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## Review article

# COVID-19 and disease-modifying therapies in patients with demyelinating diseases of the central nervous system: A systematic review

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## ABSTRACT

**Introduction:** The Coronavirus disease-19 (COVID-19) pandemic continues to expand across the world. This pandemic has had a significant impact on patients with chronic diseases. Among patients with demyelinating diseases of the central nervous system (CNS), such as Multiple Sclerosis (MS) or Neuromyelitis Optica Spectrum Disorder (NMOSD), concerns remain about the potential impact of COVID-19 on these patients given their treatment with immunosuppressive or immunomodulatory therapies. In this study, we review the existing literature investigating the impact of disease-modifying therapies (DMT) on COVID-19 risks in this group of patients.

**Method:** For this systematic review, we searched PubMed from January 1, 2020, to December 3, 2020. The following keywords were used: “COVID-19” AND “Multiple Sclerosis” OR “Neuromyelitis Optica.” Articles evaluating COVID-19 in patients with demyelinating diseases of CNS were included. This study evaluates the different aspects of the DMTs in these patients during the COVID-19 era.

**Results and conclusion:** A total of 262 articles were found. After eliminating duplicates and unrelated research papers, a total of 84 articles met the final inclusion criteria in our study. Overall, the experiences of 2493 MS patients and 37 NMOSD patients with COVID-19 were included in this review. Among them, 46 (1.8%) MS patients died (the global death-to-case ratio of Covid-19 was reported about 2.1%). Among DMTs, Rituximab had the highest mortality rate (4%). Despite controversies, especially concerning anti-CD20 monoclonal antibody therapies, a relation between DMT-use and COVID-19 disease-course was not found in many studies. This observation reinforces the recommendation of not stopping current DMTs. Other variables such as age, higher expanded disability status scale (EDSS) scores, cardiac comorbidities, and obesity were independent risk factors for severe COVID-19.

Despite the risks of infection, most patients were willing to continue their DMT during the pandemic because of more significant concern about the risk of relapse or worsening MS symptoms. After the infection, an immune response's attenuation was seen in the patients on Fingolimod and anti-CD20 monoclonal antibodies. This may be a critical finding in future vaccinations.

## 1. Introduction

Coronavirus disease-19 (COVID-19) pandemic continues to expand globally with a significant impact on health care systems and economies. (Sharifian-Dorche et al., 2020). Patients with chronic diseases and those

receiving immunosuppressive therapies have an increased risk of infection and severe complications. (Sahraian et al., 2020a) Especially in the latter group of patients, the pandemic affects many aspects of their disease management, from therapeutic strategies to scheduling routine clinical follow-up and rehabilitation plans. Patients with demyelinating

