

Improving pediatric multiple sclerosis interventional phase III study design: a meta-analysis

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Abstract

Background: To support innovative trial designs in a regulatory setting for pediatric-onset multiple sclerosis (MS), the study aimed to perform a systematic literature review and meta-analysis of relapse rates with interferon β (IFN β), fingolimod, and natalizumab and thereby demonstrate potential benefits of Bayesian and non-inferiority designs in this population.

Methods: We conducted a literature search in MEDLINE and EMBASE from inception until 17 June 2020 of all studies reporting annualized relapse rates (ARR) in IFN β -, fingolimod-, or natalizumab-treated patients with pediatric-onset relapsing–remitting MS. These interventions were chosen because the literature was mainly available for these treatments, and they are currently used for the treatment of pediatric MS. Two researchers independently extracted data and assessed study quality using the Cochrane Effective Practice and Organization of Care – Quality Assessment Tool. The meta-analysis estimates were obtained by Bayesian random effects model. Data were summarized as ARR point estimates and 95% credible intervals.

Results: We found 19 articles, including 2 randomized controlled trials. The baseline ARR reported was between 1.4 and 3.7. The meta-analysis-based ARR was significantly higher in IFN β -treated patients (0.69, 95% credible interval: 0.51–0.91) versus fingolimod (0.11, 0.04–0.27) and natalizumab (0.17, 0.09–0.31). Based on the meta-analysis results, an appropriate non-inferiority margin versus fingolimod could be in the range of 2.29–2.67 and for natalizumab 1.72–2.29 on the ARR ratio scale. A Bayesian design, which uses historical information for a fingolimod or natalizumab control arm, could reduce the sample size of a new trial by 18 or 14 patients, respectively.

Conclusion: This meta-analysis provides evidence that relapse rates are considerably higher with IFNs versus fingolimod or natalizumab. The results support the use of innovative Bayesian or non-inferiority designs to avoid exposing patients to less effective comparators in trials and bringing new medications to patients more efficiently.

Keywords: annualized relapse rate, clinical trial design, fingolimod, interferon, natalizumab, pediatric-onset multiple sclerosis, systematic review

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Introduction

Multiple sclerosis (MS), an autoimmune disorder of the central nervous system, is characterized by inflammation and neurodegeneration, leading to disability accumulation.¹ The onset of disease is

generally observed in adulthood (age 20–40 years); however, the global incidence (0.05–2.85 per 100,000 children) and prevalence (0.69–26.92 per 100,000 children) rates in pediatric-onset MS have been on the rise.²

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Although the underlying pathology is similar to adult-onset MS, pediatric-onset MS is associated with higher relapse rates and radiological activity.³ Compared with adult-onset patients, children with pediatric-onset MS reach the secondary progressive disease stage and manifest prominent levels of cognitive impairment at younger age, leading to longer time lived with disability.⁴ Furthermore, the symptoms of depression and fatigue impact the daily functioning and psychosocial well-being of children at school.⁵ These symptoms may be associated with poor academic performance, social interactions, behavioral aspects, and quality of life of the child during the key formative years of development, impacting the attainment of educational and career milestones.⁶

Historically, most pediatric MS patients have been treated with first-line injectable therapies – interferon (IFN) β and glatiramer acetate – as evidenced by the data available from retrospective and observational studies.⁷ The efficacy of these treatments has never been demonstrated in a controlled clinical trial in pediatric patients, and up to 30% of the treated patients experience breakthrough disease activity and require disease-modifying therapies (DMTs) that have demonstrated higher efficacy in adult patients.⁸ The available literature for DMTs in pediatric MS is mainly for IFN β , fingolimod, natalizumab, or teriflunomide, which are largely based on the observational or retrospective studies except the phase III randomized, double-blind clinical trials – PARADIGMS in fingolimod⁹ and TERIKIDS in teriflunomide.¹⁰ Fingolimod is a sphingosine-1-phosphate receptor modulator and demonstrated superior reduction in annualized relapse rate (ARR) and magnetic resonance imaging activity versus IFN β in patients with MS, including pediatric-onset MS.^{4,9,11} Another treatment, natalizumab, is an anti-very late antigen-4, humanized monoclonal antibody which has been shown to be effective in adult MS, including pediatric-onset MS patients with highly active MS based on observational/retrospective studies;^{12–16} however, there are no pediatric data available from phase III randomized controlled trials. Recently, TERIKIDS study in 166 relapsing MS patients (aged 10–17 years) investigating efficacy of safety of teriflunomide, a dihydroorotate dehydrogenase inhibitor,¹⁷ did not meet its primary endpoint (reduction in relapse rate: 34% vs placebo, i.e. rate ratio of 0.66 [95% confidence interval from 0.39 to 1.11], $p=0.29$; NCT02201108).¹⁰ In addition to the above studies, several clinical trials in pediatric MS are

ongoing to determine the effect of DMTs in pediatric-onset MS, including LemKids (NCT03368664) for alemtuzumab, CONNECT (NCT02283853) for dimethyl fumarate, and an open-label phase II study (NCT04075266) for ocrelizumab. Overall, there remains a strong medical need for phase III trials for new treatment options in pediatric MS with proven efficacy based on controlled clinical trials.

