A Network Meta-Analysis of Randomized Controlled Trials to Evaluate the Comparative Efficacy of Disease-Modifying Therapies for Patients with Relapsing Multiple Sclerosis

P047

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Summary

- Given that not all disease-modifying therapies (DMTs) for relapsing multiple sclerosis (RMS) have been compared head-to-head in randomized controlled trials (RCTs) and there are differences in how confirmed disability progression (CDP) is defined across trials, a network meta-analysis (NMA) was conducted to estimate the relative efficacy of all available therapies and explore the influence of different CDP definitions.
- For the outcome of annualized relapse rate, the three most efficacious treatments versus placebo were alemtuzumab, ofatumumab, and ublituximab.
- For the outcome of 3-month CDP, the three most efficacious treatments versus placebo were alemtuzumab, ocrelizumab, and ofatumumab. However, the rank order of these treatments varied based on the CDP definition used to calculate ofatumumab ASCLEPIOS I/II trial data included in the NMA.
- For the outcome of 6-month CDP, the three most efficacious treatments versus placebo varied based on the CDP definition used: alemtuzumab, natalizumab, and ocrelizumab using the per-protocol definition; and alemtuzumab, natalizumab, and ofatumumab using an alternative definition aligned with RCTs for several DMTs in the NMA.
- Generally, monoclonal antibody therapies were the most efficacious DMTs for RMS. This finding was robust to changes in the CDP definition used for two trials in the NMA. Of the included DMTs, only alemtuzumab and ofatumumab ranked among the three most efficacious treatments for both reducing relapse frequency and delaying disability progression.

Introduction and Objective

- The availability of many disease-modifying therapies (DMTs) for relapsing multiple sclerosis (RMS) and the complex nature of this condition can complicate selecting the best treatment option for individual patients.
- Since not all DMTs have been compared head-to-head in randomized controlled trials (RCTs), indirect treatment comparison methods such as network meta-analysis (NMA) can be used to estimate the relative efficacy of all available therapies.
- As an additional complexity, the definition of confirmed disability progression (CDP), a common trial endpoint, varies between trials (e.g., Expanded Disability Status Scale [EDSS] score increases from baseline needed to confirm progression) and so may influence NMA results.
- **The objective of this study was to use NMA to assess the relative efficacy of DMTs for patients with RMS and explore the influence of different CDP definitions**.

Methods

- This NMA is an update of a previously published NMA of DMTs for RMS.[1]
- A systematic literature review (SLR) was conducted to identify relevant RCTs, which involved searches of biomedical databases, conference proceedings, and trial registries up to March 2022.
- The NMA included RCTs meeting the following criteria: (1) population was ≥75% RMS; (2) interventions and comparators included DMTs approved for RMS by the United States Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) or undergoing FDA and/or EMA review as of June 2022; (3) outcomes included at least one of annualized relapse rate (ARR), time to 3-month CDP (3mCDP), or time to 6-month CDP (6mCDP); (4) the duration of the initial randomized portion of the trial was ≥48 weeks; and (5) a full-text pivotal publication was available for the trial.
- A feasibility assessment was performed to ensure an NMA was appropriate, which included an investigation of network structure and a qualitative assessment of cross-trial differences in trial and patient characteristics.
- Bayesian analyses were conducted for ARR, 3mCDP, and 6mCDP.
- Two different CDP definitions were used to calculate the ofatumumab ASCLEPIOS I/II[2] trial data included in the analyses for 3mCDP and 6mCDP (see below).

Predefined CDP	EDSS-Aligned CDP
•As per the ASCLEPIOS I/II[2] protocol	•Aligned with the OPERA I/II[3], TEMSO[4], TOWER[5], ULTIMATE I/II[6] trials, based on the required increases in EDSS score from baseline needed to confirm progression

Results

Literature Review and Feasibility Assessment

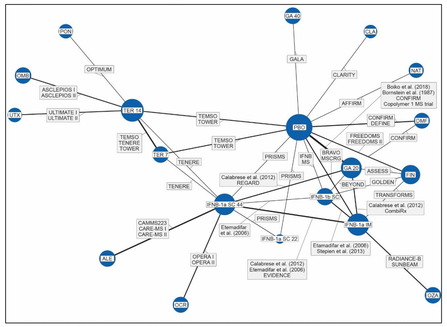
- Overall, 39 RCTs identified from the SLR were included in the NMA.
- Cross-trial differences were evident for some trial and patient characteristics, but these did not preclude conducting an NMA.

Network Meta-Analysis

- For each outcome, a network diagram visualizing the evidence base is provided, along with a forest plot comparing each treatment in the network with placebo.
- A network is made up of nodes (treatments) and connecting lines (where two treatments were compared in an included RCT).
- In the forest plots, rate ratios and hazard ratios below 1.0 indicate an improved outcome for the DMT relative to placebo.

