Emerging data on the treatment of multiple sclerosis

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ABSTRACT

Background and objectives. In the past few years, a myriad of new studies were aimed to find better ways to manage MS. As a result, a bunch of new molecules were found to have good efficacy, therefore FDA and EMA approved a series of treatments in the last few years, the last one receiving green light from EMA on March 30th, 2021 (Ofatumumab – Kesimpta®). The aim of this study was to evaluate and classify three of the newest drugs approved by the FDA and EMA.

Material and methods. All the studies were chosen on the basis of pre-determined inclusion criteria and in accordance with PRISMA guidelines. We searched Pubmed and Cochrane Library for all studies published up until the end of 2020. For the data analysis we used MetaInsight®, a statistical web-based tool for meta-analyses and NMAs performing both Frequentist and Bayesian hierarchical model analyses, each one being seen as a sensitivity check for the other.

Outcomes. The best therapeutic agent in reported efficacy amongst the three analyzed was Ofatumumab, ranked first in hierarchy, Ozanimod and Cladribine following in the second and third place, respectively.

Conclusions. According to ABN’s 2015 guidelines, Cladribine was ranked between the most effective medicines for the treatment of MS; given the results from this study, other two may be considered as high efficacy alongside Natalizumab, Alemtuzumab and Ocrelizumab.

Keywords: multiple sclerosis, network meta-analysis, immunomodulatory drugs, Frequentist NMA, Bayesian NMA

INTRODUCTION

Multiple sclerosis is a chronic neurodegenerative disorder of unknown etiology. There are now over 150 years since Charcot’s neurological triad was first described, albeit given the complexity of the disease, the attempts of finding the missing link which, alongside genetic proneness and environmental factors could be responsible for the autoimmune assault against CNS, reached no definite answer (1).

A recent epidemiological study comprising prevalence data from 75 countries found a 50% higher prevalence reported in 2020 than in 2013 (2), a worryingly insight. Likewise, a systemic analysis of all epidemiological data from 1990 until 2016 showed consistency regarding anterior findings in the latitude gradient distribution of SM, higher mortality in women, higher prevalence in whites and lower in children (3).

The last five years were prosperous. Four new drugs showed good efficacy in randomized clinical trials; therefore, FDA and EMA approved their use. Cladribine, Ofatumumab, Ozanimod and Ocrelizumab (including a shorter two-hour infusion dosed twice yearly), despite their proved efficacy against placebo or an active first-generation drug, lack evidence in head-to-head trials.
The rationale of this study was to generate a hierarchy based on indirect data comparison of the newly approved drugs (Cladribine, Ofatumumab, Ozanimod) using the ARR reported in the primary studies and following an analytical technique known as an extension of a conventional meta-analysis to a network meta-analysis.

MATERIAL AND METHODS

The data from randomized controlled trials conducted before January 1st, 2021, underwent statistical analysis in a NMA for ARR. We looked for all studies which directly compared Cladribine, Ofatumumab and Ozanimod with an active or inactive agent and had, as a primary or secondary outcome, efficacy evaluation through ARR.

Sources

We used Pubmed and Cochrane Library for literature search purposes and via the latter we found additional information of finished and ongoing studies from EMBASE, Clinicaltrials.gov and ICTRP (International Clinical Trials Platform).

Search strategy

We obtained the search results using the PICOT search strategy in MEDLINE's search engine and Cochrane Library. Searches with synonymous terms were performed automatically.

Study selection

Inclusion and exclusion criteria were necessary for study selection. We excluded the studies which had no ARR calculated as an outcome, non-randomized-controlled trials, follow-up under six months, different drug administration protocol and other studies not relevant for the current analysis. All search results were carefully evaluated and selected in preparation for data extraction.

Data extraction and manipulation

All necessary data required to perform this analysis was extracted and modified in compliance with international protocols and recommendations for systematic reviews and NMAs.

For each therapeutic arm we extracted aARR (adjusted ARR) expressed by M (Mean), SD (Standard Deviation) and N (Number of patients). None of the studies reported the SD value, therefore we extracted it indirectly using Cochrane's Software - Review Manager (4) based on the 95%CI (Confidence Interval) associated with M and the demonstrated symmetry around the mean. Likewise, where needed, we deducted SD using SE (standard error) or ARR's MD (mean difference) and the associated p value.

Quality assessment

All studies were evaluated in order to eliminate the risk of bias. Thereinafter, we used the Cochrane Collaboration's tool for assessing risk of bias in RCTs and the criteria for judging risk of bias for each domain (5).