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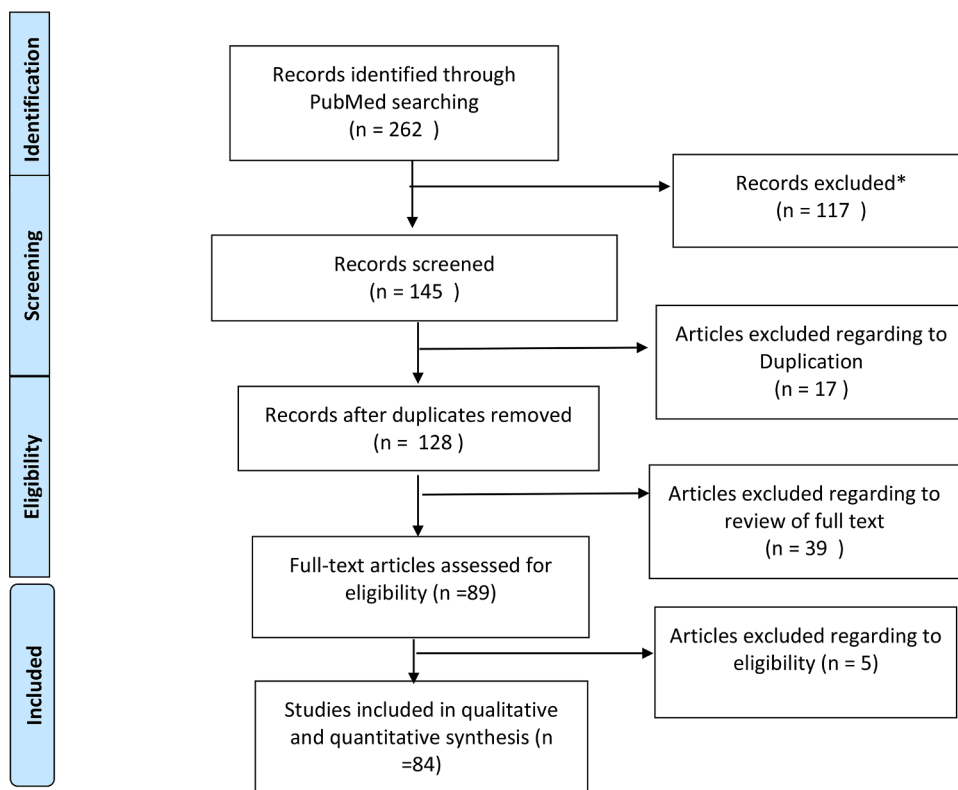
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disorders of the central nervous system (CNS) such as Multiple Sclerosis (MS) or Neuromyelitis Optica Spectrum Disorder (NMOSD) deserve particular consideration due to their need for immunosuppressive or immunomodulatory therapies and regular monitoring of disease activity and response to treatment. (Sahraian et al., 2020a) In this study, we review the latest evidence on 1) the effect of different disease-modifying therapies (DMT) on the risk of contracting SARS-CoV-2 infection and severe COVID-19 complications; 2) the effect of these therapies on the ability to develop immune responses to vaccines, and 3) the psychological impact of COVID-19 pandemic on patients with chronic demyelinating diseases.

## 2. Search strategy and selection criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1), (Hutton et al., 2015), we searched PubMed from January 1, 2020, to December 3, 2020. These keywords were used: “COVID-19” AND “Multiple Sclerosis” OR “Neuromyelitis Optica” We included articles that were written in English. The authors evaluated the titles and abstracts of each article. Articles evaluating COVID-19 in patients with demyelinating diseases of CNS were included. This study focuses on evaluating different aspects of the disease-modifying therapies (DMT) in the COVID-19 time (possible increased risk of infection, their effect on the future vaccine, and patients’ attitudes to continue or discontinue the medication during a pandemic) in patients with MS and NMOSD.

Studies presented as original articles, case series, case reports, letters, correspondence, or short communications were considered. We evaluated the full text of included articles for the detection of clinical features of the patients. Duplicated results were removed. The final list of included articles was generated according to relevance to the topics covered in this review. Data from each article was extracted into the Microsoft Excel software.



