

Relating Treatment Effect on Relapses with Disability Worsening in Multiple Sclerosis Patients: Age Matters

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Abstract

Objective: To determine whether treatment efficacy on relapses do enable to predict treatment efficacy on disability worsening in multiple sclerosis patients and whether that efficacy is dependent on age.

Methods: The relevant features of published randomized controlled clinical trials in MS were extracted according to defined criteria namely data on age baseline information relapses and proportion of progressing patients. Regression analyses were performed to analyse the relationship between treatment efficacy on relapses and on confirmed disability progression over trials duration as well as between age and those clinical outcomes.

Results: Fifty-three trials comprising 76 comparison arms and totalising 34.765 patients were selected and engaged in the subsequent analyses. Significant correlation was observed between the treatment effect on relapses and on confirmed disability progression (adjusted $R^2=0.3872$). A strong association was found between the baseline EDSS and baseline age (adjusted $R^2=0.6243$) and a significant association was registered between the treatment effect on confirmed disability progression and age (adjusted $R^2=0.3179$). A weighted multiple linear regression between the treatment effect on confirmed disability progression and the interaction of the treatment effect on relapses with the age at disease onset interacting with disease duration exhibited a strong association (adjusted $R^2=0.5846$).

Conclusion: These findings demonstrate that age is a significant determinant of disability, the treatment effect on relapses is correlated with its effects on disability worsening being such association affected by age and that the efficacy of disease modifying therapies in multiple sclerosis decreases with age. The results reinforce the importance of early treatment initiation with high efficacy drugs as well as the need for treatments with targets other than relapses particularly for older patients.

Keywords: Multiple sclerosis; Relapses; Disability progression; Age; Treatment effect; Clinical trials

Abbreviations: MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; ARR-ratio: Treatment effect on the annualized relapses rate; CDP-ratio: Treatment effect on confirmed disability progression

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system in which about 85% of patients begin with a relapsing phase. Relapses and disability progression are two important clinical phenomena of multiple sclerosis and in patients with relapsing-remitting multiple sclerosis (RRMS) disability can result either from incomplete recoveries from relapses or development of secondary progressive MS (SPMS) [1]. Relapses are deemed to be the clinical expression of inflammation and are commonly used as primary endpoints of clinical trials due to the presumed effect of the drugs on the inflammatory component of the disease. From randomized controlled clinical trials of disease modifying therapies (DMTs) exists unequivocal evidence of a drug effect on reducing relapse rates over trials periods. Conversely the evidence of a drug effect on reducing confirmed disease progression is not impressive or is controversial. On the other hand natural history studies have shown that relapses are age and time dependent the role of patient age but not disease duration is an important determinant of decline in relapse incidence and that the development of a progressive disease course is an age-dependent process [2-10].

Therefore an important issue is to analyse the association of age and relapses with disability progression as well as their role as mediators on the treatment effect on disability progression in multiple sclerosis patients. For such purpose data from the published randomized trials on MS reporting data on relapses age and disability progression were analysed.

Methods

Electronic databases such as PubMed and Clinicaltrials.gov were searched to identify randomised placebo or active-controlled trials in relapsing-remitting multiple sclerosis (RRMS) fulfilling the following inclusion criteria: baseline data including patients age and the time from disease onset first event reporting data on relapses and the proportion of patients with confirmed disability progression (a change in the Expanded Disability Status Scale (EDSS) confirmed in a subsequent follow-up visit after 3 or 6 months). Additional details about the selection process are provided in the respective PRISMA flowchart (Figure 1) [11].

