Relapse Reduction by Disease-modifying Therapies for Relapsing Multiple Sclerosis: A Network Meta-analysis

P919

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Introduction

- Numerous disease-modifying therapies (DMTs) are available for patients with relapsing multiple sclerosis (RMS)
- Several DMTs including ofatumumab, ozanimod, and ponesimod have been approved for the treatment of RMS in the United States and Europe since 2020
- Randomised controlled trials (RCTs) evaluating the efficacy of DMTs are often restricted to a comparison with placebo or a single active comparator
- Indirect treatment comparison methods such as network meta-analysis (NMA) are required to understand the efficacy of newer therapies relative to both each other and older DMTs

Objective

- Assess the relative efficacy of newly approved and established DMTs for patients with RMS based on annualised relapse rate (ARR), the primary endpoint for many phase III clinical trials of DMTs for RMS

Methods

- This work is an extension of a previously published NMA of DMTs for RMS[1]

Figure 1. Methods Flow Diagram

A systematic literature review was conducted from inception until Dec 2019

- Biomedical databases (including Embase, MEDLINE, and Cochrane Central Register) and relevant conference and health technology assessment agency websites were searched
- All RCTs evaluating DMTs for adult patients with RMS were included

Additional inclusion criteria were applied to select RCTs for the NMA

- Trial duration ≥48 weeks and the endpoint of ARR was reported

A feasibility assessment was performed to ensure an NMA was appropriate

- Cross-trial differences were qualitatively assessed for trial and patient population characteristics

A Bayesian NMA was conducted to compare treatments based on ARR

- Analyses were conducted as per National Institute for Health and Care Excellence guidance[2]
- A Poisson model with random effects was used
- DMT doses/schedules were from RCTs and not always in clinical use
- Results were provided as rate ratios for comparisons of interest

Results

Literature Review

Figure 2. PRISMA Flow Diagram

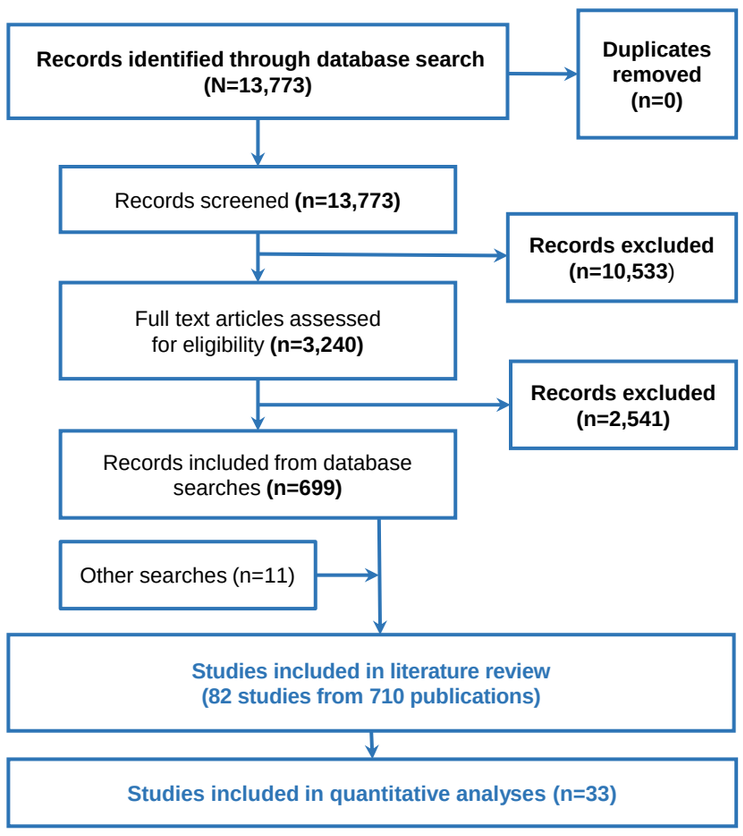


Table 1. NMA Summary Measures

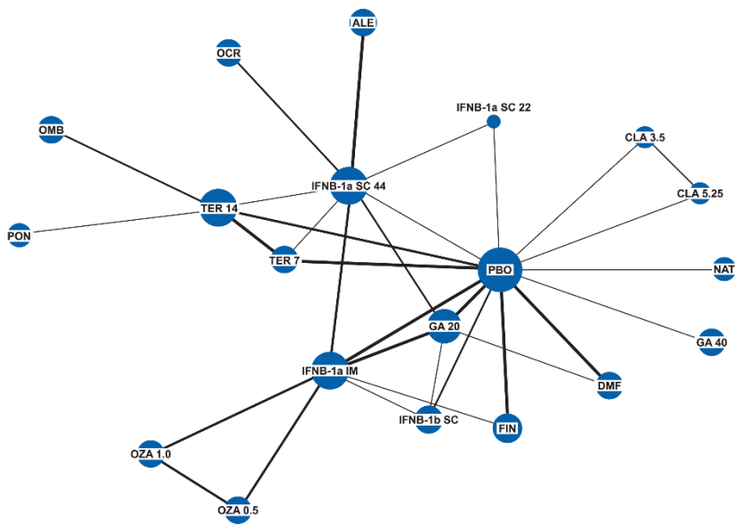
Treatment	Mean SUCRA (%)	Mean *P*-Best (%)
Alemtuzumab 12 mg	97	55
Ofatumumab 20 mg	92	25
Natalizumab 300 mg	89	14
Ocrelizumab 600 mg	87	5
Cladribine 3.5 mg/kg	71	0
Ozanimod 1.0 mg	68	0
Cladribine 5.25 mg/kg	65	0
Fingolimod 0.5 mg	65	0
Ponesimod 20 mg	64	0
Dimethyl fumarate 240 mg	58	0
Ozanimod 0.5 mg	43	0
Glatiramer acetate 20 mg	37	0
IFNB-1a SC 44 µg	36	0
Glatiramer acetate 40 mg	30	0
Teriflunomide 14 mg	28	0
IFNB-1b SC	25	0
IFNB-1a SC 22 µg	24	0
IFNB-1a IM	10	0
Teriflunomide 7 mg	10	0
Placebo	0	0

