Πανεπιστήμιο Θεσσαλίας

Τμήμα Ιατρικής

Πρόγραμμα Μεταπτυχιακών Σπουδών

Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική

Καθηγητής: Η. Ζιντζαράς

Μεταπτυχιακή εργασία με τίτλο:

"Επίδραση ανοσοτροποποιητικής αγωγής στην εξέλιξη της αναπηρίας σε ασθενείς με πολλαπλή σκλήρυνση: Μετα-ανάλυση κλινικών μελετών"

Φοιτητής: Δαρδιώτης Ευθύμιος

Supervisor: Γ.Μ. Χατζηγεωργιου

Evaluator 1: Η. Ζιντζαράς

Evaluator 2: Ι. Στεφανίδης

Αύγουστος 2015

Title:

The effect of disease modifying therapies on disease progression in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis

Abstract:

Background: A number of officially approved disease-modifying drugs (DMD) are currently available for the early intervention in patients with relapsing-remitting multiple sclerosis (RRMS). The aim of the present study was to systematically evaluate the effect of DMDs on disability progression in RRMS using from all available placebo-controlled randomized clinical trials (RCT).

Methods: A systematic review and meta-analysis was conducted according to PRISMA guidelines of all available placebo-controlled RCTs of RRMS patients that reported absolute numbers or percentages of disability progression during each study period.

Results: DMDs for RRMS were found to have a significantly lower risk of disability progression compared to placebo (RR=0.72, 95%CI: 0.66-0.79; p<0.001), with no evidence of heterogeneity or publication bias. In subsequent subgroup analyses, neither dichotomization of DMDs as "first" and "second" line RRMS therapies [(RR=0.72, 95% CI=0.65-0.81) vs. (RR= 0.72, 95%=0.57-0.91); p=0.99] nor the route of administration (injectable or oral) [RR=0.75 (95% CI=0.63-0.88) vs. RR= 0.74 (95% CI=0.66-0.83); p=0.93] had a differential effect on the risk of disability progression. Either considerable (5-20%) or significant (>20%) rates of loss to follow-up were reported in all included study protocols, while financial and/or other support from pharmaceutical industries with a clear conflict of interest on the study outcomes was documented in all included studies.

Conclusion: Available DMDs appear to be effective in reducing disability progression in patients with RRMS, independent of the route of administration and their classification as "first" or "second" line therapies. Attrition bias needs to be taken into account in the interpretation of these findings.

Introduction:

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease that manifests with acute relapses and progressive disability[1]. Expanded Disability Status Scale (EDSS) change is the main outcome measure used in MS clinical studies[2], as a potential indicator of neurological improvement that correlates directly with the quality of patients' life[3]. A number of officially approved disease-modifying drugs (DMD), including novel oral agents, are currently available for the aggressive early intervention in patients with relapsing-remitting MS (RRMS), promising higher treatment goals and long-term outcomes improvement[4].

The aim of the present systematic review and meta-analysis was to systematically evaluate the effect of all available DMDs on disability progression in RRMS using follow-up data from all available placebo-controlled randomized clinical trials (RCT). Moreover, we sought to evaluate potential sources of heterogeneity regarding the potential differential effect of DMD subgroups on disability progression.

Methods:

Trial identification and data abstraction:

This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses[5]. Eligible placebo-control RCTs that reported absolute numbers or percentages of RRMS patients with disability progression during the study period were identified by searching MEDLINE, SCOPUS and the CENTRAL Register of Controlled Trials. The combination of search strings that was used in all database searches included the terms: “relapsing-remitting multiple sclerosis”, “RRMS”, “disability” and “EDSS change”. No language or other restrictions were imposed. Last literature search was conducted on February 7th, 2015. Reference lists of all articles that met the criteria and of relevant review articles were examined to identify studies that may have been missed by the database search.