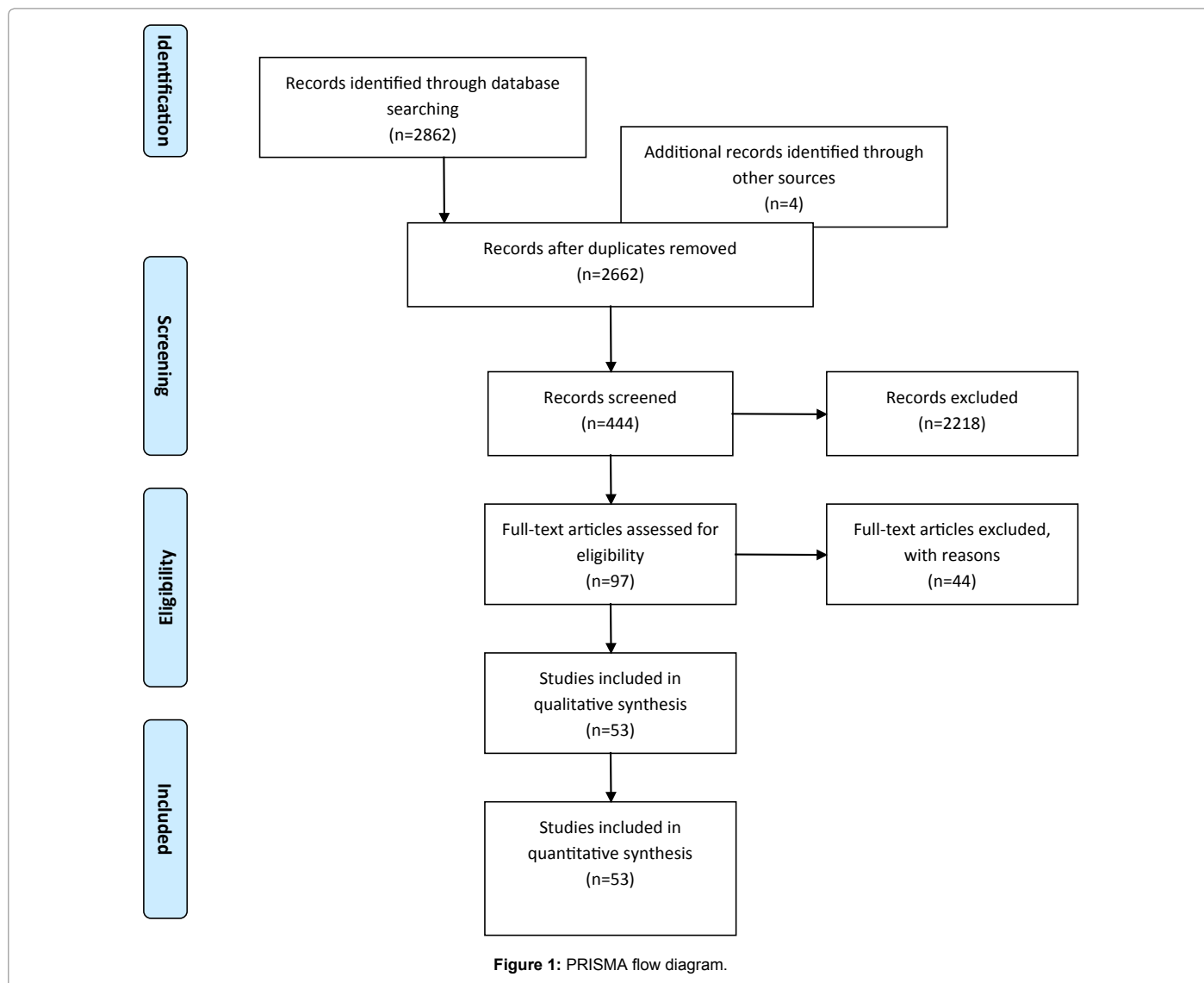
The following data was extracted from each trial: year of publication, author, drug, control group (placebo or active comparator) and, per trial arm, the number of randomized patients, the baseline data, the annualized relapse rate (ARR) the proportion of patients with relapses and the proportion of patients with confirmed disease progression (CDP). For trials with multiple arms, each experimental arm was compared with the control arm. The weight for each comparison was calculated multiplying the trial size by the squared root of the trial duration, as proposed in. For trials with more than two arms the

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number of patients in the control arm was divided into equal parts for each comparison [12].

Treatment effect was estimated by means of the ratio between the experimental and the control arm: ARR-ratio (between the annualized relapses rates), relapses-ratio (between the proportions of patients with relapses, and CDP-ratio (between the proportions of patients with confirmed disability progression). In order to harmonize the data to analyse the associations between the outcomes and age/time related variables, there was the necessity to estimate the drugs' efficacy against placebo in the trials using an active principle as control. For such purpose, the ARR-ratio and CDP-ratio of every trial using an active drug as control were recalculated by multiplying the trial results by some reference value of the respective drug. Rate ratio estimates for ARR and the relative risk estimated for disability progression reported in a recent network meta-analysis of DMTs for the correspondent drugs were utilized as the references values [13].

