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Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis

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ABSTRACT

Background: COVID-19 may spread through various ways ranging from asymptomatic to severe forms, until respiratory failure, critical conditions and death occurs. There is a particular concern for patients affected by multiple sclerosis, especially for those under disease-modifying treatments. Some studies have found an association between anti-CD20 therapies (especially rituximab) and severe COVID-19. However, results were not always clear and thus a systematic review was helpful.

Methods: A systematic literature search was performed independently by two authors on the main search tools considering as key inclusion criterion the presence of data on patients under ocrelizumab or rituximab positive to COVID-19. The quality of the included studies was evaluated based on a modified version of the Dutch Cochrane center critical review checklist proposed by MOOSE and in case of missing data an email was sent to the corresponding authors asking for missing information. After excluding case-reports, a random effects meta-analysis of proportions was conducted using the continuity correction and the $I^2$ statistic was calculated to measure heterogeneity.

Results: 29 articles were included in the analysis and the median quality of the articles reached 4/5 after having integrated the additional details provided by the authors. The articles included 5173 patients, of whom 770 (14.8%) and 455 (8.8%) were, respectively, under ocrelizumab and rituximab. Pooled estimates of hospitalization, pneumonia and intensive care unit admission were 18.1%, 14.8% and 3.3%, respectively, while pooled estimate for death was 1.8% overall and 1.6% and 4.5%, respectively, for patients under ocrelizumab and rituximab.

Conclusion: Patients treated with rituximab seem to be at higher risk of severe COVID-19 outcomes compared to patients under other treatments.

1. Introduction

Even if most of the COVID-19 cases are classified as mild, disease course can be severe or critical, possibly leading to serious pneumonia, hospitalization, admission to intensive care unit (ICU), and death (Wu and McGoogan, 2020). Furthermore, there is a particular concern for patients affected by multiple sclerosis (MS) and especially for those who take disease-modifying treatments (DMTs) that impact on the immune system and that can increase the risk of infections (Winkelmann et al., 2016).

Several studies have investigated associations between the use of DMTs and COVID-19 severity among patients with MS. A pooled analysis from an Italian and French cohort found a significant relationship of anti-CD20 therapies (rituximab and ocrelizumab) with COVID-19 severity, confirming previous results from a smaller Italian cohort (Sormani et al., 2021; Sormani et al., 2021). Consistently, in a North American study, both ocrelizumab and rituximab were associated with hospitalization, but association was stronger for rituximab (Salter et al., 2021).

However, the role of anti-CD20 treatments in the COVID-19 severity were not always confirmed (BSTEH et al., 2021; LOUAPRE et al., 2020). Therefore, it is relevant to undertake a comprehensive systematic review.
for estimating the mortality rate among patients under these therapies, for exploring all their available characteristics and in general for estimating their rates of severe COVID-19 events.

2. Methods

2.1. Article selection

A systematic literature search covering studies published until 31st July 2021, was performed in Scopus, Web of Science, PubMed and among the abstracts presented at the 2020 ECTRIMS meeting. Search strategy is detailed in Table 1.

The key inclusion criterion was that the study presented data on COVID-19 course for MS patients treated with ocrelizumab or rituximab.

Two authors independently conducted the literature search and screened titles and abstracts based on the criteria reported above. They also collected the full texts and evaluated the eligibility of each study. Duplicated manuscripts among the sources, with clearly or suspicious overlapping patients, and those out of topic were excluded. The following data were extracted from the identified studies: authors, title, country, sample size, number of suspected/confirmed COVID-19 cases, number of males/females, mean age with range, number of patients with progressive MS, number of patients with relapsing MS, median last EDSS, mean MS duration with range, use and frequencies of MS treatments (cladribine, alemtuzumab, azathioprine, glatiramer acetate, daclizumab, dimethyl fumarate, fingolimod, interferon, methotrexate, mitoxantrone, natalizumab, ocrelizumab, rituximab, teriflunomide, natalizumab, ocrelizumab, rituximab).