All retrieved studies were scanned to include only placebo-control RCTs that reported either the absolute or the percent numbers of RRMS patients with disability progression during the study period in both treatment and placebo subgroups. Excluded from the final analysis were: 1. Observational studies, 2. case series, 3. case reports, 4. RCTs without placebo subgroups and 5. studies reporting the use of RRMS therapies that are not still officially

approved.

In each study that met the inclusion criteria for the quantitative analysis a predefined 7-point quality control was used to address for biases. For each quality item the corresponding risk of bias was categorized as low, high or unclear according to the suggestions by Higgins et al[6]. Complete outcome data were judged as "low risk" when the percentage of participants lost to follow-up was lower than 5% and "high risk" when the reported loss to follow up was more than 20%. In studies reporting loss to follow up between 5%-20% the risk of attrition bias was categorized as "unclear"[7]. In the “other bias” category all other potential sources of bias, including the source of funding reported in each protocol were included[8]. Quality control and bias identification was also performed.

Absolute or percent numbers of RRMS patients with disability progression during the study period were extracted from the studies. The active treatment arm with the finally approved dose of DMD was selected in each trial for comparisons versus the placebo arm.

Statistical analyses

Risk ratios (RRs) were calculated in each study protocol to express the comparison of disability progression in RRMS patients treated with a DMD and those RRMS patients receiving placebo. RR values smaller than 1 denote that the treatment under investigation has a positive effect in the number of RRMS patients with disability progression compared to placebo. A random-effects model (DerSimonian Laird) was used to calculate the pooled RRs. The equivalent z test was performed for each pooled RR, and if $p < 0.05$ it was considered statistically significant.

Heterogeneity between studies was assessed with the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity, as per the Cochrane Handbook.[9] Publication bias (i.e. assessment of bias across studies) was graphically evaluated using a funnel plot[10] and with the Egger’s statistical test for funnel plot asymmetry.[11]

Subsequently subgroup analyses were conducted according to (i) current categorization of eligible DMDs as “first line” (INFb-1b, glatiramer acetate, INFb-1a, teriflunomide, dimethyl fumarate) and “second line” (natalizumab & fingolimod) RRMS

treatments (ii) the DMT route of administration: injectable subcutaneously (IFNβ-1a, IFNβ-1b and glatiramer acetate) or intramusculary (IFNβ-1a) vs. oral (fingolimod, teriflunomide, dimethyl fumarate).

The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, a random effects model (DerSimonian Laird) was used to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. I assumed the study-to-study variance (tau-squared) to be the same for all subgroups. Tau-squared was first computed within subgroups and then pooled across subgroups.