Current regulations by the US Food and Drug Administration (FDA) and European Union require that any new product or drug developed for the treatment of MS in the adult population must also be investigated for efficacy and safety in the pediatric patient population.¹⁸ Several planned or ongoing trials in pediatric MS patients compete for a small pool of available patients, which causes feasibility constraints.¹⁹ Moreover, the testing of new drugs in classical randomized controlled clinical trials poses ethical and feasibility challenges and calls for more innovative trial designs.²⁰ At the start of a new trial in pediatric participants, data from adult patients are often available. As biology of the disease is similar between adult- and pediatric-onset MS, a new trial in pediatric patients could make use of the data from adult patients, which is often available, in a Bayesian framework to reduce sample size requirements and gain efficiency for a pediatric trial. In addition, it would be desirable to minimize the use of placebo and low-efficacy treatment control groups to reduce the risk of relapse. One way to achieve this is to demonstrate that the relapse rates are equally low on treatment with a new drug as on a concurrent efficacious control and distinctly lower than those historically reported in untreated or IFN β -treated patients.

To support innovative trial designs in a regulatory setting for patients with pediatric-onset MS, this study aimed to (1) perform a systematic literature review and meta-analysis of studies investigating relapse rates in pediatric MS patients treated with IFN β , fingolimod, or natalizumab and (2) demonstrate potential benefits of Bayesian and non-inferiority designs in this population using the meta-analysis results.

Methods

Study population and intervention selection

For a study to be considered for inclusion, the study population and outcomes had to be typical

of pediatric-onset MS or at least informative for a new regulatory study in pediatric MS. For instance, studies conducted in special populations, such as patients with highly active MS or children below the age of 10 years, or with unusual endpoint definitions were excluded because such studies would not be informative in the context of a new regulatory trial. Interventions considered in the literature search were in line with the regulatory context and included (1) fingolimod because of its proven efficacy and safety in a randomized controlled phase III study; (2) IFN β because it is the de facto standard of care among platform therapies and has been used as a comparator to demonstrate efficacy against new treatment as per regulatory guidelines (intramuscular IFN β -1a was tested in a limited number of pediatric patients²¹); and (3) natalizumab because of its high efficacy in adult MS patients and its de facto use in pediatric patients. Although natalizumab is not approved yet in pediatric patients, it was considered informative to summarize relapse rates as a potential alternative control treatment in a non-inferiority design.

Data sources and literature search strategy

A systematic review and a meta-analysis of studies were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²² We conducted a literature search of all studies in MEDLINE and EMBASE through the Ovid platform from inception to 17 June 2020, reporting relapse rates in patients with pediatric-onset relapsing–remitting MS. Search terms included MS AND (adolescents OR children OR juvenile OR pediatric OR early onset) AND (interferon OR betaseron OR betaferon OR Avonex OR Rebif OR fingolimod OR Gilenya OR natalizumab OR Tysabri OR placebo OR untreated OR no treatment).

Selection criteria

Eligible records were screened first by title and abstract, and those that did not meet the search criteria, such as case reports, conference material, editorials/letters, short surveys, or review papers, were excluded. The remaining publications were excluded if they did not report any information about relapses (e.g. ARR, total number of relapses, or patient-level information about relapses). An overview of the inclusion criteria for the systematic search is summarized in Table S1.

Data extraction

The literature search was conducted by a researcher (A.S.) based on the described search methodology. All studies that were retrieved from the databases were evaluated for study design, patient population, intervention, and outcomes. Titles and abstracts at the first stage and full articles at the second stage were evaluated by two researchers (M.T. and A.S.) independently to determine their potential relevance. The included studies were validated and clinically confirmed by another researcher (J.L.). Any disagreements or discrepancies were resolved through joint article review and discussion.

Quality assessment

The level of evidence and quality assessment were evaluated using the Cochrane Effective Practice and Organization of Care – Quality Assessment Tool for the included studies.²³ In this analysis, we assigned total scores of ≤ 4 , 5–7, and 8–10 for low, moderate, and high quality of studies, respectively.

Outcomes

The ARR, defined as the mean number of confirmed relapses per patient per year, that is, adjusted for the individual follow-up time, was assessed in this study. ‘Relapse’ was commonly defined as ‘new or worsening symptoms that last 24 h, occurring in the absence of fever or infection’.²⁴ Definitions of ‘relapse’ varied across pediatric studies that used the Poser criteria,²⁵ modified McDonald criteria,^{26–28} IPMSSG criteria,^{29,30} and/or Lublin criteria³¹ and are summarized in Table S2. Uncertainty in ARR estimates was captured based on confidence interval (CI) or standard error (SE) if these were available. However, not all studies reported measures of uncertainty (in the form of either CI or SE) for the ARRs.

