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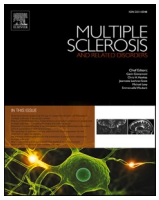

Correspondence

Severity of COVID19 infection among patients with multiple sclerosis treated with interferon-β

A B S T R A C T

Background: Interferon-β, a disease-modifying therapy (DMT) for MS, may be associated with less severe COVID-19 in people with MS.

Results: Among 5,568 patients (83.4% confirmed COVID-19), interferon-treated patients had lower risk of severe COVID-19 compared to untreated, but not to glatiramer-acetate, dimethyl-fumarate, or pooled other DMTs.

Conclusions: In comparison to other DMTs, we did not find evidence of protective effects of interferon-β on the severity of COVID-19, though compared to the untreated, the course of COVID19 was milder among those on interferon-β. This study does not support the use of interferon-β as a treatment to reduce COVID-19 severity in MS.

1. Background

While several studies have shown association of anti-CD20 disease-modifying therapies (DMTs) with severe COVID-19 (e.g., hospitalization, ICU admission, requiring artificial ventilation, and death) in people with MS, some have suggested a potential beneficial association of interferon-β on COVID-19 severity. Louapre and colleagues found patients treated with interferon-β or glatiramer-acetate may experience less severe COVID-19 compared to the untreated (Louapre et al., 2020). Sormani and colleagues showed that, compared to the untreated, patients treated with interferon-β had a 65% lower risk of experiencing severe COVID-19 (Sormani et al., 2021a), this also evident in a pooled French-Italian study (n = 1787) (Sormani et al., 2021b). Salter and colleagues assessed a combined US-Canadian sample (n = 1626), finding interferon-β treatment was inversely associated with hospitalization (OR=0.37, p = 0.11) compared to the untreated, though no associations with ICU admission, requiring artificial ventilation, or death were seen (Salter et al., 2021).

We previously assessed COVID-19 severity in an international sample of 2460 people with MS (Simpson-Yap et al., 2021), finding that interferon-β was not associated with COVID-19 severity compared to dimethyl-fumarate. Here, we compared severity of COVID-19 between patients treated with interferon-β and the untreated, as well as patients treated with dimethyl-fumarate or glatiramer-acetate, or pooled other DMTs.

2. Methods

As described previously (Peeters et al., 2020; Simpson-Yap et al., 2021), this was an international cross-sectional study (2020–2022) that evaluated determinants of COVID-19 severity among patients with MS having suspected or confirmed COVID-19. Data were acquired via an online central data-entry platform, hosted by QMENTA®, through which 11 independent registries and cohorts from 27 countries contributed. Study participation was restricted to MS patients aged ≥18 years with suspected or confirmed COVID-19. Ethics approval was granted by Hasselt University [CME2020/025]; individual data-sources obtained additional ethics approval, as required.

Clinicians entered demographic, lifestyle, and MS- and COVID-19-specific clinical characteristics(Simpson-Yap et al., 2021). As described previously (Simpson-Yap et al., 2021), data were entered either directly, indirectly accumulated by each data-source and entered *en masse* onto the platform, or via aggregated data sharing where the data-sources provide multidimensional contingency tables which were merged and an anonymised dataset reconstructed.

Confirmed COVID-19 was based on positive SARS-CoV-2 PCR test; suspected COVID-19 was based on clinician assessment and its alignment with COVID-19 as per physician judgement. Hospitalization, ICU admission, need for artificial ventilation, and death due to COVID-19 constituted the outcome measures of severity.

Sex was queried as male/female. Age was categorised as 18–49/50–69/≥70 years. MS phenotype was categorised as relapsing-remitting MS (RRMS) and progressive MS (SPMS/PPMS). Disability was assessed by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983, D'Souza et al., 2017) and dichotomised as 0–6.0 and >6.0. Current smoker status was queried. Current DMT use included alemtuzumab, cladribine, dimethyl-fumarate, fingolimod, glatiramer-acetate, interferon-β, natalizumab, ocrelizumab, rituximab, siponimod, teriflunomide, or another DMT.

