Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Efficacy classification of modern therapies in multiple sclerosis

Imtiaz A Samjoo[1], Evelyn Worthington[1], Christopher Drudge[1], Melody Zhao[1], Chris Cameron*[,2], Dieter A Häring[3], Dee Stoneman[3], Luisa Klotz[4] & Nicholas Adlard[3]

[1]EVERSANA™, Burlington, ON, Canada
[2]EVERSANA™, Sydney, NS, Canada
[3]Novartis Pharma AG, Basel, Switzerland
[4]Department of Neurology, University Hospital Münster, Westfälische-Wilhelms-University Münster, Münster, Germany
*Author for correspondence: chris.cameron@eversana.com

Background: The Association of British Neurologists (ABN) 2015 guidelines suggested classifying multiple sclerosis therapies according to their average relapse reduction. We sought to classify newer therapies (cladribine, ocrelizumab, ofatumumab, ozanimod) based on these guidelines. **Materials & methods:** Therapies were classified by using direct comparative trial results as per ABN guidelines and generating classification probabilities for each therapy based on comparisons versus placebo in a network meta-analysis for annualized relapse rate. **Results:** For both approaches, cladribine and ofatumumab were classified as high efficacy. Ocrelizumab and ozanimod (1.0 mg) were classified as moderate or high efficacy depending on the approach used. **Conclusion:** Cladribine and ofatumumab have an efficacy comparable with therapies classified in the ABN guidelines as high efficacy.

First draft submitted: 1 December 2020; Accepted for publication: 5 February 2021; Published online: 23 February 2021

Keywords: cladribine • disease-modifying therapy • network meta-analysis • ocrelizumab • ofatumumab • ozanimod • relapsing multiple sclerosis • treatment guidelines

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system that is characterized by inflammation, demyelination and degenerative changes, including neuroaxonal loss and progressive atrophy [1]. The exact etiology of MS is not well understood, although several genetic and environmental risk factors have been identified [1]. Four MS phenotypes exist: clinically isolated syndrome, relapsing–remitting (RRMS), secondary progressive and primary progressive [2]. The term relapsing MS (RMS) has been used to describe both RRMS and secondary progressive patients with superimposed relapses [3]. There are many disease-modifying therapies (DMTs) indicated for patients with RMS/RRMS, the earliest of which was IFN-β-1b. Most MS therapies target various immune cells involved in the inflammatory cascade. Overall, DMTs are more efficacious in the earlier stages of RRMS and decrease in effectiveness as the disease progresses [4].

Decisions regarding the optimal DMTs for patients with RMS/RRMS are informed by numerous factors including the level of disease activity and other patient characteristics, the relative efficacy, tolerability and safety of therapies, and the likelihood of adherence and access to therapies. Several guidelines covering the use of DMTs for patients with RMS/RRMS have recently been published, including those from the American Academy of Neurology (AAN) [5], the Association of British Neurologists (ABN) [6], the Brazilian Academy of Neurology working jointly with the Brazilian Committee on Treatment and Research in Multiple Sclerosis (BAN/BCTRIMS) [7] and the European Committee of Treatment and Research in Multiple Sclerosis working jointly with the European Academy of Neurology (ECTRIMS/EAN) [8]. Of these four guidelines, only the ABN and BAN/BCTRIMS guidelines proposed approaches to classifying DMTs based on their efficacy to help inform treatment decisions. Instead of broadly classifying DMTs, the guidelines from the AAN and ECTRIMS/EAN identified specific therapies as being more efficacious than others. The AAN guidelines included conclusions regarding the superiority of individual DMTs compared with placebo or other DMTs based on outcomes such as annualized relapse rate (ARR) that were

Future Medicine

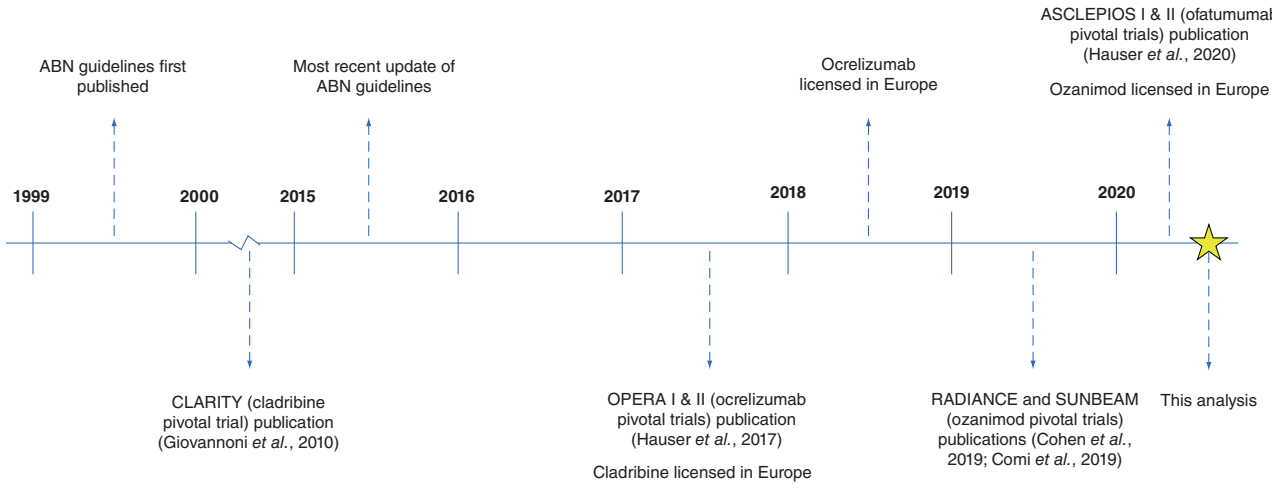

Figure 1. Timeline of Association of British Neurologists guidelines and recent multiple sclerosis therapies.
ABN: Association of British Neurologists.

measured in clinical trials. The ECTRIMS/EAN guidelines identified interferon and glatiramer acetate as relatively less efficacious therapies but recommended selecting among the many available DMTs based on factors such as patient characteristics and comorbidities, disease severity and the safety profile and accessibility of each therapy.

The ABN first published guidelines on the use of MS DMTs in 1999, and these were most recently updated in 2015 [6]. The 2015 iteration of the ABN guidelines included seven DMTs: alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β preparations, natalizumab and teriflunomide [6]. The ABN guidelines suggested dividing these seven therapies into two broad classes: high efficacy, defined as average relapse reduction substantially more than 50% (alemtuzumab and natalizumab) and moderate efficacy, defined as average relapse reduction between 30 and 50% (dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β preparations and teriflunomide) [6]. Similar to the ABN guidelines, the BAN/BCTRIMS guidelines mentioned two groups of DMTs, those associated with a moderate reduction in the ARR in comparison to placebo (around 30%) and those of higher potency (associated with a reduction greater than 50% in the ARR, usually compared with placebo) [7]. Since the publication of these 2015 guidelines, several newer DMTs have been approved for the treatment of MS, including cladribine, ocrelizumab, ofatumumab and ozanimod, that have not yet been classified in this manner (Figure 1).

