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COMPARATIVE EFFECTIVENESS IN MULTIPLE SCLEROSIS: A METHODOLOGICAL COMPARISON

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KEYWORDS

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INTRODUCTION

In the absence of evidence from randomised controlled trials, observational data from large clinical registries can be used to emulate clinical trials and guide clinical decisions.[1] **Target trial emulation requires an explicit target-trial protocol and methodologic proficiency.** Whereas the process of randomisation ensures comparable treatment groups in clinical trials, observational studies need to carefully identify and account for potential confounders and sources of bias.[1] **Non-random treatment exposure (treatment indication bias) is inherent in clinical decision-making, as patient characteristics inform both treatment selection and clinical outcomes. Two potential techniques to reduce indication bias are propensity score (PS) matching, and marginal structural models (MSM).**

In PS matching, patients are matched at baseline on their propensity of receiving either of the compared therapies, **similar to a randomised trial.[2-4] Real-world treatment decisions do not, however, occur at a single timepoint, but are periodically reassessed. Marginal structural model (MSM), allows a continuous readjustment for potential confounders of serial treatment decisions.[2-4] The influence of time-varying covariates on the assessment of treatment response is not unique to observational data, and has also been reported to influence the interpretation of randomised clinical trials.[5]**

It remains uncertain whether simple comparisons of disease modifying therapies in cohorts with multiple sclerosis (MS) should repeatedly re-balance compared groups or a single balancing at baseline is sufficient. We have chosen a well described clinical MS scenario, the comparative effectiveness of fingolimod (FTY) and natalizumab (NAT), to **compare and contrast clinical outcomes using both PS matching and MSMs.**

METHODS

Patients with clinically isolated syndrome or relapsing-remitting MS were identified from MSBase, a global MS registry. Included patients were treated with either NAT or FTY after 2011 **(when both treatments were available, in order to satisfy the positivity assumption),** and were not previously treated with the comparator therapy. **Baseline was the first date of treatment commencement**. Patients required assessment of disability with the Expanded Disability Status Scale (EDSS) at baseline, two subsequent timepoints >= 6 months apart, and annually thereafter. **While no minimal treatment period was specified, at least one post-baseline visit had to be recorded while treated with study therapy. Patients were censored at the time of treatment discontinuation, or at the last available visit (whichever occurred first).** To compare results from the two analytical approaches, relapses, 6-month confirmed disability accrual and improvement were studied after PS matching and with MSMs. First, propensity scores were calculated using a multivariable logistic regression model and the following covariates at baseline: MS course, age, sex, disability, MS duration, number of relapses in the prior year, number of previous MS therapies. Patients were matched, without replacement, in a 2:1 ratio using nearest-neighbour matching within 0.1 SD of the PS. Second, inverse probability of treatment weights were calculated at 6-monthly intervals using the above variables.[4] This reflected the probability of patients' treatment status at each interval given their demographic and disease history**. Covariate balance was assessed by standardised mean difference. Cumulative hazard of relapses, 6-month confirmed disability accumulation and 6-month confirmed disability improvement** were assessed with Cox proportional hazards models, and marginal structural Cox models,

respectively. **A cluster term was included per individual patient. Disability outcomes were adjusted for visit density.**

Four hundred Monte Carlo simulations using 80% of the cohort, without replacement, were performed for each outcome to estimate the differences in mean hazard ratio (HR) and 95% confidence intervals (CI) between the two analytical approaches.

RESULTS

4,608 patients fulfilled the inclusion criteria (NAT 1,659, FTY 2,949). Baseline characteristics differed between groups, with higher rates of relapse (NAT:1.24 [0.96], mean [SD], vs FTY:0.89 [0.86]), higher EDSS (NAT:2.94 [1.63] vs FTY:2.36 [1.56]) and younger age (NAT:36.1 [10.3] vs FTY:38.1 [9.9]) in the natalizumab group. Covariate balance was improved by both PS matching and MSM reweighting at 6-monthly intervals, with a sustained standardised difference of <=20% for most variables (Fig 1). **Propensity score matching retained 86% of the included cohort (natalizumab 1574, fingolimod 2390). Characteristics of the PS matched and MSM cohorts were thus comparable.**

The comparisons of outcomes were consistent between the two methods. Treatment with natalizumab was associated with a lower probability of relapse **(PS matching: HR 0.67 [95%CI 0.60-0.76] Fig 2A.a; MSM 0.71 [0.62-0.80] Fig2B.a)** and higher probability of disability improvement **(PS matching: 1.21 [1.02-1.43] Fig 2A.c; MSM 1.43 [1.19-1.72] Fig2B.c). We did not find evidence for a difference in disability accumulation between the studied therapies with either analytical approach (PS matching: 0.96 [0.79-1.16] Fig 2A.b;**