Data analyses

Meta-analysis. Meta-analysis estimates were obtained using a Bayesian random effects model fitted to the log ARRs and SEs from individual studies, under the assumption of equal between-trial variability for all treatments. If the SE (or CI) was not available from the individual study, the values were calculated based on the reported relapse rates and follow-up times, with assumption

of similar over-dispersion of relapses as in the PARADIGMS study.⁹ For a study reporting zero relapses,³² a non-zero ARR estimate derived from a Bayesian negative binomial model³³ was used in the meta-analysis.

For the meta-analysis, weakly informative normal (0, 5) priors were used for the population means for each treatment. For the between-trial standard deviation, a half-normal prior with a scale parameter of 0.5 was used.³⁴ Results were summarized in forest plots showing ARR point estimates and 95% credible intervals for individual studies and meta-analysis estimates. Heterogeneity across the studies was assessed by the estimated between-trial variability parameter in the model.

Sensitivity analyses were performed to assess the robustness of the meta-analysis results to the model assumptions and priors. These analyses included fitting the model, assuming different between-trial variability for IFN β versus natalizumab and fingolimod, and a less informative prior scale for the between-trial standard deviation. In addition, the meta-analysis was repeated without some outlier studies that reported ARR > 1 for IFN β .

To supplement the data from the literature review, individual patient data from adult fingolimod phase III studies (24-month FTY720 Research Evaluating Effects of Daily Oral therapy in MS (FREEDOMS; NCT00289978),³⁵ FREEDOMS II (NCT00355134),³⁶ and 12-month Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting MS (TRANSFORMS; NCT00340834)³⁷) were used in a supplementary analysis to obtain extrapolated relapse rate estimates in children on fingolimod and IFNs using negative binomial models adjusting for age and baseline number of relapses on individual data. All analyses were performed using R version 3.6.1 (R Core Team, Vienna, Austria).³⁸

Informing future innovative trial designs. Based on historical data from meta-analysis results, features of innovative designs for future pediatric MS studies were explored. These included non-inferiority trials versus highly effective treatments (which would show superiority over placebo or low-efficacy treatments indirectly based on historical control data) and Bayesian designs using the historical information (e.g. based on completed trials for the same medication) to reduce the number of patients required in the new study.³⁹

To explore the possibility of the use of completed adults study data to inform the newly planned pediatric trial, a supplementary meta-analysis, including adult studies, was performed. Non-inferiority margins for a non-inferiority study of a new test drug versus fingolimod or natalizumab were derived using the inverse of the upper bound of the credible intervals for the ARR ratios of fingolimod/natalizumab versus IFN β . Showing non-inferiority of a new test drug versus a concurrent fingolimod or natalizumab control using these margins would guarantee superior efficacy over IFN β (and placebo). In addition, the meta-analytic predictive (MAP) approach⁴⁰ was used to obtain prior distributions for the ARR in a new pediatric study with a Bayesian design. Effective sample size (ESS) can be used to quantify the information included in the priors and represents the number of patients by which the sample size for a trial can be reduced, when using MAP-priors for the control arm. The ESS for MAP priors was calculated using the expected local information ratio approach proposed by Neuenschwander *et al.*⁴¹

Data availability statement

Anonymized data that support the findings of this study will be made available to qualified external researchers, with requests reviewed and approved by an independent review panel on the basis of scientific merit.

Results

Identified studies

A total of 1751 studies were identified during the initial database search (Figure 1). After removing the duplicates ($n = 264$) and screening based on titles and abstracts, full texts of 82 studies were considered. Of these, 19 studies met the inclusion criteria as defined in Table S1. The average study duration follow-up ranged from 0.72 to 6.7 years. Among these studies, 2 were randomized controlled clinical trials in patients with pediatric MS, while 17 were observational studies. An overview of 19 studies summarizing the study design, patient population, and treatment interventions is presented in Table S2.

Patient disposition and baseline characteristics

The key demographic and baseline characteristics of patients from the 19 studies that met the selection

criteria are presented in Table 1. The mean age of the patients ranged from 11.0 to 16.7 years across studies. Approximately 44%–85% of patients were female. The mean disease duration ranged from 0.4 to 5.1 years. The ARR reported at baseline before observation was between 1.4 and 3.7 when available. In most studies (11/19), patients were treatment-naïve at study entry. In one study, the presence or absence of prior treatment was not reported, and in the remaining seven studies, 37%–100% of patients had received prior MS treatment.

ARR on different DMTs

The ARR reported in the individual publications for 19 studies are summarized in Table 2.

In the randomized controlled trials ($n=2$), ARR with IFN β was 0.679⁹ and 0.5942⁴² (Table 2). In the remaining trials of varying study designs ($n=11$), ARR ranged from 0.21 to 1.6 in the IFN β group. The ARR with fingolimod was 0.12 in the randomized trial of PARADIGMS⁹ and 0.08 in the non-randomized trial based on a Brazilian database.⁴⁴ In non-randomized studies ($n=5$), ARR with natalizumab treatment ranged from 0.00 to 0.4.

