Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

COVID-19 in persons with multiple sclerosis treated with ocrelizumab – A pharmacovigilance case series

Dear Editor,

We read with great interest the *Case Report* by Novi and colleagues (Novi et al., 2020) of an ocrelizumab-treated patient with multiple sclerosis (MS) who developed COVID-19 without serious complications. The emergence of the COVID-19 pandemic presents a new challenge for neurologists treating persons with MS (pwMS) (Brownlee et al., 2020). At the time of writing, over 3.5 million confirmed COVID-19 cases (243,401 fatal) have been reported worldwide (World Health Organization 2020). This has triggered the release of various and diverse guidelines on the use of disease-modifying therapies (DMTs) in MS during the pandemic. However, there are no unified, evidence-based recommendations. A better understanding of COVID-19, its implications for pwMS, and the effects of DMTs in the context of this novel disease are only just beginning to emerge, and evidence is scarce (Novi et al., 2020; Sormani et al., 2020). The pilot phase of an Italian MS COVID-19 registry reported a mild disease course of COVID-19 (defined as no pneumonia or mild pneumonia) in the majority (223/232; 96%) of patients, largely receiving DMTs. This was described as slightly reassuring (Sormani et al., 2020). As highlighted in the *Editorial* (Giovannoni, 2020a) accompanying the *Case Report* by Novi, more real-world data on COVID-19 in pwMS are needed to help the MS community find answers to the questions of potential risks associated with MS and the use of DMTs during the COVID-19 pandemic.

To date, over 160,000 pwMS worldwide have been treated with ocrelizumab (Roche, data on file, 2020). Here we present a summary of the available data, as of 30 April 2020, from ocrelizumab-treated pwMS with confirmed or suspected COVID-19 adverse event (AE) reports extracted from the Roche/Genentech global safety databases.

Cases are defined as valid when at least an identifiable reporter, a single identifiable patient, a medicinal product and a suspected AE are provided (EMA, Guideline on GVP, 2017). AE reports can be flagged by the reporter as serious, based on their judgement, and are also designated serious by the company when regulatory definitions are met (EMA, ICH Harmonised Tripartite Guideline E2A, 1995). Patient characteristics such as age, gender, MS type, country of report, and details of ocrelizumab treatment are usually also provided.

In the absence of an agreed COVID-19 severity classification, cases were assigned to categories based on the information provided: *asymptomatic* if it was explicitly stated that no symptoms were present, *mild* if non-hospitalised symptoms such as low-grade fever or cough were described, *moderate* if shortness of breath was reported, *severe* if pneumonia was present, and *critical* if requiring intensive care and/or mechanical ventilation. Outcome was classified as *recovered, recovering* (e.g. “doing well at home”, or “improving”), *fatal*, or *not reported*. Where no information was provided on a given parameter, this was captured as *not reported*.

As of 30 April 2020, Roche/Genentech have received 100 validated AE reports of confirmed or suspected COVID-19 in ocrelizumab-treated pwMS as part of standard post-marketing pharmacovigilance. Details of these cases are presented in Table 1.

Time from last ocrelizumab dose to onset of COVID-19 could be calculated in 40 cases (40%). The mean time was 12.5 weeks (median, 8.7 weeks; range, 3 days to 7.5 months). Total exposure to ocrelizumab at the time of COVID-19 could be calculated in 46 cases (46%). The mean exposure was 84.2 weeks (median, 67.0 weeks; range, 1 week to 8.3 years).

Twenty-six cases were considered suspected COVID-19. These reports described symptoms or signs consistent with COVID-19 and where SARS-CoV-2 infection was suspected, but not confirmed by laboratory testing.

Seventy-four cases were reported as confirmed COVID-19. Thirty-two explicitly described a positive test result.

No suspected cases were hospitalised. Twenty-six of the 74 confirmed cases were reported as either hospitalised at the time of report ($n=12$), or previously hospitalised ($n=14$).