Weighted regression models were performed in all the datasets. The coefficient of determination (R^2) was used to assess the goodness-of-fit of the linear models. In all the regressions, an analysis of the residuals was performed, and the Shapiro-Wilk test was used to evaluate normality of

the data in the linear regressions. In order to assess the stability of the fitted models, weighted linear regressions were performed for different subgroups of trials: 1/trials for RRMS where only approved drugs for MS were utilized; 2/trials for RRMS/SPMS where only approved drugs for MS were utilized; 3/trials with a duration equal or superior to 96 weeks; 4/trials including placebo in the control arm.

All analyses were performed with the statistical software R Studio Version 1.1.456 [14,15].

Results

Fifty-three trials, comprising seventy-six comparison arms, and totalising 34.765 patients, were selected and used for the subsequent analyses (data set available as a supplementary file 1). This data set includes six trials in SPMS reporting data in relapses and disability progression. The mean age of patients at baseline was 37.44 (± 3.65) years and the mean time from disease onset to baseline was 6.69 (± 3.24) years [2,3,16-66].

The mean recalculated confirmed disability progression (CDP) ratio was 0.704 \pm 0.227 (median=0.708) and the mean recalculated annualized relapse rate (ARR) ratio was 0.635 \pm 0.263 (median=0.642).

The statistically relevant associations with the treatment effect on confirmed disability progression are discriminated (Table 1).

Relating the treatment effect on relapses with the treatment effect on confirmed disability progression

A statistically significant association was observed between the treatment effect on disability progression and those on relapses utilizing the original data, either on the ARR-ratio (adjusted $R^2=0.3872$, $p=1.183e-09$), or on the percentage of patients with relapses (adjusted $R^2=0.4183$; $p<0.001$). A statistically significant association was also noted between the recalculated CDP-ratio and the recalculated ARR-ratio (adjusted $R^2=0.4153$; $p=2.017e-10$) (Figure 2A).

The role of age

A strong association was found between the baseline EDSS and the baseline age (adjusted $R^2=0.6243$; $p<2.2e-16$), as well as in a weighted multiple regression using age at disease onset plus the mean time from disease onset to baseline (adjusted $R^2=0.6974$; $p<2.2e-16$). A similar result was obtained running an equivalent regression in the subgroup of trials including only placebo in the control arm (adjusted $R^2=0.7255$; $p=1.667e-13$).

A weak association was observed between recalculated ARR-ratio and mean age at baseline (adjusted $R^2=0.089$; $p=0.0051$), mean age at the end of trials (adjusted $R^2=0.0873$; $p=0.0055$), and mean age at disease onset (adjusted $R^2=0.0850$; $p=0.0061$). There was no association of the recalculated ARR-ratio with disease duration neither with the year of trial publication.

Conversely a significant association was found between the treatment effect on confirmed disability progression (recalculated CDP-ratio) and age (adjusted $R^2=0.3179$; $p=6.836e-08$) and a strong association was registered between the treatment effect on confirmed disability progression (recalculated CDP-ratio) and the interaction of recalculated ARR-ratio with age at disease onset interacting with disease duration (adjusted $R^2=0.5846$; $p=2.265e-14$) (Figure 2B and Figure 2C).

Sensitivity analysis

Weighted linear regressions using different subgroups of trials were undertaken in order to assess the stability of fitted models). Excluding the analysis of the association between recalculated CDP ratio and age in the data set including only approved drugs in RRMS trials, all the other results were quite consistent, with adjusted R^2 ranging from 0.3263 to 0.6132 (Table 2).

Recalculated CDP-ratio (treatment effect on disability progression)		
Independent variables	Adj.R ²	p-value
Age at the onset of trial (baseline)	0.3179	<0.001
Age at the end of trial (current)	0.3158	<0.001
Disease duration	0.2029	<0.001
Baseline EDSS	0.2676	<0.001
Recalculated-ARR ratio	0.4153	<0.001
Recalculated ARR-ratio+Baseline EDSS	0.5284	<0.001
Interaction of Recalculated ARR ratio with Age at disease onset interacting with disease duration	0.5846	<0.001

Table 1: Statistically relevant associations with disability progression ratio (treatment effect on disability progression).