Meta-analysis. The results of the meta-analysis based on the literature review of 19 studies (IFN β , 12; fingolimod, 2; and natalizumab, 5) are depicted in Figure 2. These studies were considered informative for a new trial in pediatric MS. The combined estimate for the ARR (95% credible interval) in IFN β -treated patients was 0.69 (0.51–0.91) across all studies versus 0.11 (0.04–0.27) with fingolimod and 0.17 (0.09–0.31) with natalizumab. ARR reported in the fingolimod and natalizumab studies were lower than all ARRs reported in the IFN β studies, with the exception of one IFN β study.⁵¹ The between-trial standard deviation on the log-ARR scale was estimated to be 0.45 (0.27–0.72), indicating considerable between-trial heterogeneity.

For all sensitivity analyses conducted, results were consistent with the main analysis and showed no overlap in the estimated ARR credible intervals between IFNs and fingolimod/natalizumab (Table S3).

Innovative trial designs

The results of the meta-analysis, in particular the high relapse rates with IFNs compared with the

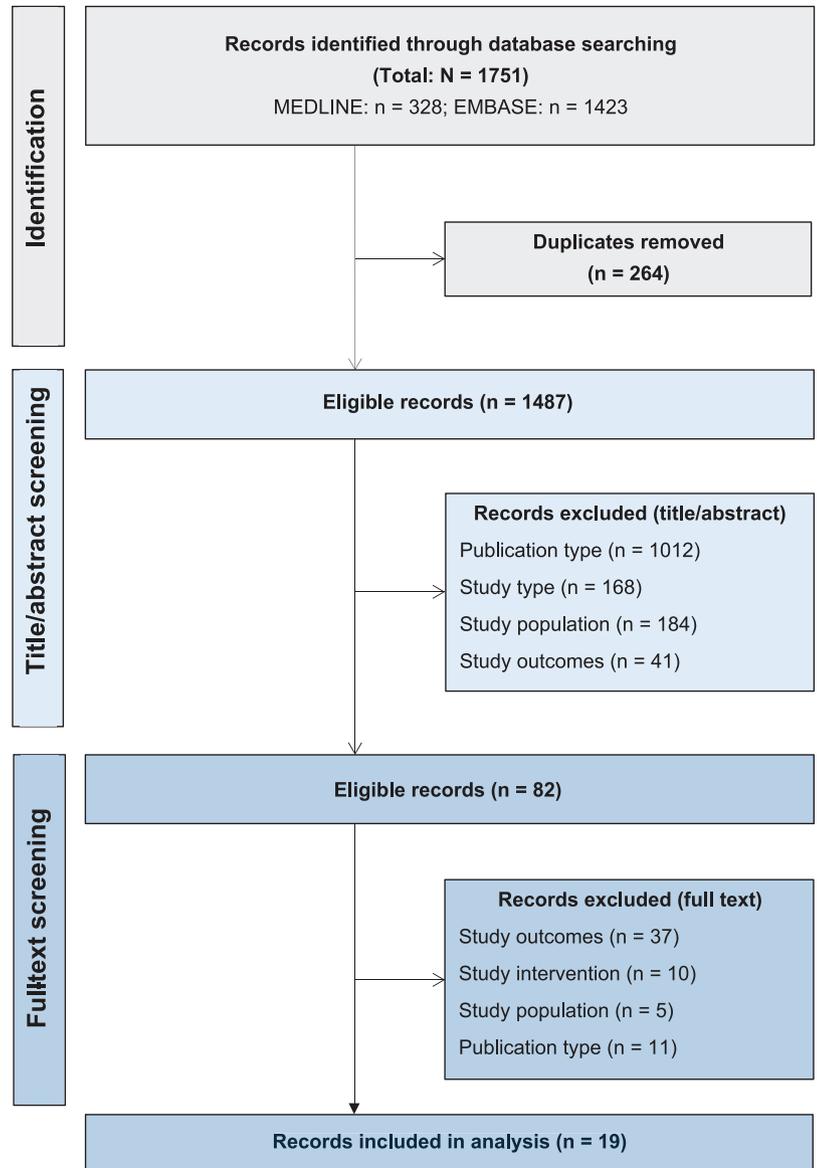


Figure 1. PRISMA diagram for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

higher efficacy therapies, justify the use of innovative trial designs to avoid unnecessary risk of relapse during the trial. Possible innovative design options we would like to highlight here include non-inferiority designs versus an effective treatment (e.g. fingolimod), where the objective of the trial is to indirectly demonstrate superiority to IFN β by showing that a new treatment is non-inferior (i.e. not worse in terms of relapse rate) to an established effective treatment within a pre-specified margin. This margin can be chosen based on historical data so that superiority over IFN β is guaranteed when the objective of

Table 1. Patient demographics and baseline characteristics of trial populations.