## 3. Results

The PRISMA flow chart of this study is shown in Fig. 1. A total of 262 articles were found. After removing duplicates and unrelated research papers, a total of 84 articles met the final inclusion criteria in our study. Overall, the data of 2493 MS patients and 37 NMOSD patients were reported with COVID-19. (Tables 1 and 2) (Sahraian et al., 2020a; Safavi et al., 2020; Bowen et al., 2020; Louapre et al., 2020a; Dalla Costa et al., 2020; Parrotta et al., 2020; Barzegar et al., 2020a; Ciampi et al., 2020a; Mantero et al., 2020a; Sahraian et al., 2020b; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Shalhoub, 2020; Delbue et al., 2007; Berger and Brandstadter, 2020; Maillart et al., 2020; Ciampi et al., 2020b; Mantero et al., 2020b; Crescenzo et al., 2020; Mehta et al., 2019; Maghzi et al., 2020; Möhn et al., 2020; Bollo et al., 2020; Ciardi et al., 2020; Valencia-Sanchez and Wingerchuk, 2020; Foerch et al., 2020; Barzegar et al., 2020b; Chiarini et al., 2020; Gomez-Mayordomo et al., 2020; Mallucci et al., 2020; Giovannoni et al., 2020; Borriello and Ianniello, 2020; Louapre et al., 2020b; Aguirre et al., 2020; Rimmer et al., 2020; Luna et al., 2019; Carandini et al., 2020; Matias-Guiu et al., 2020; Guevara et al., 2020; Fernández-Díaz et al., 2020; Amor et al., 2020; Fiorella and Lorna, 2020; Dersch et al., 2020; De Angelis et al., 2020; Celius, 2020; Jack et al., 2020; Suwanwongse and Shabarek, 2020; Ghajarzadeh et al., 2020; Montero-Escribano et al., 2020; Novi et al., 2020; Hughes et al., 2020; Meca-Lallana et al., 2020; Conte, 2020; Lucchini et al., 2020; Thornton and Harel, 2020; Iannetta et al., 2020; Soresina et al., 2020; Devogelaere et al., 2020; Woo et al., 2020; Wurm et al., 2020; Sormani et al., 2020; Olivares Gazca et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020; Fan et al., 2020; Creed et al., 2020; Mirmosayyeb et al., 2020; Louapre et al., 2020c; Preziosa et al., 2020; Kataria et al., 2020)

### 3.1. Risk of infection in patients on DMTs

One of the essential concerns of neurologists involved in patient care with demyelinating CNS diseases during the COVID-19 pandemic is the

Fig. 1.. PRISMA chart of this study.

\*Among the selected articles, those with relation to the rate of infection in patients on DMTs, articles related to psychiatric problems and anxiety in MS and NMOSD patients during pandemic (with focus on the articles which evaluated the risk of different DMT and attitude of the patients about continuing or discontinuing of the DMT) and articles related to vaccination were included. Other articles were excluded (to have a more focused review).

**Table 1.**

DMTs in MS patients who were infected with COVID-19, Abbreviations: RRMS: Relapsing-Remitting MS, SPMS: Secondary progressive MS, PPMS: Primary Progressive MS, DMF: Dimethyl fumarate, GA: Glatiramer acetate, ICU: Intensive care unit.