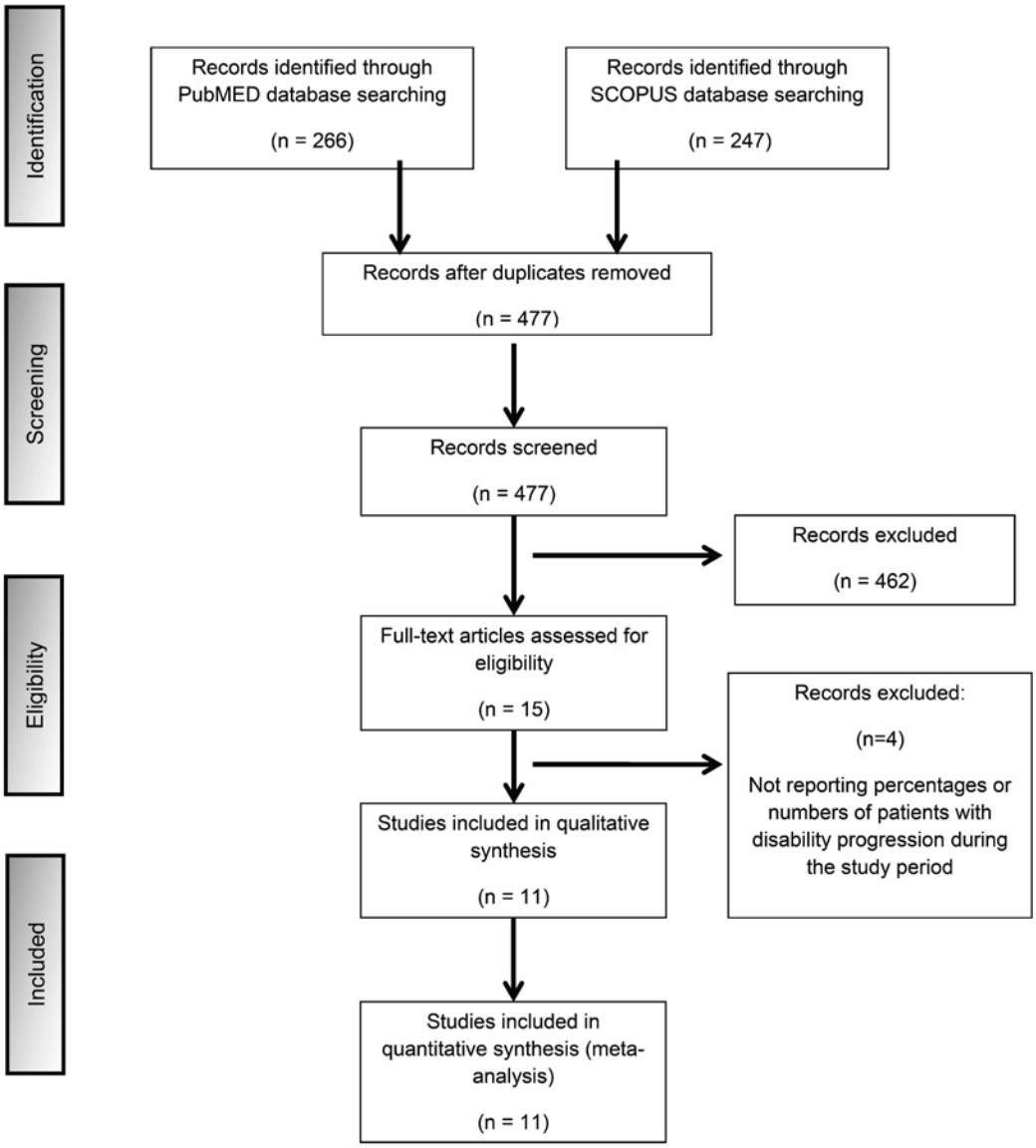
Statistical analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Comprehensive Meta-analysis Version 2 software (Borenstein M, Hedges L, Higgins J, Rothstein H, Biostat, Englewood NJ, 2005).

Results

Study selection and study characteristics

Systematic search of MEDLINE and SCOPUS databases yielded 266 and 247 results respectively. Subsequent search in the CENTRAL Register of Controlled Trials retrieved no additional RCTs. After removing duplicates, the titles and abstracts from the remaining 477 studies were screened and 15 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 15 studies, 4 studies were excluded because they provided neither percentages nor numbers of patients with disability progression during the study period.[12-15] Finally 11 studies that met the study protocol's inclusion criteria were included both in the qualitative and quantitative synthesis **(Figure 1)**.[16-26] The characteristics of the included studies, comprising 6872 patients are summarized in **Table 1**. The following treatment arms (including only placebo arms and active arms with approved doses of available DMD) of the 11 selected RCT were included in the present analyses: INFb-MS (INFβ-1b subcutaneous),[16] Copolymer (glatiramer acetate subcutaneous),[17] MSCRG (INFβ-1a intramuscular),[18] PRISMS (INFβ-1a subcutaneous),[19] AFFIRM (natalizumab),[20]