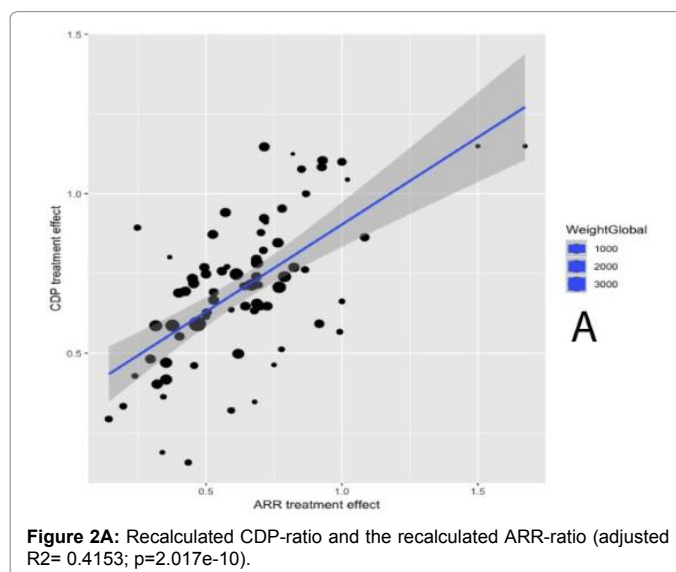


Figure 2A: Recalculated CDP-ratio and the recalculated ARR-ratio (adjusted $R^2= 0.4153$; $p=2.017e-10$).

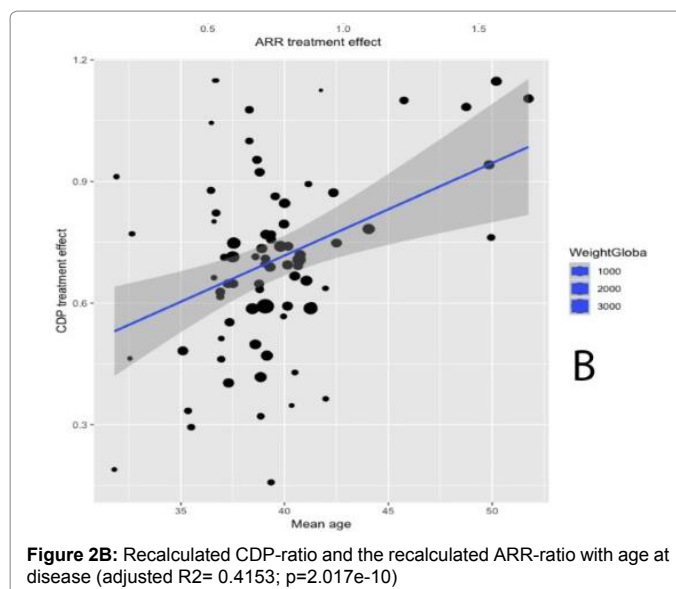


Figure 2B: Recalculated CDP-ratio and the recalculated ARR-ratio with age at disease (adjusted $R^2= 0.4153$; $p=2.017e-10$)

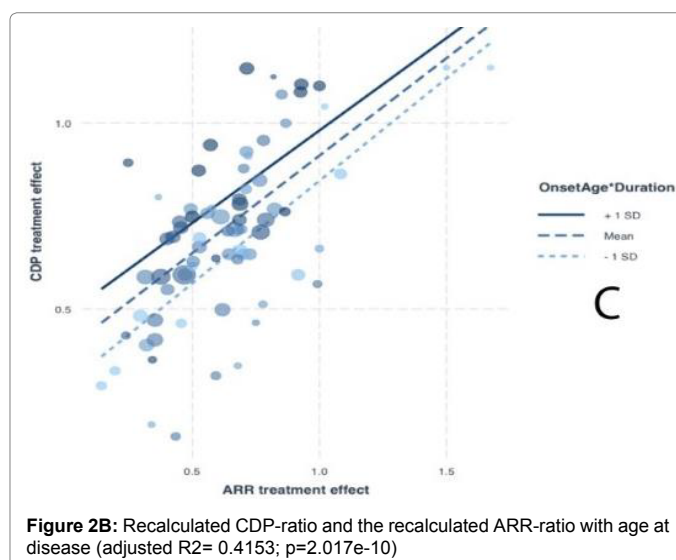


Figure 2B: Recalculated CDP-ratio and the recalculated ARR-ratio with age at disease (adjusted $R^2= 0.4153$; $p=2.017e-10$)