MSM 0.85 [0.69-1.04] Fig2B.b). There was no statistical evidence of a difference in the magnitude of the effect size between the two methods, with point estimates of the difference in means close to null and the 95% confidence intervals including 0 (relapses [mean, 95%CI]: -0.03 [-0.17-0.11]; disability accumulation: 0.07 [-0.19-0.34]; disability regression: -0.16 [-0.43-0.10].

DISCUSSION

Here we have used observational data from MSBase, a large international MS registry, to emulate a head-to-head trial comparing clinical outcomes after treatment with two widely used MS therapies, FTY and NAT. The purpose of this methodological study of a well-described comparison of disease modifying therapies was to compare the efficiency of two statistical methods aimed at reducing indication bias and confounding: PS matching at baseline, and MSM with repeated re-weighting of compared groups. Results from both approaches were comparable, and consistent with the existing literature: compared to FTY, NAT reduced the risk of relapse by 29-33%, increased the chance of disability improvement by 4-15%, and had a comparable effect on disability accumulation.[6, 7] Despite the analytical advantages of MSM to account for time-varying confounding and indication bias, the results were consistent with PS matching.

Observational data have been used to guide clinical decision-making across the breadth of medicine.[8] In the fields of MS in particular, comparative effectiveness studies using observational data have replicated the findings from randomised controlled trials, and have frequently confirmed clinician intuition.[9, 10]

Since randomised controlled trials are not always feasible, the responsible and effective use of observational data is essential. The relative effectiveness of two therapies with similar structures of confounding and mediation of treatment effects can therefore be efficiently compared by either of these two methods when applied in clearly defined clinical contexts, with the use of adequately powered cohorts, and if the assumptions of causal inference are met.

REFERENCES

1. Hernán MA and Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol*. 2016, pp.758-764.
2. Hernan MA, Brumback B and Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000; 11: 561-570. 2000/08/24. DOI: 10.1097/00001648-200009000-00012.
3. Kalincik T, Brown JWL, Robertson N, et al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol* 2017; 16: 271-281. 20170211. DOI: 10.1016/S1474-4422(17)30007-8.
4. Kalincik T, Diouf I, Sharmin S, et al. Effect of Disease-Modifying Therapy on Disability in Relapsing-Remitting Multiple Sclerosis Over 15 Years. *Neurology* 2021; 96: e783-e797. 2020/12/30. DOI: 10.1212/WNL.0000000000011242.
5. Toh S, Hernandez-Diaz S, Logan R, et al. Estimating absolute risks in the presence of nonadherence: an application to a follow-up study with baseline randomization. *Epidemiology* 2010; 21: 528-539. DOI: 10.1097/EDE.0b013e3181df1b69.
6. Kalincik T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol* 2015; 77: 425-435. Comparative Study 2014/12/30. DOI: 10.1002/ana.24339.
7. Andersen JB, Sharmin S, Lefort M, et al. The effectiveness of natalizumab vs fingolimod-A comparison of international registry studies. *Mult Scler Relat Disord* 2021; 53: 103012. 2021/06/12. DOI: 10.1016/j.msard.2021.103012.

8. Kitsios GD. Propensity score studies are unlikely to underestimate treatment effects in critical care medicine: a critical reanalysis. *J Clin Epidemiol* 2015; 68: 467-469. 20141204. DOI: 10.1016/j.jclinepi.2014.10.012.
9. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol* 2016; 79: 950-958. 20160420. DOI: 10.1002/ana.24651.
10. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; 358: 676-688. DOI: 10.1056/NEJMoa0706383.

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CONFLICT OF INTEREST

Izanne Roos served on scientific advisory boards for Novartis and Merck and received conference travel support and/or speaker honoraria from Roche, Novartis, Biogen, Teva, Sanofi-Genzyme and Merck.

Ibrahima Diouf did not declare any competing interests.

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Alexandre Prat did not declare any competing interests.

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Rana Karabudak did not declare any competing interests.

Chris McGuigan did not declare any competing interests.

Elisabetta Cartechini did not declare any competing interests.

Michael Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck and Novartis.

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Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck, Roche, and Novartis; has received travel grants from Biogen, Merck, Roche, and Novartis; has participated in clinical trials by Biogen and Merck. She has received research grant support from Biogen.