| SOURCE         | STRING                                                                 |
|----------------|------------------------------------------------------------------------|
| Scopus         | (TITLE-ABS-KEY (coronavirus OR covid) AND TITLE-ABS-KEY (rituximab OR ocrelizumab) AND TITLE-ABS-KEY (ms OR multiple AND sclerosis)) AND NOT DOCTYPE (re) AND (LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020)) |
| Web of Science | TOPIC: (Covid or coronavirus) AND TOPIC: (rituximab or ocrelizumab) AND TOPIC: (ms or multiple sclerosis) NOT DOCUMENT TYPES: (Review) Refined by: PUBLICATION YEARS: (2021 OR 2020) |
| PubMed         | Search: (((MS or multiple sclerosis) AND (Covid OR coronavirus)) AND (rituximab OR ocrelizumab)) NOT (Review[Publication Type]) NOT (Meta-Analysis[Publication Type]) NOT (Systematic Review[Publication Type]) Filters: from 2020 to 2021 Sort by: Most Recent |
| Ectrims 2020   | Search: (Covid OR coronavirus) AND (rituximab OR ocrelizumab) NOT (Review[Publication Type]) NOT (Meta-Analysis[Publication Type]) NOT (Systematic Review[Publication Type]) |

Table 1 - Search strategy.
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Table 2