CDP ~ ARR analysis (raw data)		
Data sets	Adj.R ²	p-value
Approved drugs (only RRMS trials. N=31)	0.429	<0.001
Approved drugs (RRMS+SPMS trials. N=36)	0.3973	<0.001
Only trials with at least 96 weeks duration. N=45	0.404	<0.001
Subgroup control arm=placebo. N=50	0.3712	<0.001
CDP ~ ARR analysis (recalculated data)		
Approved drugs (only RRMS trials. N=31)	0.3429	<0.001
Approved drugs (RRMS+SPMS trials. N=36)	0.3811	<0.001
Only trials with at least 96 weeks duration. N=45	0.4265	<0.001
Subgroup control arm=placebo. N=50	0.3712	<0.001
CDP ~ Age analysis (recalculated data)		
Approved drugs (only RRMS trials. N=31)	0.0705	0.0380
Approved drugs (RRMS+SPMS trials. N=36)	0.3473	<0.001
Only trials with at least 96 weeks duration. N=45	0.3399	<0.001
Subgroup control arm=placebo. N=50	0.3785	<0.001
CDP ~ Interaction of ARR with Age at disease onset interacting with disease duration		
Approved drugs (only RRMS trials. N=31)	0.6132	<0.001
Approved drugs (RRMS+SPMS trials. N=36)	0.4651	<0.001
Only trials with at least 96 weeks duration. N=450.3785	0.5828	<0.001

Table 2: Sensitivity analysis. Assessment of the association between the treatment effect on confirmed disability progression with the treatment effect on relapses in subgroup data sets (using original/raw and recalculated data), and with age in the same subgroups (using recalculated data) CDP–confirmed disability progression; ARR– annualized relapse rate; RRMS–relapsing-remitting multiple sclerosis; SPMS–secondary progressive multiple sclerosis; N–number of comparison arms

Discussion

This analysis of randomized controlled trials in multiple sclerosis demonstrates that age is an important determinant of disability. The treatment effect on relapses is correlated with its effects on disability being such association affected by age and that the efficacy of DMTs decreases with age. Before discussing the implications of these findings, a few limitations of this study have to be acknowledged. The lack of access to the individual patient's data prevents us to make predictions for the individual patient and does not allow data validation. Despite of only randomized controlled trials are included in the present study any potential bias affecting the results of a trial cannot be excluded. Different definitions of the clinical outcomes are used amongst the trials; moreover, disability outcomes based on 3-6 months confirmed disability progression may overestimate the accumulation of permanent disability [67]. The short duration of the trials (1 to 3 years) only allows us to correlate treatment effects at a short-term. Lack of trials in which the mean age of included patients is below 30 years old. As these trials were designed to assess treatment efficacy of some drug their inclusion criteria usually required (high) disease activity therefore excluding patients with a less severe course. The way recalculated CDP-ratios were estimated in the trials in which active drugs were used as controls deserves an additional comment. Weideman et al. proposed a distinct methodology to perform such recalculations based on the coefficients obtained from weighted regressions of Interferons beta and glatiramer acetate in the trials against placebo using CDP ratio as response variable and the current age as the predictive variable. Applying such methodology in the present data set a similar mean recalculated CDP-ratio was obtained (0.704 ± 0.226). This similarity of the mean recalculated CDP-ratios and of the determination coefficients (R^2) of the models analysing the association between the treatment effect on confirmed disease progression and age as calculated by the two distinct methodologies (adjusted $R^2=0.3562$ vs. 0.3179 ; $p<0.001$) provide confidence to the results [68].

Despite the limitations, this study provides findings that deserve some discussion. In the present study the treatment effect on confirmed

disability progression is clearly associated with the treatment effect on relapses over the years of trials' duration. However these results are not as significant as the ones published in the study of Sormani et al. in which the adjusted R^2 value of the weighted regression on the association between the treatment effect on relapses and disability progression was 0.71 as opposite to 0.3872 here in reported [69]. The reasons for such discrepancy are not obvious from the current analysis. The main differences between these two studies are the number of included trials (19 against 53) and the inclusion of new drugs such as the oral DMTs alemtuzumab, cladribine, daclizumab and ocrelizumab. In both cases the sensitivity analysis utilizing different subsets of trials confirmed the stability of the models. The study of Fahrbach, which included 40 trials, also described a significant association (adjusted $R^2=0.7501$) between disability progression and ARR ratio [70]. However, this result is not comparable with the value 0.71 reported in the work of Sormani et al. because of the differences in the weighted regressions realized (no intercept vs. with intercept).