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Angel Perez Sempere did not declare any competing interests.

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FIGURE LEGENDS

Figure 1: Covariate balance adjusted by propensity score matching at baseline (A) and inverse probability of treatment weighting at 6-monthly intervals in the marginal structural model (B)

Figure 2: Relapse and disability outcomes in natalizumab and fingolimod

As evaluated by propensity score matching (A) and marginal structural models (B):

Cumulative hazard of relapse (A.a, B.a), 6-month confirmed disability accumulation (A.b, B.b), 6-month confirmed disability improvement (A.c, B.c)

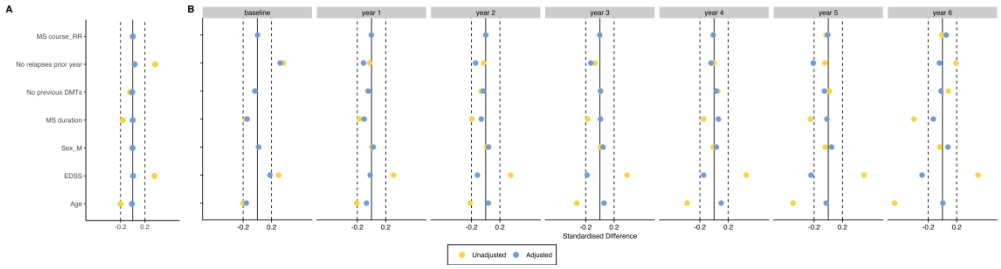

Figure 1: Covariate balance adjusted by propensity score matching at baseline (A) and inverse probability of treatment weighting at 6-monthly intervals in the marginal structural model (B)

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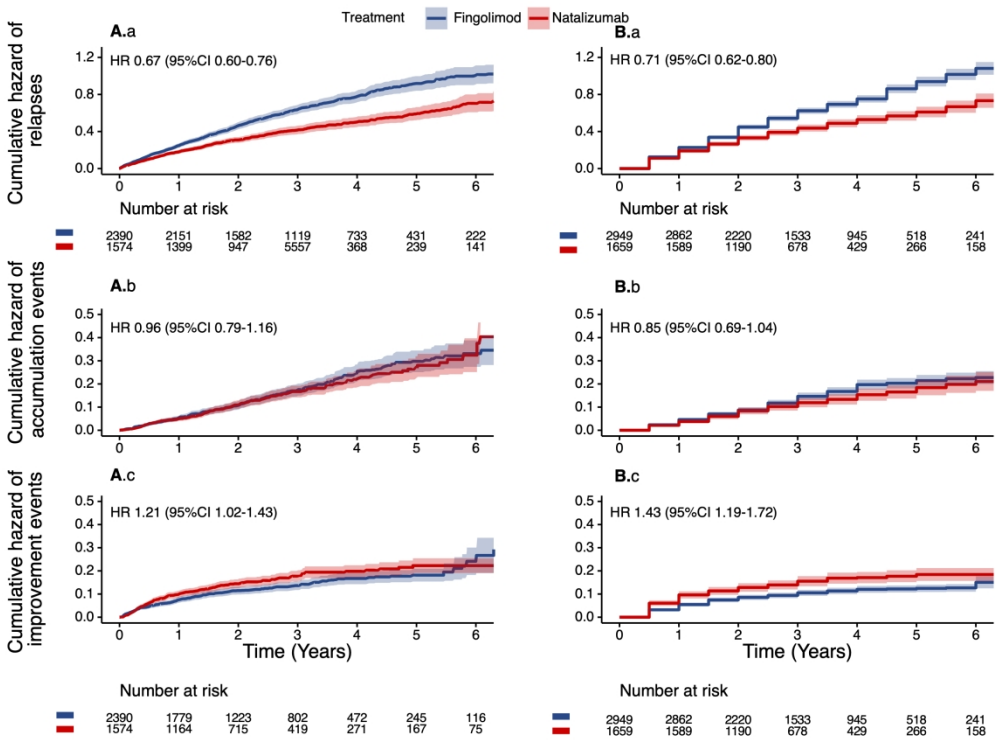

Figure 2: Relapse and disability outcomes in natalizumab and fingolimod
As evaluated by propensity score matching (A) and marginal structural models (B): Cumulative hazard of relapse (A.a, B.a), 6-month confirmed disability accumulation (A.b, B.b), 6-month confirmed disability improvement (A.c, B.c)

1058x793mm (72 x 72 DPI)