3. Statistical analysis

We compared ordered COVID-19 severity between people with MS treated with interferon-β vs. untreated, glatiramer-acetate, dimethyl-

Abbreviations: COVID-19, Coronavirus disease of 2019; ICU, Intensive care unit; OR, Odds ratio; DMT, Disease modifying therapy.

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fumarate, and all Other non-interferon-β DMTs. Mixed-effect ordered probit regression, random-effects representing data-source, was used to evaluate associations with ordered COVID-19 severity, categorised in ordered fashion as none, hospitalization, ICU admission/requiring artificial ventilation, and death. For the ordered categorical term, people are allocated to the most severe outcome level they reach, so not double counted. For instance, if a patient has gone to ICU/ventilation, they are considered to have been hospitalised as well, but their allocation is to the ICU/ventilation level. From these, an overall coefficient, as well as marginal effects of each covariate level, relative to its reference, were estimated as means of model covariates. All models were adjusted for age, sex, MS phenotype, and disability. Model covariates were selected based on a priori justification from literature, though also limited to these four based on the way data was aggregated; thus, adjustment for comorbidities was not possible for all persons.

All statistical analyses were undertaken in STATA/SE 16.0 (StataCorp, College Station, USA).

4. Results

The analysis sample comprised 5568 participants with suspected/confirmed COVID-19 (83.4% confirmed COVID-19). Participants were predominantly female (73.1%), <50 years (66.3%), of RRMS phenotype (84.3%), and with low disability (EDSS 0–6; 81.8%). Most patients were treated with DMTs (91.3%), including 5.4% with interferon-β. The characteristics of the subsample with confirmed COVID-19 were similar (data not shown). Patients treated with interferon-β were younger than the untreated, and more typically diagnosed with RRMS and of EDSS 0–6. Compared to those treated with other DMTs, interferon-β-treated patients were slightly older and more commonly diagnosed with progressive MS (Supplementary Table 1). The outcomes indicating more severe course of COVID-19 were less frequent among interferon-β-treated or Other DMT-treated than untreated patients. The frequency of these outcomes did not differ between the interferon-treated or Other DMT-treated patients. Similar observations were made among the patients with confirmed COVID-19 only (data not shown).

Compared to the untreated, interferon-β-treated patients had lower risks of severe COVID-19, including 6% lower hospitalisations, and 2% lower ICU admission/requiring artificial ventilation, and 2% lower death rates (Table 1). Compared to pooled Other DMTs, however, there was no evidence for difference in COVID-19 severity. Indeed, what inverse trend that was evident was merely a function of comparison to the anti-CD20 DMTs, as excluding these from the Other DMT comparator completely abrogated any association with less severe COVID-19. This observation was replicated when comparing the severity of COVID-19 course among patients treated with interferon-β vs. dimethyl-fumarate or glatiramer-acetate (data not shown).

Table 1
Ordered probit regression of leveled outcomes by interferon treatment status.

	aβ (95% CI)	Marginal effects (95% CI)			
		None	Hospitalization	ICU/ Ventilation	Death
Untreated	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Interferons	**−0.34 (−0.59, −0.08) *p* = *0.010***	**0.10 (0.02, 0.18) *p* = *0.012***	**−0.06 (−0.10, −0.01) *p* = *0.011***	**−0.02 (−0.05, −0.00) *p* = *0.022***	**−0.02 (−0.04, −0.00) *p* = *0.044***
Pooled Other DMT[a]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Interferons	−0.18 (−0.39, 0.02) *p* = *0.074*	0.05 (−0.01, 0.10) *p* = *0.079*	−0.03 (−0.05, 0.00) *p* = *0.075*	−0.01 (−0.03, 0.00) *p* = *0.085*	−0.01 (−0.02, 0.00) *p* = *0.11*
Pooled Other DMT[b]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Interferons	−0.03 (−0.24, 0.17) *p* = *0.76*	0.01 (−0.05, 0.06) *p* = *0.76*	−0.00 (−0.03, 0.02) *p* = *0.76*	−0.00 (−0.02, 0.01) *p* = *0.76*	−0.00 (−0.01, 0.01) *p* = *0.76*

