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Updated Results of the COVID-19 in MS Global Data Sharing Initiative

Anti-CD20 and Other Risk Factors Associated With COVID-19 Severity

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Abstract

Background and Objectives

Certain demographic and clinical characteristics, including the use of some disease-modifying therapies (DMTs), are associated with severe acute respiratory syndrome coronavirus 2 infection severity in people with multiple sclerosis (MS). Comprehensive exploration of these relationships in large international samples is needed.

Methods

Clinician-reported demographic/clinical data from 27 countries were aggregated into a data set of 5,648 patients with suspected/confirmed coronavirus disease 2019 (COVID-19). COVID-19 severity outcomes (hospitalization, admission to intensive care unit [ICU], requiring artificial ventilation, and death) were assessed using multilevel mixed-effects ordered probit and logistic regression, adjusted for age, sex, disability, and MS phenotype. DMTs were individually compared with glatiramer acetate, and anti-CD20 DMTs with pooled other DMTs and with natalizumab.

Results

Of 5,648 patients, 922 (16.6%) with suspected and 4,646 (83.4%) with confirmed COVID-19 were included. Male sex, older age, progressive MS, and higher disability were associated with more severe COVID-19. Compared with glatiramer acetate, ocrelizumab and rituximab were

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Glossary

aβ = adjusted β; **BMI** = body mass index; **COVID-19** = coronavirus disease 2019; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **ICU** = intensive care unit; **MS** = multiple sclerosis; **RRMS** = relapsing-remitting MS.

associated with higher probabilities of hospitalization (4% [95% CI 1–7] and 7% [95% CI 4–11]), ICU/artificial ventilation (2% [95% CI 0–4] and 4% [95% CI 2–6]), and death (1% [95% CI 0–2] and 2% [95% CI 1–4]) (predicted marginal effects). Untreated patients had 5% (95% CI 2–8), 3% (95% CI 1–5), and 1% (95% CI 0–3) higher probabilities of the 3 respective levels of COVID-19 severity than glatiramer acetate. Compared with pooled other DMTs and with natalizumab, the associations of ocrelizumab and rituximab with COVID-19 severity were also more pronounced. All associations persisted/enhanced on restriction to confirmed COVID-19.

Discussion

Analyzing the largest international real-world data set of people with MS with suspected/confirmed COVID-19 confirms that the use of anti-CD20 medication (both ocrelizumab and rituximab), as well as male sex, older age, progressive MS, and higher disability are associated with more severe course of COVID-19.

The ongoing coronavirus disease 2019 (COVID-19) pandemic has had significant effects on health and wellbeing worldwide. Beyond its general effects, however, there is interest in the effects on patient populations, including people with multiple sclerosis (MS). Several clinic-based and other studies have been undertaken to assess the epidemiology of COVID-19 severity among people with MS.[1-4] The Covisep clinical registry study in France studied 347 people with MS with suspected or confirmed COVID-19[1]; finding disease-modifying therapies (DMTs) with a higher infection risk were associated with more than 4 times greater risk of more severe COVID-19. Sormani and colleagues described the results of the national Musc-19 Italian registry study, including 593 suspected and 191 confirmed COVID-19[2]; finding anti-CD20 DMTs, ocrelizumab and rituximab, were associated with 2.4 and 2.7 times greater risk of more severe COVID-19, respectively, compared with the untreated and with dimethyl fumarate. These results were replicated in a pooled analysis comprising 1,066 Italian and 721 French patients with confirmed COVID-19, finding anti-CD20 DMT use was associated with 2.1 times greater risk of more severe COVID-19 than the untreated, although evaluating each DMT individually, the association of rituximab was twice as strong as ocrelizumab (OR 3.78 vs 1.79).[4] In the United States/Canada, Salter and colleagues conducted the large multicenter CoviMS study, comprising 281 suspected and 1,345 confirmed COVID-19,[3] evaluating DMTs compared with the untreated, and the authors found rituximab and ocrelizumab were associated with greater risk of hospitalization; however, only rituximab showed positive trends for intensive care unit (ICU) admission/artificial ventilation and death. Langer-Gould and colleagues used data from the Kaiser Permanente patient population to evaluate COVID-19 severity between 1,895 people with MS treated with rituximab and 4.8 million non-MS patients; finding rituximab-treated patients with MS was more likely to be hospitalized because of COVID-19, although none died.[5]

Although there has been some variability in the comparators used, including DMTs with less infection risk,[1] dimethyl fumarate,[2] and no treatment,[2-4] broadly, these studies show a detrimental association of the anti-CD20 DMTs, ocrelizumab and rituximab. We have previously examined COVID-19 severity among 2,340 people with MS and suspected or confirmed COVID-19 up to October 2020; finding older age, progressive MS phenotype, and greater disability were each associated with more severe COVID-19, including hospitalization, admission to ICU, artificial ventilation, and death.[6] We also showed ocrelizumab and rituximab were associated with higher frequencies of hospitalization, admission to ICU, and need for artificial ventilation.

In this full and final analysis data set, we applied an ordered probit regression methodology to an expanded cohort of people with MS followed until September 2021 to describe the associations of severity of COVID-19 with clinical and treatment-related factors, with a goal to confirm our previous findings[6] and to unify the analytical approach.

Methods

Study Design

This was a multicenter cross-sectional study; patients with suspected or confirmed COVID-19 were assessed for the characteristics of COVID-19 severity outcomes. Data were acquired through an international online central data-entry platform and 11 independent registries and cohorts from 27 countries, including Argentina (n = 173), Australia (n = 11), Azerbaijan (n = 2), Bahamas (n = 1), Belgium (n = 36), Brazil (n = 225), Bulgaria (n = 3), Chile (n = 15), Colombia (n = 14), Czech Republic (n = 14), Denmark (n = 157), Ecuador (n = 26), France (n = 2), Germany (n = 168), Honduras (n = 3), Italy (n = 30), Kuwait (n = 102), Mexico (n = 5), the Netherlands (n = 65), New Zealand (n = 1), Paraguay (n = 1),

Romania (n = 3), Saudi Arabia (n = 6), Serbia (n = 3), Spain (n = 273), Sweden (n = 880), Turkey (n = 412), the United Kingdom (n = 26), and Canada/the United States (n = 2,911). Some of the constituent registries and cohorts included multiple countries, but the enumeration of these data sources is platform (n = 114), source 1 (n = 880), source 2 (n = 664), source 3 (n = 214), source 4 (n = 3), source 5 (n = 90), source 6 (n = 25), source 7 (n = 157), source 8 (n = 214), source 9 (n = 79), source 10 (n = 2,910), and source 11 (n = 218).

