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

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Abstract

Background: Interferon-β, a disease-modifying therapy (DMT) for multiple sclerosis (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.

Background

While several studies have shown association of anti-CD20 disease-modifying therapies (DMTs) with severe COVID-19 (e.g., hospitalisation, ICU admission, requiring artificial ventilation, and death) in people with multiple sclerosis (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=1,787)(Sormani et al., 2021b). Salter and colleagues assessed a combined US-Canadian sample (n=1,626), finding interferon-β treatment was inversely associated with hospitalisation (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 2,460 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.

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 onto the centralised platform, hosted by QMENTA®, 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. Hospitalisation, ICU admission, need for artificial ventilation, and death due to COVID-19 constituted the outcome measures of severity.

Patient 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.

Statistical analysis

We compared ordered COVID-19 severity between people with MS treated with interferon-β vs. untreated, glatiramer-acetate, dimethyl-fumarate or all other grouped 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, hospitalisation, 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 is estimated, 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).

Results

The analysis sample comprised 5,568 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 patients 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-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-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-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).

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; Sormani et al., 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 as we have done, there are other unmeasured potential risk factors, both clinical and behavioural, which our study was not able to account for. We are thus inclined to not interpret the suggested inverse associations of interferons compared to the untreated as indicative of a potential protective effect, but instead as statistical artifact. If there were any protective effect to be ascertained, this should only be assessed in a clinical trial design where treatment allocations are not potentially affected by indication bias or other spurious drivers of effect.

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, slightly more than half of the sample evaluated here 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. However, analyses evaluating the period of recruitment did not show evidence of a consistent association with COVID-19 severity outcomes, and likewise adjustment for period of recruitment had no effect on associations (data not shown). We are loath to make any conclusions about the impacts, or

lack thereof, of anti-SARS-CoV-2 vaccination on COVID-19 outcomes, from these data and will leave it to other studies specifically designed for such purpose to make such conclusions

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

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Contributorship

SSY: Data analysis taskforce, lead of HOLISM, running key analyses, drafted initial manuscript draft;

AP: Data wrangling taskforce;

EDB: Data analysis taskforce, running key analyses, contributing author;

LMP: Project lead, contributing author;

LG: Project coordinator; **TP**: Data wrangling taskforce;

AH: Stakeholder engagement and communications lead, project delivery, contributing author;

JH: Data analysis taskforce, lead of Swedish MS register, contributing author;

YM: Data analysis taskforce; **GE**: Data analysis taskforce;

TS: Data analysis taskforce; **SS**: Statistical guidance for ordered probit analyses;

RMcB: Lead for iConquerMS data-source, contributing author;

HS: Lead for iConquerMS data-source; **AB**: Lead for NTD data-source;

SB: Lead for NTD data-source; **ASt**: Lead for German MS Registry data-source;

RM: Lead for UK MS Register data-source. **AS**: Lead for COViMS data-source, contributed to analysis approach; **BB**: Lead for COViMS;

AvdW: Lead of MSBase COVID-19 study and Australian and New-Zealand Cohort, contributed to data analysis approach, contributing author;

HB: Co-Lead of Australian and New-Zealand Cohort and MSBase COVID-19 study, contributed to data analysis approach;

SO: Co lead Turkish MS Covid Cohort; **RK**: Co lead Turkish MS Covid Cohort; **CB**: Co lead Turkish MS Covid Cohort;

RAl: Contributed to MSBase data collection;

JIR: Lead for RELACOEM data-source; **IvdM**: Lead for AMSLS data-source; **GSdO**: Lead for ABEM data-source.

MM: Lead for Danish MS Registry data-source; **RA**: Lead for RELACOEM data-source;

RN: Lead for UK MS Register data-source; **AC**: Lead for EMA data-source;

AZ: Lead for CEM-CAT data-source; **GA**: Lead for CEM-CAT data-source, contributing author;

NN: Lead for HOLISM data-source, contributing author; **AD**: Lead for icometrix data-source;

LC: Lead for icometrix data-source; **RD**: PI for OPTIMISE:MS;

AM: OPTIMISE:MS Senior Clinical Project Manager;

PR: Lead for central platform collecting the data-sources;

VP: Lead for central platform collecting the data-sources;

GC: Core dataset taskforce, conceptualisation, contributing author;

TK: Data analysis taskforce, contributing author.

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

SSY & AP contributed equally to this paper.

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 centre.

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.

Research subject protection was sought from the Washington University in St Louis (WUSTL) Institutional Review Board for housing COViMS Registry data, who determined it to be "not human subjects" research and therefore exempt from active IRB oversight at WUSTL and did not require patient consent.

The patient data sent to analyses resulting in the study "Associations of DMT therapies with COVID-19 severity in multiple sclerosis" originated from a study approved by the ethics Committee of the Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP) under the internal review board number (IRB) CAAE 31021220.2.0000.5411. All participants signed a written informed consent form before enrollment.

The Cemcat cohort study was approved by the ethics committee of the Vall d'Hebron University Hospital (XMG-INT-2014-01) and all patients have signed an informed consent.

Data sharing

Persons interested in acquiring the anonymised data underlying this analysis can inquire with Professor Dr Liesbet M. Peeters to make requests.

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