: observational study of 12, 24 or 73 weeks; PML: Progressive Multifocal Leukoencephalopathy.

[a] including cysts and polyps.

[b] chest discomfort, chest pain, systemic reaction, brainstem syndrome, chest pain and flushing, chest pain without flushing, flushing without chest pain, need for rehabilitation therapy and rhinitis.



Graph	Discontinuation due to adverse event	Headache	Serious adverse events	Any adverse event
Outcome				
Nodes	13	13	9	8
Edges	15	15	10	9
Studies	19	16	10	10
Density	0,19	0,19	0,25	0,32
Median thickness	1,27	1,07	1,00	1,11
Common comparators	0,54	0,54	0,56	0,63
Strong edges	0,33	0,20	0,20	0,33
Patients	14,093	12,099	9,364	8,270

Fig. 2. Network characteristics of outcomes more reported by clinical trials.
Network geometry: each node represents a therapy, and the lines represent direct comparisons in the literature; thicker lines represent largest number of studies identified, and larger nodes represent the largest number of studies for a therapy; A: GA40TIW; AA: PIFN125Q2W; C: GA20QD; CC: PLA; D: ALE12; F: BG240BID; I: CLA3.5; M: FING0.5QD; Q: IFNA30QW; R: IFNA44TIW; T: IFNB250EOD; X: NAT300Q4W; Z: OCRE600Q6M;.

conduction of a systematic review, which resulted in the inclusion of 47 studies (26,892 participants). Recent NMAs of DMTs in RRMS (Hamidi et al., 2018; Siddiqui et al., 2018; Xu et al., 2018) were limited to RCTs and considered few safety outcomes, being restricted only to discontinuation due to adverse events, incidence of any adverse or serious adverse events. Therefore, in our study, we attempted to summarise more comprehensively the safety of DMTs by expanding the number of safety outcomes and type of trial design, in order to fully capture the incidence of adverse events in these patients.

Considering the meta-analyses on clinical trials, discontinuation due to adverse events was the most reported outcome, followed by incidence of any adverse event and serious adverse event. Specific adverse events such as any hepatic dysfunction, increase of alanine transferase, any infection, upper respiratory tract infection, urinary tract infection, lymphocytopenia, neoplasia, depression, hypertension and rash were poorly reported. This may be related to the rarity of these events, and, if they occur, they will probably be detected in long-term studies. Additionally, when meta-analysing results, one cannot infer that the omission of a report means a report of null prevalence, which precludes the conduction of more robust meta-analyses including more comparisons. However, it is paramount to precisely estimate the incidence of specific adverse events in RRMS, because some particular populations have an increased risk of developing some adverse events (Clerico et al., 2017; Coles et al., 2017; Croteau et al., 2018; DTB, 2018; Hellwig, 2011; McGinley; Cohen, 2017).

The inspection of the geometry of the networks showed that we found lower values than the reported in the literature for other NMAs, when concerning the median number of studies per edge, number of nodes and edges, thickness, common comparator and strong edges. These results suggest weakly connected networks with a limited amount of direct evidence. Therefore, the data should be interpreted with caution. Despite of the high number of safety outcomes, they were not reported in a standardized manner throughout the studies, which precluded the construction of a precise network with a high number of studies, resulting, instead, in several less robust small networks. Tonin et al. have conducted systematic review of NMAs of pharmacological interventions, where they identified higher median of studies (22), nodes (8), edges (10), thickness (2.0), common comparator (68%), and strong edge (53%) (Tonin et al., 2019).

It is important to observe that although inconsistency (node-split) analyses have shown consistency (i.e., coherence) for four outcomes, clinical aspects cannot be overlooked (e.g., it is not reliable to affirm that IFNA30 is safer than placebo for serious adverse events). Thus, consistency in node-split should be interpreted with caution. Additionally, inconsistency analyses were not possible for most of the safety outcomes.