Name	Ref.	Confirmed patients	Death	Suspicious patients	TotalPatients	TotalDeath (%)
<b>Interferon beta</b>	(Safavi et al., 2020; Bowen et al., 2020; C Louapre et al., 2020; Parrotta et al., 2020; M Barzegar et al., 2020; E Ciampi et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	61		74	135	0
<b>Interferons/GA</b>	(Dalla Costa et al., 2020; Nesbitt et al., 2020)	-	-	84	84	0
<b>GA</b>	(Bowen et al., 2020; C Louapre et al., 2020; Parrotta et al., 2020; MA Sahraian et al., 2020; Maillart et al., 2020; Chaudhry et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020; Kataria et al., 2020)	67	1-71 -year-old, Male, SPMS Comorbidities: Venus Thrombo embli and obesity ( Parrotta et al., 2020) 2-64 -year-old, Male, RRMS, EDSS: 2, no comorbidity. (Sormani et al., 2020)	73	140	2(1.4%)
<b>DMF</b>	(C Louapre et al., 2020; Parrotta et al., 2020; M Barzegar et al., 2020; E Ciampi et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; V Mantero et al., 2020; Crescenzo et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020; Kataria et al., 2020)	119	1-68 -year-old, Male, SPMS, EDSS:6 Comorbidities: cerebrovascular disease, Hypertension (Sormani et al., 2020)	195	314	1(0.3%)
<b>DMF/Teriflunomide</b>	(Nesbitt et al., 2020; Dalla Costa et al., 2020)			108	108	0
<b>Teriflunomide</b>	(Safavi et al., 2020; Bowen et al., 2020; C Louapre et al., 2020; E Ciampi et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Maillart et al., 2020; Crescenzo et al., 2020; Maghzi et al., 2020; Möhn et al., 2020; Bollo et al., 2020; Ciardi et al., 2020; Valencia-Sanchez and Wingerchuk, 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	83	1-55 -year-old Female, SPMS, EDSS:7.5, Comorbidities: myotonic dystrophy (Bowen et al., 2020)	49	132	1(0.7%)
<b>Fingolimod</b>	(Safavi et al., 2020; Bowen et al., 2020; C Louapre et al., 2020; Dalla Costa et al., 2020; Parrotta et al., 2020; M Barzegar et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Crescenzo et al., 2020; Bollo et al., 2020; Valencia-Sanchez and Wingerchuk, 2020; Foerch et al., 2020; M Barzegar et al., 2020; Chiarini et al., 2020; Gomez-Mayordomo et al., 2020; Mallucci et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	111	1-42 -year-old Female, RRMS, EDSS 6.0 Comorbidities: severe cognitive impairment, history of struma treated with radioiodine, refused ICU admission. (Loonstra et al., 2020)	146	257	1(0.3%)
<b>Siponimod</b>	(Parrotta et al., 2020)	2			2	0
<b>Ponesimod</b>	(Sormani et al., 2020)			1	1	0
<b>Natalizumab</b>	(C Louapre et al., 2020; Dalla Costa et al., 2020; Parrotta et al., 2020; E Ciampi et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Maillart et al., 2020; Crescenzo et al., 2020; Borriello and Ianniello, 2020; C Louapre et al., 2020; Aguirre et al., 2020; Rimmer et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	97	1- 60 -year-old Female, RRMS, Comorbidities: Coronary artery disease, Hypertension and obesity. (Parrotta et al., 2020) 2-51 -year-old Female, EDSS: 6.5, Comorbidities: obesity and hypertension. (Rimmer et al., 2020) 3-52 -year-old Female, RRMS, EDSS:5, no Comorbidity . (Sormani et al., 2020)	136	233	3(1.2%)
<b>Alemtuzumab</b>	(C Louapre et al., 2020; E Ciampi et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Carandini et al., 2020; Matías-Guiu et al., 2020; Guevara et al., 2020; Fernández-Díaz et al., 2020; Fiorella and Lorna, 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	14		23	37	0
<b>Alemtuzumab/Cladribine</b>	(Dalla Costa et al., 2020)			15	15	0
<b>Cladribine</b>		35		56	91	0

(continued on next page)

Table 1. (continued)