| Nr | First Author | Title |
|----|--------------|-------|
| 01 | Arrambide G. | SARS-CoV-2 Infection in Multiple Sclerosis (Arrambide et al., 2021) |
| 02 | Barzegar M. | Characteristics of COVID-19 disease in multiple sclerosis patients (Barzegar et al., 2020) |
| 03 | Btch G. | COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: Insights from a nation-wide Austrian registry (Btch et al., 2021) |
| 04 | Bose G. | Reactivation of SARS-CoV-2 after Rituximab in a Patient with Multiple Sclerosis (Bose and Galetta, 2021) |
| 05 | Chaudhry F. | COVID-19 in multiple sclerosis patients and risk factors for severe infection (Chaudhry et al., 2020) |
| 06 | Ciampi E. | COVID-19 in MS and NMOSD: A multicentric online national survey in Chile (Ciampi et al., 2020) |
| 07 | Conte WL. | Attenuation of antibody response to SARS-CoV-2 in a patient on ocrelizumab with hypogammaglobulinemia (Conte, 2020) |
| 08 | Czarnowska A. | Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies-the Polish experience (Czarnowska et al., 2021) |
| 09 | D’Afram A. | Prolonged and severe SARS-CoV-2 infection in patients under B-cell-depleting drug successfully treated: A tailored approach (D’Afram et al., 2021) |
| 10 | Develgare J. | Coronavirus disease 2019: favorable outcome in an immunosuppressed patient with multiple sclerosis (Develgare et al., 2020) |
| 11 | Fernandez-Diaz E. | Real-world experience of ocrelizumab in multiple sclerosis in a Spanish population (Fernandez-Diaz et al., 2021) |
| 12 | Fragojo G. | Coronavirus disease 2019 in Latin American patients with multiple sclerosis (Fragojo et al., 2021) |
| 13 | Gibson E.G. | Prolonged SARS-CoV-2 Illness in a Patient Receiving Ocrelizumab for Multiple Sclerosis (Gibson et al., 2021) |
| 14 | Hervas-Garcia J.V. | Seroprevalence of sars-cov-2 in multiple sclerosis patients under immunomodulatory treatment in Lleida (study emcovid-19) (Hervas-Garcia et al., 2020) |
| 15 | Louapre C. | Clinical Characteristics and Outcomes in Patients with Coronavirus Disease 2019 and Multiple Sclerosis (Louapre et al., 2020) |
| 16 | Loonstra FC. | COVID-19 in multiple sclerosis: The Dutch experience (Loonstra et al., 2020) |
| 17 | Montero-Escribano R. | Anti-C20 and COVID-19 in multiple sclerosis and related disorders: A case series of 60 patients from Madrid, Spain (Montero-Escribano et al., 2020) |
| 18 | Olivas-Gasca JC. | Mélange intéressante: COVID-19, autologous transplants and multiple sclerosis (et al., 2020) |
| 19 | Sadeghi M. | Types of pharmaceutical intervention in patients with multiple sclerosis (ms): a fine line between immunosuppressive and risk of covid-19 infection (Sadeghi Maryam et al., 2021) |
| 20 | Sahraian MA. | Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis (Sahraian et al., 2020) |
| 21 | Saltor A. | Outcomes and Risk Factors Associated With SARS-CoV-2 Infection in a North American Registry of Patients With Multiple Sclerosis (Saltor et al., 2021) |
| 22 | Sen S. | The outcome of a national MS-COVID-19 study: What the Turkish MS cohort reveals? (Sen et al., 2021) |
| 23 | Sormani MP. | Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis (Sormani et al., 2021) |
| 24 | Spelman T. | Increased rate of hospitalization for COVID-19 among rituximab-treated multiple sclerosis patients: A study of the Swedish multiple sclerosis registry (Spelman et al., 2021) |
| 25 | Suwanwongse K. | Benign course of COVID-19 in a multiple sclerosis patient treated with Ocrelizumab (Suwanwongse and Shabarek, 2020) |
| 26 | Thornton JR. | Negative SARS-CoV-2 Antibody Testing Following COVID-19 Infection in Two MS Patients Treated with Ocrelizumab (Thornton and Harel, 2020) |
| 27 | Woo MS. | Control of SARS-CoV-2 infection in rituximab-treated neuroimmunological patients (Woo et al., 2021) |
| 28 | Wurm H. | Recovery from COVID-19 in a B-cell-depleted multiple sclerosis patient (Wurm et al., 2020) |
| 29 | Wallach A. | The presence of SARS-CoV2 antibodies in MS patients (Armstrong et al., 2021; Arrambide et al., 2021; Barzegar et al., 2020, 2021; Bose and Galetta, 2021; Btch et al., 2021; Chaudhry et al., 2020; Czarnowska et al., 2021; D’Abramo et al., 2021; Develgare et al., 2021; Fernandez-Diaz et al., 2021; Fragojo et al., 2020; Hervas-Garcia, 2020; Louapre et al., 2020; Montero-Escribano et al., 2020; Olivas-Gasca et al., 2020; Sahraian et al., 2020; Salter et al., 2021; Sen et al., 2021; Sormani et al., 2021; Spelman et al., 2021; Stroup et al., 2020; Suwanwongse and Shabarek, 2020; Thornton and Harel, 2020; Wallach and Picone, 2021; Winkelmann et al., 2016; Woo et al., 2021; Wu and McGoogan, 2020; Wurm et al., 2021; The Multiple Sclerosis International Federation 2020; Gibson et al., 2021; Sadeghi Maryam et al., 2021) |

Table 3

Assessment of the quality of included studies by a modified MOOSE criteria.

| Nr (study) | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
|------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Clear definition of study population | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Clear definition of outcomes and outcome assessment | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Independent assessment of outcome parameters | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | No* | Yes | Yes | Yes | Yes |
| Important confounders and prognostic factors identified | Yes | No | No* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Quality Score on published data | 4 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 3 | 3 | 4 | 3 | 1 | 3 | 3 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 3 | 3 | 4 | 4 | 2 |
| Quality Score revised with data provided by authors | 4 | 3 | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | 4 | 3 | 4 | 4 | 2 |

Data provided by the authors but not published.

other), number of hospitalizations, number of patients admitted to the ICU, number of patients with pneumonia, number of deaths, number of deceased patients treated with ocrelizumab, number of deceased patients treated with rituximab. In case of missing data, an email was sent to the corresponding authors asking to complete the missing information.