Cladribine is a purine antimetabolite that was evaluated in a Phase III randomized controlled trial (RCT), CLARITY (NCT00213135) [9]. The CLARITY trial investigated oral (PO) cladribine (3.5 or 5.25 mg/kg cumulative dose) versus placebo in patients with RRMS. This trial met its primary end point: ARR was significantly lower in cladribine-treated patients compared with patients who received placebo (0.14 and 0.15 for the 3.5 and 5.25 mg/kg doses, respectively, vs 0.33; both $p < 0.001$).

Ocrelizumab is a humanized monoclonal anti-CD20 antibody that was evaluated in two identically designed Phase III RCTs, OPERA I (NCT01247324) and OPERA II (NCT01412333) [10]. The OPERA trials investigated intravenous ocrelizumab 600 mg versus subcutaneous (SC) IFN-β-1a 44 µg in patients with RMS. Both OPERA I and II met their primary end point: ARR was significantly lower in ocrelizumab-treated patients compared with patients treated with IFN-β-1a (OPERA I: 0.16 vs 0.29; OPERA II: 0.16 vs 0.29; both $p < 0.001$).

Ofatumumab is a human monoclonal anti-CD20 antibody that was evaluated in two identically designed Phase III RCTs, ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231) [11]. The ASCLEPIOS trials investigated SC ofatumumab 20 mg versus PO teriflunomide 14 mg in patients with RMS. Both ASCLEPIOS I and II met their primary end point: ARR was significantly lower in ofatumumab-treated patients compared with patients treated with teriflunomide (ASCLEPIOS I: 0.11 vs 0.22; ASCLEPIOS II: 0.10 vs 0.25; both $p < 0.001$) [11].

Ozanimod is an S1P1 modulator that was evaluated in two Phase III RCTs, RADIANCE (NCT02047734) [12] and SUNBEAM (NCT02294058) [13]. The RADIANCE and SUNBEAM trials investigated PO ozanimod (0.5 or 1.0 mg) versus intramuscular (IM) IFN-β-1a 30 µg. Both trials met their primary end point: ARR was significantly

lower in ozanimod-treated patients compared with patients treated with IFN-β-1a (RADIANCE: 0.22 and 0.17 for the 0.5 and 1.0 mg doses, respectively, vs 0.28; SUNBEAM: 0.24 and 0.18 for the 0.5 and 1.0 mg doses, respectively, vs 0.35; $p < 0{\cdot}0167$ for RADIANCE ozanimod 0.5 mg vs IFN-β-1a and $p < 0{\cdot}0013$ for SUNBEAM ozanimod 0.5 mg vs IFN-β-1a but $p < 0.001$ for both ozanimod 1.0 mg comparisons) [12,13].

When the ABN guidelines were released, all high-efficacy DMTs in MS (i.e., alemtuzumab and natalizumab) were intravenously administered monoclonal antibody therapies. Safety concerns associated with alemtuzumab and/or natalizumab include serious infusion reactions or acute hypersensitivity reactions even under supervision and premedication, serious or opportunistic infections and organ-specific toxicities. Accordingly, based on their risk–benefit ratio it was recommended that the high-efficacy DMTs be reserved for use later in the disease course [4,6]. However, recent evidence suggests early treatment with high-efficacy therapies may lead to improved disease control [14,15]. The efficacy-based classification of newer DMTs not yet included in the ABN guidelines is expected to improve the ability of patients and clinicians to select treatment options that optimize patient care [16].

The aim of this study was to classify contemporary DMTs based on their efficacy in accordance with the guidelines set by the ABN. In addition to a direct comparative approach that closely followed the ABN guidelines, we employed an additional classification approach that used a network meta-analysis (NMA) to incorporate both direct and indirect comparative evidence to estimate DMT efficacy relative to a common comparator, placebo.

Materials & methods

Identification & selection of relevant trials

A systematic literature review (SLR) was conducted in December 2019 and employed a robust methodology for identification of evidence as recommended by the National Institute of Health and Care Excellence (NICE) [17]. Implementation and reporting of the systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. The aim of the review was to identify all RCTs assessing the efficacy and safety of DMTs used for the treatment of patients with RMS. Briefly, a search of databases (including Embase, MEDLINE and Cochrane), neurology/MS conference abstracts (2017–2019), health technology assessment websites and clinical trials registries was conducted in December 2019. Two reviewers independently screened titles and abstracts against eligibility criteria and then evaluated potentially eligible articles in full-text form using the same criteria, with disagreements resolved by a third independent reviewer. Eligible trials for this study were RCTs with a duration of at least 48 weeks involving adult patients with relapsing forms of MS (excluding trials wherein >25% of patients had non-relapsing forms of MS). Trials were only included if one of their objectives was to directly compare the efficacy of any of a list of interventions (alemtuzumab, cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer acetate, IFN-β-1a, IFN-β-1b, natalizumab, ocrelizumab, ofatumumab, ozanimod, peginterferon β-1a and teriflunomide) to any other included DMT or placebo. Only licensed (by the US FDA and/or EMA) and clinically relevant regimens of these DMTs were considered. Full details of the SLR search strategy have been described previously [19].

Classification of DMTs

According to the 2015 ABN guidelines, DMTs can be divided into two broad classes: drugs of high efficacy, defined as average relapse reduction substantially more than 50% and drugs of moderate efficacy, defined as average relapse reduction between 30 and 50% [6]. This classification approach was based on between-trial comparisons made using direct comparative results reported by pivotal RCTs. Because the meaning of 'substantially' was not clearly stated in the guidelines and so was subjective, we used a 50% threshold to define the high-efficacy class. Regardless of how the classes were defined, we expected there to be a gradation in efficacy within the class groupings.

In the present analysis, we employed two approaches to classify DMTs. The first approach closely followed the ABN guidelines, which grouped DMTs based on direct comparative results reported by RCTs for relapse reduction [6]. Because of the lack of reporting details (e.g., how average relapse reduction was calculated) in the guidelines, we developed our own definition for average relapse reduction. Specifically, for each DMT we qualitatively considered the relative reduction in relapse risk (DMT vs comparator) using the outcome of ARR as reported by RCTs included in the evidence base. We classified a DMT as high efficacy if the relative reduction in relapse risk was ≥50% for all trials reporting a comparison for the therapy.