Name	Ref.	Confirmed patients	Death	Suspicious patients	TotalPatients	TotalDeath (%)
<b>Ocrelizumab</b>	(C Louapre et al., 2020; Nesbitt et al., 2020; Castillo Álvarez et al., 2020; Dersch et al., 2020; De Angelis et al., 2020; Celius, 2020; Jack et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020; Preziosa et al., 2020)	202	1- 51 -year-old Male, SPMS, and history of prostatic cancer. (Parrotta et al., 2020) 2- 59 -year-old Male, SPMS, EDSS 5.5, Comorbidities: Chronic obstructive pulmonary disease (COPD), refused ICU admission. (Loonstra et al., 2020) 3-50 -year-old Female, SPMS,EDSS:6, no comorbidity . (Sormani et al., 2020)	104	306	3(0.9%)
<b>Rituximab</b>	(Safavi et al., 2020; C Louapre et al., 2020; Parrotta et al., 2020; M Barzegar et al., 2020; Montero-Escribano et al., 2020; Meca-Lallana et al., 2020; Devogelaere et al., 2020; Woo et al., 2020; Wurm et al., 2020; MA Sahraian et al., 2020; Maillart et al., 2020)	88	1-42 -year-old Male, RRMS, Comorbidities: history of Hodgkin lymphoma and venous thrombosis (Parrotta et al., 2020) 2- 46 -year-old Female, SPMS, EDSS:6.5 and history of hypothyroidism (M Barzegar et al., 2020) 3-54 -year-old Female, SPMS, EDSS:7 (65) Two other patients (MA Sahraian et al., 2020)	25	113	5(4%)
<b>Anti-CD20 monoclonal antibodies</b>	(Dalla Costa et al., 2020; Nesbitt et al., 2020)			49	49	0
<b>Mycophenolate Mofetil</b>	(C Louapre et al., 2020)	3			3	0
<b>Cyclophosphamide</b>	(C Louapre et al., 2020)	1			1	0
<b>Methotrexate</b>	(C Louapre et al., 2020; Sormani et al., 2020)	1		1	2	0
<b>Azathioprine</b>	(MA Sahraian et al., 2020; Crescenzo et al., 2020; Sormani et al., 2020)	8		4	12	0
<b>Mitoxantrone</b>	(Sormani et al., 2020)			1	1	0
<b>Hematopoietic Cell Transplant</b>	(Olivares Gazca et al., 2020; Loonstra et al., 2020)	1		4	5	0
<b>Steroid</b>	(Chaudhry et al., 2020)	2			2	0
<b>IVIG</b>	(Parrotta et al., 2020; Loonstra et al., 2020)	4			4	0
<b>No Medication</b>	(Bowen et al., 2020; C Louapre et al., 2020; Parrotta et al., 2020; M Barzegar et al., 2020; V Mantero et al., 2020; MA Sahraian et al., 2020; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Crescenzo et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020)	166	1-84 -year-old Male SPMS, EDSS:8.5, Comorbidities: Congestive heart disease, Diabetic Mellitus, Chronic obstructive pulmonary disease, cardiomegaly (Bowen et al., 2020) 2-63 -year-old Male, SPMS, EDSS:7 Comorbidities: Diabetic Mellitus (Sormani et al., 2020) 3-65 -year-old Male, PPMS, EDSS:7.5, Comorbidities: Congestive heart disease, Diabetic Mellitus, HBV (Sormani et al., 2020) 4-63 -year-old Male, SPMS, EDSS:6.5, Comorbidities: Diabetic Mellitus (Sormani et al., 2020) 5-50 -year-old Female, Comorbidities: Hypertension, Obesity, Hypothyroid (Parrotta et al., 2020) 6-65 -year-old Female, Comorbidities: Neurogenic Bladder, Non-Ambulatory (Parrotta et al., 2020) 7- 74 -year-old Male, SPMS, EDSS: 7 (Castillo Álvarez et al., 2020) 8- 57 -year-old Male, EDSS 7,	213	379	14(3.6%)

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**Table 1.** (continued)

Name	Ref.	Confirmed patients	Death	Suspicious patients	TotalPatients	TotalDeath (%)	
			Comorbidities: asthma and hypertension, refused intensive care unit admission. (Loonstra et al., 2020) 9- 59 -year-old Male, PPMS, EDSS 4, Comorbidities: obesity, no intubation, and ICU admission due to fulminant disease. (Loonstra et al., 2020) 10-57 -year-old Female, EDSS: 9, SPMS, no comorbidity. (Sormani et al., 2020) 11-76 -year-old Male, SPMS, EDSS:6.5, Comorbidities: Congestive heart disease, hypertension, dyslipidemia, depression (Sormani et al., 2020) 12-59 -year-old Male, SPMS, EDSS:9, no comorbidity. (Sormani et al., 2020) 13-68 -year-old Female, SPMS, EDSS:5.5, no comorbidity. (Sormani et al., 2020) 14-60 -year-old Male, SPMS, EDSS:9, Comorbidities: Congestive heart disease, Hypertension, Cardiovascular disease. (Sormani et al., 2020)				
<b>Undetermined</b>	(C Louapre et al., 2020; M Barzegar et al., 2020; Chaudhry et al., 2020; Sormani et al., 2020)		16	67	67	16(23%)	
<b>Total</b>		1065	46	1428	2493	46(1.8%)	

