Introduction

- Approximately 20 treatment options are approved for use in adult patients with multiple sclerosis (MS), while in patients with paediatric MS (PedMS), fingolimod is the only successfully tested and world-wide approved therapy, and so a high unmet need continues to exist.
- The pathophysiology of PedMS and adult-onset MS patients is fundamentally similar; however, young patients, and particularly PedMS patients experience more frequent relapses and associated neurological symptoms compared to adult MS patients.
- Robust annualized relapse rates (ARR) in Interferon beta (IFNβ)- or fingolimod-treated PedMS patients. The point sizes of individual studies are proportional to the effective sample sizes. Dashed line for meta estimates show the predictive 95% pointwise CI.
- Extrapolations from adult data to PedMS patients can be done and needs to account for differences in inflammatory disease activity in PedMS patients compared to that of adult MS patients.
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Objective

- To systematically review and summarize the current knowledge on relapse rates in PedMS based on existing literature and patient-level data, and to leverage this information in the newly planned NEOS Phase 3 trial of ofatumumab and siponimod in PedMS patients using a Bayesian framework.

Methods

- A systematic literature search was conducted in the MEDLINE and EMBASE databases through the Ovid platform, from inception until June 17, 2020, for all studies reporting annualized relapse rate (ARR) in Interferon beta (IFNβ)- or fingolimod-treated PedMS patients.
- ARR data from adult Phase 2 and 3 studies of IFNβ, fingolimod, siponimod, or ofatumumab-treated MS patients were analyzed to obtain age-based extrapolations of the ARR in PedMS patients.
- A meta-analysis was conducted from all available data sources (historical PedMS studies, and extrapolations from adult MS trials to PedMS) to summarize prior knowledge of the ARR on different treatments (IFNβ, fingolimod, ofatumumab, siponimod) and to quantify the uncertainty.
- Bayesian meta-analytic predictive priors were used to incorporate the historical information in the Bayesian design of the new study.
- The amount of information in priors was quantified using the effective sample size.

Results

- Age-based extrapolation from adults to PedMS
  - Age-based extrapolation from the adult Phase 3 TRANSFORMS trial (fingolimod vs IFNβ) conducted in year 2010 was highly accurate in predicting the outcome of the PARADIGMS trial (fingolimod vs IFNβ in PedMS patients) in year 2017. Similar results were obtained for other Phase 3 fingolimod studies.
  - Extrapolation of ARR from adults to PedMS patients can be done but needs to consider that relapse rates in paediatric patients may be higher than in adults.

Figure 2 Extrapolation of ARR from Phase 3 adult studies to PedMS patients, and superimposed ARR of pediatric MS patients

- Extrapolation of the ARR from adult healthy efficacy disease modifying therapy (fingolimod) would conclusively suggest superiority of the new drugs (siponimod and ofatumumab) over IFNβ.
- A meta-analytic framework with the Bayesian meta-analytic priors obtained from the historical information have an effective sample sizes of 48, 7, and 30 for fingolimod, siponimod, and ofatumumab, respectively.

Conclusions

- Extrapolation of the ARR from adult data to PedMS patients can be done and needs to account for differences in inflammatory disease activity in PedMS patients compared to that of adult MS patients.
- Extrapolation of ARR from adult data to PedMS patients can be done and needs to account for differences in inflammatory disease activity in PedMS patients compared to that of adult MS patients.

References


Disclosures

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