A pragmatic literature review of network meta-analyses of disease-modifying drugs in the treatment of multiple sclerosis

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Introduction

- Technical network meta-analyses (NMAs) have evaluated disease-modifying drugs (DMs) in relapsing–remitting multiple sclerosis (RRMS).
- Analysis is based on a consensus criteria, methodology, and types of statistical analyses.
- Most NMAs fail to provide a definitive basis for clinical guidance. This is in part because studies are selected over limited periods, whereas the effects of these treatments are generally unclear beyond 2 years in a therapeutic area that may extend up to 40 years in duration.
- A consensus array of inclusion and exclusion criteria, endpoints, and statistical models will result in better practice in matching clinical evidence to guide clinical decision in RRMS.

Objective

- To conduct a pragmatic literature review to identify NMAs of DMs for the treatment of RRMS and to evaluate methodological trends and positions.

Methods

- Publications including PubMed, MEDLINE, EMBASE, and the Cochrane Library were searched to identify NMAs and common properties including inclusion/exclusion criteria, study endpoints, analytic approaches, independence and covariance, and tools for consistency and sensitivity. The complete search strategy is shown in Table 1.

Results

- Twenty-nine were identified as relevant in PubMed/Cochrane Library, 6 conference abstracts (CIOMS, 1; CSTM, 1; ESPR; 4), and 100 abstracts/tables (ASC, 1; CSTM, 1; CIOMS, 12; CIOMS, 1; CIOMS, 1; CIOMS, 1; CIOMS, 1; CIOMS, 1; CIOMS, 1; CIOMS, 1).
- The most frequent inclusion criteria for studies evaluated in the NMA were RRMS and/or matched control subjects (Figure 1A). Several studies explicitly stated that only patients with RRMS could be included. In five of the 26 studies, the patient populations were defined as ≥1 relapses within the last 10 years. One study, the population was defined as >100 RRMS. Other common inclusion criteria were:
  - Duration of disease (5 studies; 10–36 months; 1 study 1 year).
  - Reporting the percentage of patients with various adverse effects (4 studies).
  - Patient data at baseline (1 study), detailed characteristics not reported.

- The most common analysis framework was Frequentist (70% of studies), followed by Bayesian analysis (50% of studies; Figure 2). The analysis framework was not reported in the remaining studies.
- In Frequentist analysis, the Bayesian approaches were limited in the design of a clinical trial but not in the design of the analysis. In contrast, Bayesian statistical models are sought after in clinical trials with limited information on the design and conduct of the trial, and at the analysis stage. The Bayesian approach can also be applied at post-market surveillance and in meta-analysis. The basic tenets of good trial design are the same for both approaches.

- Bayesian analysis has been increasingly used since 2012, and was used in only 11 recent articles. The current review reports that the Bayesian approach is being applied to compete against results obtained by the Frequentist approach.
- The number of studies over time that can review whether the impact of covariates was examined in use of meta-regression models. Furthermore, there was a wide variability across sources in the use of reporting meta-regression in model selection, with the highest rate of reporting in the Bayesian analysis. Of the studies, 20% used exploratory analyses to investigate meta-regression parameters, with the highest rate of reporting in the Bayesian analysis. Of the studies, 20% used exploratory analyses to investigate meta-regression parameters, with the highest rate of reporting in the Bayesian analysis.
- When reporting, common covariates included age, sex, year of publication, baseline EDSS score, duration of disease, and number of relapses in prior year(s), baseline lesion volume, baseline number of gadolinium-enhancing lesions, and patients with adverse events (4 studies).
- Patient data at baseline (1 study), detailed characteristics not reported.

- Most studies did not report sensitivity analyses (Figure 3). HTPA analyses were rarely focused on factors to impact sensibility analyses on other treatment groups. Bayesian approaches (40%), publications (22.2%), and other (16%).
- Bayesian approaches evaluated variations in study design and population, compared random-effects versus fixed-effects efficiency distributions, assessed the impact of blockings of different pairs, and used meta-analyses with models of treatment networks by adding vaccine without interaction.

Conclusions

- A pragmatic literature review was conducted to identify NMAs recently performed in CHRRM. Most clinical trials approached have been network meta-analyses (NMAs) in RRMS, including considerations for endpoints, methodological approaches, potential pitfalls, and emerging solutions, and tools for consistency and sensitivity.
- Endpoints that are most relevant to patients with RRMS (eg, proportion of patients with relapse-free proportion of patients with disease progression) should be explored in any efficacy-focused analysis.
- Most NMAs failed to provide a definitive basis for clinical guidance. This is in part because studies are selected over limited periods, whereas the effects of these treatments are generally unclear beyond 2 years in a therapeutic area that may extend up to 40 years in duration.
- Although inconsistency tests were not frequently reported, these should be included in order to report the validity of results. Consistency in any method commonly employed with RRMS include pairwise versus indirect comparisons and computation of ranks using an inconsistency model.
- Possible limitations of the current analysis include the following:

  - The pragmatic literature review was limited in the time horizon investigated (2000–present). PubMed and Cochrane Library were used for primary and secondary analyses, and Table 1 (see Additional file 1).

- HTPA analysis is often compared across studies. The low rate of reporting in the Bayesian analysis is a common model. The Bayesian approach can also be applied at post-market surveillance and in meta-analysis. The basic tenets of good trial design are the same for both approaches. Further, the effects of covariates were examined in use of meta-regression models. Furthermore, there was a wide variability across sources in the use of reporting meta-regression in model selection, with the highest rate of reporting in the Bayesian analysis. Of the studies, 20% used exploratory analyses to investigate meta-regression parameters, with the highest rate of reporting in the Bayesian analysis. When reporting, common covariates included age, sex, year of publication, baseline EDSS score, duration of disease, and number of relapses in prior year(s), baseline lesion volume, baseline number of gadolinium-enhancing lesions, and patients with adverse effects (4 studies). Patient data at baseline (1 study), detailed characteristics not reported.