Figure 1: Flow chart presenting the selection of eligible studies



FREEDOMS I (fingolimod),[21] FREEDOMS II (fingolimod),[22] TEMSO (teriflunomide),[23] TOWER (teriflunomide),[24] CONFIRM (dimethyl fumarate),[25] DEFINE (dimethyl fumarate).[26] The duration of studies varied from 1 year to 3 years. One year follow-up was reported in 3 study protocols,[17, 21, 22] approximately 1,5 year follow-up in one study protocol,[24] two year follow-up in 4 studies,[18, 19, 25, 26] approximately 2,5 years in one study[20] and three year follow-up in two studies.[16,23]

Risk of bias for independent studies

Risk of bias in the included studies is summarized in **Figures 2A&2B**. Random sequence generation and allocation concealment was adequately reported in all trials, except for two.[16,17] Blinding of participants, personnel and outcome assessment was sufficient in all protocols. Six of the study protocols reported loss to follow up percentages between 5%-20%,[16-21] while the remaining 5 studies reported loss to follow up more than 20% of the baseline number of participants.[22-26] Selective reporting bias was detected in only one study.[20] All study protocols were supported financially partly[17,18] or solely[19-26] by the pharmaceutical companies that produce and market the drug under consideration in each study. Funding sources were not reported in the disclosures of one study protocol,[16]providing thus insufficient information to permit judgment.

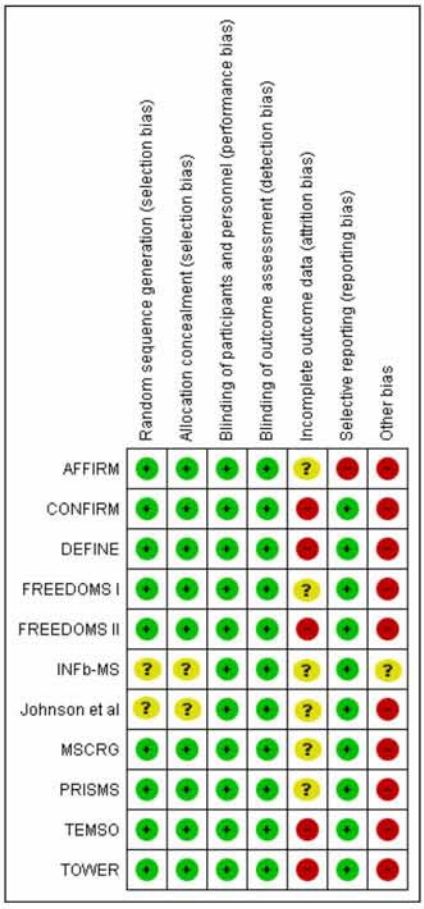
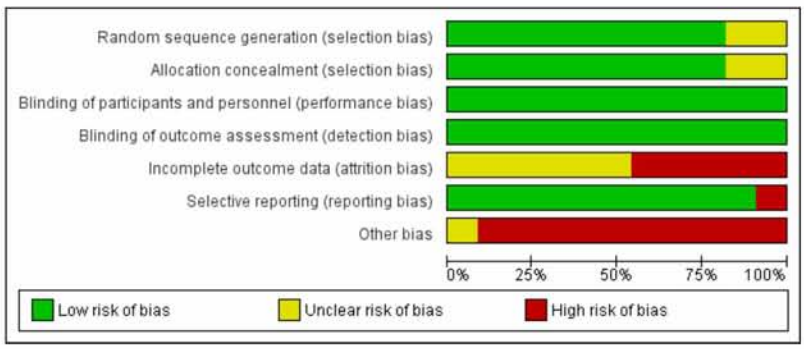


Figure 2A: *Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

Figure 2B. *Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.*



Overall analysis and subgroup analyses

Patients receiving approved DMDs for RRMS were found to have a significantly lower risk of disability progression compared to those receiving placebo (RR=0.72, 95%CI: 0.66-0.79; p<0.001; **Figure 3**).