Data were entered in 3 fashions: (1) direct entry to the central platform, (2) patient-level data-sharing through participating registries/cohorts which uploaded their COVID-19 core data set into the central data platform at interval, and (3) aggregated data-sharing through participating registries/cohorts as described previously.[6] Multidimensional contingency tables from the constituent data sources were merged, and from this, a combined anonymized data set was reconstructed. Data were entered for each given participant once, but information for that participant could be reentered, this then replacing the original record.

Clinicians entered demographic, lifestyle, and MS-specific and COVID-19–specific clinical characteristics, as described previously.[7] In this article, only age, sex, MS phenotype, disability, DMT use, glucocorticoid use, smoking status, body mass index (BMI), comorbidities, COVID-19 status, hospitalization, ICU admission, artificial ventilation, and death are described. Study participation was restricted to patients with MS aged 18 years or older with suspected or confirmed COVID-19. Confirmed COVID-19 was based on a positive PCR test, while suspected COVID-19 was based on clinician judgement of the clinical presentation and its alignment with COVID-19.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the ethical committee of Hasselt University (CME2020/025). Other ethics information from data custodians, MSBase data were provided with the consent of individual participants and principal investigators at each MSBase participating center. The GMSR was first approved by the ethics committee of the 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 signed an informed consent. Research subject protection was sought from the Washington University in the St. Louis 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 under internal review board number 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 signed an informed consent.

Variables

Definitions for all terms were provided to data partners and were available on the MS Data Alliance platform: msdataalliance.com/wp-content/uploads/2020/04/Data-Dictionary-for-COVID-19-in-people-with-MS.docx. As described previously,[6] hospitalization was queried as Admission in hospital because of COVID-19 (suspicious) infection? ICU admission was queried as Stay in ICU because of COVID-19 (suspicious) infection? Requiring artificial ventilation was queried as Ventilation needed during hospital stay? Death due to COVID-19 was queried as Did the patient die because of the (suspected) COVID-19 infection? Clinicians made all judgements regardless of how data were entered.

As described previously,[6] patient age was categorized into 3 groups: 18–49, 50–69, and ≥70 years. MS phenotype was grouped into relapsing-remitting MS (RRMS) and progressive MS (secondary progressive MS and primary progressive MS). Disability was assessed by the Expanded Disability Status Scale (EDSS)[8,9] and dichotomized into 0–6.0 and >6.0. Comorbidities were queried, including cardiovascular disease, hypertension, diabetes, chronic liver disease, kidney disease, other neurologic/neuromuscular disorder, lung disease, or malignant neoplasia. BMI was categorized as nonobese (BMI ≤30) and obese (BMI >30). Current smoker status was queried as yes or no. Current DMT use was queried, including alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferons, natalizumab, ocrelizumab, rituximab, siponimod, teriflunomide, or another DMT, this latter queried as On another drug not listed. In addition, the use of glucocorticoids was queried; although dose and frequency were queried, this was insufficiently completed and so only dichotomous glucocorticoid use was evaluated. Data on DMT dose and duration were not queried.

Statistical Analysis

Mixed-effects ordered logistic regression was assessed, but models failed the proportional odds assumption. Accordingly, mixed-effects ordered probit regression, random effects grouped by data source, was used to evaluate associations with ordered COVID-19 severity, categorized as none, hospitalization, ICU admission/requiring artificial ventilation, and death. All models were adjusted for age, sex, MS phenotype, and disability. From these, the marginal effects of each covariate level relative to its reference were estimated at means of model covariates.

In addition, associations with dichotomous hospitalization, ICU admission, artificial ventilation, and death outcomes were assessed using multilevel mixed-effects logistic regression, random effects grouped by data source, as univariable and adjusted for age, sex, MS phenotype, and disability.

Adjustment for multiple comparisons was undertaken using the family-wise Holm step-down method such that within each hypothesis and within models 1 and 2, statistical tests were ranked by lowest p value and significance threshold evaluated relative to the number of statistical tests within that family. Associations reaching significance after this adjustment are annotated as such in tables.

Subgroup analyses were also undertaken where data on comorbidities, BMI, and smoking were available, allowing additional adjustment for these covariates. Due to the way data were aggregated, these covariates could not be assessed in the ordered probit regression analyses. All analyses were complete-case.

Individual DMT associations with outcomes were assessed relative to glatiramer acetate because it has little immunosuppressive activity that might affect infection risk and, thus, represents an ideal comparator. Next, ocrelizumab and rituximab, as well as the untreated, were evaluated relative to all other pooled DMTs. Afterward, ocrelizumab and rituximab were evaluated relative to natalizumab to account for a possibility of ascertainment bias due to treatment with high-efficacy DMT.

In addition, with a goal to assess whether DMT associations were just a function of underlying COVID-19 severity risk predisposing characteristics, stratified analyses by age (≥70 vs <70 years), MS phenotype (progressive vs RRMS), and EDSS (>6 vs ≤6) were undertaken. These were assessed by including a product term between the interaction covariate and the primary predictor, the significance of this term denoting the significance of the intergroup difference.

Intergroup differences were accounted for by mixed-effects regression. Leave-one-out analyses serially excluding each data source were also undertaken (data not shown).

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

Data Availability

Data used in this study are in the custody of the participating registries and databases. For further enquiries, those interested in access to the data liaise with the MS Data Alliance.

Results

The cohort comprised 5,568 participants with suspected or confirmed COVID-19, of whom 83.4% were confirmed COVID-19. In evaluating COVID-19 severity outcomes between data sources, those patients in the platform, source C-3, and source C-11 had higher rates of hospitalization, but source C-4 and source C-5 had lower hospitalization. ICU admission was more frequent among patients in the platform and did not occur in source C-4 and source C-6, but otherwise did not differ. Requiring artificial ventilation was more common among patients in the platform, source C-3, and source C-5, and less common in source C-4 and source C-7. Death was more common among patients in source C-7 but did not occur in sources C-4, C-5, C-6, C-8, and C-9.