Study author (Study acronym)	Treatment (Sample size, N)	Mean age \pm SD (and/or range) (years)	Female (n, %)	Mean \pm SD disease duration (and/or range) (years)	Mean ARR \pm SD (and/or range)	Prior treatment (n, %)
Randomized controlled clinical trials						
Chitnis <i>et al.</i> ⁹ (PARADIGMS)	Fingolimod (107) IFN β (107)	15.3 \pm 1.8	134 (62)	2.1 \pm 1.9 [0.2–10.9]	1.2 \pm 1.4 [0–4.5]	79 (37)
Pakdaman <i>et al.</i> ⁴²	IFN β (8) No treatment (8)	12.9	10 (63)	1.72	1.42	0 (0)
Non-randomized controlled clinical trials						
Margoni <i>et al.</i> ³²	Natalizumab (20)	14.2 \pm 2.5	13 (65)	0.5 \pm 0.33	2.1 \pm 0.3	20 (100)
Huppke <i>et al.</i> ⁴³	IFN β (249) GA (51)	13.7 \pm 2.7	N/R	1	N/R	0 (0)
Fragomeni <i>et al.</i> ⁴⁴	IFN β (45) GA (15)	15.0 [4.5–17.9]	N/R	N/R	N/R	0 (0)
Ben Achour <i>et al.</i> ⁴⁵	IFN β (17)	11 [3–17]	13 (76)	N/R	2.0 [0.25–4]	0 (0)
Gärtner <i>et al.</i> ⁴⁶ (BETAPAEDIC)	IFN β (65)	14.2 \pm 1.3	50 (77)	0.4 \pm 1.4 [0–9.2]	2.2 \pm 1.4	0 (0)
Alroughani <i>et al.</i> ¹²	Natalizumab (32)	15.7 \pm 1.9 [8–17]	23 (72)	5.1 \pm 3.1 [1–11]	1.66 \pm 0.5	21 (66)
Fragoso <i>et al.</i> ⁴⁷	Fingolimod (17)	16.1 [14–17]	10 (59)	N/R	2.8 [0–8]	13 (76)
Ghezzi <i>et al.</i> ¹⁵	Natalizumab (101)	14.7 \pm 2.4	69 (68)	2.1 \pm 1.94	2.3 \pm 1.3	66 (65)
Arnal-Garcia <i>et al.</i> ¹³	Natalizumab (9)	15.3 [9.8–17.7]	4 (44)	4.0 [2–7]	3.0 [1–8]	8 (89)
Kornek <i>et al.</i> ¹⁴	Natalizumab (20)	16.7 \pm 1.1	16 (80)	1.5 \pm 0.33	3.7	19 (95)
Tenembaum <i>et al.</i> ⁴⁸	IFN β (307)	14.0 \pm 3.0	190 (62)	0.8	1.79	0 (0)
Basiri <i>et al.</i> ⁴⁹	IFN β (13)	14.7 \pm 1.9	11 (85)	N/R	N/R	N/R
Ghezzi <i>et al.</i> ⁵⁰	IFN β (Avonex [®]) (77)	11.4 \pm 3.1	47 (61)	1.94 \pm 1.33	2.5 \pm 1.9	0 (0)
Ghezzi <i>et al.</i> ⁵⁰	IFN β (Rebif [®] /Betaferon [®]) (39)	12.6 \pm 2.6	25 (64)	1.6 \pm 1.43	3.2 \pm 2.5	0 (0)
Tenembaum <i>et al.</i> ⁵¹	IFN β (19)	15.9 [11.3–17.9]	N/R	3.4 [0.3–13.9]	1.8 [1–3]	0 (0)
Pohl <i>et al.</i> ⁵²	IFN β (51)	14.6 [8.1–17.9]	36 (71)	2.0 [0.1–6.7]	1.9 [0.4–7.6]	0 (0)
Waubant <i>et al.</i> ⁵³	IFN β (9)	12.7 [8–15]	7 (78)	N/R	1.4	0 (0)

ARR, annualized relapse rate; GA, glatiramer acetate; IFN, interferon; N/R, not reported; SD, standard deviation.

non-inferiority is reached. A second option is the use of a Bayesian trial design, where historical data on the control treatment can be directly incorporated in the form of priors. This would

then allow for comparison against an IFN β to show superiority and for reduction in the number of patients required for a new study (as some information is already included in the priors).

Table 2. ARR in pediatric patients with MS.