2.2. Quality assessment

All selected articles were rigorously appraised by two authors according to a modified version of the Dutch Cochrane center critical review checklist proposed by MOOSE (Stroup et al., 2000). Key domains assessed by the MOOSE tool include: (I) Clear definition of study population; (II) Clear definition of outcomes and outcomes assessment; (III) Independent assessment of outcome parameters; (IV) Sufficient
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Table 4
Baseline characteristics.

| Nr  | First Author       | Demography Sample | Age, yrs (range) | MS data Progressive /RR | Last EDSS | MS duration, yrs (range) | Disease Modifying Treatments | Un treated |
|-----|-------------------|-------------------|-----------------|-------------------------|----------|-------------------------|-------------------------------|------------|
| 01  | Arrambide G.      | 326 221/105       | 63/263          | 2                       | 59       | 6                       | 18                            | 013        |
| 02  | Baranzegar M.     | 9 8/1             | 29 - 50         | 2/6                     | 1 - 27   | 2                       | 0                            | 01        |
| 03  | Bhat G.           | 126 90/36         | 21 - 79         | 28/98                   | 36       | 2                       | 2                            | 11        |
| 04  | Boc G.            | 1 1/0             | 32 - 32         | 0/1                     | 1.5      | 12 - 12                 | 0                            | 09        |
| 05  | Chaudhry F.       | 40 24/16          | 28 - 84         | 9/30                    | 2 - 31   | 8                       | 0                            | 3         |
| 06  | Clampi E.         | 14 10/4           | 17 - 57         | 0/14                    | 1 - 2 - 14| 0                       | 2                            | 0         |
| 07  | Conte WL          | 1 1/0             | 48 - 48         |                         |          | 0                       | 0                            | 0         |
| 08  | Czarnowska A.     | 396 282/114       | 18 - 68         | 24/372                  | 2 - 0 - 33| 0                       | 5                            | 4         |
| 09  | D'Abramo A.       | 1 1/0             | 54 - 54         | 1.5                     | 0        | 0                       | 0                            | 0         |
| 10  | Devogelaere J.    | 1 1/0             | 53 - 33         | 0/1                     | 6        | 0                       | 0                            | 0         |
| 11  | Fernandez-Diaz E. | 3 0/3             | 32 - 49         | 2/1                     | 6        | 0                       | 0                            | 0         |
| 12  | Fragozo J.        | 73 50/23          | 17 - 72         | 4/69                    | 2 - 0 - 26| 3                       | 1                            | 10        |
| 13  | Gibson EG.        | 1 1/0             | 46 - 46         | 0/1                     | 0        | 0                       | 0                            | 0         |
| 14  | Hervas-Garcia JV. | 19 12/7           | 41 - 67         | 1/18                    | 2 - 3 - 24| 0                       | 1                            | 0         |
| 15  | Lounape C.        | 347 249/98        | 65/276          | 2                      | 63       | 3                       | 1                            | 33        |
| 16  | Leontra FC.       | 86 60/26          | 20 - 71         | 14/69                   | 3 - 6.8 - 32.8| 12       | 0                       | 1                | 4         |
| 17  | Montero-Escubias P.| 9 7/2             | 41 - 55         | 4/4                     | 5 - 30   | 0                       | 0                            | 0         |
| 18  | Olivares Guza JC.| 4 3/1             | 39 - 54         | 1/3                     | 5.8      | 3 - 21                   | 0                            | 0         |
| 19  | Sedghi M.         | 371 235/136       | 39 - 43.5       | 104/267                 | 1 - 1 - 13| 7                       | 0                            | 0         |
| 20  | Suharst MA.       | 68 56/12          | 3/60            |                         | 200       | 0                       | 0                            | 1         |
| 21  | Saltor A.         | 1626 1202/421     | 280/1235        |                         | 237       | 14                      | 0                            | 84        |
| 22  | Sen S.            | 309 219/90        | 18 - 66         | 32/277                  | 1.5       | 0.2 - 31                 | 26                            | 0         |
| 23  | Sonnemi MP.       | 644 593/251       | 18 - 82         | 135/676                 | 2         | 151                     | 11                            | 14        |
| 24  | Spelman T.        | 476 346/136       | 19 - 78         | 67/407                  | 2         | 0.0 - 0.40.7             | 18                            | 8         |
| 25  | Suwanzongwe K.    | 1 0/1             | 31 - 31         |                         | 0        | 0                       | 0                            | 0         |
| 26  | Thornton JR.      | 2 1/1             | 39 - 42         | 0/2                     | 1.5      | 4 - 5                   | 0                            | 0         |
| 27  | Wies MS.          | 1 1/0             | 44 - 44         | 0/1                     | 2         | 21 - 21                 | 0                            | 0         |
| 28  | Warm H.           | 1 1/0             | 59 - 59         | 1/0                     | 6        | 4 - 4                   | 0                            | 0         |
| 29  | Wallace A.        | 17 13/4           | 32 - 67         |                         | 2        | 0                       | 0                            | 1         |