Cohort characteristics of the sample were typical for MS, being majority female (73.1%), predominantly younger than 50 years (66.3%), and largely of RRMS phenotype (84.3%) and EDSS <6 (81.8%, Table 1). The most commonly used DMTs were ocrelizumab (19.8%), rituximab (11.4%), and dimethyl fumarate (11.1%). In the subgroup of participants with data on these parameters, 2,479 of 4,890 (50.7%) were of MS duration >10 years, 1,932 of 4,347 (44.4%) had comorbidities, 1,089 of 2,998 (36.3%) were of obese BMI, 141 of 3,635 (3.9%) were taking glucocorticoid medication, and 1,209 of 5,568 (21.7%) were current smokers. Of the total sample, 14.6% were hospitalized, 3.7% admitted to ICU, 3.4% required artificial ventilation, and 1.6% died (Table 2). Similar proportions were seen on restriction to confirmed COVID-19.

Characteristics of COVID-19 Severity According to MS Therapy

We first evaluated the demographic and clinical characteristics of COVID-19 severity as an ordered polychotomous term, ranging from no hospitalization, hospitalization, ICU admission/requiring artificial ventilation, and death. Evaluating the predicted probabilities of these outcomes by patient characteristics,

Table 1 COVID-19 and Demographic Cohort Characteristics

	Suspected and confirmed (n = 5,568)	Confirmed (n = 4,646)
Confirmed COVID-19 status	4,646 (83.4)	4,646 (100.0)
Hospitalization	815 (14.6)	761 (16.4)
ICU admission	208 (3.7)	201 (4.3)
Artificial ventilation	187 (3.4)	170 (3.7)
Death	89 (1.6)	82 (1.8)
Sex, female	4,069 (73.1)	3,381 (72.8)
Age		
18–49	3,691 (66.3)	3,026 (65.1)
50–69	1,688 (30.3)	1,459 (31.4)
≥70	147 (2.6)	129 (2.8)
Missing	52 (0.8)	32 (0.7)
BMI		
<30	1,909 (34.3)	1,660 (35.7)
≥30	1,089 (19.6)	994 (21.4)
Missing	2,570 (46.2)	1,992 (42.9)
Current smoker	1,209 (21.7)	1,035 (22.3)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; ICU = intensive care unit.
Data are presented as n (%) unless otherwise specified.

female patients were less likely to have more severe COVID-19 (adjusted β [aβ] −0.21, 95% CI −0.31 to −0.12), while older age (>50–70 years: aβ 0.31, 95% CI 0.21–0.40; >70 years: aβ 0.56, 95% CI 0.30–0.81), progressive MS phenotype (aβ 0.22, 95% CI 0.08–0.35), and higher disability (aβ 0.69, 95% CI 0.56–0.81) were associated with more severe COVID-19 (Table 2), persisting on restriction to confirmed COVID-19 (eTable 1, links.lww.com/NXI/A739). Similar results were seen evaluating the 4 outcomes as separate dichotomous terms by multilevel mixed-effects logistic regression (eTables 2–5). In the analyses where data were available, glucocorticoids and comorbidities were associated with all 4 dichotomous outcomes, while higher BMI was associated with increased risks of hospitalization, ICU admission, and requiring artificial ventilation, and smoking was associated with increased risk of death (Tables 3 and 4).

Table 2 Clinical Cohort Characteristics

	Suspected and confirmed (n = 5,568)	Confirmed (n = 4,646)
RRMS MS phenotype	4,694 (84.3)	3,913 (84.2)
EDSS 0–6	4,553 (81.8)	3,799 (81.8)
MS duration		
0–10 y	2,411 (43.3)	2,038 (43.9)
>10 y	2,479 (44.5)	2,086 (44.9)
Missing	678 (12.2)	522 (11.2)
Has comorbidities	1,932 (34.7)	1,658 (35.7)
Missing	1,221 (21.9)	910 (19.6)
Taking glucocorticoids?	141 (2.5)	123 (2.7)
Missing	1,933 (34.7)	1,520 (32.7)
DMT		
Untreated	484 (8.7)	431 (9.3)
Alemtuzumab	59 (1.1)	53 (1.1)
Cladribine	85 (1.5)	71 (1.5)
Dimethyl fumarate	619 (11.1)	518 (11.2)
Fingolimod	527 (9.5)	440 (9.5)
Glatiramer acetate	286 (5.1)	237 (5.1)
Interferon beta	300 (5.4)	247 (5.3)
Natalizumab	558 (10.0)	477 (10.3)
Ocrelizumab	1,100 (19.8)	948 (20.4)
Rituximab	636 (11.4)	504 (10.9)
Siponimod	29 (0.5)	26 (0.6)
Teriflunomide	303 (5.4)	246 (5.3)
Other DMT	158 (2.8)	125 (2.7)
Missing	424 (7.6)	323 (7.0)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis. Data are presented as n (%) unless otherwise specified.

Evaluating individual DMTs relative to glatiramer acetate, the untreated were 5% (95% CI 2–8) more likely to be hospitalized, 3% (95% CI 1–5) more likely to require ICU admission/ventilation, and 1% (95% CI 0–3) more likely to die (Table 2). Patients on treatment with ocrelizumab and rituximab were 4% (95% CI 1–7) and 7% (95% CI 4–11) more likely to be hospitalized (Figure 1), 2% (95% CI 0–4) and 4% (95% CI 2–6) more likely to require ICU admission/artificial ventilation (Figure 2), and 1% (95% CI 0–2) and 2% (95% CI 1–4) more likely to die (Figure 3). Compared with pooled other DMTs combined, ocrelizumab and rituximab users were 5% (95% CI 3–7) and 8% (95% CI 6–11) more likely to admit to hospital, 3% (95% CI 1–4) and 5% (95% CI 3–6) more likely to require ICU admission/artificial ventilation, and 1% (95% CI 0–2) and 2% (95% CI 1–4) more likely to die. Compared with natalizumab, ocrelizumab and rituximab users were 7% (95% CI 4–10) and 11% (95% CI 8–15) more likely to admit to hospital, 4% (95% CI 2–6) and 6% (95% CI 3–9) more likely to require ICU admission/artificial ventilation, and 1% (95% CI 0–3) and 2% (95% CI 1–4) more likely to die. On restriction to confirmed COVID-19, the results were generally comparable, although probabilities for the anti-CD20 s were slightly enhanced (eTable 1, links.lww.com/NXI/A739). Similar results were seen evaluating the 4 outcomes as separate dichotomous terms by multilevel mixed-effects logistic regression (eTables 6–7).

Adjustment for BMI in the subgroup where data were available found BMI to be a weak positive confounder (eTable 8, links.lww.com/NXI/A739).