- Of the 12 cases that were still hospitalised at the time of report:
  - Four were classified as critical: one was in Intensive Treatment Unit (ITU), one was reported to be on a ventilator, one had been in ITU on a ventilator but was weaned off after 5 days and recovering with supplemental oxygen in hospital, and one required non-invasive ventilation for 4 days and was described as stable
  - Eight were classified as severe: four were recovering and four did not report an outcome

In cases where COVID-19 symptom severity was provided ($n=77$), 49 were asymptomatic/mild/moderate (64%), 23 severe (30%) and five critical (6%). All cases where outcome of COVID-19 was provided were reported as either recovered or recovering (64/64, 100%).

There are several limitations to the use of pharmacovigilance data in this context which could lead to bias. AE reporting is voluntary, information reported is often limited and incomplete, while follow-up data may be challenging to obtain and may be delayed. These limitations may be accentuated during this unprecedented time of great strain on healthcare systems. Incomplete reporting of COVID-19 cases

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Table 1
COVID-19 patient demographics, symptom severity and outcomes in ocrelizumab-treated pwMS patients.

	All cases ($n=100$)	Confirmed cases ($n=74$)	Hospitalised cases* ($n=26$)
Mean age (range)	42.3 (23–59)†	42.9 (23–59)‡	44.1 (30–59)§
Gender, *n* (%)			
Male	28 (28)	21 (28)	11 (42)
Female	48 (48)	34 (46)	14 (54)
Not reported	24 (24)	19 (26)	1 (4)
Type of MS, *n* (%)			
Relapsing forms	30 (30)	22 (30)	11 (42)
Progressive forms	15 (15)	12 (16)	9 (35)
Not reported	55 (55)	40 (54)	6 (23)
Geographical location (*n*)			
Australia	4	4	0
Austria	1	1	0
Belgium	1	0	0
Brazil	1	0	0
Canada	6	2	0
Chile	2	2	1
Czech Republic	1	1	1
France	1	1	1
Germany	13	9	2
Israel	1	1	0
Italy	4	3	2
Spain	20	19	5
Switzerland	1	1	1
UK	2	2	0
US	42	28	13
Case seriousness			
Reported as serious, *n* (%)	33 (33)	31 (42)	26 (100)
COVID-19 severity			
Asymptomatic, *n* (%)	1 (1)	0 (0)	0 (0)
Mild, *n* (%)	34 (34)	22 (30)	0 (0)
Moderate, *n* (%)	14 (14)	7 (9)	1 (4)
Severe, *n* (%)	23 (23)	23 (31)	20 (77)
Critical, *n* (%)	5 (5)	5 (7)	5 (19)
Not reported, *n* (%)	23 (23)	17 (23)	0 (0)
Outcomes			
Recovered, *n* (%)	46 (46)	35 (47)	14 (54)
Recovering, *n* (%)	18 (18)	13 (18)	5 (19)
Fatal, *n* (%)	0 (0)	0 (0)	0 (0)
Not reported, *n* (%)	36 (36)	26 (35)	7 (27)

† Calculated on all cases where age was reported (63%, $n=63$).
‡ Calculated on all confirmed cases where age was reported (62%, $n=46$).
§ Calculated on all hospitalised cases where age was reported (84%, $n=22$).
* All cases reported as hospitalised were also reported as confirmed.

may arise due to differences in national testing capacity and strategy.

It is currently unknown whether pwMS are at increased risk of a SARS-CoV-2 infection or a more severe course of COVID-19 compared with the general population and whether the different DMTs play any role (Giovannoni et al., 2020b; Giovannoni, 2020a). Differences in the classification of severity (categories used and assignment criteria) make direct comparisons between case series challenging. Nevertheless, the data presented in this pharmacovigilance-based case series appear to be broadly in line with larger case series of COVID-19 patients (Guan et al., 2020; Wu and McGoogan, 2020; Zhou et al., 2020). The rate of severe COVID-19 in patients with other immune-mediated inflammatory diseases largely receiving DMTs did not appear to differ from the local population (Haberman et al., 2020).

It is anticipated that the number of COVID-19 cases will increase and as a result it is likely that the number of COVID-19 cases (including fatal outcomes) in pwMS treated with DMTs will also rise. While it is too early to draw conclusions, based on the limited data available to date, there is no evidence at this time to suggest a more severe course of COVID-19 in ocrelizumab-treated pwMS.

Declaration of Competing Interest

Drs Hughes, Pedotti, and Koendgen are employees of F. Hoffmann-La Roche Ltd. There was no funding to this research.

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