Patient's age certainly has also a relevant role in the treatment effect on disability progression. Age alone explains about 62% of the variance of the EDSS at baseline, and age plus the mean time from disease onset to baseline explain around 70% of the variance of the EDSS at baseline. Age is likewise independently associated with the treatment effect on relapses and, especially with the treatment effect on confirmed disability progression over trials duration, explaining about 32% of its variance. In the work of Weideman et al. a significant association between the treatment effect on disability progression and age was also described, with mean age explaining approximately 42% (using a simple regression, and 67% with a multiple regression) of the variance in the treatment effect on disability. Causes for treatment effect decline on disability worsening with age are not known. A decline of inflammatory activity with age, in line with relapse rate reduction, could be a plausible explanation. Inflammatory demyelination is an important cause of axonal transection and subsequent axonal degeneration and there is clinical-pathological evidence that axonal loss is the pathological substrate of established disability in multiple sclerosis as well as clinical-radiological evidence of axonal damage, determining disability from the early stages of MS. Vascular disease, which is another age related disorder, has been increasingly associated with MS and may also serve as a contributing factor. Accordingly, small vessels disease has been recently reported as a potential contributor to neurodegeneration in multiple sclerosis [70-77].

Notwithstanding the limitations the role of age concerning the treatment effect of DMTs has implications for the analysis and interpretation of the results of MS clinical trials as well as for comparing the efficacy between treatments. For instance in a subgroup analysis of the DEFINE trial (dimethyl fumarate vs. placebo) the hazard ratio regarding the proportion of patients with confirmed disease progression at two years for patients with less than 40 years old was 0.38 (0.22-0.63) as opposed to 0.92 (0.58-1.43) for patients with 40 years old or more [78]. Accordingly a meta-analysis of randomized trials of subgroups of multiple sclerosis patients shows that treatment effects on ARR and disability progression were significantly higher in younger than in older patients [79]. Interestingly, the dispersion graph (Figure 2B) correlating the treatment effect on confirmed disability progression with mean age shows that there is no high efficacy treatment effect (i.e. recalculated CDP-ratio less than the median 0.708) after 40 years age.

The results herein presented may also have implications for the clinical practice. The significant association between the treatment effect on relapses and on confirmed disability accumulation suggests that at least in part the treatment impact on disability worsening during

the trials is derived from the treatment impact on relapses. Moreover the interaction of the treatment effect on relapses with age at disease onset interacting with disease duration is clearly associated with the treatment effect on disability progression (adjusted $R^2=0.5846$ $p<0.001$) suggesting that age affects the relationship between the treatment effect on relapses with the treatment effect on disability progression.

Obviously from the present study, one cannot assume any treatment effect as to long-term disability progression. Nevertheless there is evidence from natural history studies that relapses in the earlier phase of the disease (first 2 to 5 years) are associated with long-term disability milestones and/or SPMS or that relapses in the first 5 years of disease have impact on disease progression, and that such association typically diminished with time. Despite the differences between the patients enrolled in these natural history studies and today's patients, mainly because of the anticipation of MS diagnosis through the improvement of the diagnostic process/criteria those natural history studies demonstrate an association between relapses and disability progression. On the other hand, there is also evidence that early relapses contribute to permanent damage to the central nervous system and that relapses can be directly associated with residual disability [80-86]. Accordingly, the treatment of relapses should promote a reduction on disability worsening, as the current results demonstrate during the trials' period. Taking into account the relation of early relapses and long-term disability, the treatment of relapses, particularly in the early phases of the disease course, during the young ages, may contribute to prevent some disability accumulation and, eventually, delay the onset of secondary progression. In line with this, a contemporary work comprising 2477 patients showed that time from onset of MS to treatment was associated with disability, and that early treatment with DMTs is associated with a significantly reduced risk of disability pension. Finally the present results cannot be extrapolated to the individual level because the findings were drawn from group analysis based on mean outcomes within the trials. In order to make predictions at the patient level, it would be necessary to utilize individual patient data from the variety of randomized trials. That could enable for instance, to use models to profile patients in terms of their disease evolution and expected outcomes.

Conclusion

The present analysis of randomized controlled clinical trials shows that patients' age is a determinant of the treatment efficacy of available disease modifying therapies in multiple sclerosis reinforces the importance of early treatment initiation with high efficacy drugs, targeting specially younger ages, and underlines the need for new drugs with different targets than relapses particularly to treat older patients with MS.

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