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 III trials 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.
- 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

- 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 NMA were conducted to compare DMTs based on 6mCDP and 3mCDP:
  - Analyses were conducted as per National Institute for Health and Care Excellence guidance.
  - 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, NMA were conducted using ASCLEPIOS III data based on three different CDP definitions (see below).

Results

- Time to 6mCDP NMA

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

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

Figure 4. Network Diagram for 3mCDP

Abbreviations: ALE = alemtuzumab 12 mg; CLA = cladribine 3.5 mg/day; OLE = ocrelizumab 30 mg; IFNB = interferon beta-1a subcutaneous 44 μg/week; GA = glatiramer acetate 40 mg/day; PBO = placebo; TEIR = teriflunomide 7 mg; TIR + = 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


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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