Network Meta-analysis of Disease-modifying Therapies for Relapsing Multiple Sclerosis Based on Confirmed Disability Progression: Investigating the Influence of Cross-trial Differences in Endpoint Definition

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Introduction

- Many disease-modifying therapies (DMTs) are available for patients with relapsing multiple sclerosis (RMS) but direct head-to-head results from randomised controlled trials (RCTs) are not available for all therapies
- Ofatumumab is a relatively newly anti-CD20 monoclonal antibody DMT investigated in the ASCLEPIOS I/II trials[1] and approved in the US and Europe
- Indirect treatment comparison methods such as network meta-analysis (NMA) are often used to understand the relative efficacy of ofatumumab compared to other DMTs for RMS
  - The other available anti-CD20 therapy approved for RMS is ocrelizumab, investigated in the OPERA I/II trials[2]
- Confirmed disability progression (CDP) is a common endpoint in clinical trials of DMTs for RMS; however, the definition of CDP often differs between trials
- The influence of different CDP definitions used in clinical trials on the results of an NMA for this endpoint is not well understood

Objective

- Investigate the influence of CDP definition on relative disability reduction by various DMTs for patients with RMS, as estimated by NMA

Methods

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 endpoints of interest (6-month CDP [6mCDP] and/or 3-month CDP [3mCDP]) were reported

A feasibility assessment was performed to ensure an NMA was appropriate
- Cross-trial differences were qualitatively assessed with regards to trial and patient population characteristics

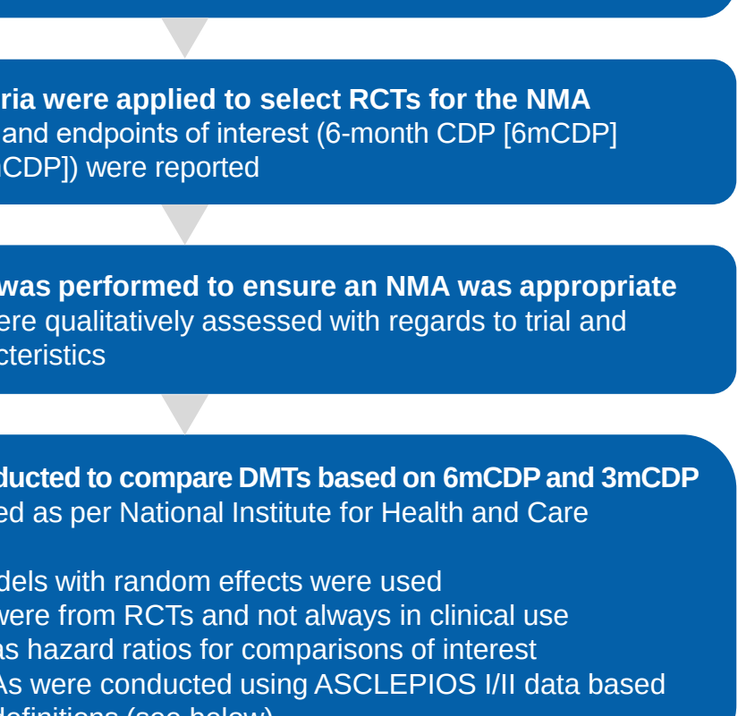
Bayesian NMAs were conducted to compare DMTs based on 6mCDP and 3mCDP
- Analyses were conducted as per National Institute for Health and Care Excellence guidance[3]
- Continuous survival models with random effects were used
- DMT doses/schedules were from RCTs and not always in clinical use
- Results were provided as hazard ratios for comparisons of interest
- For each endpoint, NMAs were conducted using ASCLEPIOS I/II data based on three different CDP definitions (see below)

Predefined CDP	EDSS Only CDP	OPERA-aligned CDP
• As per the ASCLEPIOS I/II protocol	• Aligned with the OPERA I/II trials only for the definition component related to the magnitude of increase in EDSS score from baseline required for CDP • ASCLEPIOS I/II CDP data were recalculated	• Fully aligned with the definition reported for the ocrelizumab OPERA I/II trials • ASCLEPIOS I/II CDP data were recalculated