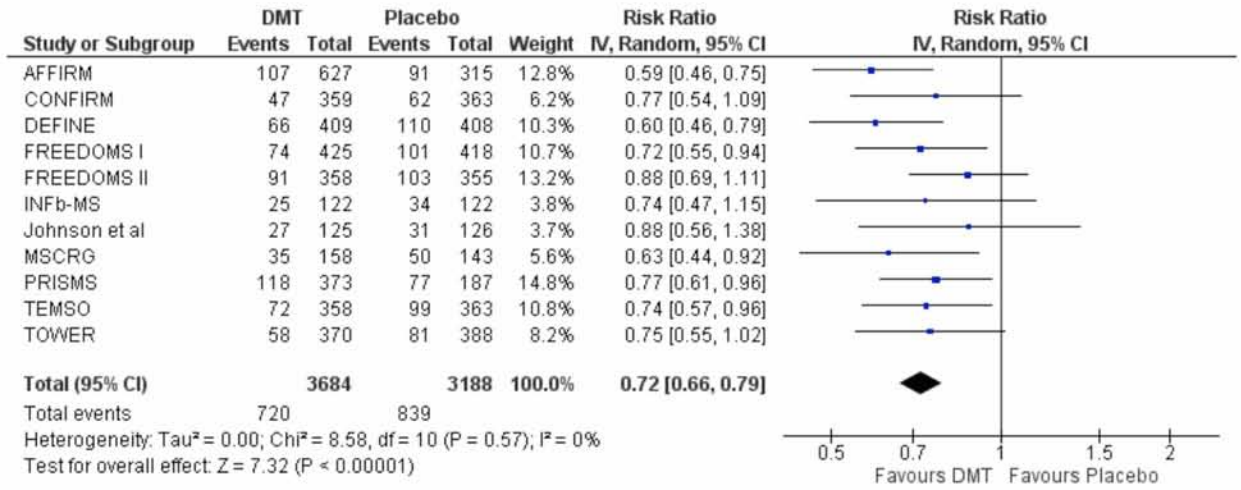


Figure 3. *Overall analysis of disability progression in placebo-control randomized clinical trials of different disease modifying therapies in patients with relapsing-remitting multiple sclerosis.*

No evidence of heterogeneity was found between estimates (I^2=0%, p=0.57). Moreover, no evidence of publication bias was detected in the funnel plot inspection (**Figure 4**) or in the Egger's statistical test (p=0.615).

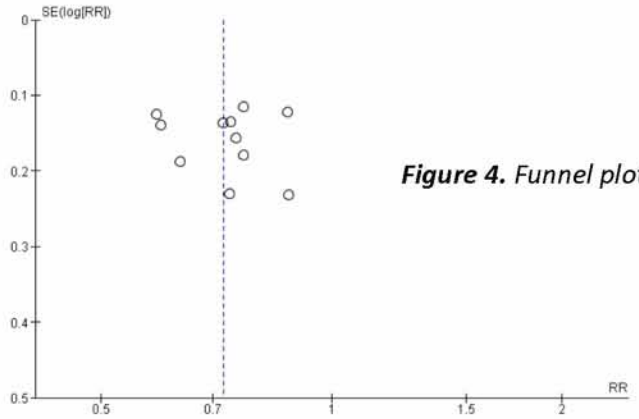


Figure 4. *Funnel plot for the risk of publication bias.*

In subsequent subgroup analyses, neither dichotomization of DMTs as "first" and "second" line RRMS therapies [RR=0.72 (95% CI=0.65-0.81) vs. RR= 0.72 (95%=0.57-0.91); p=0.99; **Figure 5**] nor the route of administration (injectable or oral) [RR=0.75 (95% CI=0.63-0.88) vs. RR= 0.74 (95% CI=0.66-0.83); p=0.93; **Figure 6**] had a differential effect on the risk of disability

progression throughout each study follow-up period. In both the aforementioned analyses no evidence of substantial heterogeneity was found both within and between subgroups ($p>0.05$ for Cochran Q test & $I^2<75\%$).