Considering the limitations of clinical trials in identifying some adverse events, mainly because of study duration, inclusion of patients without comorbidities or reduced statistical power, one can expect that observational studies may significantly contribute to this outcome. Observational studies were considered essential to monitor safety outcomes (Baudart et al., 2016) by facilitating the identification of adverse events in the real world. However, many observational RRMS studies are not comparative studies, and therefore cannot be included in the systematic review with NMAs. Hence, only three outcomes could be summarised in small meta-analyses (i.e., any adverse event, discontinuation due to adverse event and influenza-like illness).

Taking into account that certain drugs have the potential to cause serious adverse events, a safety outcome trial was defined by the US Food and Drug Administration as a ‘prospective, randomised, controlled trial that is specifically designed and adequately powered to test a safety hypothesis, prior to approval of certain drugs’ (CDER, 2016). However, we did not identify any study fulfilling these criteria, even though DMTs may have worrisome safety profiles. In part, the absence of safety outcome trials can be justified by the variability among the adverse events caused by DMTs in RRMS, which contributes to the lack of a common safety outcome set. Therefore, to allow a comprehensive comparison of safety among the DMTs, future studies should monitor and report critical adverse events described in previous studies of other drugs used for the same disease.

Some limitations of our study should be mentioned. As in any systematic search, the chance of missing studies exists. However, the manual searches found no additional studies, reinforcing the quality of our search. Due to the variability in the safety outcomes reported, we could not conduct meta-analyses for all the safety outcomes identified.

In conclusion, safety outcomes are poorly reported in primary studies of DMTs in RRMS, precluding the conduction of robust meta-analyses. Therefore, the current available data on safety of these drugs

Table 3
Comparison for DAE and SAE in clinical trials - risk ratio (95% CrI).

GA20	3.358 (1.447, 8.963)	2.589 (0.609, 13.701)	0.896 (0.621, 1.307)	1.110 (0.272, 5.948)	1.078 (0.745, 1.561)	1.390 (0.568, 3.364)	1.296 (0.813, 2.050)	1.004 (0.591, 1.733)	2.909 (0.785, 14.061)	0.990 (0.463, 2.200)	1.282 (0.689, 2.444)	1.593 (0.399, 8.064)
0.890 (0.576, 1.385)	PIFN	0.755 (0.144, 4.661)	0.266 (0.106, 0.573)	0.324 (0.065, 2.033)	0.319 (0.125, 0.716)	0.409 (0.123, 1.262)	0.383 (0.149, 0.865)	0.296 (0.111, 0.708)	0.844 (0.183, 5.018)	0.292 (0.088, 0.914)	0.379 (0.138, 0.962)	0.464 (0.095, 2.794)
	1.393 (1.005, 1.939)	GA40	0.347 (0.069, 1.394)	0.434 (0.196, 0.954)	0.420 (0.082, 1.745)	0.544 (0.088, 2.642)	0.494 (0.098, 2.050)	0.389 (0.073, 1.635)	1.131 (0.640, 2.025)	0.381 (0.063, 1.980)	0.497 (0.092, 2.185)	0.622 (0.300, 1.294)
1.237 (0.934, 1.668)			PLA	1.227 (0.318, 6.457)	1.203 (0.931, 1.562)	1.543 (0.715, 3.485)	1.441 (1.094, 1.893)	1.118 (0.753, 1.674)	3.217 (0.942, 15.267)	1.100 (0.497, 2.580)	1.427 (0.885, 2.396)	1.763 (0.467, 8.541)
				ALE	0.977 (0.183, 3.885)	1.234 (0.206, 6.038)	1.159 (0.220, 4.742)	0.906 (0.163, 3.656)	2.599 (1.501, 4.660)	0.885 (0.144, 4.522)	1.156 (0.210, 4.843)	1.435 (0.694, 2.984)
1.009 (0.751, 1.367)	1.133 (0.774, 1.672)		0.815 (0.667, 1.005)		BG	1.282 (0.567, 2.978)	1.199 (0.826, 1.754)	0.928 (0.582, 1.505)	2.690 (0.739, 12.840)	0.911 (0.411, 2.163)	1.187 (0.685, 2.117)	1.482 (0.375, 7.396)
1.551 (0.906, 2.712)	1.739 (0.997, 3.126)		1.250 (0.791, 2.041)		1.539 (0.925, 2.581)	CLA	0.931 (0.396, 2.123)	0.724 (0.292, 1.739)	2.110 (0.476, 11.380)	0.713 (0.230, 2.273)	0.928 (0.355, 2.353)	1.155 (0.240, 6.832)
1.119 (0.775, 1.642)	1.260 (0.836, 1.906)		0.905 (0.711, 1.152)		1.111 (0.803, 1.520)	0.724 (0.420, 1.211)	FING	0.775 (0.509, 1.179)	2.237 (0.631, 10.718)	0.763 (0.330, 1.825)	0.995 (0.581, 1.750)	1.234 (0.318, 6.140)
0.821 (0.536, 1.273)	0.923 (0.581, 1.464)		0.663 (0.477, 0.922)		0.814 (0.549, 1.197)	0.529 (0.299, 0.934)	0.733 (0.516, 1.044)	IFNA30	2.895 (0.800, 14.054)	0.987 (0.430, 2.357)	1.277 (0.693, 2.427)	1.595 (0.398, 7.971)
									IFNA44	0.336 (0.064, 1.538)	0.441 (0.088, 1.721)	0.550 (0.346, 0.846)
0.868 (0.645, 1.190)	0.979 (0.574, 1.666)		0.702 (0.459, 1.068)		0.862 (0.566, 1.316)	0.561 (0.299, 1.036)	0.775 (0.480, 1.262)	1.059 (0.614, 1.802)		IFNB250	1.302 (0.489, 3.361)	1.642 (0.335, 9.103)
0.970 (0.661, 1.441)	1.093 (0.719, 1.663)		0.785 (0.610, 1.025)		0.962 (0.699, 1.354)	0.627 (0.366, 1.065)	0.866 (0.614, 1.242)	1.180 (0.785, 1.814)		1.120 (0.678, 1.846)	NAT	1.238 (0.294, 6.310)
												OCRE