Results

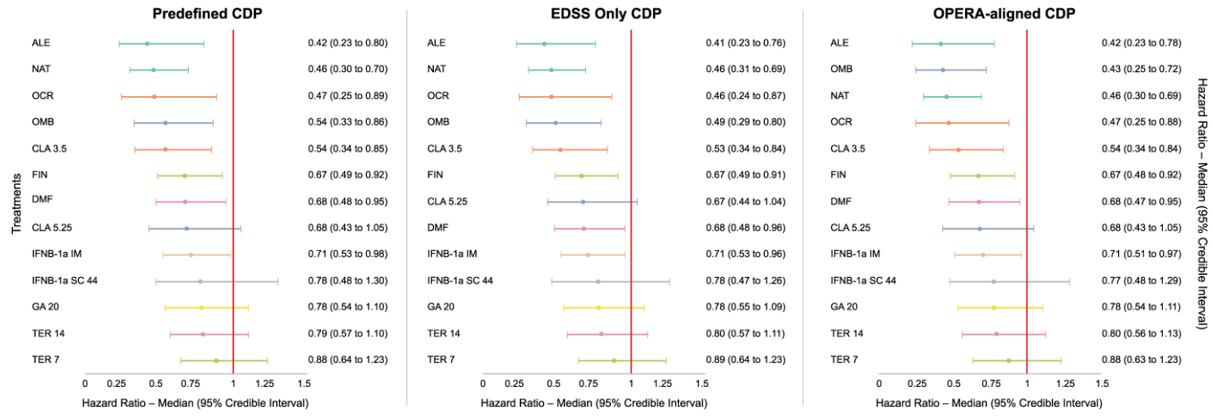
Time to 6mCDP NMA Results

Figure 2. Network Diagram for 6mCDP



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; IFNB-1a IM = interferon beta-1a intramuscular 30 µg; IFNB-1a SC 44 = interferon beta-1a subcutaneous 44 µg; NAT = natalizumab 300 mg; OCR = ocrelizumab 600 mg; OMB = ofatumumab 20 mg; PBO = placebo; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg.

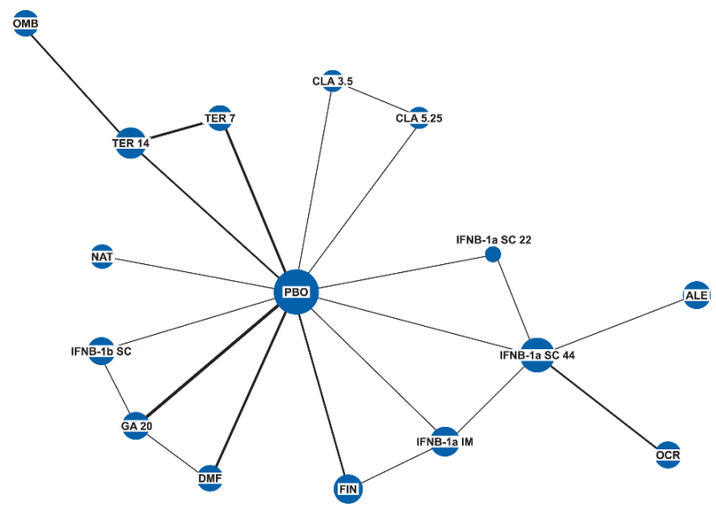
Figure 3. Forest Plots (DMT vs. Placebo) for 6mCDP NMA



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

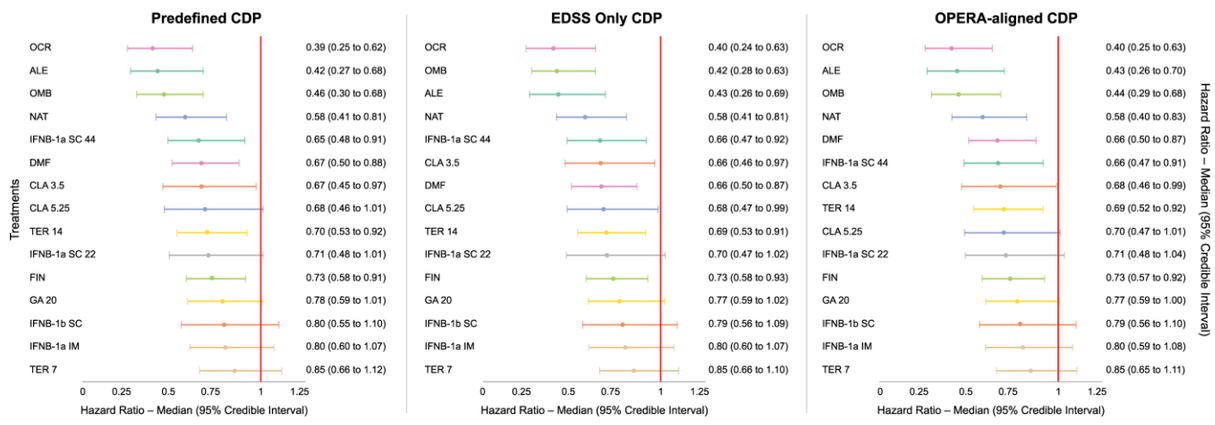
Time to 3mCDP NMA Results

Figure 4. Network Diagram for 3mCDP



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; 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; PBO = placebo; TER 7 = teriflunomide 7 mg; TER 14 = teriflunomide 14 mg.

Figure 5. Forest Plots (DMT vs. Placebo) for 3mCDP NMA



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

Conclusions

- The monoclonal antibody therapies ofatumumab, ocrelizumab, natalizumab, and alemtuzumab were the most efficacious DMTs compared with placebo for reducing the accumulation of disability in RMS
- For both 6mCDP and 3mCDP, the rank order of the four therapies varied depending on the definition of disability progression used
- The definition used for CDP can impact the ranking of DMTs in an NMA for this endpoint

References

1. Hauser SL, et al. *N Engl J Med.* 2020;383(6):546–557. **2.** Hauser SL, et al. *N Engl J Med.* 2017; 376(3):221–234. **3.** 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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