Data analysis

We analyzed our data using MetaInsight tool – a web-based platform for conducting NMAs (6). The strategy was to perform a two-way check of the results using R packages netmeta and gemtc, specifically both Frequentist and Bayesian hierarchical model analyses. The two statistical models differ, albeit the results should be similar, thus confirming the results' validity.

OUTCOMES

We ran a search applying the described strategy in the specified databases and found 393 studies, out of which 9 were included in this analysis. The PRISMA flowchart in figure 1 recounts reasons for the exclusion of some studies.

FIGURE 1. PRISMA flowchart. One study consists of two interventions ASCLEPIOS I and ASCLEPIOS II which have been treated as individual studies, therefore resulting 9 total studies in the network.
The selected studies can be found in table 1.

The preliminary results showed the network being connected, thus permitting us to proceed with the analysis. The total number of possible pairwise comparisons was 15, out of which 5 with direct data, and comprised a total of 7031 patients in the network. In figure 2 we obtained an overview for all studies included in the NMA based on the input of the extracted data.

The forest plot allowed us to observe the evidence available for each comparison and to examine the heterogeneity between studies.

The network plot (Figure 3) provided a visual display of the head-to-head compared interventions in the trials. There have been 6 interventions, 9 pairwise comparisons and one sub-network.

Frequentist NMA results

In the associated forest plot (Figure 4) we displayed the pooled effect estimates and 95% confidence intervals for all interventions compared to the reference treatment, in this case - Placebo.

Inconsistency was assessed for all studies and did not appear to be any important estimated differences between direct and indirect evidence.

Bayesian hierarchical model results

Similar to the Frequentist result, the Bayesian result (figure 5) also shown Ofatumumab (Ofat_20mg) as having the best pooled estimate

| Author          | Year | Study   | Treatment/Dose                                      | References |
|-----------------|------|---------|----------------------------------------------------|------------|
| Cohen JA        | 2019 | RADIANCE| Ozanimod 1 mg vs. Interferon b1a IM 30 ug           | 7          |
| Comi G          | 2019 | SUNBEAM | Ozanimod 1 mg vs. Interferon b1a IM 30 ug           | 8          |
| Vollmer TL      | 2014 | BRAVO   | Interferon b1a IM 30 ug vs. Placebo                | 9          |
| Jacobs LD       | 1996 | MSCRG   | Interferon b1a IM 30 ug vs. Placebo                | 10         |
| Giovannoni G    | 2010 | CLARITY | Cladrribina 3.5 mg/kg vs. Placebo                  | 11         |
| Hauser SL       | 2020 | ASCLEPIOS I | Ofatumumab 20 mg vs. Teriflunomid 14 mg   | 12         |
| Hauser SL       | 2020 | ASCLEPIOS II | Ofatumumab 20 mg vs. Teriflunomid 14 mg | 12         |
| O’Conner P      | 2011 | TEMSO   | Teriflunomid 14 mg vs. Placebo                     | 13         |
| Confavreux C    | 2014 | TOWER   | Teriflunomid 14 mg vs. Placebo                     | 14         |
compared with placebo but with larger uncertainty depicted by the 95% credible interval.

The convergence assessment plots for Bayesian NMA model showed that the simulated models converged. Per-arm residual deviance for all studies showed contribution around one, indicating good fit in the model and lower residuals. Also, the analysis did not indicate evidence of inconsistency for any study arm.

**DISCUSSION**

The network consisted of nine studies which have been integrated in an extended statistical analysis. The two analytical methods reached similar outcomes, displaying the superiority of all therapeutic agents over placebo and ranking them according to ARR's reduction (figure 6).

The Bayesian inconsistency indexes showed similar influence of the studies on the overall NMA results, although the algorithms had limited power in assessing inconsistency in the Frequentist analytical method.

![FIGURE 6. Ranking with all studies – NMA median rank chart](image)

From the available data analyzed, we found Ofatumumab in doses of 20 milligrams administered in a monthly subcutaneous dose as being the most efficacious for the treatment of multiple sclerosis. The following ranked treatments were Ozanimod (1 milligram), Cladribine (3.5 milligrams), Teriflunomide (14 milligrams) and Interferon beta 1a (30 micrograms). The sensitivity analysis performed showed the results are robust.

The results look very promising and, with the extended range of treatments made available, the patients might experience less relapses and an overall good quality of life over the years lived with the disease.
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