Time-patterns of annualized relapse rates in randomized placebo-controlled clinical trials in relapsing multiple sclerosis: A systematic review and meta-analysis
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Introduction

It is known that the annualized relapse rate (ARR) in patients with multiple sclerosis (MS) changes as the disease develops. However, in the design and analysis of trials in relapsing multiple sclerosis (RMS) constant ARRs are commonly assumed. To our knowledge no systematic investigation of this assumption exists to date, although recent reviews have identified a decrease in trial relapse rates over the past 20 years. Furthermore, whether the treatment effects are constant over time or vary with time is of increasing interest in clinical practice. Increasing options for therapy, short trial designs and a drive to identify effective therapies as early as possible make it important to recognize whether a treatment effect is waning or increasing over the timeframe of a study to enable timely choices about therapy to be made. This paper aims to assess time-patterns of trial ARR by conducting a systematic review of randomized, placebo-controlled trials in RMS.

Abstract

Background: Although it is known that the annualized relapse rate (ARR) in patients with multiple sclerosis (MS) changes as disease progresses, in the design and analysis of trials in relapsing multiple sclerosis (RMS) constant ARRs are assumed.

Objectives: This paper aims to assess time-patterns of trial ARR by conducting a systematic review of randomized, placebo-controlled trials in RMS.

Methods: A systematic literature search was conducted by searching PubMed for randomized, placebo-controlled trials in RMS. In meta-analyses the following comparisons of trial ARR were carried out for the placebo controls and active treatment arms: months 1–6 vs. months 7–12, and months 1–12 vs. months 13–24.

Results: A total of 52 trials was identified. Out of these, information on the time-dependence of trial ARR could be extracted from 13 trials. The ARR was by 25% (p = 0.0005) and 40% (p < 0.0001) higher in months 1–12 compared with months 13–24 for placebo and active treatments, respectively. Consequently, the treatment effects were by 13% (p = 0.23) larger in the second year compared with the first year. Within the first year of follow-up the ARR was by 4% (p = 0.75) and 23% (p = 0.06) higher in months 1–6 compared with months 7–12 for placebo controls and active arms, respectively.

Conclusions: Trial ARR decreases during a trial in RMS, which is in line with epidemiological findings and has implications for design and analysis of future trials. The observed decrease in trial ARR might be at least partially explained by regression to the mean. Individual patient data analyses are warranted.

Keywords
relapsing multiple sclerosis, annualized relapse rate, systematic review, meta-analysis

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Methods

Literature review

A systematic literature review was carried out by searching PubMed on 8 August 2011 without date or language restrictions, but limiting the search to clinical trials. The search was conducted with “(multiple sclerosis OR demyelinating disease) AND (relapsing OR relapsing remitting) AND placebo” as search strategy. We also assessed for inclusion in this analysis the publications included in two recent systematic reviews\(^3,4\) that had searched PubMed, Ovid Medline and the Cochrane Register of Controlled Trials for randomized, placebo-controlled trials in RMS. One trial\(^5\) in these reviews\(^3,4\) was excluded since this trial investigated an add-on treatment and all patients received a form of active treatment. For a trial to be included in the present systematic review it had to be randomized, single or double blind, placebo controlled, conducted in RMS, assessing the efficacy of disease-modifying drugs (i.e. not symptomatic therapies), and reporting data on clinical relapses. Trials were excluded if the following applied: the control group received active treatment, the disease type was not RMS (e.g. primary progressive MS), or the study was an extension of a previous randomized trial.

Data extraction

For the meta-analysis, the rate ratios comparing the ARRs for the different time periods, i.e. months 1–6 vs. 7–12 and months 1–12 vs. 13–24, and the ratios of the treatment effect rate ratios for each period were extracted as well as their standard errors on the log scale. If ARRs for the time periods were reported in the articles, these were used to calculate their ratio. Otherwise the ARRs were estimated as the ratio of the number of relapses and the total follow-up time per patient. If the latter was not reported in the paper, it was calculated as the number of patients (at the beginning of the specific period) times the planned follow-up time per patient. The standard error (SE) of the log rate ratio is commonly estimated by \(\sqrt{1/D_1+1/D_2}\) with \(D_1\) and \(D_2\) being the numbers of relapses within the two time periods.\(^6\) The SE of the log ratio of the treatment effect rate ratios for the two periods was accordingly estimated by \(\sqrt{1/D_{A1}+1/D_{A2}+1/D_{C1}+1/D_{C2}}\) where \(D_{A1}\) and \(D_{A2}\) are the numbers of events of the first and second period for the active treatment and \(D_{C1}\) and \(D_{C2}\) for the placebo control. If the numbers of relapses were not given by time period, they were estimated as the ARR times the number of patients at the beginning of that time period (preference) or the number of patients randomized. For the 6-month periods the numbers of relapses were divided by two.