Follow-up; (V) No selective loss during follow-up; and (VI) Important confounders and prognostic factors identified. Each domain could be filled in with “yes”, “no” or “unclear” and rated as follows: yes (1 point), no/unclear (0 points) based on published data.

However, since two domains (IV and V) were considered irrelevant for the purpose of this study, only four (I, II, III, VI) were combined in an overall reporting quality score (ranging from 0 to 4 points). A study was defined of highest quality if all criteria were rated as “yes” because free from intra-study bias.

2.3. Statistical analysis

To estimate the mortality rate among patients treated with ocrelizumab and rituximab and to evaluate the overall rate of mortality, hospitalization, and ICU admission, a random effects meta-analysis of proportions using the continuity correction was conducted, with the I² statistic to measure heterogeneity. Case reports were excluded from the meta-analysis to avoid misleading results and to not overestimate the rate of severe outcomes (case reports usually describe more serious cases rather than mild disease courses).

Meta-analysis was performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

3. Results

Out of 269 articles retrieved from investigated databases, 29 were included in the final analysis (Fig. 1) (Table 2).

The quality of selected studies ranged from 1 to 4 points (median = 3) by considering original published data, whereas with implemented details provided by authors the total quality score of manuscripts improved to 2 to 4 points (median = 4) (Table 3).

These studies involved 5173 patients (81% with confirmed COVID-19), with an age ranging from 17 to 84 years, and 71% of the participants were females. The sample size for the included studies ranged from 1 (single case report) to 1626 cases. As about MS history, 80.6% of the sample presented a relapsing remitting form of disease, 770 (14.8%) patients were in treatment with ocrelizumab and 455 (8.8%) with rituximab (Table 4).

Frequencies of COVID-19 outcomes and results from the meta-analysis are reported in Table 5. A total of 888 patients were hospitalized (pooled estimate: 18.1%; 95%CI = [14.5%;21.6%]), 436 cases reported pneumonia (pooled estimate: 14.8%; 95%CI = [9.6%;20.1%]); 200 patients were admitted to ICU and 115 died. Fifteen (1.9%) and ten (2.2%) fatal events occurred respectively among patients on ocrelizumab and on rituximab.

4. Discussion

The pooled estimate of the hospitalization rate was 18.1%, slightly lower compared to the rate observed in a systematic review which included studies on MS and COVID-19 without restrictions based on the treatment type (20.7%) (Barzegar et al., 2021).

