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Postmarketing evidence of disease-modifying drugs in multiple sclerosis

Maria Trojano · Damiano Paolicelli · Aurora Fuiani · Fabio Pellegrini · Pietro Iaffaldano · Vita Direnzo · Mariangela D'Onghia

Abstract There is growing interest in the use of observational data to estimate treatment effects in chronic diseases such as multiple sclerosis (MS). The main results derived from postmarketing evaluations, in the last 2 years, of short- and long-term disease modifying drugs (DMDs) effectiveness will be reported in this Review. Moreover, some of the methodological improvements that may be useful to enhance the quality of observational studies will also be discussed.

Keywords Multiple sclerosis · Disease-modifying drugs · Disability progression · Long-term effect · Observational study

M. Trojano (✉) · D. Paolicelli · A. Fuiani · F. Pellegrini · P. Iaffaldano · V. Direnzo · M. D'Onghia
Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy
e-mail: mtrojano@neurol.uniba.it

F. Pellegrini
Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy

Review

Randomized Controlled trial (RCT) is undoubtedly the ideal way for providing evidence on drug efficacy. However, particularly for answering long-term questions in chronic diseases such as multiple sclerosis (MS), RCTs are often infeasible because of their size, time, ethical constraints and costs [1]. Even if an RCT is feasible, interest often focuses on estimating treatment effects in "real-world" settings, outside the tightly controlled confines of an RCT. A major issue is that observational studies are more exposed to biases, which can partly be addressed through rigorous study design or statistical analysis [2]. Several possible methodological improvements (matching, stratification, partitioning, adjustment, and restriction) have been recently proposed and are available to ensure validity when randomization is absent. Propensity score (PS)-adjusted analysis, which can create groups of patients who have similar likelihood of receiving a therapy, is the most common device currently used to reduce bias in treatment comparisons in observational studies [3]. PS analysis, taking into consideration parameters of interest that would likely affect the outcome, can create balanced groups that have a similar likelihood of receiving a therapy and resemble randomized cohorts of patients [4].

By applying this method in a previous paper [5] we evaluated the risk of worsening according to the length of exposure to interferon beta (IFNβ) in a large cohort of 2,090 multiple sclerosis patients collected by the Italian MS Database Network. Overall 44,140 patient visits with a follow-up of 22,143 patient years were evaluated. Forty-one percent of patients were exposed to IFNβ for up to 2 years, 39% for 2–4 years, and 20% for more than 4 years. A Cox regression model was used to analyze two clinical outcomes: disability progression and worsening of relapse

rate. The technique of propensity score was applied to reduce bias in the comparison of nonrandomized groups. The risks of disability progression (HR=0.23; 95% CI: 0.17–0.30) and worsening of relapse rate (HR=0.19; 95% CI: 0.14–0.27) were reduced by about four- to fivefold in patients exposed to IFNβ for more than 4 years, compared with patients exposed for up to 2 years. The propensity score technique confirmed the findings. The proportion of days covered by IFNβ treatment was lower ($p<0.0001$) in patients exposed to IFNβ for up to 2 years than in other groups. The results suggest that a clinical stabilization over 2 years of IFNβ exposure may predict a subsequent good clinical response to treatment.

In a more recent paper [6] we report beneficial effects of IFNβ treatment in 1,504 patients with relapsing-remitting (RR) MS followed prospectively for up to 7 years. Seventy-three percent of the patients were treated with IFNβ; the remaining patients were not treated. Cox proportional hazards regression adjusted for PS showed significantly reduced probabilities of worsening to secondary progression (hazard ratio, 0.38 [0.24–0.58]), Extended Disability Status Scale (EDSS) 4.0 (hazard ratio, 0.70 [0.53–0.94]), or EDSS 6.0 (hazard ratio, 0.60 [0.38–0.95]) in the IFNβ-treated group. A sensitivity analysis [7], conducted to evaluate the possible impact of potential unmeasured confounding variables, confirmed these findings. In a more recent analysis we evaluated the impact of early (<=1 year from disease onset) vs. delayed (>1 year from disease onset) IFNβ treatment on long-term disability in a cohort of 2,283 RR MS treated with IFNβ (N.625 in early group; N.1,655 in delayed group) for up to 7 years in 15 Italian MS Centers. Cox proportional hazards regression adjusted for PS showed that an early treatment reduced significantly the risk of EDSS 4 (HR, 0.50, 95% CI, 0.28–0.91, $p=0.024$) and EDSS 6 (HR, 0.22, 95% CI, 0.05–0.91, $p=0.037$) compared with a delayed treatment.

Brown et al. [8] analyzed DMD effectiveness, in a cohort of 590 RRMS collected in a large database in Nova Scotia, by an interesting pre-post treatment analysis of change in EDSS. This study made it possible to demonstrate a significant and robust impact of DMDs on disability progression and an EDSS increase more rapid in years following drug switches and treatment stops, while RCTs were unable to address these issues.

In other words, data derived from observational studies complement results of RCTs.

Any attempt to assess treatment effectiveness within the framework of properly conducted observational studies, once overt and hidden bias are taken into account, should not have to be dismissed a priori [9]. Methodological improvements to enhance the quality of observational studies are to be stressed given the availability of large longitudinal observational data in a number of databases that are being used by MS clinicians and researchers around the world [10].

Conflict of Interest statement The Authors declare that they have no conflict of interest related to the publication of this manuscript

References

1. McKee M, Britton A, Black N et al (1999) Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. BMJ 319:312–315
2. D'Agostino RB Jr, D'Agostino RB Sr (2007) Estimating treatment effects using observational data. JAMA 297:314–316
3. Rubin DB (2007) The design versus the analysis of observational studies for causal effects: parallels with the design of randomized studies. Stat Med 26:20–36
4. D'Agostino RB Jr (1998) Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17:2265–2281
5. Trojano M, Russo P, Fuiani A et al (2006) The Italian Multiple Sclerosis Database Network (MSDN): the risk of worsening according to IFN exposure in multiple sclerosis. Mult Scler 12:1–8
6. Trojano M, Pellegrini F, Fuiani A et al (2007) New natural history of Interferon-b-treated relapsing Multiple Sclerosis. Ann Neurol 61:300–306.
7. Lin DY, Psaty BM, Krommal RA (1998) Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 54:948–963
8. Brown MG, Kirby S, Skedgel C et al (2007) How effective are disease modifying drugs in delaying progression in relapsing-onset MS? Neurology 69:1498–1507
9. Trojano M (2007) Editorial: is it time to recognize the use of observational data to estimate treatment effectiveness in multiple sclerosis? Neurology 69:1478–1479
10. Butzkueven H, Chapman J, Cristiano E et al (2006) MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Mult Scler 12:769–774