Ocrelizumab and COVID-19 Pharmacovigilance Data

Main takeaways

- While it is too early to draw definitive conclusions, based on the limited information that is available from pharmacovigilance data, the risk factors for severe COVID-19 outcomes do not indicate a difference between ocrelizumab-treated patients[1] and the general population,[2–10] and may suggest that COVID-19 follows a similar course in ocrelizumab-treated patients with MS as in the general population[1–10]
  - These risk factors for severe COVID-19 include old age and presence of comorbidities, such as hypertension, diabetes, obesity, smoking, and cardiovascular and lung disease[1–4,8,9]
- The known benefit/risk profile of ocrelizumab remains unchanged

Incidence of COVID-19 cases in ocrelizumab-treated patients[1]

- As of May 31, 2020, 201 cases of COVID-19 in ocrelizumab-treated patients were identified in pharmacovigilance reports; all cases were conservatively considered as having confirmed COVID-19 (including the cases with missing information on diagnosis confirmation, eg, by PCR)
- More than 160,000 people with MS have been treated with ocrelizumab globally, in clinical trial and real-world settings; data continue to show a consistent and favorable benefit/risk profile
- Patients receiving ocrelizumab that are either exposed to SARS-CoV-2 or confirmed to have COVID-19 should contact their neurologist or other medical professional right away, and patients should consult their neurologist or other medical professional before discontinuing their medication

Seriousness and outcomes of COVID-19 in ocrelizumab-treated patients[1]

- Of the 201 cases, 61% (n=122/201) were reported as not serious, and 39% (n=79/201) were reported as serious
  - Included in the serious cases were:
    - 2.0% (n=4/201) reported as life-threatening and 5.5% (n=11/201) reported as fatal outcome
    - 65% (n=51/79) of cases classified as serious were done so on the basis of hospitalization
    - Reasons for hospitalization were variable and included (but were not limited to) the following: treatment of pneumonia and treatment in ICU
    - At the time of reporting, 32% (n=25/79) of the serious cases were reported as recovered/recovering, and 33% (n=26/79) of the serious cases had an unknown outcome

Table 1: Reported outcomes by most serious seriousness criterion[a] for all serious cases (n=79)[1]

		Reported Outcome					
		Fatal	Recovered	Recovering	Not recovered	Missing information	Total
Most serious seriousness criterion	All serious cases	**11**	**15**	**10**	**17**	**26**	**79**
	Medically significant	0	3	2	2	5	12
	Hospitalization	0	11	8	14	18	51
	Disability	0	0	0	0	1	1
	Life-threatening	0	1	0	1	2	4
	Death	11	0	0	0	0	11

Details of 11 cases with a fatal outcome[1]

- For the 11 cases with fatal outcomes, the reported causes of death were: COVID-19 (n=8); COVID-19 pneumonia (n=1); coronavirus infection (n=1); and respiratory failure (n=1)
  - None of the 11 cases had an available autopsy report
- Patient demographics for these cases were as follows: Sex: male (n=7), female (n=3), unspecified (n=1); Age range 43–66 years (n=10), unspecified (n=1)
- The majority (n=7) of the 11 cases with fatal outcomes had risk factors known to be associated with severe COVID-19 outcomes in the general population
  - Reported previous DMTs (n=2); of note, as indicative of more advanced MS
  - Reported EDSS 6.0–9.0 (n=5), indicating a more severe course; MS registries identified MS severity as risk factor for severe COVID-19 outcomes
  - Risk factors were identified for all patients with COVID-19 confirmed by RT-PCR (n=4) and all patients who received mechanical ventilation (n=5)
  - Two patients were not assessable; follow-up for missing information is ongoing
- Time from starting ocrelizumab to outcome ranged from 1.5 to 3 years, but was unknown in 2 cases

Interpreting COVID-19 real-world data

- COVID-19 is caused by a new strain of coronavirus called SARS-CoV-2, so knowledge about how it may affect people with MS remains limited[11,12]
  - The limited data that are emerging on COVID-19 in people with MS are mainly derived from real-world data sources and it is important to recognize the limitations (and biases) inherent in these sources[13,14]
- From the limited real-world evidence available globally, the MS population in general does not seem to be at higher risk from COVID-19 and no association between any DMTs and fatal COVID-19 outcomes has been reported
  - Major risk factors identified for severe/fatal COVID-19 in the MS population are advanced age (>50 years old), high levels of disability, progressive form of MS, and presence of comorbidities, such as hypertension, diabetes, obesity, smoking, and cardiovascular and lung disease[9,15,16]
  - Treatment decisions should therefore be made between a patient and their treating neurologist or other medical professional based on a benefit/risk assessment specific to the individual patient
- We are aware of many efforts to collect real-world evidence to inform communities' understanding of COVID-19 and the impact on patients with MS, including the COVISEP (French) and MuSC-19 (Italian) registries[4,9,15]
- Real-world evidence is complex and challenging to interpret as there are many limitations and biases in the datasets, including significant unknown and/or unreported data, differences in data collection and reporting (patient-reported vs healthcare professional-reported), suspected vs confirmed COVID-19 cases, identification of other comorbidities, and generally a reporting bias towards more severe cases

Table 2: Number of cases and deaths in the general population, as of July 14, 2020[16]

Country	France	Italy	USA	Global
Confirmed COVID-19 cases, n[b]	209,640	243,230	3,363,056	13,127,030
COVID-19 deaths, n[b]	30,032	34,967	135,605	573,663
Case–fatality rate, %	14.3	14.4	4.0	4.4

Table 3: Number of cases and deaths in MS datasets, including reported ocrelizumab cases

MS datasets	COVISEP France[9] (as of May 21, 2020)	MuSC-19 Italy[17] (as of May 31, 2020)	COViMS North America[18] (as of July 14, 2020)	MSDA/MSIF Global[16,19,c] (as of June 10, 2020)
COVID-19 cases (OCR cases), n[b]	347 (38)	789 (83)	362 (110)	457[d] (85)
COVID-19 deaths (OCR cases), n	12 (0)	13 (1)	24 (4)	18 (3)
Case–fatality rate (OCR cases), %	3.5 (0.0)	1.6 (1.2)	6.6 (3.6)	3.9 (3.5)
NB: numbers and percentages in parentheses indicate ocrelizumab cases				

- Due to limitations of real-world data and countries being affected differently by the pandemic, there may be differences in emerging data and interpretations
  - Publication in peer-reviewed journals of the real-world evidence will provide a robust assessment of the data quality and analytical methods, especially accounting for potential confounders and biases, which is essential to understand the impact of COVID-19 in MS

The Prescribing Information is the primary source of information on the known and potential risks associated with ocrelizumab.

Footnotes:
[a]Serious event is defined as one that requires in-patient hospitalization, prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is life-threatening or fatal; [b]includes both clinically suspected and cases; [c]includes data from Germany, Sweden, Denmark, Brazil, and North America; [d]overall dataset includes 527 cases, with alive/death status available for 457 laboratory-confirmed patients.

Abbreviations:
COVID-19=coronavirus disease 2019; COViMS=COVID-19 Infections in MS & Related Diseases; COVISEP=Epidemiological Characteristics of COVID-19 in Patients With MS or NMO; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; ICU=intensive care unit; MS=multiple sclerosis; MuSC-19=Multiple Sclerosis and COVID-19; OCR=ocrelizumab; PCR=polymerase chain reaction; PPMS=primary progressive MS; RMS=relapsing MS; RT-PCR=reverse transcription PCR; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

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