DAE: discontinuation due to adverse events (upper); SAE: serious adverse events (bottom); Interpretation: right therapy compared to left therapy, for example, PIFN is less safe than GA20 with an RR of 3.358 (95% CrI: 1.447; 8.963) (DAE, upper) and RR of 1.393 (95% CrI: 1.005; 1.939) (SAE, bottom). GA20: glatiramer acetate, 20 mg per day; PIFN: peginterferon; GA40: glatiramer acetate, 40 mg three times a week; PLA: placebo; ALE: alemtuzumab; BG: dimethyl fumarate; CLA: cladribine; FING: fingolimod; IFNA30: interferon 1a beta, 30 μg every week; IFNA44: interferon 1a beta 44 μg three times a week; IFNB250: interferon 1b beta, 250 μg, every other day; NAT: natalizumab; OCRE: ocrelizumab.

may not be sufficiently contributing to regulatory and evidence-based clinical decision making, as adverse events are not being given the same importance as efficacy outcomes. To overcome this issue, researchers should ensure that all studies declare the prevalence of adverse events, including the null prevalence of critical safety outcomes, reported for drugs used for the same condition. Furthermore, comparative observational studies should be conducted to allow long-term comparison of effectiveness and safety between drugs. Finally, safety outcomes trials for DMTs for RRMS should be required by regulatory authorities.

The manuscript does not contain clinical studies or patient data.

Conflicts of interest

Rosa Lucchetta reports personal fees from Biogen and Roche; and Jefferson Becker reports grants and personal fees from Biogen, Novartis, Roche and Teva and personal fees from Bayer, Ipsen, Merck Serono, Sanofi, outside the submitted work. Letícia Leonart, Roberto Pontarolo, Fernando Fernandez-Llimós and Astrid Wiens declare that they have no conflict of interest.

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Supplementary materials

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