Analysis by multilevel mixed-effects ordered probit regression, estimating β (95% CI). All models adjusted for age, sex, MS phenotype, and EDSS. Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale.
Results in boldface denote statistical significance ($p<0.05$).
Note: Other DMT was queried as "On another drug not listed".
[a] Pooled Other DMT includes alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, rituximab, siponimod, teriflunomide, and other DMTs not specifically queried.
[b] Pooled Other DMT includes alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, siponimod, teriflunomide, and other DMTs not specifically queried, but specifically excludes ocrelizumab and rituximab.

5. Discussion

We tested the hypothesis that treatment with interferon-β was associated with less severe COVID-19 among patients with MS. Using the composite international COVID-19 database, collated by the MS Data Alliance and MS International Federation on behalf of the Global Data Sharing Initiative, we showed that treatment with interferon-β was not associated with less severe COVID-19 compared to treatment with Other DMTs. On the other hand, patients who remained untreated, were at a slightly higher risk of experiencing severe COVID-19 than those treated with interferon-β.

A few observational studies, including our own, have described the severity of COVID-19 among people with MS, especially in relation to their demographic and clinical characteristics and treatment with high-efficacy DMTs. So far, no randomised clinical trials have studied the effects of interferon-β on the severity of COVID-19. Studies in French and Italian MS registries suggested that patients treated with interferon-β are less likely to require hospitalization, ICU admission, artificial ventilation, or die as the result of COVID-19 than those who are untreated at the time of acquiring the infection (Louapre et al., 2020; Sormani et al., 2021a, 2021b). However, given the lack of difference between the COVID-19 severity on interferon-β and other, more immunosuppressive DMTs, one may speculate that this difference is driven by the higher underlying clinical and demographic risks which are typically more prevalent among patients who remain untreated (Simpson-Yap et al., 2022). While our and other studies controlled for some of the demographic and clinical participant characteristics, such as age, sex, MS phenotype, and disability, there are other unmeasured potential risk factors, both clinical and behavioural, which our study was not able to account for. We therefore interpret the suggested marginal difference in the outcomes between interferon-β and the untreated patients as a result of the unadjusted differences between the compared groups.

Our study did not systematically query anti-SARS-CoV-2 vaccination to allow assessment of these effects, and indeed the majority of the data collection for this study preceded the advent of these vaccines. Nonetheless, over half of our study sample was recruited after 2021 when anti-SARS-CoV-2 vaccines had become available and thus some unknown proportion of participants may have been exposed to these vaccines. The analyses evaluating the period of recruitment did not show evidence of its association with COVID-19 severity, and likewise adjustment for period of recruitment had no effect on the reported associations (data not shown). However, this study was not designed to answer the question of the potential impact of anti-SARS-CoV-2 vaccination on COVID-19 serverity outcomes.

Our study does not support the use of interferon-β as a treatment to reduce COVID-19 severity in people with MS.