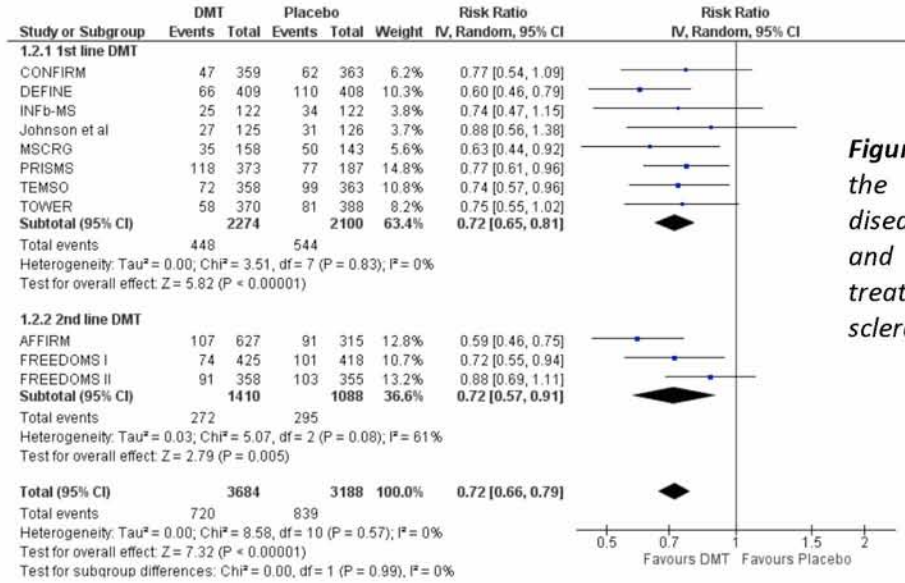


Figure 5. *Subgroup analysis according to the current categorization of eligible disease modifying therapies as "first line" and "second line" drug options for the treatment of relapsing-remitting multiple sclerosis.*

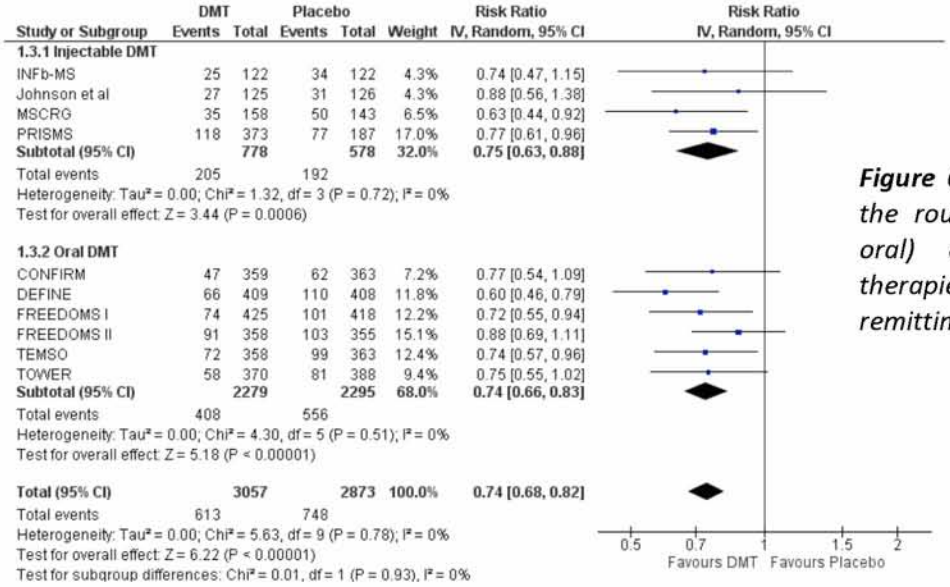


Figure 6. *Subgroup analysis according to the route of administration (injectable vs. oral) of eligible disease modifying therapies for the treatment of relapsing-remitting multiple sclerosis.*

Discussion

The study showed that currently approved DMD for RRMS are effective in reducing disability progression compared to placebo. Moreover, no significant heterogeneity in the risk reduction of disability progression across different subgroup analyses was detected including "first" vs. "second" line DMD and oral vs. injectable route of administration.