The second approach was to group DMTs based on their rate ratio (RR) versus placebo as derived from an NMA with ARR as the outcome. An RR ≤0.5 corresponded to high efficacy and an RR >0.5 and ≤0.7 corresponded to moderate efficacy. In addition to these two classes, a 'modest efficacy' class was defined as average relapse reduction

<30% or RR >0.7. The probability that a DMT was high efficacy, moderate efficacy or modest efficacy was based on the RR versus placebo value generated for each iteration of the NMA for the outcome of ARR. The sum of these probabilities was 100% for each DMT. Each DMT was assigned the efficacy class for which it had the greatest probability in the NMA. The use of NMA allowed us to incorporate both direct and indirect comparative evidence and estimate DMT efficacy relative to a common comparator, placebo. We selected placebo as the comparator to obtain a relative reduction in relapse risk value for each DMT, which was the measure used to classify therapies in the ABN guidelines.

We selected ARR as the efficacy outcome of interest for this study because it was the primary outcome of most Phase III clinical trials in RMS including the CLARITY cladribine trial, the OPERA I and II ocrelizumab trials, the ASCLEPIOS I and II ofatumumab trials and the RADIANCE and SUNBEAM ozanimod trials. Other outcomes were not considered for the efficacy classification of DMTs because the ABN guidelines classified therapies based solely on relapse reduction and the NMA-based classification approach used in this study was not feasible for outcomes such as time to confirmed disability progression that are reported as relative values between DMTs.

Network meta-analysis

Methods of indirect treatment comparison such as NMA permit the comparison of DMTs not directly evaluated in an RCT, provided the therapies can be linked via a network of direct comparisons made in RCTs. For example, a DMT for which only RCTs comparing it to an active comparator are available can be indirectly compared with placebo if that active comparator was compared with placebo in one or more other RCTs included in the analysis.

In accordance with published recommendations regarding the evaluation of NMA feasibility [20–22], a rigorous qualitative assessment of between-trial clinical heterogeneity was conducted based on trial design, patient eligibility criteria, baseline patient characteristics, placebo response and trial-specific outcome definitions. We previously reported an NMA feasibility assessment for a similar evidence base, which included a detailed comparison of patient eligibility criteria and baseline characteristics [19]. Although we noted between-trial heterogeneity in some baseline patient characteristics and placebo arm ARR outcome values in our assessment, these differences did not preclude an NMA. This conclusion aligns with recently published NMAs that used an evidence base similar to this study and conducted sensitivity analyses showing this heterogeneity did not appreciably impact NMA results [19,23–26]. We previously found that older trials (1987–2003) were more likely to have elevated placebo-arm (i.e., baseline risk) relapse rates, which likely reflects changes in MS natural history and improving diagnostic criteria and standard of care over time. However, excluding these older trials as a sensitivity analysis did not appreciably change the results of the ARR NMA [19]. Although heterogeneity in an NMA can be accounted for with meta-regression, this method was not considered appropriate given the limited number of trials connecting treatments in the network. Nevertheless, to further investigate the influence of clinical heterogeneity between trials, we conducted a baseline risk adjusted NMA. This analysis permitted us to control for between-trial differences in baseline risk (i.e., placebo-arm relapse rates), which are known to reflect potentially important differences in measured and unmeasured confounders across trials. As such, we were able to adjust for multiple cross-trial differences. A forest plot summarizing the results of this NMA is provided in Appendix A of the Supplementary Materials. The results of the baseline risk adjusted NMA closely aligned with the NMA we used to classify DMTs, supporting our assertion that imbalances in baseline patient characteristics did not preclude an NMA. Accounting for heterogeneity by conducting sensitivity analyses in which trials with a divergent value for a baseline patient characteristic were excluded was not considered appropriate because this exclusion would be based on arbitrary thresholds and so would introduce uncertainty in the resultant indirect effect estimates.

The ARR NMA was performed using standard Bayesian approaches based on the Markov Chain Monte Carlo simulation as described in the NICE Evidence Synthesis Decision Support Unit Technical Support Document series [27]. The NMA used a random effects model because it makes less stringent assumptions about the consistency of effects [28]. A Poisson model was used with vague priors for treatment effects and between-trial variances. Inputs for the model were ARR (mean), trial duration and patient number. For each study, trial duration was extracted in weeks; where only the number of months or years was reported by a study, it was assumed that 1 year = 52 weeks and 12 months = 1 year. The analysis was conducted using R version 3.6.1, Just Another Gibbs Sampler (JAGS) version 4.3.0 and WinBUGS version 1.4.3, and was based on burn-in and sampling durations of 60,000 iterations each. To assess whether the model had adequate fit to the data, we compared the posterior mean of the residual deviance from the NMA to the corresponding number of unconstrained data points (approximately equal if the

fit is adequate), as well as the deviance information criterion. The Brooks-Gelman-Rubin statistic was assessed to ensure that convergence was reached [29].

Results

Literature search & trial selection

Briefly, 36 RCTs were identified based on an SLR. Four of these RCTs were excluded from our analysis. The ASSESS trial (fingolimod 0.5 mg vs glatiramer acetate 20 mg) was excluded because the data were from a conference proceeding and were therefore insufficient for inclusion in the analysis [30]. The ADVANCE trial (pegylated IFN-β-1a 125 μg vs placebo) [31] and INCOMIN trial (IFN-β-1a IM 30 μg vs IFN-β-1b SC 250 μg) [32] were excluded because their results were not reflective of clinical practice. Specifically, the ADVANCE trial was excluded because the NICE committee determined this trial to be an outlier and disregarded its impact in the technology appraisal guidance for ocrelizumab [33]. Unlike other head-to-head IFN trials, INCOMIN reported significantly different efficacy results between interferon therapies [34]. Finally, one trial was excluded as it was a noninferiority trial comparing different formulations of glatiramer acetate 20 mg [35]. The list of 32 included RCTs is provided in Table 1. Full search and selection details, quality assessment, feasibility assessment and discussion of the included trials (with the exception of ozanimod trials) have been reported previously [19].

Classification of DMTs

Eighteen DMTs were classified in this study. For the first classification approach (i.e., aligning with the approach described in the ABN guidelines), the relative reduction in relapse risk for each DMT based on ARR values reported by included RCTs is provided in Table 1. Of the 41 comparisons, 19 (46%) were versus placebo, 19 (46%) were versus an IFN-β preparation and 3 (7%) were versus teriflunomide 14 mg. Except for the placebo-controlled cladribine CLARITY trial, all RCTs for the newer DMTs (ocrelizumab, ofatumumab and ozanimod) used an active comparator. Based on the approach described in the ABN guidelines, the high-efficacy class included alemtuzumab, cladribine (both doses), natalizumab and ofatumumab; and the moderate efficacy class included dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β preparations, ocrelizumab, ozanimod (both doses) and teriflunomide.