Information was extracted from graphs (e.g. Kaplan–Meier curves of time to first relapse) using Engauge Digitizer 4.1 (http://digitizer.forgesource.net), or the quantities were measured with a ruler from enlarged printouts.

The data extraction was carried out by one author (SP or TF) and independently verified by another (SS).

Baseline characteristics were extracted including age, gender, the Expanded Disability Status Scale (EDSS),\(^7\) disease duration (from onset), and type of MS. If available, the mean is reported but in some cases only the median was available.

Data analysis

The log ARR ratios comparing the different time periods were formally combined in a random-effects meta-analysis with inverse variance weighting (see for example Whitehead).\(^8\) The combined estimates are reported with 95% confidence intervals (CI) and \(p\)-values testing the null hypothesis of no difference between the time intervals. Between-study heterogeneity was estimated and is reported as the heterogeneity measure \(I^2\), which is the ratio of the between-trial variance and the total variance, alongside the \(p\)-values of the chi-square test of heterogeneity.\(^9\) Forest plots giving the ratios of the individual studies and the combined effect allow visual assessments of the heterogeneity and provide an overview of the results. The meta-analyses were conducted using the RevMan 5.1 software (http://ims.cochrane.org/revman).

To further investigate the time-patterns of relapses, one-parameter exponential curves of the form \(\exp(-2^{*}t)\) were fitted to Kaplan–Meier curves of time to first relapse extracted from selected papers using the statistics software STATISTICA 9.1 (www.statsoft.com).

Results

A total of 52 trials was identified as potentially eligible for this systematic review. Information on the time-dependence of trial ARR was extracted from 13 trials\(^10-22\) with a total number of \(n = 4758\) patients. ARR could be extracted from eight (12 active treatment arms) and seven (eight active treatment arms) trials for the comparison of months 1–6 vs. 7–12 and months 1–12 vs. 13–24, respectively. Table 1 gives baseline characteristics of these studies. One trial\(^22\) provided information on 9 and 18 months only and was not included in the analyses.

ARR in the first and second year of follow-up

In the first 12 months of follow-up the ARR was 25% (95% CI [10%, 43%]; \(p = 0.0005\)) higher compared with months 13–24 for patients in the placebo control groups. No between-trial heterogeneity was observed (\(I^2 = 0\%\), \(p = 0.53\)). In Figure 1(a) the ratios for the individual trials are displayed. For patients on active treatment the difference was 40% (95% CI [19%, 63%]; \(p < 0.0001\)), even larger than with placebo. Again, no between-trial heterogeneity was detected (\(I^2 = 0\%\), \(p = 0.45\)). The rate ratios of the individual trials are displayed in Figure 1(b).
Table 1. Baseline characteristics of the 12 randomized, placebo-controlled trials included in this systematic review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Sample size</th>
<th>Female gender</th>
<th>Age [y]</th>
<th>MS type</th>
<th>EDSS</th>
<th>Disease duration [y]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camenga (1986)</td>
<td>Recombinant α-2 Interferon</td>
<td>98</td>
<td>59%</td>
<td>–</td>
<td>RMS</td>
<td>3.7</td>
<td>–</td>
</tr>
<tr>
<td>Goodkin (1991)</td>
<td>Azathioprine</td>
<td>54</td>
<td>67%</td>
<td>36.0</td>
<td>RRMS</td>
<td>3.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Lycke et al. (1996)</td>
<td>Acyclovir</td>
<td>60</td>
<td>67%</td>
<td>32.8</td>
<td>RRMS</td>
<td>1.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Fazekas et al. (1997)</td>
<td>Immunoglobulin</td>
<td>148</td>
<td>75%</td>
<td>37.0</td>
<td>RRMS</td>
<td>3.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Millefiorini et al. (1997)</td>
<td>Mitoxantrone</td>
<td>51</td>
<td>69%</td>
<td>29.9</td>
<td>RRMS</td>
<td>3.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Achiron et al. (1998)</td>
<td>Immunoglobulin</td>
<td>40</td>
<td>80%</td>
<td>34.6</td>
<td>RRMS</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Lenercept SG (1999)</td>
<td>Lenercept</td>
<td>168</td>
<td>74%</td>
<td>35.3</td>
<td>RMS</td>
<td>2.6</td>
<td>–</td>
</tr>
<tr>
<td>Romine et al. (1999)</td>
<td>Cladribine</td>
<td>52</td>
<td>69%</td>
<td>41.7</td>
<td>RRMS</td>
<td>2.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Filippi et al. (2006)</td>
<td>Glatiramer acetate</td>
<td>1644</td>
<td>74%</td>
<td>36.5</td>
<td>RRMS</td>
<td>2.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Polman et al. (2006)</td>
<td>Natalizumab</td>
<td>942</td>
<td>70%</td>
<td>36.0</td>
<td>RMS</td>
<td>2.3</td>
<td>5.0*</td>
</tr>
<tr>
<td>Hauser et al. (2008)</td>
<td>Rituximab</td>
<td>104</td>
<td>78%</td>
<td>40.2</td>
<td>RRMS</td>
<td>2.5*</td>
<td>9.6</td>
</tr>
<tr>
<td>Giovannoni et al. (2010)</td>
<td>Cladribine</td>
<td>1326</td>
<td>68%</td>
<td>38.6</td>
<td>RMS</td>
<td>2.9</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Mean values are given, if not specified otherwise. * Median
EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis; RMS: Relapsing MS; RRMS: Relapsing–remitting MS.