In the pairwise comparison of a recent network meta-analysis on the currently available immunomodulator and immunosuppressive treatments for multiple sclerosis natalizumab and subcutaneous IFNß-1a were found to be significantly more effective (OR=0.62, 95%CI:0.49-0.78 and OR=0.35, 95%CI:0.17-0.70, respectively) than intramuscular IFNß-1a in the reduction of disability progression in patients with RRMS at 2 years follow-up. However, the confidence in this result was graded as moderate by the authors, due to the moderate quality of evidence derived from the trials.[27] The present results are not directly comparable to this network meta-analysis since the aim of this study was not to compare individual DMD against each other. Instead, the potential sources of heterogeneity in the effect of DMD on disability progression was systematically evaluated using sensitivity analyses.

The observation of the current study regarding the lack of differential effect in disability progression between "oral" and "injectable" DMD is intriguing. This finding appears to be in line with available data from individual head-to-head comparisons in RCT: (i) TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis) comparing oral fingolimod to intramuscular IFNß-1a,[28] (ii) TENERE (the Terfiflunomide and Rebif study) comparing oral teriflunomide to subcutaneous IFNß-1a[29] and (iii) CONFIRM[25] (Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis) comparing oral dimethyl fumarate to subcutaneous glatiramer acetate. Interestingly, oral DMD did not reduce disability progression in comparison to the injectable therapies in any of the three trials. Similarly, our finding regarding the lack of differential effect on disability progression between "first" and "second" line DMD is not contradicted by the available data from a single RCT (TRANSFORMS).[28] Notably, no direct comparisons were performed in the SENTINEL (Safety and Efficacy of Natalizumab in combination with Interferon Beta-1a in patients with Relapsing Remitting Multiple Sclerosis)

trial between natalizumab and intramuscular IFNß-1a since the active treatment group was allocated to combination therapy with natalizumab and IFNß-1a.[30]

Certain limitations need to be acknowledged in the interpretation of the study results. First, in the current systematic review and meta-analysis only the effect of disability worsening was evaluated, without reporting data on other established markers of disease activity (freedom of relapse, lack of new/enlarging T2 lesions and gadolinium-enhancing lesions on magnetic resonance imaging)[31] or brain volume loss.[32] However, in a large multicentre study both brain atrophy and lesion volumes were also found to be significant predictors of long term disability in patients with MS.[33] Likewise, progression in disability (measured with the EDSS scale) was found be directly associated with regional grey matter atrophy in a follow-up MRI evaluation study of patients with RRMS.[34] Furthermore, it was recently reported that DMD for RRMS appear to be effective in attenuating brain atrophy using a similar meta-analytical approach, while DMD benefit on brain volume loss increased linearly with longer treatment duration.[35] Second, four potentially eligible studies were excluded from the final quantitative assessment (meta-analysis) because they provided neither percentages nor numbers of patients with disability progression during the study period.[12-15] As for the included study protocols there is also an unclear risk for selection bias in 2 of them due to non adequate report in random sequence generation and allocation concealment.[16,17] Third, all of the study protocols reported either considerable (5-20%)[16-21] or significant (>20%)[22-26] rates of loss to follow-up during the study period. Finally, bias related to funding source can not be excluded, as all study protocols had financial and/or other support from pharmaceutical industries with a clear conflict of interest on the study outcomes.

In conclusion available DMD appear to be effective in reducing the disability progression in patients with RRMS, independent of the route of administration and their classification as “first” or “second” line therapies. However, attrition and funding source biases need to be taken into account in the interpretation of these findings.

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