For the second classification approach (i.e., deriving classification probabilities from an ARR NMA), the RR versus placebo values for each DMT from the ARR NMA are provided in Figure 2. Relative to placebo, ofatumumab reduced relapse rate by 70%, ocrelizumab by 67%, cladribine by 58% (3.5 mg/kg) or 55% (5.25 mg/kg) and ozanimod by 55% (1.0 mg) or 41% (0.5 mg). The probabilities of each DMT being classified as high efficacy, moderate efficacy and modest efficacy are presented in Figure 3. The probabilities that alemtuzumab, cladribine 3.5 and 5.25 mg/kg, fingolimod, natalizumab, ocrelizumab, ofatumumab and ozanimod 1.0 mg were high-efficacy therapies were ≥50% and were ≥99% for alemtuzumab, natalizumab, ocrelizumab and ofatumumab. The probabilities that dimethyl fumarate, glatiramer acetate 20 and 40 mg, IFN-β-1a SC 22 and 44 μg, IFN-β-1b SC, ozanimod 0.5 mg, teriflunomide 14 mg were moderate-efficacy therapies were ≥50%. Finally, the probabilities that IFN-β-1a IM and teriflunomide 7 mg were modest-efficacy therapies were ≥50%.

Discussion

The 2015 update to the ABN guidelines divided licensed DMTs for MS into two broad classes (drugs of high efficacy and drugs of moderate efficacy) based on average relapse reduction. To our knowledge, this classification has not been revised since the 2015 guideline update. Newer therapies have since been introduced, including cladribine, ocrelizumab, ofatumumab and ozanimod. Furthermore, the direct comparative approach described in the ABN guidelines does not account for the use of different comparators (active or placebo) across the trials included in the evidence base. In the present study, classification of these newer DMTs was estimated in the context of the ABN guidelines using two approaches: using direct comparative ARR results from RCTs as per the guidelines, and using classification probabilities based on the RR versus placebo for ARR in a Bayesian NMA. The latter approach allows for more consistent classification because it leverages both direct and indirect comparative evidence to compare all therapies in the evidence base to a common comparator, placebo. Although the NMA-based approach used DMT versus placebo effect estimates to align with the ABN guidelines, future classification approaches could focus on comparisons with alemtuzumab and natalizumab, the two therapies identified in the guidelines as high efficacy. Therapies classified in the 2015 ABN guidelines as high efficacy (alemtuzumab and natalizumab) and moderate efficacy (dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β preparations and teriflunomide), remained as

Table 1. Relapse rate reduction values reported by randomized controlled trials included in this study.

Intervention	Comparator	Trial name	Relative reduction in relapse risk (vs comparator)†	Ref.
Alemtuzumab 12 mg	IFN-β-1a SC 44 μg	CAMMS223	69%	[36]
Alemtuzumab 12 mg	IFN-β-1a SC 44 μg	CARE-MS I	54%	[37]
Alemtuzumab 12 mg	IFN-β-1a SC 44 μg	CARE-MS II	50%	[38]
Cladribine 3.5 mg/kg	Placebo	CLARITY	58%	[9]
Cladribine 5.25 mg/kg	Placebo	CLARITY	55%	[9]
Dimethyl fumarate 240 mg BID	Placebo	CONFIRM	44%	[39]
Dimethyl fumarate 240 mg BID	Placebo	DEFINE	53%	[40]
Fingolimod 0.5 mg	Placebo	FREEDOMS	55%	[41]
Fingolimod 0.5 mg	Placebo	FREEDOMS II	48%	[42]
Fingolimod 0.5 mg	IFN-β-1a IM 30 μg	TRANSFORMS	52%	[43]
Glatiramer acetate 20 mg	IFN-β-1b SC 250 μg	BEYOND	6%	[44]
Glatiramer acetate 20 mg	Placebo	Bornstein *et al.* (1987)	78% ‡	[45]
Glatiramer acetate 20 mg	IFN-β-1a IM 30 μg	Calabrese *et al.* (2012)	0%	[46]
Glatiramer acetate 20 mg	IFN-β-1a IM 30 μg	CombiRx	31%	[47]
Glatiramer acetate 20 mg	Placebo	CONFIRM	29%	[39]
Glatiramer acetate 20 mg	Placebo	Copolymer 1 MS trial	30%	[48]
Glatiramer acetate 20 mg	IFN-β-1a SC 44 μg	REGARD	3%	[49]
Glatiramer acetate 40 mg	Placebo	GALA	34%	[50]
IFN-β-1a IM 30 μg	Placebo	BRAVO	24%	[51]
IFN-β-1a IM 30 μg	Placebo	MSCRG	18%	[52]
IFN-β-1a IM 30 μg	IFN-β-1b SC 250 μg	Stepien *et al.* (2013)	19%	[53]
IFN-β-1a SC 22 μg	Placebo	PRISMS	29% ‡	[54]
IFN-β-1a SC 44 μg	IFN-β-1a IM 30 μg	Calabrese *et al.* (2012)	20%	[46]
IFN-β-1a SC 44 μg	IFN-β-1a IM 30 μg	EVIDENCE	16%	[55]
IFN-β-1a SC 44 μg	Placebo	PRISMS	32% ‡	[54]
IFN-β-1b SC 250 μg	Placebo	IFNB MS	34%	[56]
Natalizumab 300 mg	Placebo	AFFIRM	68%	[57]
Ocrelizumab 600 mg	IFN-β-1a SC 44 μg	OPERA I	47%	[10]
Ocrelizumab 600 mg	IFN-β-1a SC 44 μg	OPERA II	47%	[10]
Ofatumumab 20 mg	Teriflunomide 14 mg	ASCLEPIOS I	50%	[11]
Ofatumumab 20 mg	Teriflunomide 14 mg	ASCLEPIOS II	60%	[11]
Ozanimod 0.5 mg	IFN-β-1a IM 30 μg	RADIANCE	21%	[12]
Ozanimod 0.5 mg	IFN-β-1a IM 30 μg	SUNBEAM	31%	[13]
Ozanimod 1.0 mg	IFN-β-1a IM 30 μg	RADIANCE	39%	[12]
Ozanimod 1.0 mg	IFN-β-1a IM 30 μg	SUNBEAM	49%	[13]
Teriflunomide 7 mg	Placebo	TEMSO	31%	[58]
Teriflunomide 7 mg	IFN-β-1a SC 44 μg	TENERE	-86%	[59]
Teriflunomide 7 mg	Placebo	TOWER	22%	[60]
Teriflunomide 14 mg	Placebo	TEMSO	32%	[58]
Teriflunomide 14 mg	IFN-β-1a SC 44 μg	TENERE	-18%	[59]
Teriflunomide 14 mg	Placebo	TOWER	36%	[60]

†Relative reduction in relapse risk calculated using ARR values reported by treatment arm.
‡ARR values calculated using reported number of relapses per patient over a specified time period.
ARR: Annualized relapse rate; BID: Twice a day; IFN: Interferon; IM: Intramuscular; RCT: Randomized controlled trial; SC: Subcutaneous.

such according to the direct comparative approach, but fingolimod was classified as high efficacy according to the NMA-based approach.