Stratified Analyses by Age, MS Type, and Disability

With a goal to assess whether DMT associations with COVID-19 severity reflected underlying disease propensity, we next evaluated models of DMTs stratified by age (≥70 vs <70 years), MS phenotype (progressive vs RRMS), and EDSS (>6 vs ≤6). Among participants with suspected + confirmed and confirmed-only COVID-19, in the ordered probit regression analyses, there was no indication that the associations of anti-CD20 DMTs with the COVID-19 severity level were a function of underlying demographic/clinical risk profile (eTables 9 and 10, links.lww.com/NXI/A739), nor did associations with hospitalization, ICU admission, requiring artificial ventilation, and death either seem solely evident among persons in the lower risk group (<70 years) (eTables 11 and 12), RRMS phenotype (eTables 13 and 14), EDSS ≤6 (eTables 15 and 16) or did not statistically differ.

Discussion

Evaluating COVID-19 severity as a single ordered 4-level outcome upheld our previous findings[6] showing demographic and clinical characteristics, particularly DMT exposure, were associated with increased COVID-19 severity in people with MS. Regardless of the comparator, rituximab and ocrelizumab

Table 3 Demographic/Clinical Characteristics of COVID-19 Severity by Ordered Probit Regression, Suspected + Confirmed

		Marginal effects (95% CI)			
	aβ (95% CI)	None	Hospitalization	ICU/artificial ventilation	Death
Average predicted probabilities (95% CI)		0.79 (0.74 to 0.85)	0.13 (0.10 to 0.16)	0.05 (0.03 to 0.07)	0.03 (0.01 to 0.04)
Sex					
Female	**−0.21 (−0.31 to −0.12)[a]**	**0.06 (0.03 to 0.08)**	**−0.03 (−0.04 to −0.02)**	**−0.02 (−0.03 to −0.01)**	**−0.01 (−0.01 to −0.00)**
	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* = 0.003**
Age					
50–69	**0.31 (0.21 to 0.40)[a]**	**−0.08 (−0.11 to −0.05)**	**0.04 (0.03 to 0.06)**	**0.02 (0.01 to 0.03)**	**0.01 (0.00 to 0.02)**
≥70	**0.56 (0.30 to 0.81)[a]**	**−0.14 (−0.21 to −0.07)**	**0.08 (0.04 to 0.12)**	**0.04 (0.02 to 0.07)**	**0.02 (0.01 to 0.04)**
	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* = 0.001**
MS phenotype, progressive					
Progressive	**0.22 (0.08 to 0.35)[a]**	**−0.06 (−0.09 to −0.02)**	**0.03 (0.01 to 0.05)**	**0.02 (0.01 to 0.03)**	**0.01 (0.00 to 0.02)**
	***p* = 0.002**	***p* = 0.002**	***p* = 0.002**	***p* = 0.004**	***p* = 0.014**
EDSS >6					
>6	**0.69 (0.56 to 0.82)[a]**	**−0.18 (−0.23 to −0.13)**	**0.10 (0.08 to 0.12)**	**0.05 (0.04 to 0.07)**	**0.03 (0.01 to 0.04)**
	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**

Abbreviations: aβ = adjusted β; COVID-19 = coronavirus disease 2019; EDSS = Expanded Disability Status Scale; ICU = intensive care unit; MS = multiple sclerosis.
Analysis by multilevel mixed-effects ordered probit regression, estimating aβ (95% CI). All models adjusted for age, sex, MS phenotype, and EDSS. Results in boldface denote statistical significance ($p < 0.05$).
[a] Significant after family-wise Holm step-down multiple comparison adjustment.

were associated with more severe COVID-19, although associations of rituximab were consistently of greater magnitudes. This is consistent with our previous comparison against dimethyl fumarate[6] and persists across both polychotomous and separate dichotomous analysis methods. Our results are consistent with both our and other groups' previously reported findings.[1-4,6] Indeed, despite a fairly heterogeneous set of comparators used across the studies, including glatiramer acetate/interferons,[1] dimethyl fumarate,[2,6] the untreated,[2-4] and glatiramer acetate, the anti-CD20 DMTs have shown a remarkable consistency in being associated with more severe COVID-19. Moreover, anti-CD20 DMTs associations with COVID-19 severity were not only seen among those of older age, progressive MS phenotype, and disability but were more pronounced in the low-risk groups, suggesting these associations were not merely reflective of underlying clinical predisposition. Thus, although these characteristics are factors to consider when describing the severity of COVID-19, the anti-CD20 DMTs, particularly rituximab, independently contribute to the risk of more severe COVID-19. Taken together, this internal and external consistency is strongly indicative of a greater risk of more severe COVID-19 course among patients treated with anti-CD20 DMTs.

Our previous study evaluated each of the 4 severity outcomes as separate dichotomous variables.[6] This method fails to capture the interrelated nature of these outcome levels, with increasing severity necessarily a function of the preceding severity increments. Some of the previous studies have endeavored to reflect this in their methods but with some limitations, either having to consolidate outcome ICU and death or not capturing the ordered nature of their outcome variable. In this article, we have improved on the methods of previous studies, evaluating a 4-level ordered COVID-19 severity variable by statistical methods that capture this ordered nature. The ordered probit regression method estimates marginal probabilities, rather than odds ratios, and so precludes direct comparison of magnitudes with previous studies. It is necessary to evaluate the magnitudes in the context of their particular outcome. That is, differences in the probabilities of outcomes must be considered relative to the average predicted probabilities of each. Therefore, for example, the marginal probabilities for rituximab vs glatiramer acetate for hospitalization (7%), ICU admission/ventilation (4%), and death (2%) are not indicative of weaker effects on ICU/ventilation and death but rather should be considered relative to the total average probabilities of these outcomes of 13%, 5%, and 3%. In that context, the associations of

Table 4 DMT Characteristics of COVID-19 Severity by Ordered Probit Regression, Suspected + Confirmed