Figure 1. Ratios of the ARRs from months 1–12 vs. months 13–24 in the (a) placebo groups and (b) the active treatment groups for seven studies included in the meta-analysis.

SE: Standard error; ARR: Annualized relapse rate.
Ratios of the individual trials are displayed in Figure 2(b). The ARR in the first 6 months and months 7–12

### ARR in the first 6 months and months 7–12

Within the first 6 months of follow-up the ARR was 4% (95% CI [-17%, 29%]; p = 0.75) higher compared with months 7–12 for placebo patients. The between-trial heterogeneity was estimated as $I^2 = 38\%$ ($p = 0.13$). In Figure 2(a) the ARR ratios for the individual trials are displayed. For patients on active treatment the difference was 23% (95% CI [-1%, 53%]; p = 0.06), again larger than with placebo. The between-trial heterogeneity was $I^2 = 56\%$, also larger and statistically significant ($p = 0.01$). The ARR ratios of the individual trials are displayed in Figure 2(b).

### Treatment effects in the first and second year of follow-up

Treatment effects, i.e. the relative reductions of the ARR in the active treatment compared with placebo, tended to be stronger in the second year compared with the first year. The relative treatment effects in the second year compared with the first year for the individual trials are displayed in Figure 3. In months 13–24 the treatment effects were on average 13% (95% CI [-7%, 37%]; p = 0.23) larger compared with the first 12 months of follow-up. No between-trial heterogeneity was observed ($I^2 = 0\%$, p = 0.85), even
though the treatments investigated in the included trials were diverse and some were deemed ineffective at the end of the trial. A schematic illustration of the relative changes over time in ARRs and the resulting time changes in the treatment effects is given in Figure 4. Compared with the relapse rate in the first 6 months of follow-up, the relapse rate is typically reduced in months 7–12 and even more so in the second year, both for placebo and for the active treatments.

**Time to first relapse**

Figure 5 shows the Kaplan–Meier curves of time to first relapse for the placebo controls in Giovannoni et al. and Kappos et al. with superimposed exponential curves. The ARRs derived from these exponential models are 0.31 and 0.44; they are in close agreement with the reported ARRs of 0.33 and 0.40, respectively. As is apparent from the figure, the Kaplan–Meier curves deviate from the exponential curves by being lower within the first year and higher in the second, with the Kaplan–Meier and exponential curves crossing at about week 60 for both studies. This corresponds to higher relapse rates in the first year and lower rates in the second year, and is in agreement with the findings from the meta-analyses described above. However, an alternative explanation for the apparent time-dependence in the time-to-relapse data could be between-patient heterogeneity, i.e. unexplained biological or clinical variation between patients.

**Discussion**

In this paper we demonstrate the time-dependence of trial ARR over the period of 2 years. Overall, the relapse rate decreased as the trials progressed. The PRISMS study was identified as a randomized-controlled trial in relapsing–remitting MS in our systematic review, but had to be excluded from analyses since the original publication did not report any relapses for different time intervals. As was pointed out during the peer review of this publication, a very recent paper in this journal by Sormani and colleagues provides relapse data for the first and the first 2 years of follow-up. We did not formally include these data in our meta-analysis since the data reported by Sormani et al. are not based on the intention-to-treat analysis and are combined for two interferon β-1a (IFNβ-1a) dose groups. However, the data reported by Sormani and colleagues support the downward trend in relapse rates over time. The relapse rates for placebo and IFNβ-1a are 1.51