CRediT authorship contribution statement

Steve Simpson-Yap: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Visualisation, Writing Original, Writing Review/Editing; **Ashkan Pirmani:** Data Curation, Software, Writing Review/Editing; **Edward De Brouwer:** Data Curation, Software, Writing Review/Editing; **Liesbet M. Peeters:** Conceptualization, Funding, Project Administration, Writing Review/Editing; **Lotte Geys:** Project Administration, Writing Review/Editing; **Tina Parciak:** Data Curation, Writing Review/Editing; **Anne Helme:** Project Administration, Funding, Writing Review/Editing; **Jan Hillert:** Data Curation, Project Administration, Writing Review/Editing; **Yves Moreau:** Data Curation, Writing Review/Editing; **Gilles Edan:** Data Curation, Writing Review/Editing; **Tim Spelman:** Data Curation, Writing Review/Editing; **Sifat Sharmin:** Methodology, Writing Review/Editing; **Robert McBurney:** Data Curation, Project Administration, Writing Review/Editing; **Hollie Schmidt:** Data Curation, Project Administration, Writing Review/Editing; **Arnfin Bergmann:** Data Curation, Project Administration, Writing Review/Editing; **Stefan Braune:** Data Curation, Project Administration, Writing Review/Editing; **Alexander Stahmann:** Data Curation, Project Administration, Writing Review/Editing; **Rodden Middleton:** Data Curation, Project Administration, Writing Review/Editing. **Amber Salter:** Data Curation, Project Administration, Writing Review/Editing; **Bruce Bebo:** Data Curation, Project Administration, Writing Review/Editing; **Anneke van der Walt:** Data Curation, Project Administration, Writing Review/Editing; **Helmut Butzkueven:** Data Curation, Project Administration, Writing Review/Editing; **Serkan Ozakbas:** Data Curation, Project Administration, Writing Review/Editing; **Rana Karabudak:** Data Curation, Project Administration, Writing Review/Editing; **Cavit Boz:** Data Curation, Project Administration, Writing Review/Editing; **Raed Alroughani:** Data Curation, Project Administration, Writing Review/Editing; **Juan I Rojas:** Data Curation, Project Administration, Writing Review/Editing; **Ingrid van der Mei:** Data Curation, Project Administration, Writing Review/Editing; **Guilherme Sciascia do Olival:** Data Curation, Project Administration, Writing Review/Editing. **Melinda Magyari:** Data Curation, Project Administration, Writing Review/Editing; **Ricardo Alonso:** Data Curation, Project Administration, Writing Review/Editing; **Richard Nicholas:** Data Curation, Project Administration, Writing Review/Editing; **Anibal Chertcoff:** Data Curation, Project Administration, Writing Review/Editing; **Ana Zabalza:** Data Curation, Project Administration, Writing Review/Editing; **Georgina Arrambide:** Data Curation, Project Administration, Writing Review/Editing; **Nupur Nag:** Data Curation, Project Administration, Writing Review/Editing; **Annabel Descamps:** Data Curation, Project Administration, Writing Review/Editing; **Lars Costers:** Data Curation, Project Administration, Writing Review/Editing; **Ruth Dobson:** Data Curation, Project Administration, Writing Review/Editing; **Aleisha Miller:** Data Curation, Project Administration, Writing Review/Editing; **Paulo Rodrigues:** Data Curation, Project Administration, Writing Review/Editing; **Vesna Prčkovska:** Data Curation, Project Administration, Writing Review/Editing; **Giancarlo Comi:** Conceptualisation, Data Curation, Project Administration, Writing Review/Editing; **Tomas Kalincik:** Conceptualization, Methodology, Resources, Data Curation, Project Administration, Writing Original, Writing Review/Editing.

All authors contributed to the final revision of the manuscript and approve it for submission.

SSY & AP contributed equally to this paper.

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Ethics approval

This study was approved by the ethical committee of Hasselt University [CME2020/025]. Other ethics information from data custodians includes:

MSBase data is provided with the consent of individual participants and principal investigators at each MSBase participating center.

The GMSR was first approved by ethics committee of Julius-Maximilians-University of Würzburg (vote number 142/12). After switching to the web-based documentation system, further positive votes e.g., by the ethics committee of the Thuringia state chamber of physicians, followed by several ethics' committees of different universities, were given and all patients have signed an informed consent.

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Data sharing

People interested in the data that were used for the analyses in this study can inquire with Prof. Dr. Liesbet M. Peeters.

Declaration of Competing Interest

Steve Simpson-Yap has no conflicts of interests to disclose.

Ashkan Pirmani has no conflicts of interests to disclose.

Edward De Brouwer has no conflicts of interests to disclose.

Liesbet M. Peeters has no personal pecuniary interests to disclose, other than being the chair of The MS Data Alliance (MSDA), which received income from a range of corporate sponsors, recently including Biogen, BristolMyersSquibb (formerly Celgene), Janssen Pharmaceuticals, Merck, Novartis, QMENTA, and Roche.

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Supplementary materials

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