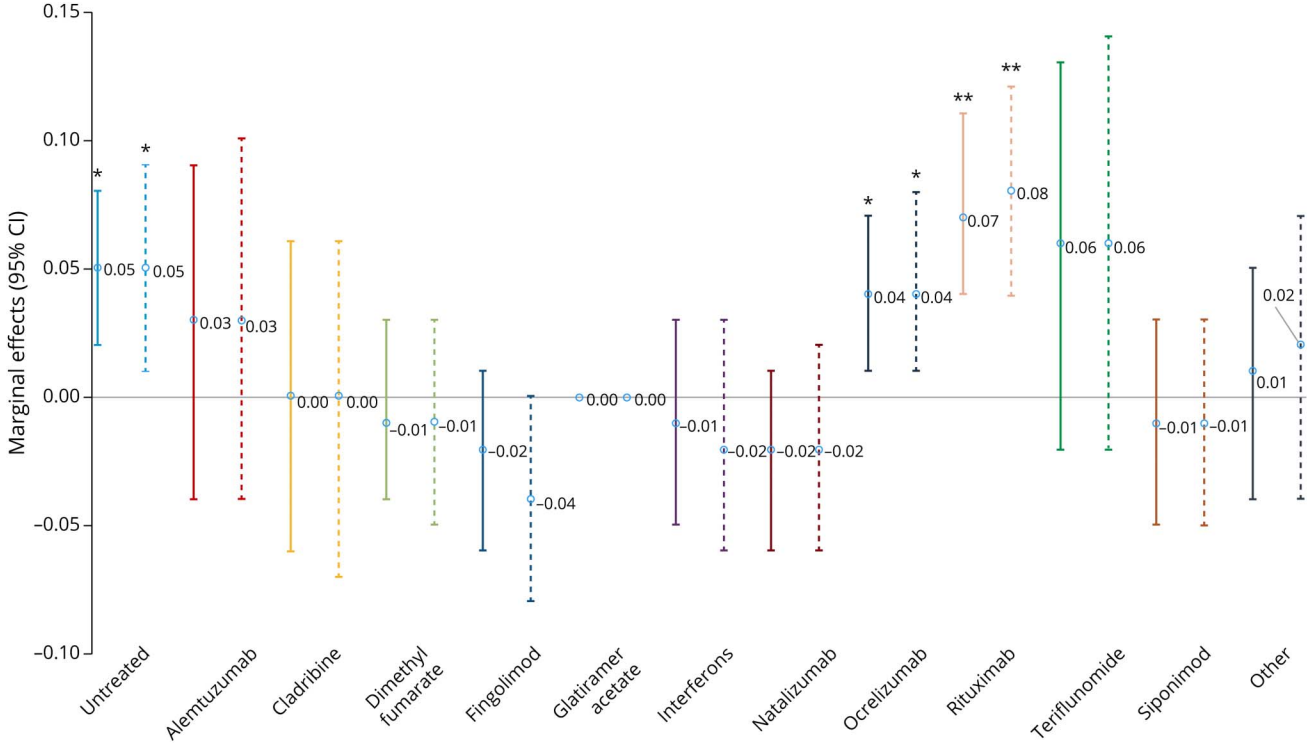
		Marginal effects (95% CI)			
	aβ (95% CI)	None	Hospitalization	ICU/artificial ventilation	Death
Average predicted probabilities (95% CI)		0.79 (0.74 to 0.85)	0.13 (0.10 to 0.16)	0.05 (0.03 to 0.07)	0.03 (0.01 to 0.04)
DMT					
Untreated	**0.35 (0.12 to 0.59)[a]**	**−0.09 (−0.15 to −0.03)**	**0.05 (0.02 to 0.08)**	**0.03 (0.01 to 0.05)**	**0.01 (0.00 to 0.03)**
Alemtuzumab	0.20 (−0.26 to 0.65)	−0.05 (−0.17 to 0.07)	0.03 (−0.04 to 0.09)	0.02 (−0.02 to 0.05)	0.01 (−0.01 to 0.03)
Cladribine	0.02 (−0.40 to 0.44)	−0.01 (−0.11 to 0.10)	0.00 (−0.06 to 0.06)	0.00 (−0.03 to 0.03)	0.00 (−0.02 to 0.02)
Dimethyl fumarate	−0.05 (−0.29 to 0.19)	0.01 (−0.05 to 0.08)	−0.01 (−0.04 to 0.03)	−0.00 (−0.02 to 0.01)	−0.00 (−0.01 to 0.01)
Fingolimod	−0.17 (−0.43 to 0.08)	0.04 (−0.02 to 0.11)	−0.02 (−0.06 to 0.01)	−0.01 (−0.03 to 0.01)	−0.01 (−0.02 to 0.00)
Glatiramer acetate	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Interferon	−0.09 (−0.36 to 0.19)	0.02 (−0.05 to 0.09)	−0.01 (−0.05 to 0.03)	−0.01 (−0.03 to 0.01)	−0.00 (−0.01 to 0.01)
Natalizumab	−0.16 (−0.42 to 0.09)	0.04 (−0.02 to 0.11)	−0.02 (−0.06 to 0.01)	−0.01 (−0.03 to 0.01)	−0.01 (−0.02 to 0.00)
Ocrelizumab	**0.27 (0.06 to 0.49)**	**−0.07 (−0.13 to −0.01)**	**0.04 (0.01 to 0.07)**	**0.02 (0.00 to 0.04)**	**0.01 (0.00 to 0.02)**
Rituximab	**0.52 (0.28 to 0.77)**	**−0.14 (−0.20 to −0.07)**	**0.07 (0.04 to 0.11)**	**0.04 (0.02 to 0.06)**	**0.02 (0.01 to 0.04)**
Siponimod	0.40 (−0.12 to 0.92)	−0.10 (−0.24 to 0.03)	0.06 (−0.02 to 0.13)	0.03 (−0.01 to 0.07)	0.02 (−0.01 to 0.04)
Teriflunomide	−0.06 (−0.33 to 0.22)	0.01 (−0.06 to 0.09)	−0.01 (−0.05 to 0.03)	−0.00 (−0.03 to 0.02)	−0.00 (−0.01 to 0.01)
Other DMT	0.06 (−0.26 to 0.37)	−0.01 (−0.10 to 0.07)	0.01 (−0.04 to 0.05)	0.00 (−0.02 to 0.03)	0.00 (−0.01 to 0.01)
Pooled other DMT	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Ocrelizumab	**0.34 (0.22 to 0.45)[a]**	**−0.09 (−0.12 to −0.05)**	**0.05 (0.03 to 0.07)**	**0.03 (0.01 to 0.04)**	**0.01 (0.00 to 0.02)**
Rituximab	**0.59 (0.44 to 0.74)[a]**	**−0.15 (−0.20 to −0.10)**	**0.08 (0.06 to 0.11)**	**0.05 (0.03 to 0.06)**	**0.02 (0.01 to 0.04)**
No DMT	**0.41 (0.27 to 0.56)[a]**	**−0.11 (−0.15 to −0.06)**	**0.06 (0.04 to 0.08)**	**0.03 (0.02 to 0.05)**	**0.02 (0.01 to 0.03)**
Natalizumab	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]	0.00 [Ref]
Ocrelizumab	**0.44 (0.25 to 0.64)[a]**	**−0.12 (−0.18 to −0.06)**	**0.07 (0.04 to 0.10)**	**0.04 (0.02 to 0.06)**	**0.01 (0.00 to 0.03)**
Rituximab	**0.72 (0.50 to 0.94)[a]**	**−0.20 (−0.26 to −0.13)**	**0.11 (0.08 to 0.15)**	**0.06 (0.03 to 0.09)**	**0.02 (0.01 to 0.04)**

