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Long-term impact of interferon or Glatiramer acetate in multiple sclerosis: A systematic review and meta-analysis

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ABSTRACT

Background: In recent years the impact of disease-modifying drugs on long-term progression in multiple sclerosis (MS) was assessed both in observational studies and in extension of randomized controlled trial (RCT). Aim of this work was to quantitatively summarize by a meta-analysis the long-term impact of immunomodulatory drugs (Interferon-Beta (IFN-β) or Glatiramer Acetate (GA)) in relapsing-remitting (RR) MS patients.

Methods: We collected all published observational studies reporting the long-term efficacy of IFN-β or GA in RRMS patients. The primary outcome was the treatment effect on progression to a sustained EDSS score of 6 or to the Secondary Progressive (SP) phase. A non-parametric approach was adopted to test the overall treatment effect significance, while a random effect model was used to obtain a pooled quantitative estimate of the treatment benefit, in terms of hazard-ratios (HR) or Relative Risks, with their 95% confidence interval (CI).

Results: Fourteen studies, on a total of 13,238 RRMS patients, were included in the meta-analysis. All studies but two reported a consistent effect of immunomodulatory treatment on long-term disease progression; the pooled effect on progression to EDSS 6 or SP was significant ($p < 0.01$) when tested by the non-parametric test. The quantitative estimate of the treatment effect in reducing progression to EDSS 6 in the subset of studies reporting this outcome was $HR_{pooled} = 0.49$ (95% CI: 0.34–0.69), $p < 0.001$.

Conclusions: Treatment with immunomodulators seems to reduce long-term probability of disability progression. Additional well-designed observational studies could help to confirm these findings.

1. Introduction

A large number of observational studies has been recently conducted to verify whether the efficacy of the disease modifying drugs approved for the treatment of multiple sclerosis (MS), demonstrated in randomized clinical trials (RCT), can be translated into a clinically significant delay in disease progression over the long term in real-world settings (Trojano et al., 2007, 2009; Veugelers et al., 2009; Patrucco et al., 2010; Bergamaschi et al., 2012; Shirani et al., 2012; Drulovich et al., 2013; Tedeholm et al., 2013; Cocco et al., 2015). All of these observational studies evaluated the impact of different preparation of Interferon beta (IFN) or Glatiramer Acetate (GA), the drugs that accumulated more than 20 years of observation, on the risk of reaching high levels of disability. A recent review (Sormani and Bruzzi, 2015) summarized the evidence coming from observational studies in MS, focusing on a critical revision of all the several potential biases that can affect such studies, where subjects are not randomly assigned to the treatment. In the present study we tried to quantitatively summarize, through a formal meta-analysis, the effect of IFN or GA as estimated in these observational studies. Despite these studies are affected by biases that can be both in favor or against the treatment effect, according to the different designs used, and the results are somehow discordant, it could be useful to have a quantitative overall estimate of the average tendency emerging from the whole picture, in an era when new drugs started to be extensively used and their effects will accumulate in the near future sufficient follow up time to be studied in the long-term.

2. Methods

2.1. Search strategy and selection criteria

We searched electronic databases (Ovid MEDLINE [1950-19

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March 2015], PubMed [1965-19 March 2015] and The Cochrane Library with the same time limits), to identify studies fulfilling the following inclusion criteria: observational studies or extension of randomized controlled trials (RCT) reporting information on the long-term effect of Interferon-β (IFN) or Glatiramer acetate (GA) in patients with Relapsing Remitting Multiple Sclerosis (RRMS).

We used search terms for the disease ("multiple sclerosis") and treatment ("Interferon", "glatiramer acetate", "immunomodulating", "immunomodulatory", "disease-modifying"), combining then terms for indexing articles in Medline/Pubmed (Interferon OR immunomodulating OR immunomodulatory OR disease-modifying) AND (long-term OR disability progression) AND (multiple sclerosis).

No language restriction was used.

Abstracts were independently screened by two reviewers (AS and MPS) and relevant information were extracted from the full papers. To find any additional studies, reference lists of included studies and contingent systematic reviews were evaluated.

2.2. Data extraction

Data extraction was done independently by two authors (AS, MPS) and the accuracy of extraction was validated by consensus.

For each study, data were collected on year of publication, follow-up length, criteria to define the treatment and the control group, criteria to define the treatment start and the duration of treatment, endpoint and measures used to assess the treatment effect. In the extensions of RCT the proportion of patients evaluated at the end of the study as compared to those originally randomized (retention fraction) was also extracted. Treatment effect estimates along with their 95% Confidence Intervals (CI) were extracted where explicitly reported or derived from figures and Tables where possible.

Assessment of study quality of observational studies was done according to a modified version of the Newcastle-Ottawa scale (Wells et al., 2000) and the GRACE checklist (Dreyer et al., 2014).