Study	Treatment group (N)	Comparator group (N)	ARR (treatment group) (95% CI)	ARR (comparator group) (95% CI)
I. Randomized controlled clinical trials				
Chitnis <i>et al.</i> ⁹ (PARADIGMS)	Fingolimod (107)	IFNs (107)	0.12 (0.08–0.19)	0.67 (0.52–0.89)
Pakdaman <i>et al.</i> ⁴²	IFN β (8)	No treatment (8)	0.59 (0.38–0.93) ^a	1.09 (N/R) ^a
II. Non-randomized controlled clinical trials				
Margoni <i>et al.</i> ³²	Natalizumab (20)	–	0.0 (N/R)	–
Huppke <i>et al.</i> ⁴³	IFN β (249)	GA (51)	0.79 (0.70–0.90)	0.89 (0.7–1.1)
Fragomeni <i>et al.</i> ⁴⁴	IFN β (45; 32 on high dose, 13 on low dose)	GA (15)	1.38 (N/R) on high dose 1.24 (N/R) on low dose	0.53 (N/R)
Alroughani <i>et al.</i> ¹²	Natalizumab (32)	–	0.06 (0.01–0.25) ^b	–
Ben Achour <i>et al.</i> ⁴⁵	IFN β (17)	–	0.42 (N/R)	–
Gärtner <i>et al.</i> ⁴⁶ (BETAPAEDIC)	IFN β (65)	–	0.70 (0.51–0.96) ^b	–
Fragoso <i>et al.</i> ⁴⁷	Fingolimod (17)	–	0.08 (N/R)	–
Ghezzi <i>et al.</i> ¹⁵	Natalizumab (101)	–	0.10 (0.06–0.18) ^b	–
Arnal-Garcia <i>et al.</i> ¹³	Natalizumab (9)	–	0.38 (N/R)	–
Kornek <i>et al.</i> ¹⁴	Natalizumab (20)	–	0.40 (N/R)	–
Tenembaum <i>et al.</i> ⁴⁸	IFN β (307)	–	0.47 (N/R)	–
Basiri <i>et al.</i> ⁴⁹	IFN β (13)	–	0.41 (0.15–1.09) ^a	–
Ghezzi <i>et al.</i> ⁵⁰	IFN β (Avonex) (77)	–	0.40 (0.32–0.49) ^b	–
Ghezzi <i>et al.</i> ⁵⁰	IFN β (Rebif/ Betaferon) (39)	–	0.90 (0.63–1.3) ^b	–
Tenembaum <i>et al.</i> ⁵¹	IFN β (19)	–	0.21 (N/R)	–
Pohl <i>et al.</i> ⁵²	IFN β (51)	–	0.80 (N/R)	–
Waubant <i>et al.</i> ⁵³	IFN β (9)	–	1.60 (N/R) ^a	–
ARR, annualized relapse rate; CI, confidence interval; GA, glatiramer acetate; IFN, interferon; MS, multiple sclerosis; N/R, not reported. Avonex® (intramuscular IFN β -1a [Biogen Netherlands BV, Badhoevedorp, Netherlands]). Betaferon® (IFN β -1b [Bayer AG, Leverkusen, Germany]). Rebif® (subcutaneous IFN β -1a [Merck Europe BV, Amsterdam, Netherlands]). Betaseron® (IFN β -1b [Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA]). ^a ARR calculated from reported individual patient data. ^b CI was derived from reported standard deviation/standard error.				

When using historical data to inform non-inferiority margins for a new trial or for a Bayesian prior, all relevant data should be considered. In the pediatric setting, this includes data from adult patients, if accurate extrapolation of data from adults to children is

possible.⁵⁴ In MS, it is possible to extrapolate adult data to children.⁵⁵ Therefore, in the setting of pediatric MS relevant, data from adult studies should be included when informing non-inferiority margins or forming Bayesian priors for a new trial.