Abbreviations: IFNB = interferon beta; IM = intramuscular; *P*-Best = probability of being best; SC = subcutaneous; SUCRA = surface under the cumulative ranking curve.

ARR NMA Results

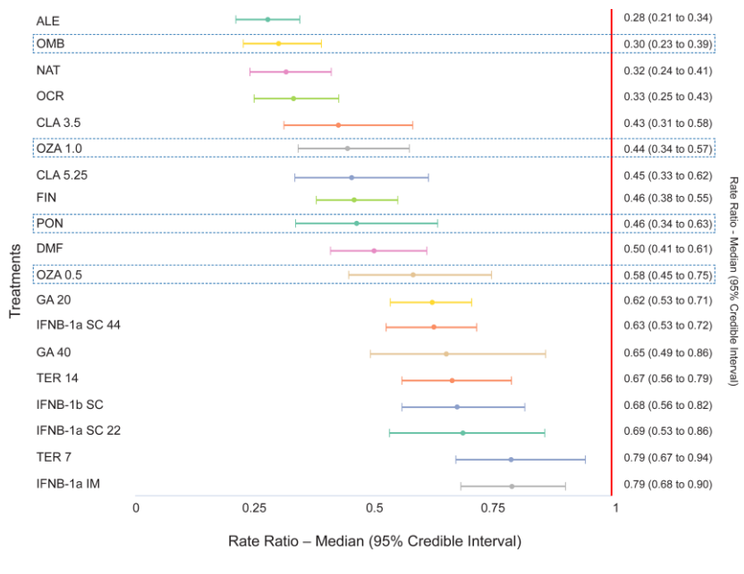
- The NMA network consisted of 20 treatments (including placebo) from 33 RCTs

Figure 3. Network Diagram



Abbreviations: ALE = alemtuzumab 12 mg; CLA 3.5 = cladribine 3.5 mg/kg; CLA 5.25 = cladribine 5.25; DMF = dimethyl fumarate 240 mg twice a day; FIN = fingolimod 0.5 mg; GA 20 = glatiramer acetate 20 mg; GA 40 = glatiramer acetate 40mg; IFNB-1a IM = interferon beta-1a intramuscular 30 µg; IFNB-1a SC 22 = interferon beta-1a subcutaneous 22 µg; IFNB-1a SC 44 = interferon beta-1a subcutaneous 44 µg; IFNB-1b SC = interferon beta-1b subcutaneous 250 µg; NAT = natalizumab 300 mg; OCR = ocrelizumab 600 mg; OMB = ofatumumab 20 mg; OZA 0.5 = ozanimod 0.5 mg; OZA 1.0 = ozanimod 1.0 mg; PBO = placebo; PON = ponesimod 20 mg; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg.

Figure 4. Forest Plot (DMT vs. Placebo)



= Newer therapy

Note: A rate ratio below 1.0 indicates an improved outcome for the DMT.

Conclusions

- Monoclonal antibody therapies were the most efficacious DMTs for treating MS relapse
  - The top DMTs compared with placebo in the NMA for ARR, in order of their efficacy, were alemtuzumab (rate ratio [RR]: 0.28, 95% credible interval [CrI] 0.21–0.34), ofatumumab (RR: 0.30, 95% CrI 0.23–0.39), natalizumab (RR: 0.32, 95% CrI 0.24–0.41), and ocrelizumab (RR: 0.33, 95% CrI 0.25–0.43)
- Among the newly approved DMTs (since 2020) ofatumumab was the most efficacious therapy
  - Ofatumumab was superior to ozanimod 0.5 mg (RR: 0.51, 95% CrI 0.35–0.74), ozanimod 1.0 mg (RR: 0.67, 95% CrI 0.46–0.97), and ponesimod (RR: 0.65, 95% CrI 0.45–0.91)
- Ofatumumab was identified as a highly effective treatment option for reducing relapse risk in patients with RMS among both recently approved and established DMTs

References

1. Samjoo IA, et al. *J Comp Eff Res*. 2020;9(18):1255–1274.
2. Dias S, et al. *Med Decis Making*. 2013;33(5):607–617.

Disclosures

D. Stoneman, D.A. Häring, and N. Adlard are employees of Novartis Pharma AG. C. Drudge, M. Zhao, E. Worthington, C. Cameron, and I.A. Samjoo 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™.

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