**Table 3.** Time dependence of treatment effects. The treatment effects in active treatment groups at months 1–12 are compared with the treatments effects at months 13–24 for seven studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Rate Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Rate Ratio 95% CI</th>
<th>Rate Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 Goodkin [11]</td>
<td>0.5101</td>
<td>0.5083</td>
<td>3.9%</td>
<td>1.67 [0.61, 4.51]</td>
<td></td>
</tr>
<tr>
<td>1996 Lycke [12]</td>
<td>0.0155</td>
<td>0.3274</td>
<td>9.3%</td>
<td>1.02 [0.53, 1.93]</td>
<td></td>
</tr>
<tr>
<td>1997 Fazekas [13]</td>
<td>-0.2945</td>
<td>0.3058</td>
<td>10.7%</td>
<td>0.74 [0.41, 1.36]</td>
<td></td>
</tr>
<tr>
<td>1997 Millefiorini [14]</td>
<td>0.0039</td>
<td>0.4867</td>
<td>4.2%</td>
<td>1.00 [0.39, 2.61]</td>
<td></td>
</tr>
<tr>
<td>1998 Achiron [15]</td>
<td>0.3427</td>
<td>0.4987</td>
<td>4.0%</td>
<td>1.41 [0.53, 3.74]</td>
<td></td>
</tr>
<tr>
<td>2006 Polman [19]</td>
<td>0.2142</td>
<td>0.1772</td>
<td>31.8%</td>
<td>1.24 [0.88, 1.75]</td>
<td></td>
</tr>
<tr>
<td>2010 Giovannoni [21] (1)</td>
<td>0.0459</td>
<td>0.2324</td>
<td>18.5%</td>
<td>1.05 [0.66, 1.65]</td>
<td></td>
</tr>
<tr>
<td>2010 Giovannoni [21] (2)</td>
<td>0.2222</td>
<td>0.2378</td>
<td>17.7%</td>
<td>1.25 [0.78, 1.99]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.13 [0.93, 1.37] Heterogeneity: Tau² = 0.00; Chi² = 3.35, df = 7 (p = 0.85); I² = 0%
Test for overall effect: Z = 1.20 (p = 0.23)

(1) Cladribine 3.5 mg/kg
(2) Cladribine 5.0 mg/kg

**Figure 3.** Time dependence of treatment effects. The treatment effects in active treatment groups at months 1–12 are compared with the treatments effects at months 13–24 for seven studies included in the meta-analysis.

**Figure 4.** Illustration of the decrease in ARR (in %) as the trial progressed. We have compared the early (months 1–6) with later time periods (months 7–12 and months 13–24) and demonstrate how this contributes to a differential effect of active treatment and placebo by the end of the trial. ARR: Annualized relapse rate.
and 0.96 in the first year and 1.09 and 0.86 in the second year, respectively, which translates into 28% and 10% reductions from year 1 to year 2 for placebo and IFNβ-1a, respectively.

This systematic review has a number of limitations. We did not have access to individual patient data but rather had to rely on summary data from publications, with information presented differently across papers. Furthermore, we did not differentiate between different active treatments. This is a possible explanation for the heterogeneity observed in the comparison of months 1–6 vs. 7–12.

It is known that the relapse rate reduces by 17% every 5 years as MS develops. The timeframe of our observations showing a 25% reduction over a year is larger and implies another cause. The timeframe of the drop in ARR is similar to that seen in the phenomenon of regression to the mean, which has been seen in relapse rates in prospective studies in MS where subjects fitting trial entry criteria were followed prospectively for 1 year. A decrease in pre-study ARR to on-study ARR of about 40% was observed and attributed to this effect, which is an artefact of choosing subjects with a recent flurry of attacks who are then likely to settle down. This is of course different from the situation considered in this paper, where on-study relapses from different time periods are compared. The regression to the mean phenomenon is well known in epilepsy, where 20–50% of the reductions in seizures seen in patients treated with active agents are actually due to such non-pharmacological effects. Although the overall drop in ARR was larger in the treated group, the finding that the improvement occurring between months 6–12 and 13–24 is almost the same for placebo and treated groups raises doubts as to whether there really is an increased treatment effect in the second year; it may be an artefact. However, it is biologically plausible that active treatments take time to build up maximum efficacy, thus more treatment effect could be seen in year 2. This should be borne in mind when reporting yearly ARRs.

Other potential causes for the reduction in relapse rates over time include the use of rescue medication. In trials, use of rescue medication (e.g. steroids) could impact on the ARR if it was employed more commonly as a trial progressed. However, this is not characteristic of MS trials, and the consistency of our findings across a wide range of therapies goes against this. Furthermore, patients with high relapse rates may drop out early. However, the effect we described was more evident in the treatment groups across a range of therapies where dropouts should be less common than with placebo, due to treatment benefits.

In conclusion, the time-dependence in trial ARR described in this report should be considered in the design, analysis and interpretation of trials in RMS. Analysis of individual patient data from large datasets would enable more precise and methodologically consistent evaluation of time trends.

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Conflict of interest statement
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