In the CLARITY trial, the relative reductions in relapse risk for cladribine 3.5 mg/kg and cladribine 5.25 mg/kg versus placebo were 58 and 55%, respectively. In the ASCLEPIOS I and ASCLEPIOS II trials, the relative reductions in relapse risk for ofatumumab versus teriflunomide were 50 and 60%, respectively. We therefore classified cladribine

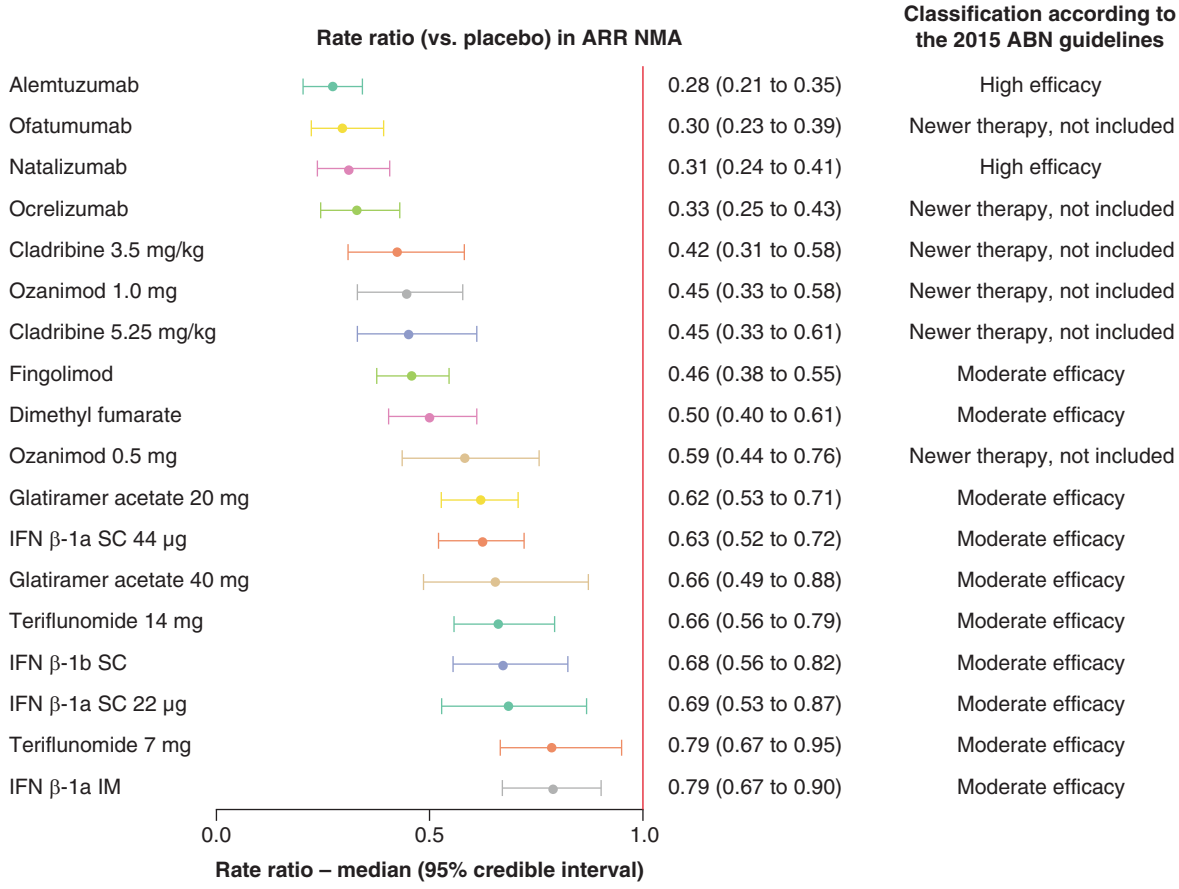

Figure 2. Annualized relapse rate network meta-analysis forest plot (versus placebo) with efficacy class for each disease-modifying therapies (2015 Association of British Neurologists guidelines). Rate ratios from the ARR NMA may not directly align with the relapse rate reduction values used by the ABN to group the DMTs. The ABN guidelines were published in 2015, so the NMA estimates were informed by additional more recently published trials.
ABN: Association of British Neurologists; ARR: annualized relapse rate; DMT: Disease-modifying therapy; IFN: Interferon; IM: Intramuscular; NMA: Network meta-analysis; SC: Subcutaneous.

(3.5 and 5.25 mg/kg doses) and ofatumumab as high efficacy based on the direct comparative approach described in the ABN guidelines. According to the ARR NMA-based approach, these DMTs had the greatest probability of being classified as high efficacy. Collectively, these results suggest that the ABN guidelines should be updated to expand the high efficacy class to include cladribine and ofatumumab.

In the OPERA I and OPERA II trials, the relative reduction in relapse risk for ocrelizumab versus IFN-β-1a was 47%. In the RADIANCE trial, the relative reductions in relapse risk for ozanimod 0.5 mg and ozanimod 1.0 mg versus IFN-β-1a were 21 and 39%, respectively. In the SUNBEAM trial, the relative reductions in relapse risk for ozanimod 0.5 mg and ozanimod 1.0 mg versus IFN-β-1a were 31 and 49%, respectively. We classified ocrelizumab and ozanimod 1.0 mg as moderate efficacy based on the direct comparative approach described in the ABN guidelines. However, according to the ARR NMA-based classification approach, these DMTs, along with another therapy classified as moderate efficacy in the ABN guidelines (fingolimod) [6], had the greatest probability of being classified as high efficacy. The ABN guidelines noted that fingolimod and dimethyl fumarate were particularly efficacious among moderate-efficacy DMTs [6], which was reflected in their higher probabilities of high efficacy classification compared with other therapies previously classified by the ABN as moderate efficacy. Taken together, the results of the two classification approaches suggest that the ABN guidelines could either be updated to expand the high efficacy class to include fingolimod, ocrelizumab and ozanimod 1.0 mg, or these DMTs could together be considered as a particularly efficacious subgroup of the moderate efficacy class. We classified ozanimod 0.5 mg