Abbreviations: aβ = adjusted β; COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; ICU = intensive care unit; MS = multiple sclerosis.
Analysis by multilevel mixed-effects ordered probit regression, estimating aβ (95% CI). All models adjusted for age, sex, MS phenotype, and EDSS. Results in boldface denote statistical significance ($p < 0.05$).
[a] Significant after family-wise Holm step-down multiple comparison adjustment. Note: Other DMT was queried as on another drug not listed.

rituximab with the more severe outcomes are actually stronger than those seen for hospitalization despite the smaller marginal probabilities; this in line with the results seen where individual dichotomous outcomes are assessed. This statistical methodology is superior to the separate dichotomous outcomes methods which have primarily been used in previous studies, making more efficient and comprehensive use of the ordered nature of the data. It is important that, however, regardless of the method applied, results are consistent in the deleterious nature of the demographic and characteristics of COVID-19 severity found, particularly anti-CD20 DMTs.

Rituximab consistently showed stronger associations with the COVID-19 outcomes than ocrelizumab, in agreement with our previous study[6] and other studies.[2-4,10,11] As discussed previously,[6] the binding characteristics of rituximab differ from ocrelizumab, including a differing provenance and particularly a stronger affinity to CD20 at the epitope both DMTs bind.[12] In addition, although in our present analysis, ocrelizumab shows a positive trend with the need for artificial ventilation, rituximab shows consistent associations with COVID-19 outcomes, including death. Although it is possible that these differences could result from an unmeasured confounding, particularly here where our ability to control for covariates is limited to those in the questionnaire, the consistency of this difference in associations across cohorts and over time is intriguing. Therefore, relationships of the new anti-CD20 DMT, ofatumumab, which binds a different locus on the CD20 protein,[12] with COVID-19 severity are of interest for future research.

Figure 1 Marginal Effects of Hospitalization vs None by DMT Type Relative to Glatiramer Acetate



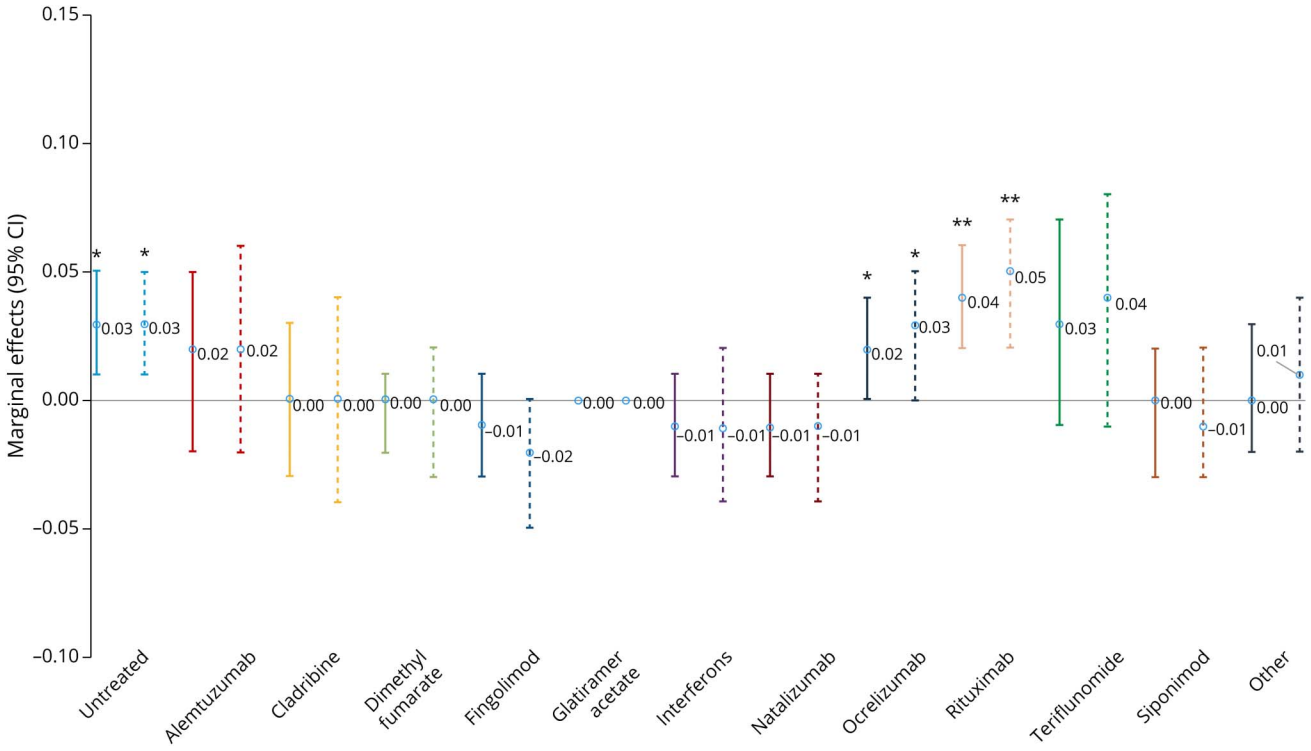
Adjusted for age, sex, MS phenotype, and disability. Full lines include suspected + confirmed COVID-19, while dashed lines are confirmed COVID-19 only. COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; MS = multiple sclerosis; * = $p < 0.05$; ** = $p < 0.001$.

It is interesting to compare the results of this work with the reports of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine response because studies have shown that people with MS on some DMTs have deficient serologic response to both the SARS-CoV-2 pathogen and vaccines, including the anti-CD20 DMTs and the S1PR modulators.[13-17] At the same time, others have evaluated post–vaccine-dose near-term reactions, finding reactions to be lower among those treated with S1PR modulators, whereas anti-CD20 DMTs were not associated with the vaccine reaction.[18] In our study, fingolimod was generally associated with less COVID-19 severity, although the other S1PR modulator, siponimod, showed no such inverse associations. Further investigation of the effect of DMTs on humoral and cellular immune response to the SARS-CoV-2 pathogen and vaccine and its protective role are needed to better understand these relationships and guide decision-making regarding DMTs and COVID-19, including vaccination.