In general, hospitalization rates were found to vary widely depending on several characteristics, including age, gender, presence of comorbidities, residence area and reference period under study (Garg et al., 2020). For a deeper analysis of these results, it is important to consider that MS population differ from the general population in distribution of several characteristics, such as age, gender, and presence of comorbidities (The Multiple Sclerosis International Federation, 2020).

In addition, the high heterogeneity (88%) found in this meta-analysis can be partially explained by the fact that data are collected from different Countries, referred to different periods of pandemic and based on different study designs. Similar considerations can be made to explain the high heterogeneity for the pneumonia rate, with lower and upper confidence interval ranged from 9.6 to 20.1%.

Furthermore, pneumonia data were not always available, probably due to the...
Table 5
Outcomes.

| Nr | First Author | Hospitalization | Pneumonia | ICU Admission | Death |
|----|--------------|-----------------|-----------|---------------|-------|
| 0  | 01 Arrambide G. | 69/326 (21%) | NA/326 (NA) | 7/326 (2%) | 7/326 (2%) |
| 0  | 02 Barzagari M. | 2/9 (22%) | 2/9 (22%) | 1/9 (11%) | 1/9 (11%) |
| 0  | 03 Batch G. | 12/126(10%) | NA/126(NA) | NA/126(NA) | 4/126(3%) |
| 0  | 04 Base G. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 05 Chaudhry F. | 3/40 (50%) | 17/40 (43%) | 3/40 (7%) | 4/40 (10%) |
| 0  | 06 Ciampi E. | 3/14 (21%) | 2/14 (14%) | 0/14 (0%) | 0/14 (0%) |
| 0  | 07 Conte WL. | 12/126 (10%) | NA/126 (NA) | NA/126 (NA) | 4/126 (3%) |
| 0  | 08 Czarnowska A. | 27/396 (7%) | NA/396 (NA) | 1/396 (0.3%) | 1/396 (0.3%) |
| 0  | 09 D Abramo A. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 10 Devogelaere J. | 0/1 (0%) | 0/1 (0%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 11 Fernandez-Diaz E. | 1/3 (33%) | NA/3 (NA) | 0/3 (0%) | 0/3 (0%) |
| 0  | 12 Fregno J. | 15/73 (21%) | 20/73 (27%) | 6/73 (8%) | 2/73 (3%) |
| 0  | 10 Gibson EG. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 14 Hervas-Garcia J. | 1/19 (5%) | 1/19 (5%) | 0/19 (0%) | 0/19 (0%) |
| 0  | 15 Loupcre G. | 73/347 (21%) | NA/347 (NA) | 4/347 (1%) | 12/347 (3%) |
| 0  | 16 Loonstra FC. | 22/86 (26%) | 4/86 (5%) | 3/86 (3%) | 4/86 (5%) |
| 0  | 17 Montero-Escribano P. | 1/9 (11%) | 1/9 (11%) | 0/9 (0%) | 0/9 (0%) |
| 0  | 18 Olivares Gascia JC. | 1/4 (25%) | 1/4 (25%) | 0/4 (0%) | 0/4 (0%) |
| 0  | 19 Sadeghi M. | 38/371 (10%) | 89/371 (24%) | 4/371 (1%) | 0/371 (0%) |
| 0  | 20 Sahraian MA. | 17/68 (25%) | NA/68 (NA) | 2/68 (3%) | 2/68 (3%) |
| 0  | 21 Saltor A. | 320/1626 (20%) | 112/1626 (7%) | 104/1626 (6%) | 54/1626 (3%) |
| 0  | 22 Sen S. | 85/309 (28%) | 81/309 (26%) | 9/309 (3%) | 3/309 (1%) |
| 0  | 23 Sormani MP. | 96/844 (11%) | 96/844 (11%) | 96/844 (11%) | 14/844 (2%) |
| 0  | 24 Spelman T. | 73/476 (15%) | NA/476 (NA) | 19/476 (4%) | 8/476 (2%) |
| 0  | 25 Tsianos K. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 26 Tsianos K. | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) | 0/2 (0%) |
| 0  | 27 Wuu MS. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 28 Wurz H. | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| 0  | 29 Wallach A. | 5/17 (29%) | NA/17 (NA) | 0/17 (0%) | 0/17 (0%) |