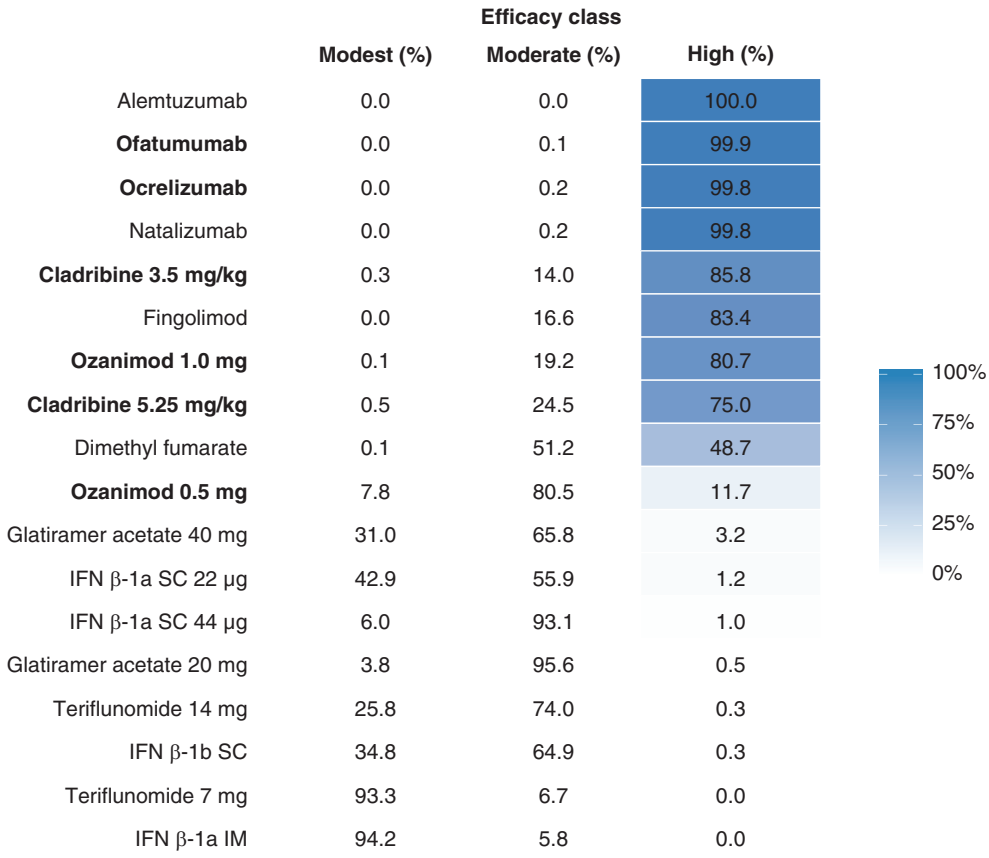

Figure 3. Heatmap of efficacy class probabilities for each disease-modifying therapies as derived from the annualized relapse rate network meta-analysis. The heatmap reports the probability that a DMT was classified as high, moderate, or modest efficacy, based on the many iterations of the NMA that were run as part of this analysis. The DMTs are ordered by high-efficacy class probability. Newer DMTs not included in the 2015 ABN guidelines are in bold.
ABN: Association of British Neurologists; ARR: Annualized relapse rate; DMT: Disease-modifying therapy; IFN: Interferon; IM: Intramuscular; NMA: Network meta-analysis; SC: Subcutaneous.

as moderate efficacy according to both the direct comparative approach described in the ABN guidelines and the ARR NMA-based approach.

Similar to the ABN guidelines, the BAN/BCTRIMS guidelines mentioned two groups of DMTs, those associated with a moderate reduction in ARR in comparison to placebo (around 30%) and those of higher potency (associated with a reduction greater than 50% in ARR, usually compared with placebo) [7]. Higher potency DMTs, which were identified as being appropriate for patients with highly active RMS, were alemtuzumab, cladribine, fingolimod, natalizumab and ocrelizumab (ofatumumab and ozanimod were not included in the guidelines because Phase III trial results were not yet released) [7]. This higher potency DMT class closely aligns with the group of therapies we identified using the ARR NMA-based approach as having the greatest probability of being classified as high efficacy.

Lucchetta *et al.* conducted NMAs to evaluate the efficacy of traditional DMTs with more recently developed therapies in adults with RRMS, prior to the release of Phase III trial results for ofatumumab and ozanimod [24]. Similar to the NMA-based classification results reported here, Lucchetta *et al.* determined that alemtuzumab, natalizumab and ocrelizumab had the highest efficacy for ARR in the treatment of RRMS, with each having a probability >80% of being the most effective therapy [24]. Although the ABN guidelines only grouped DMTs into moderate or high efficacy, Lucchetta *et al.* also identified a low-efficacy group, which included glatiramer acetate, IFN-β-1a, IFN-β-1b, peginterferon, and teriflunomide [24]. The results of the NMA-based classification reported

in the present study were similar to Lucchetta *et al.* and suggest that IFN-β-1a IM and teriflunomide 7 mg may be clustered as low- or modest-efficacy therapies.

Several NMAs have recently been conducted to compare the treatment effects of DMTs in MS [23–26] However, these publications did not include some or all the newer DMTs (cladribine, ocrelizumab, ofatumumab and ozanimod) because trial results were not available at the time of analysis. The present study builds on an SLR and NMA we have reported elsewhere [19] and provides the most up-to-date quantitative synthesis of DMTs available for the treatment of RMS.

This study had several limitations. First, neither of our classification approaches were ideal. The ABN guidelines defined high-efficacy therapies as having an average relapse reduction substantially more than 50%. Because the meaning of 'substantially' was not clearly stated in the guidelines, we used a 50% threshold to define the high-efficacy class. It is possible that some DMTs that we classified as high efficacy would be instead be classified as moderate efficacy if a higher threshold was used. For example, the effect estimate for dimethyl fumarate versus placebo from the ARR NMA was 0.50, such that the classification of this DMT as high efficacy or moderate efficacy according the NMA-based approach was highly sensitive to the threshold that we used. Both of our approaches were limited in that DMTs were classified based on point estimates and so uncertainty in these estimates was not considered. Second, although we aimed to closely align our direct comparative approach with the 2015 ABN guidelines, the lack of reporting details (e.g., how average relapse reduction was calculated) in the guidelines led us to develop to our own definition for average relapse reduction. For each DMT we qualitatively considered the relative reduction in relapse risk (DMT vs comparator) using the outcome of ARR as reported by RCTs included in the evidence base. This approach used a commonly reported measure of relapse (ARR) and permitted us to consider the relative reduction in relapse for every relevant direct comparison reported by trials included in our evidence base. Notably, all DMTs classified as high or moderate efficacy in our direct comparative approach were consistent with the 2015 ABN guidelines. Third, our NMA-based approach is valid only if the included trials are sufficiently similar such that NMA results will not be biased by underlying patient population heterogeneity. Extensive cross-trial assessments were conducted to identify imbalances that would have precluded NMAs; however, meta-regression and sensitivity analyses involving the exclusion of outlier trials with respect to baseline patient characteristics were not appropriate. Further, we previously reported that the trials included in a similar evidence base were sufficiently similar [19] and this same conclusion was reached by other recent NMAs [23–26]. Finally, the classification of DMTs was based on ARR and did not consider other efficacy outcomes or safety/tolerability outcomes commonly reported in MS trials. We focused on ARR to align with the ABN guidelines, but future efforts could consider other outcomes as well. The classification results of this study are based solely on DMT efficacy and do not consider the many other important variables that require consideration when selecting an appropriate treatment strategy. For example, the ABN guidelines note that high efficacy therapies have a more complex safety profile and recommend limiting their use to people with more active disease [6]. Despite these constraints, the evidence generated from this study provides an important extension of the current ABN guidelines with respect to DMT efficacy by incorporating a larger and newer evidence base of licensed DMTs used to treat MS. In addition, it introduces an alternative approach to DMT classification based on efficacy that leverages indirect treatment comparisons to improve treatment effect estimates and allow the use of a common comparator.