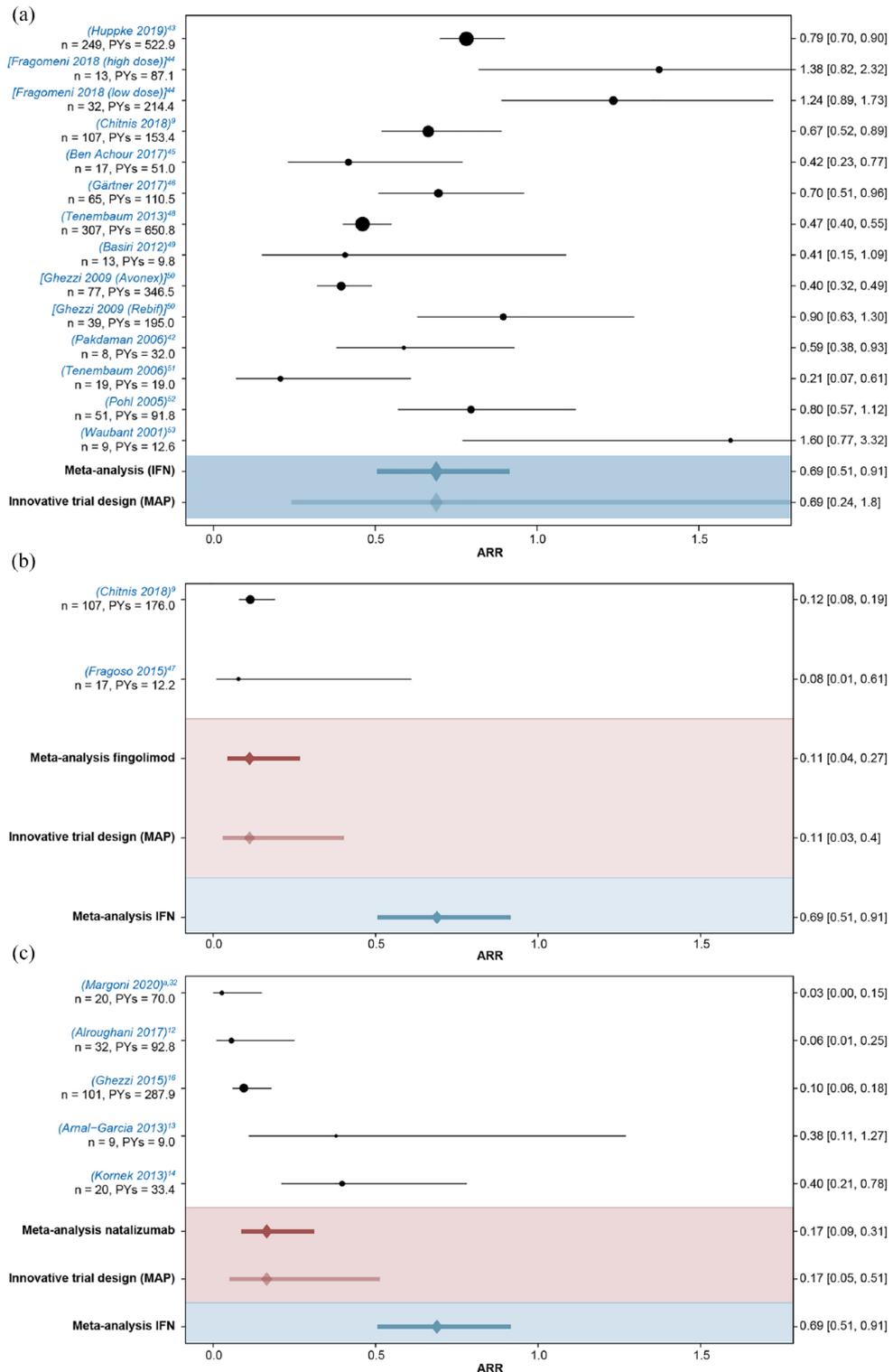


Figure 2. Meta-analysis of ARR (95% CI) reported in pediatric patients with MS. (a) IFN β studies, (b) fingolimod studies, and (c) natalizumab studies. Point sizes of individual studies are proportional to the sample size. Meta-analysis is obtained using Bayesian random effects model for the log ARR.

ARR, annualized relapse rate; CI, confidence interval; IFN, interferon; MAP, meta-analytic predictive; Meta, meta-analysis; MS, multiple sclerosis; PYs, patient-years.

^aReported ARR for this study was 0. ARR estimate and interval given here are based on a Bayesian negative binomial model to allow inclusion into the meta-analysis.

Based on the estimated ARR from the supplementary analysis, including the adult studies, approximately five times lower relapse rates were observed with fingolimod treatment compared with IFN β in children (Figure S1). The ARR ratio (95% credible interval) of fingolimod versus IFN β in children was estimated to be 0.21 (0.12–0.37). Using the upper bound of the 95% interval as a conservative estimate of the treatment effect and taking the inverse of this, a non-inferiority margin 2.67 versus fingolimod could ensure indirectly superiority over IFN β . Thus, if the ARR ratio of the investigational treatment versus fingolimod in a new trial would be smaller than 2.67, the treatment could be considered non-inferior to fingolimod and superior to interferons. Taking into account that the results are mostly based on observational data and the large between-trial variability, a smaller non-inferiority margin using the upper bound of the 99% interval could be recommended, which is approximately 2.29. Therefore, based on the historical data used for the meta-analysis, margins in the range from 2.29 to 2.67 on the ARR ratio scale could be considered to ensure indirectly superiority over IFNs. Similarly, a range of possible non-inferiority margins for natalizumab would be 1.72–2.29 on the ARR ratio scale.

To directly use the historical information on ARRs from a meta-analysis in a new study, MAP^{39,40} priors can be used to represent the range of values in the ARR that could be expected on the control treatment in the new study. A Bayesian design for a new study incorporates the historical information through the MAP priors and reduces the number of patients required in the control arm or even allows comparison only against historical data. Based on our meta-analysis, including adult studies, MAP prior estimates (95% credible interval; Table S3) would be 0.68 (0.27–1.66) for IFN β , 0.15 (0.06–0.38) for fingolimod, and 0.17 (0.06–0.47) for natalizumab. For a new 2-year study with these priors, the ESS would be 7 for IFN β , 18 for fingolimod, and 14 for natalizumab.

Discussion

This meta-analysis summarizes our knowledge of relapse rates in pediatric patients treated with IFNs, fingolimod, and natalizumab using currently available information and can inform new trials in pediatric MS. Pediatric patients treated with first-line IFN β had an ARR of 0.69 (95% CI:

0.51–0.91), which is an average of more than one relapse every other year for patients under treatment. The relapse rates were approximately five-fold higher than those observed in pediatric patients treated with either fingolimod or natalizumab, which raises concerns on the use of IFN β as a comparator in pediatric participants in future trials.