Pooled estimate
% (95% IC) 18.1% (14.5%–21.6%) 14.8% (9.6%–20.1%) 3.3% (1.8%–4.7%) 1.8% (1.0%–2.6%) 1.6% (0.6%–2.6%) 4.5% (0.8%–8.1%)

I2 88.4% 97.5% 77.1% 76.9% 0.0% 11.8%

* Case reports excluded from the meta-analysis.
difficulty in assessing its presence in retrospective studies. Concerning ICU admissions, the highest percentages of occurrence were observed from two studies (13 and 11%), but in half of the studies there were no patients admitted in ICU. However, it is relevant that for many patients included in this work (N = 591) information on ICU admissions were not available or unclear. ICU admissions should be more investigated and reported due to their relevance in COVID-19 mortality. Indeed, a meta-analysis conducted on the general population showed an ICU hand, clear and complete information on deaths were reported in all the reported due to their relevance in COVID-19 mortality. Indeed, a

meta-analysis included in this work (Btché, G., Assar, H., Hegen, H., et al., 2021. COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: insights from a nationwide Austrian registry. PLoS One 16 (7), e0255316. https://doi.org/10.1371/journal.

pone.0255316, Jul 27PMID: 34314457.

Chauhudy, F., Bulka, H., Rathnam, A.S., et al., 2020. COVID-19 in multiple sclerosis patients and risk factors for severe infection. J. Neurol. Sci. 418, 117147 https://doi.org/10.1016/j.jns.2020.117147. Nov 15Epub 2020 Sep 19. PMID: 32980678; PMCID: PMC7834402.

Conte, W.L., 2021. Attenuation of antibody response to SARS-CoV-2 in a patient on ocrelizumab with hypogammaglobulinemia. J. Neurol. Sci. 44, 102239 https://doi.org/10.1016/j.jns.2020.102239, OctEpub 2020 Jul 12. PMID: 32683306; PMCID: PMC7354374.

Gibson, E.G., Pender, M., Angerbauer, M. et al. Prolonged SARS-CoV-2 Illness in a Patient Receiving Ocrelizumab for Multiple Sclerosis. Open Forum Infect. Dis. 2021 Apr 8;7(7):ofab176. doi: 10.1093/ofid/ofab176. 34258310; PMCID: PMC8083367.

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cancer in patients under rituximab treatment with COVID-19 outcomes compared to patients under other treatments. The frequency of deaths was lower than the one observed in a previous work (Saller et al., 2021).

Patients treated with rituximab seem to be at higher risk of severe COVID-19 outcomes compared to patients under other treatments. The reason for this difference has been suggested by a sensitivity analysis from the Italian work (Sormani et al., 2021) which revealed a trend of an increased risk of anti-CD20 agents with therapy duration. In particular, as compared to patients treated with other therapies, patients on anti-CD20 therapy for less than six months had an OR = 1.65 (95% CI = 0.56–4.90, p = 0.36), patients on anti-CD20 therapy between six and twelve months had an OR = 2.24 (95% CI = 0.91–5.55, p = 0.08), and patients on anti-CD20 therapy for more than twelve months had an OR = 2.98 (95% CI = 1.37–6.46, p = 0.006).

Therefore, the increased risk of patients in Rituximab can be due to their longer therapy duration compared to that of patients in Ocrelizumab.

Declaration of Competing Interest

Schiavetti I, Ponzano M, Signori A, Bovis F, Carmisciano I. have nothing to disclose. Sormani MP received consulting fees from Merck, Biogen, Novartis, Sanofi-Genzyme, Roche, Genoveo, GSK, Medday, Immunic.

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