Conclusion

This study provides important evidence regarding the relative efficacy of contemporary DMTs compared with older approved treatments for RMS. Our findings demonstrate that the relapse reduction associated with cladribine and ofatumumab is similar to other DMTs currently classified by the ABN as drugs of high efficacy. Ocrelizumab and ozanimod 1.0 mg were classified as moderate or high efficacy depending on the classification approach used, and ozanimod 0.5 mg was classified as moderate efficacy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0267

Acknowledgments

The authors would like to thank Anja Haltner (employee of EVERSANA™) for analytical support.

Author contributions

DA Häring, D Stoneman, N Adlard, L Klotz and C Cameron conceived of and contributed to the design of the research and provided critical revisions to the manuscript. C Cameron, IA Samjoo and E Worthington contributed to research design. E Worthington, C Drudge and M Zhao extracted data, conducted analyses and discussed analytical results. IA Samjoo drafted the manuscript. All authors provided critical feedback of the research, analysis and manuscript.

Financial & competing interests disclosure

This work was funded by Novartis Pharma AG. IA Samjoo, E Worthington, C Drudge, M Zhao and C Cameron are employees of EVERSANA™. EVERSANA receives consultancy fees from major pharmaceutical and device companies, including Novartis Pharma AG. C Cameron is also a shareholder of EVERSANA. DA Häring, D Stoneman and N Adlard are salaried employees of Novartis Pharma AG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/

Summary points

- Newer therapies for relapsing multiple sclerosis (cladribine, ocrelizumab, ofatumumab and ozanimod) were classified according to treatment guidelines from the Association of British Neurologists (ABN) using two approaches.
- The first classification approach closely aligned with the ABN guidelines and used direct comparative results from relevant randomized controlled trials and considered the relative reduction in relapse risk based on the reported annualized relapse rate (ARR).
- The second classification approach used classification probabilities based on comparisons versus placebo from a network meta-analysis with ARR as the outcome.
- We identified cladribine and ofatumumab as therapies that would be classified as high efficacy according to both approaches.
- We identified ocrelizumab and ozanimod 1.0 mg as therapies that could be classified either as moderate efficacy according to the ABN guidelines or high efficacy according to the ARR network meta-analysis-based approach.
- We identified ozanimod 0.5 mg as a therapy that would be classified as moderate efficacy according to both approaches.
- We proposed a third class, modest efficacy, and identified intramuscular interferon β-1a and teriflunomide 7 mg as therapies that would be classified as such. These therapies were classified as moderate efficacy according to the ABN guidelines.
- This study provides important evidence regarding the relative efficacy of contemporary therapies compared with older approved treatments for relapsing multiple sclerosis.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Compston A, Coles A. Multiple sclerosis. *Lancet* 372(9648), 1502–1517 (2008).
2. Lublin FD, Reingold SC, Cohen JA *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 83(3), 278–286 (2014).
3. European Medicines Agency. Clinical investigation of medicinal products for the treatment of multiple sclerosis. (2015). https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-multiple-sclerosis
4. Gajofatto A, Benedetti M. Treatment strategies for multiple sclerosis: when to start, when to change, when to stop? *World J. Clin. Cases* 3(7), 545–555 (2015).

5. Rae-Grant A, Day GS, Marrie RA *et al.* Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 90(17), 777–788 (2018).
6. Scolding N, Barnes D, Cader S *et al.* Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract. Neurol.* 15(4), 273–279 (2015).

•• **Multiple sclerosis (MS) treatment guidelines from the Association of British Neurologists, which provided the basis for this study.**

7. Marques VD, Passos GRD, Mendes MF *et al.* Brazilian consensus for the treatment of multiple sclerosis: Brazilian Academy of Neurology and Brazilian Committee on Treatment and Research in Multiple Sclerosis. *Arq. Neuropsiquiatr.* 76, 539–554 (2018).
8. Montalban X, Gold R, Thompson AJ *et al.* ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multiple Scler. J.* 24(2), 96–120 (2018).
9. Giovannoni G, Comi G, Cook S *et al.* A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N. Engl. J. Med.* 362(5), 416–426 (2010).

• **The CLARITY trial was a pivotal Phase III cladribine trial investigating cladribine (3.5 or 5.25 mg/kg cumulative dose) versus placebo in patients with relapsing–remitting MS.**

10. Hauser SL, Bar-Or A, Comi G *et al.* Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N. Engl. J. Med.* 376(3), 221–234 (2017).

• **The OPERA I and II trials were pivotal Phase III ocrelizumab trials investigating ocrelizumab versus IFN-β-1a in patients with relapsing MS.**

11. Hauser SL, Bar-Or A, Cohen J *et al.* Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. *Presented at: ECTRIMS 2019.* Stockholm, Sweden (2019).

• **The ASCLEPIOS I and II trials were pivotal Phase III ofatumumab trials investigating ofatumumab versus teriflunomide in patients with relapsing MS.**

12. Cohen JA, Comi G, Selmaj KW *et al.* Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, Phase III trial. *Lancet Neurol.* 18(11), 1021–1033 (2019).

• **The RADIANCE trial was a pivotal Phase III ozanimod trial investigating ozanimod (0.5 or 1.0 mg dose) versus IFN-β-1a in patients with relapsing MS.**

13. Comi G, Kappos L, Selmaj KW *et al.* Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, Phase III trial. *Lancet Neurol.* 18(11), 1009–1020 (2019).