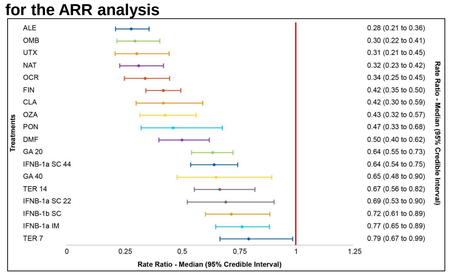
Annualized Relapse Rate

Figure 1. Network Diagram for ARR Outcome



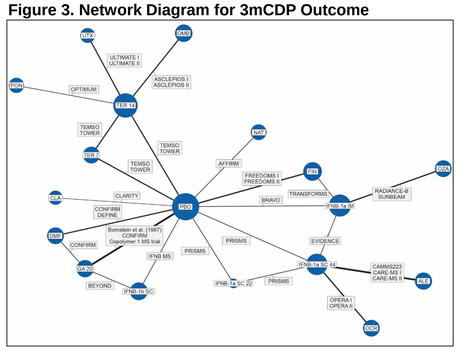
Abbreviations: ALE = alemtuzumab 12 mg; CLA = cladribine 3.5 mg/kg; DMF = dimethyl fumarate 240 mg twice a day; FIN = fingolimod 0.5 mg; GA 20 = glatiramer acetate 20 mg; GA 40 = glatiramer acetate 40 mg; IFNB-1a IM = interferon beta-1a 30 µg intramuscular; IFNB-1a SC 22 = interferon beta-1a 22 µg subcutaneous; IFNB-1a SC 44 = interferon beta-1a 44 µg subcutaneous; IFNB-1b SC = interferon beta-1b 250 µg subcutaneous; NAT = natalizumab 300 mg; OCR = ocrelizumab 600 mg; OMB = ofatumumab 20 mg; OZA = ozanimod 1.0 mg; PBO = placebo; PON = ponesimod 20 mg; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg; UTX = ublituximab 450 mg.

Figure 2. Forest plot for treatments compared with placebo for the ARR analysis



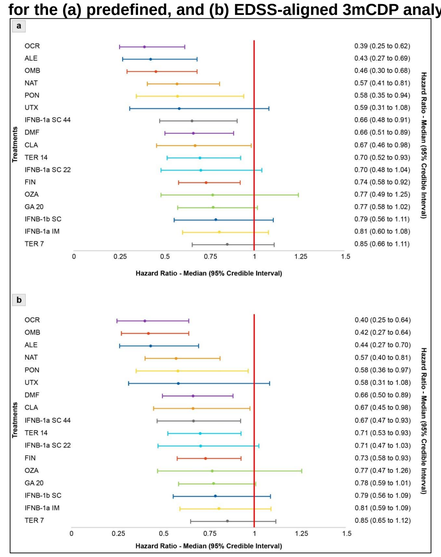
3-Month Confirmed Disability Progression

Figure 3. Network Diagram for 3mCDP Outcome



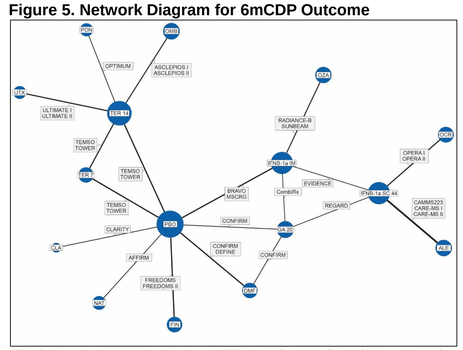
Abbreviations: ALE = alemtuzumab 12 mg; CLA = cladribine 3.5 mg/kg; DMF = dimethyl fumarate 240 mg twice a day; FIN = fingolimod 0.5 mg; GA 20 = glatiramer acetate 20 mg; IFNB-1a IM = interferon beta-1a 30 µg intramuscular; IFNB-1a SC 22 = interferon beta-1a 22 µg subcutaneous; IFNB-1a SC 44 = interferon beta-1a 44 µg subcutaneous; IFNB-1b SC = interferon beta-1b 250 µg subcutaneous; NAT = natalizumab 300 mg; OCR = ocrelizumab 600 mg; OMB = ofatumumab 20 mg; OZA = ozanimod 1.0 mg; PBO = placebo; PON = ponesimod 20 mg; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg; UTX = ublituximab 450 mg.

Figure 4. Forest plot for treatments compared with placebo for the (a) predefined, and (b) EDSS-aligned 3mCDP analyses



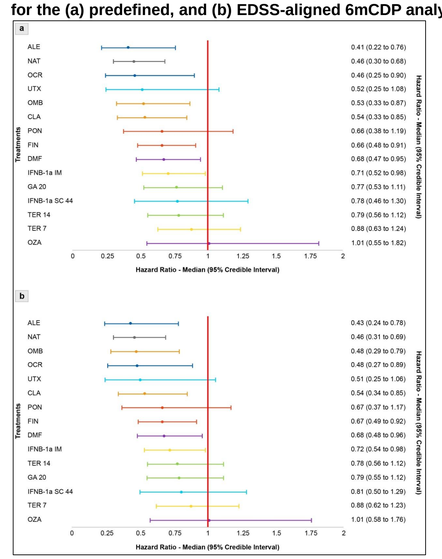
6-Month Confirmed Disability Progression

Figure 5. Network Diagram for 6mCDP Outcome



Abbreviations: ALE = alemtuzumab 12 mg; CLA = cladribine 3.5 mg/kg; DMF = dimethyl fumarate 240 mg twice a day; FIN = fingolimod 0.5 mg; GA 20 = glatiramer acetate 20 mg; IFNB-1a IM = interferon beta-1a 30 µg intramuscular; IFNB-1a SC 44 = interferon beta-1a 44 µg subcutaneous; NAT = natalizumab 300 mg; OCR = ocrelizumab 600 mg; OMB = ofatumumab 20 mg; OZA = ozanimod 1.0 mg; PBO = placebo; PON = ponesimod 20 mg; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg; UTX = ublituximab 450 mg.

Figure 6. Forest plot for treatments compared with placebo for the (a) predefined, and (b) EDSS-aligned 6mCDP analyses



References

1. Samjoo IA et al. J Comp Eff Res 2020;9(18):1255-1274; 2. Hauser SL et al. N Engl J Med 2020;383(6):546-557; 3. Hauser SL et al.. N Engl J Med 2017;376(3):221-234; 4. O'Connor P et al. N Engl J Med 2011;365(14):1293-1303; 5. Confavreux C et al. Lancet Neurol 2014;13(3):247-256. 6. Steinman L et al. N Engl J Med 2022;387(8):704-714.

Disclosures

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