In this meta-analysis, fingolimod reduced the ARR by 83% (95% credible interval 55%–94%) and natalizumab by 76% (95% CI: 54–89) versus IFN β in pediatric-onset MS. The ARR reduction reported in this meta-analysis for fingolimod versus IFN β -1a (83%) is in line with that of the pediatric PARADIGMS study, which showed a reduction of 82% (95% CI: 0.11–0.30) in the relapse rate.⁹ Similarly, results of natalizumab were in line with those of previous observational studies.^{12–16}

Regulatory phase III studies in pediatric MS are typically conducted in patients aged between 10 and 18 years; for patients younger than 10 years, a waiver is usually granted based on the rarity of the disease at that age. In the targeted age group, the biology of pediatric MS is similar to that of adult MS patients, except for a higher level of inflammatory disease activity in the pediatric-onset patients. It is therefore possible to use an age-dependent extrapolation of relapse rates from adult patients to pediatric patients. Likewise, previously, data of adult-onset MS patients from the TRANSFORMS trial were extrapolated to pediatric patients in PARADIGMS by modeling relapse rates as a function of the patient's age; this provided highly accurate predictions of the actual PARADIGMS results.⁵⁵ Similarly, comparing between the main analysis and the sensitivity analysis in this meta-analysis, extrapolated results from adults^{36,37} were in line with those obtained from pediatric patients. This is relevant for the planning of new trials in pediatric MS, as it demonstrates that extrapolation of data from adult MS trials (which are typically available at the time of the launch of a pediatric study) can in principle be used to inform a new study and help to reduce the overall sample size or the size of the control arm.

Furthermore, the findings from this systematic review suggest that it is possible to design new, feasible studies in pediatric MS that use efficacious active control treatment. This corroborates with recommendations from the International

Pediatric Multiple Sclerosis Study Group that suggest ensuring high-quality evidence-based treatment for children and adolescents with MS.²⁰

The meta-analysis provides insight on how non-inferiority margins or Bayesian priors could be used to inform designs for future pediatric MS studies based on the historical data and adult phase III studies. A recent example of a study design in pediatric MS making use of the innovative elements proposed here is the phase III NEOS study comparing ofatumumab and siponimod with fingolimod (NCT04926818). NEOS uses innovative design elements by incorporating historical data to define a non-inferiority margin versus fingolimod and also robustly borrows information from historical studies in adults and children for the analysis using MAP priors, avoiding the use of placebo or IFN comparator and optimizing sample size. The innovative design elements for this study have been discussed and agreed with the FDA and the European Committee for Medicinal Products for Human Use (CHMP), and the study started recruitment of patients in 2021.

Limitations: Most studies in pediatric-onset MS are observational. The literature review and the subsequent meta-analysis revealed high between-study heterogeneity in the ARR reported across the published studies. Although meta-regression using baseline variables (age, ARR, disease duration, and percentage of treatment-naïve patients) on the available information reveals no large variability, there could be variability resulting from (partly unknown) differences in study design, patient population, treatments, and 'relapse' definition.

Our analysis also calculated non-inferiority margins and MAP priors for natalizumab, even though natalizumab is not an approved treatment in pediatric MS. The demonstration of non-inferiority to natalizumab could theoretically be considered an adequate proof of efficacy of a new therapy; however, the acceptability and practicality of such an approach would need to be evaluated with regulatory agencies and ethical bodies before initiating such a study.

Our literature review and meta-analyses focus on efficacy with ARR as the typical primary endpoint in MS and do not consider safety endpoints. While safety is naturally also of concern in pediatric trials, due to the limited sample size,

it is generally possible to only detect strong imbalances in common adverse events, irrespective of the design of the trial. It would not be feasible to design a pediatric MS trial to detect possibly rare safety signals. Data from larger adult trials, which will typically be available at the time of pediatric development, and real-world data collected after approval can be used to assess safety topics on a more granular level.

Conclusion

Our meta-analysis suggests that relapse rates are approximately fivefold higher with IFNs than with fingolimod or natalizumab. Thus, innovative trials will improve the feasibility of recruitment and avoid the use of low-efficacy treatments as comparators in pediatric studies. Based on our results, novel trial design in pediatric patients can reduce the number of required patients using Bayesian designs or employing non-inferiority designs, which will help to establish superiority by indirect comparison to historical IFN β data.

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Author contributions

J.S.G. contributed to the study concept, design, data acquisition, and outline review and critical revision of the article; M.T. contributed to the study concept, design, execution, data acquisition, analysis and interpretation, outline review and critical revision of the article, and statistical analysis; J.L. contributed to the study concept, design, execution, interpretation of results, and outline review and critical revision of the article; A.S. contributed to the systematic literature search, analysis and interpretation, and article development, including revising and finalizing the draft for submission; A.G. contributed to the

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Conflict of interest statement

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Ethical statement

Our study did not require an ethical board approval because it is a systemic review and meta-analysis of studies identified through literature search. The authors acknowledge the patients, investigators, and staff at participating sites who participated in the trials that are included in the meta-analysis study.

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Supplemental material

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