• **The SUNBEAM trial was a pivotal Phase III ozanimod trial investigating ozanimod (0.5 or 1.0 mg dose) versus IFN-β-1a in patients with relapsing MS.**

14. Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing–remitting multiple sclerosis: a systematic review. *Autoimmun. Rev.* 16(6), 658–665 (2017).
15. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol.* 72(2), 152–158 (2015).
16. Utz KS, Hoog J, Wentrup A *et al.* Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. *Ther. Adv. Neurol. Disord.* 7(6), 263–275 (2014).
17. National Institute for Health and Care Excellence. Single technology appraisal: user guide for company evidence submission template. (2017). https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Group ATP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* 151(4), 264–269 (2009).
19. Samjoo IA, Worthington E, Drudge C *et al.* Comparison of ofatumumab and other disease-modifying therapies for relapsing multiple sclerosis: a network meta-analysis. *J. Comp. Eff. Res.* 9(18), 1255–1274 (2020).
20. Hoaglin DC, Hawkins N, Jansen JP *et al.* Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 14(4), 429–437 (2011).
21. Jansen JP, Fleurence R, Devine B *et al.* Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 14(4), 417–428 (2011).
22. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med.* 11(1), 159 (2013).
23. Institute for Clinical and Economic Review. Disease-modifying therapies for relapsing–remitting and primary-progressive multiple sclerosis: effectiveness and value. (2017).
24. Lucchetta RC, Tonin FS, Borba HHL *et al.* Disease-modifying therapies for relapsing–remitting multiple sclerosis: a network meta-analysis. *CNS Drugs* 32(9), 813–826 (2018).
25. McCool R, Wilson K, Arber M *et al.* Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Multiple Scler. Relat. Disord.* 29, 55–61 (2019).

26. Siddiqui MK, Khurana IS, Budhia S, Hettle R, Harty G, Wong SL. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis. *Curr. Med. Res. Opin.* 34(8), 1361–1371 (2018).
27. Dias S, Sutton AJ, Ades A, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med. Decis. Making* 33(5), 607–617 (2013).
28. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res. Synth. Meth.* 1(2), 97–111 (2010).
29. Spiegelhalter D, Thomas A, Best N. *WinBUGS User Manual.* MRC Biostat Unit, Cambridge, UK (2004). https://www.mrc-bsu.cam.ac.uk/wp-content/uploads/manual14.pdf
30. Cree BaC, Corboy J, Singer B *et al.* Efficacy and safety of fingolimod versus glatiramer acetate in patients with relapsing–remitting multiple sclerosis in the ASSESS study. *Presented at: 2019 Consortium of Multiple Sclerosis Centers Annual Meeting.* Seattle, WA, USA (2019).
31. Calabresi PA, Kieseier BC, Arnold DL *et al.* Pegylated interferon beta-1a for relapsing–remitting multiple sclerosis (ADVANCE): a randomised, Phase III, double-blind study. *Lancet Neurol.* 13(7), 657–665 (2014).
32. Durelli L, Verdun E, Barbero P *et al.* Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* 359(9316), 1453–1460 (2002).
33. National Institute for Health and Care Excellence. Technology appraisal guidance TA533: ocrelizumab for treating relapsing–remitting multiple sclerosis. (2018). https://www.nice.org.uk/guidance/ta533
34. Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and Phase III studies of interferon beta products in the treatment of multiple sclerosis. *Clin. Ther.* 25(1), 105–118 (2003).
35. Boiko AN, Lashch NY, Sharanova SN *et al.* A comparative placebo-controlled clinical trial of the efficacy and safety of glatiramer acetate 20 mg in patients with remitting multiple sclerosis: first-year study results. *Neurosci. Behav. Physiol.* 48(3), 351–357 (2018).
36. CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N. Engl. J. Med.* 359(17), 1786–1801 (2008).
37. Cohen JA, Coles AJ, Arnold DL *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: a randomised controlled Phase III trial. *Lancet* 380(9856), 1819–1828 (2012).
38. Coles AJ, Twyman CL, Arnold DL *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled Phase III trial. *Lancet* 380(9856), 1829–1839 (2012).
39. Fox RJ, Miller DH, Phillips JT *et al.* Placebo-controlled Phase III study of oral BG-12 or glatiramer in multiple sclerosis. *N. Engl. J. Med.* 367(12), 1087–1097 (2012).
40. Gold R, Kappos L, Arnold DL *et al.* Placebo-controlled Phase III study of oral BG-12 for relapsing multiple sclerosis. *N. Engl. J. Med.* 367(12), 1098–1107 (2012).
41. Kappos L, Radue E-W, O'Connor P *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 362(5), 387–401 (2010).
42. Calabresi PA, Radue E-W, Goodin D *et al.* Safety and efficacy of fingolimod in patients with relapsing–remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, Phase III trial. *Lancet Neurol.* 13(6), 545–556 (2014).
43. Cohen JA, Barkhof F, Comi G *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 362(5), 402–415 (2010).
44. O'Connor P, Filippi M, Arnason B *et al.* 250 microg or microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing–remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol.* 8(10), 889–897 (2009).
45. Bornstein MB, Miller A, Slagle S *et al.* A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *N. Engl. J. Med.* 317(7), 408–414 (1987).
46. Calabrese M, Bernardi V, Atzori M *et al.* Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing–remitting multiple sclerosis. *Multiple Scler. J.* 18(4), 418–424 (2012).
47. Lublin FD, Cofield SS, Cutter GR *et al.* Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann. Neurol.* 73(3), 327–340 (2013).
48. Johnson KP, Brooks BR, Cohen JA *et al.* Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a Phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 45(7), 1268–1276 (1995).
49. Mikol DD, Barkhof F, Chang P *et al.* Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol.* 7(10), 903–914 (2008).
50. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. GALA Study Group. Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis. *Ann. Neurol.* 73(6), 705–713 (2013).

51. Vollmer TL, Sorensen PS, Selmaj K *et al.* A randomized placebo-controlled Phase III trial of oral laquinimod for multiple sclerosis. *J. Neurol.* 261(4), 773–783 (2014).
52. Jacobs LD, Cookfair DL, Rudick RA *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann. Neurol.* 39(3), 285–294 (1996).
53. Stępień A, Chalimoniuk M, Lubina-Dąbrowska N, Chrapusta SJ, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing–remitting multiple sclerosis: a 3-year longitudinal study. *Neuroimmunomodulation* 20(4), 213–222 (2013).
54. Ebers GC. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 352(9139), 1498–1504 (1998).
55. Panitch H, Goodin DS, Francis G *et al.* Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. *Neurology* 59(10), 1496–1506 (2002).
56. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 43(4), 655–655 (1993).
57. Polman CH, O'Connor PW, Havrdova E *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* 354(9), 899–910 (2006).
58. O'Connor P, Wolinsky JS, Confavreux C *et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N. Engl. J. Med.* 365(14), 1293–1303 (2011).
59. Vermersch P, Czlonkowska A, Grimaldi LM *et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled Phase III trial. *Multiple Scler. J.* 20(6), 705–716 (2014).
60. Confavreux C, O'Connor P, Comi G *et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, Phase III trial. *Lancet Neurol.* 13(3), 247–256 (2014).