The untreated patients also showed associations with more severe COVID-19, especially in the ordered probit regression analyses of the polychotomous outcome. However, in the individual dichotomous outcome analyses, this association only remained consistent when compared with pooled other DMTs. These results are in agreement with other studies, including the Covisep study which found almost 3 times greater risk of more severe COVID-19 among the untreated vs treated,[1] and the Musc-19 study which found 50–66% lower risks of more severe COVID-19 in treated vs the untreated.[2] It is likely that these associations result from unmeasured confounding in a highly selected group of untreated patients with MS. Accordingly, although we did evaluate the untreated in comparison with glatiramer acetate and with the pooled other DMTs, we did not regard these as appropriate to compare other DMTs with in the fashion performed elsewhere.[2-4]

This study's robustness and generalizability are strengthened by a particularly large global sample used to examine the severity of COVID-19 course in people with MS. This, in tandem with a comprehensive assessment of the most critical clinical and demographic characteristics relevant to COVID-19, gives us a powerful platform with which to examine the outcomes of COVID-19. In addition, our larger data set enabled us to examine DMT associations with COVID-19 severity relative to glatiramer acetate, rather than dimethyl fumarate.[6] As a non–immunosuppressive immunomodulator, glatiramer acetate can be considered a more neutral comparator in its effect on infection risk and severity than dimethyl fumarate. It should be noted that the untreated group is typically a highly selected group in regions with good access to DMTs. In

Figure 2 Marginal Effects of ICU Admission/Artificial Ventilation vs None by DMT Type Relative to Glatiramer Acetate



Adjusted for age, sex, MS phenotype, and disability. Full lines include suspected + confirmed COVID-19, while dashed lines are confirmed COVID-19 only. COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; ICU = intensive care unit; MS = multiple sclerosis; * = $p < 0.05$; ** = $p < 0.001$.

addition, our use of multiple comparison adjustment by the Holm step-down method gives confidence to the veracity of the observed associations, most of which were robust to type I error. We have used 2 complementary statistical methods to assess relationships with COVID-19 severity, expressed as an ordered polychotomous outcome, as well as the series of dichotomous outcomes for hospitalization, ICU admission, requiring artificial ventilation, and death used in our previous analysis.[6] The use of the single ordered polychotomous term, which we evaluated by ordered probit regression, allowed us to estimate marginal effects of the studied covariates across all levels of COVID-19 severity simultaneously. The consistency between these methods gives confidence in the validity of these findings.

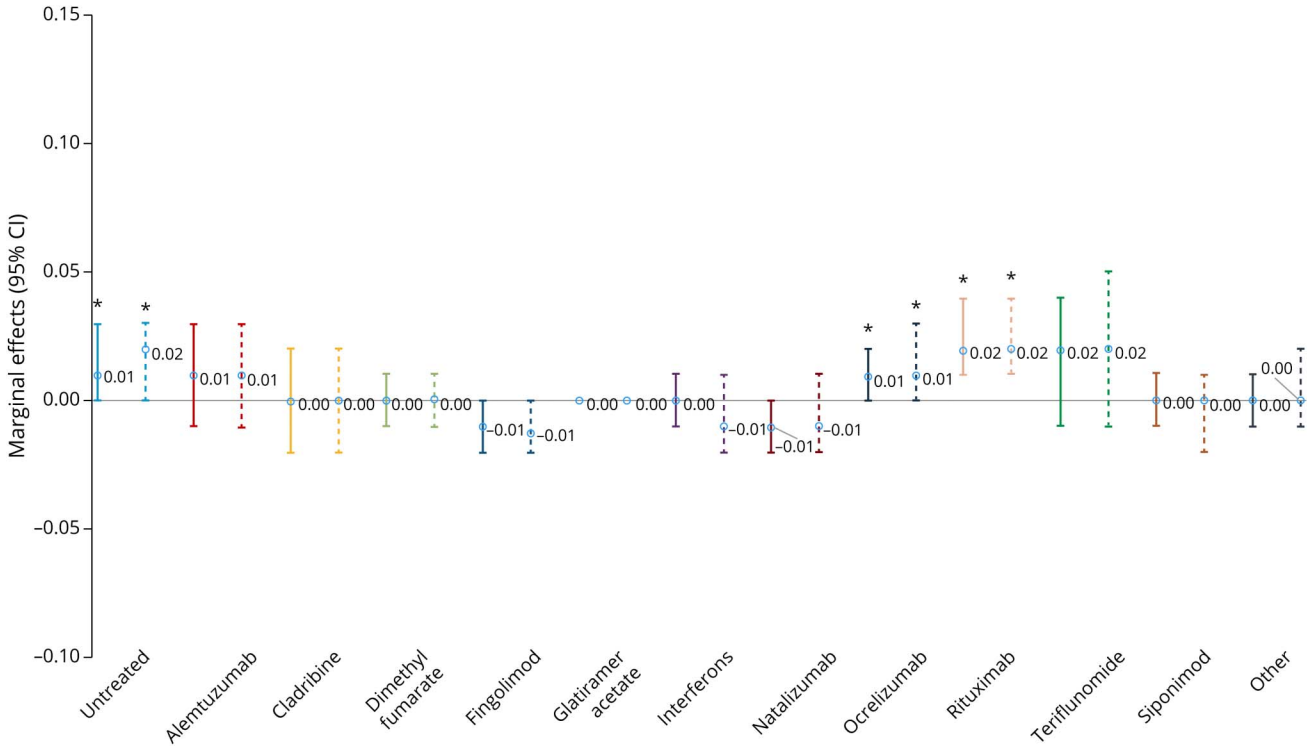
On the other hand, the scope of the questionnaire used to collate the analyzed data is limited in comparison with clinic-based registries such as the Covisep or Musc-19 studies.[1,2,4] Our data set lacks some potentially relevant information, e.g., DMT dose or frequency, pre-COVID-19 MS treatment, other MS severity measures (relapse rate or MRI), or other risk factors beyond those queried. We did endeavor in this iteration of the study to query B-cell counts and duration on DMT since last DMT treatment. However, due to high data missingness, quantitative assessments of these variables were not feasible. Our method of data aggregation was heterogeneous, utilizing individual patient data from the platform and individual registries but also multidimensional contingency tables. It is this latter data source which thus limited some aspects of our model covariates to simplified forms, including simplified categorical information about MS phenotype, disability, age, and glucocorticoid treatment. This precluded our assessment of some potentially relevant characteristics—BMI, smoking, MS duration, and exposure to glucocorticoids in the ordered probit analyses. Owing to the anonymous nature of data collection, it is possible there may be some duplication of patient entries, both over time and between data sources. Finally, the data about the dates of hospital or ICU admission/discharge were insufficient to enable analyses of the outcomes as time-dependent variables.