3. Endpoints

The meta-analysis was based on two primary endpoints, that are those most frequently used and reported as primary outcomes in long-term assessment of treatment benefit: the time to an Expanded Disability Status Scale (EDSS) score of 6 and the time to progression to the Secondary Progressive (SP) phase of MS.

Time to reach an irreversible EDSS score of 4 was also considered as secondary endpoint.

4. Statistical methods

The pooled analysis was conducted at different levels: first a rough evaluation on the overall benefit of treatment vs no treatment was run including the largest available evidence, even if heterogeneous. In this evaluation the primary endpoint was the probability to reach EDSS 6 or SP MS during the study follow up; both observational studies and long-term extension of clinical trials were included, reporting treatment effect estimates as hazard ratios (HR) (when the time to EDSS 6 or SPMS was the endpoint), or relative risks (RR), (when the proportion of patients reaching EDSS 6 was the endpoint). The statistical analysis was based on a non-parametric sign test; this simple test gives a *p*-value testing the null hypothesis that superiority or inferiority of treated arms vs placebo were randomly distributed across studies. As a consequence, no pooled estimate of treatment effect is given in this analysis, but each study is classified according to the direction and statistical significance of treatment effect, as +1 when showing a significantly favorable treatment effect, as 0 when showing a treatment effect non significantly different from 0, or as −1 when the treatment was significantly unfavorable. A more quantitative assessment of statistical significance was run on the same set of studies using a one-sample Wilcoxon Signed Rank (WSR) test, based on the ranks of the log-transformation of original effect sizes (log Hazard Ratio or log Relative Risk), then weighted according to the inverse of their variance.

Separate quantitative analyses were run on studies based on the same endpoint (time to EDSS 6, time to SP conversion, time to EDSS4) and using the same treatment effect estimate (HR). HRs with their 95% Confidence Intervals (CI) were extracted from each study and a random effect model was applied to obtain the pooled estimates of treatment effect and its significance.

Since multiple arms from the same study creates "clustered data", each contrast coming from a study with more than two arms was given a lower weight, according to a procedure previously described (Sormani et al., 2009).

Heterogeneity among studies was quantified by the I^2 coefficient (Higgins and Thompson, 2002).

The statistical package Stata (v.11; IBM Corp.) was used ("*metan*" routine) to run the meta-analyses and draw the forest plots while the software R (v.3.0.3) was used to calculate the weighted ranks and perform the nonparametric tests.

5. Results

5.1. Characteristics of included studies

10 observational studies (Trojano et al., 2007, 2009; Veugelers et al., 2009; Patrucco et al., 2010; Bergamaschi et al., 2012; Shirani et al., 2012; Drulovich et al., 2013; Tedeholm et al., 2013; Cocco et al., 2015; Goodin et al., 2011) (Table 1) and 4 long-term extension of RCT (Rudick et al., 2005; Kappos et al., 2006; Bermel et al., 2010; Ebers et al., 2010) (Table 2), including a total of 13,238 patients were selected for the analysis (Fig. 1). The median follow up time was 8.5 years (range=4.5–21 years). All the studies evaluated the effect of IFN or GA vs no treatment; in the observational studies the control group was represented by contemporary untreated patients (6 studies (Trojano et al., 2007; Patrucco et al., 2010; Bergamaschi et al., 2012; Shirani et al., 2012; Drulovich et al., 2013; Cocco et al., 2015)), historical untreated patients (2 studies (Shirani et al., 2012; Tedeholm et al., 2013)), patients with a delayed start of treatment (Trojano et al., 2009) or low exposure to treatment (Goodin et al., 2011). One study had two (both contemporary and historical) control groups (Shirani et al., 2012) and one study (Veugelers et al., 2009) compared the EDSS accumulation before and after the treatment start.

In the extensions of RCT the experimental group was treated with different preparations of IFN-β while the control group was the one originally randomized to placebo; since after the study completion all the placebo patients were switched to IFN-β, in RCT extensions the comparison was between a delayed vs an immediate IFN-β treatment start.

The time to reach each milestone in observational studies was evaluated from disease onset (5 studies (Veugelers et al., 2009; Patrucco et al., 2010; Drulovich et al., 2013; Tedeholm et al., 2013; Cocco et al., 2015)), from disease diagnosis (1 study (Bergamaschi et al., 2012)), from time of treatment start (2 studies (Trojano et al., 2009; Goodin et al., 2011)), from time of treatment eligibility (1 study (Shirani et al., 2012)) or from time of first visit (1 study (Trojano et al., 2007)).

When multiple doses of IFN-β were reported, only the approved dose was considered in the analysis (Kappos et al., 2006;