This is so far the largest study of COVID-19 severity outcomes in people with MS. It confirms that older age, higher disability, and progressive MS phenotype are associated with more severe course of COVID-19. Regarding DMTs, severe COVID-19 course is more frequent among patients treated with anti-CD20 DMTs, rituximab and ocrelizumab. These relationships are not merely a function of underlying clinical/demographic risk profile but indicate a deleterious effect of CD20 depletion. The COVID-19 risk should be considered in choosing the most appropriate DMT for people with MS.

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Figure 3 Marginal Effects of Death vs None by DMT Type Relative to Glatiramer Acetate



Adjusted for age, sex, MS phenotype, and disability. Full lines include suspected + confirmed COVID-19, while dashed lines are confirmed COVID-19 only. COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; MS = multiple sclerosis; * = $p < 0.05$.

that the results of this work may be of benefit to them and patients like them.

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Disclosure

S. Simpson-Yap and A. Pirmani have no conflicts of interests to disclose. T. Kalincik has served on scientific advisory boards for Roche, Sanofi-Genzyme, Novartis, Merck, and Biogen, steering committee for Brain Atrophy Initiative by Sanofi-Genzyme; received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL, and Merck; and received research support from Biogen. E. De Brouwer, L. Geys, and T. Parciak have no conflicts of interests to disclose. A. Helme has no personal pecuniary interests to disclose, other than being an employee of MSIF, which receives income from a range of corporate sponsors, recently including Biogen, Bristol Myers Squibb (formerly Celgene), Genzyme, Med-Day, Merck, Mylan, Novartis, and Roche. N. Rijke has no personal pecuniary interests to disclose, other than being an employee of MSIF, which receives income from a range of corporate sponsors, recently including Biogen, Bristol Myers Squibb (formerly Celgene), Genzyme, Med-Day, Merck, Mylan, Novartis, and Roche. J.A. Hillert has received honoraria for serving on advisory boards for Biogen, Celgene, Sanofi-Genzyme, Merck KGaA, Novartis, and Sandoz and speaker's fees from Biogen, Novartis, Merck KGaA, Teva, and Sanofi-Genzyme; has served as a principal investigator for projects; or received unrestricted research support from Biogen, Celgene, Merck KGaA, Novartis, Roche, and Sanofi-Genzyme,

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Rodriguez is a shareholder, employee, and member of board of directors of QMENTA. V. Prchkovska is a shareholder, employee, and member of board of directors of QMENTA. G. Comi has received consulting and speaking fees from Novartis, Teva Pharmaceutical Industries Ltd., Teva Italia Srl, Sanofi Genzyme, Genzyme Corporation, Genzyme Europe, Merck KGgA, Merck Serono SpA, Celgene Group, Biogen Idec, Biogen Italia Srl, F. Hoffman-La Roche, Roche SpA, Almirall SpA, Forward Pharma, Medday, and Excemed. L.M. Peeters has no personal pecuniary interests to disclose, other than being the chair of The MS Data Alliance (MSDA), which receives income from a range of corporate sponsors, recently including Biogen, Bristol Myers Squibb (formerly Celgene), Canopy Growth Corporation, Genzyme, Icometrix, Merck, Mylan, Novartis, QMENTA, Quanterix, and Roche. Go to Neurology.org/NN for full disclosures.

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Rana Karabudak, MD	Department of Neurology, University of Hacettepe, Turkey	Major role in the acquisition of data
Raed Alroughani, MD	Amiri Hospital, Kuwait	Major role in the acquisition of data
Juan I. Rojas, MSc	Neurology Department, Hospital Universitario de CEMIC; RELACOEM, Argentina	Major role in the acquisition of data
Ingrid A. van der Mei, PhD	The Australian MS Longitudinal Study, Menzies Institute for Medical Research, University of Tasmania	Major role in the acquisition of data
Guilherme Sciascia do Olival, PhD	ABEM–Brazilian MS Patients Association	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Melinda Magyari, PhD	The Danish Multiple Sclerosis Registry, Departement of Neurology, University Hospital Rigshospitalet, Denmark	Major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Ricardo N. Alonso, MD, MSc	RELACOEM; Multiple Sclerosis University Center, Ramos Mejia Hospital–EMA, Argentina	Major role in the acquisition of data
Richard S. Nicholas, PhD	UK MS Register, Swansea University; Imperial College London, United Kingdom	Major role in the acquisition of data
Anibal S. Chertcoff, MD	MS and Demyelinating Diseases, Hospital Británico de Buenos Aires, EMA, Argentina	Major role in the acquisition of data
Ana Zabalza de Torres, MD	Servei de Neurologia-Neuroimmunologia, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Vall d'Hebron Institut de Recerca, Vall d'Hebron Hospital Universitari, Universitat Autònoma de Barcelona, Spain	Major role in the acquisition of data
Georgina Arrambide, MD, PhD	Servei de Neurologia-Neuroimmunologia, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Vall d'Hebron Institut de Recerca, Vall d'Hebron Hospital Universitari, Universitat Autònoma de Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nupur Nag, PhD	Neuroepidemiology Unit, Melbourne School of Population & Global Health, The University of Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Annabel Descamps, MSc	icometrix, Leuven, Belgium	Major role in the acquisition of data
Lars Costers, PhD	icometrix, Leuven, Belgium	Major role in the acquisition of data
Ruth Dobson, PhD	Queen Mary University London, United Kingdom	Major role in the acquisition of data
Aleisha Miller, PhD	Imperial College London, United Kingdom	Major role in the acquisition of data
Paulo Rodrigues, PhD	QMENTA, Barcelona, Spain	Major role in the acquisition of data
Vesna Prčkovska, PhD	QMENTA, Barcelona, Spain	Major role in the acquisition of data
Giancarlo Comi, MD	Casa di Cura del Policlinico and Università Vita Salute San Raffaele, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Liesbet M. Peeters, PhD	MS Centre, Department of Neurology, Royal Melbourne Hospital, Australia	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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