**Table 2.**  
DMTs in NMOSD patients who were infected with COVID-19, ICU: Intensive care unit.

Name	Ref.	Confirmed patients	ICU admissionAnd Death	Suspicious patients	TotalPatients	TotalDeath or ICU admission
Rituximab	(MA Sahraian et al., 2020; Parrotta et al., 2020; Montero-Escribano et al., 2020; Woo et al., 2020; Creed et al., 2020; Mirmosayyeb et al., 2020; C Louapre et al., 2020)	17	1-62-year-old Male Comorbidity: obesity (Parrotta et al., 2020) 2-68 -year-old Female EDSS:8 3-41-year-old Male 4- 24 -year-old Female Comorbidity:obesity (C Louapre et al., 2020)	3	20	4(20%)
Oral Prednisolone	(E Ciampi et al., 2020; Fan et al., 2020)	3	61 -year-old Male Edss:6 Comorbidity: Hypertension, Diabetic Mellitus E Ciampi et al., 2020		3	1(33%)
Mycophenolate Mofetil	(E Ciampi et al., 2020; C Louapre et al., 2020)	3		1	4	
Azathioprine	(E Ciampi et al., 2020; C Louapre et al., 2020)	3			3	
Ofatumumab	(Maillart et al., 2020; C Louapre et al., 2020)	2			2	
Rituximab/ Azathioprine	(Mirmosayyeb et al., 2020)	4			4	
Mycophenolate Mofetil + Prednisolone	(C Louapre et al., 2020)			1	1	
<b>Total</b>		28	5	4	37	5(13%)

increased risk for infection and complications associated with immunomodulatory or immune-suppressive therapies. The risk of infection during epidemics in these patients has been studied before. For example, Ghaderi S et al. (2020) reported that influenza infection is associated with an increased risk for acute hospitalization, and vaccination could prevent this risk among MS patients. Ghaderi et al. (2020) Several studies have already reported on SARS-CoV-2 infection in patients with

MS and NMOSD and have evaluated the relation COVID-19 course with different DMTs (Tables 1 and 2). Although limited by a small sample size and multiple possible sources of bias, these papers provide essential information to understand the risk of infection in patients on different medications. Tables 1 and 2 summarizes the cases of COVID-19 in MS and NMOSD patients on different DMTs.



### 3.1.1. Interferons-beta (IFN)

Among DMTs of MS, IFN-B is associated with the lowest risk of infection. (Table 1) IFN-Bs belong to type I interferons; a class suggested to have a protective effect for COVID-19 based on the antiviral effects. Shalhoub (2020) There are very few reports of leukopenia and lymphopenia during IFN-b treatment. Delbue et al. (2007) We identified a total of 135 MS patients on IFN treatment infected with SARS-CoV-2 (Table 1), all of whom recovered completely. The use of IFN-b should not raise concerns in the context of the COVID-19 pandemic. Berger and Brandstadter (2020) SARS-CoV-2 inhibits the antiviral type 1 IFN molecules' production by the infected cells and the intracellular antioxidant nuclear factor erythroid 2-related factor 2 (NRF2) pathway. (Laroni et al., 2020) (Fig. 2) accordingly, INF-B could be a possible treatment in these patients. Sormani MP et al. (2020) found that interferon-beta's use appeared even to decrease the risk of Covid-19 in Italian MS patients.

### 3.1.2. Glatiramer acetate (GA)

It was suggested that GA causes a shift from a pro-inflammatory to an anti-inflammatory response. (Fig. 2) This shift could be potentially beneficial in case of COVID-19 infection. Furthermore, GA blocks IFN-gamma mediated activation of macrophages, which is thought to play an essential role in acute respiratory distress syndrome. (Bowen et al., 2020; Berger and Brandstadter, 2020) Moreover, there is no evidence of increased infectious risk during treatment with GA. Accordingly, GA could be a safe medication in the treatment of MS patients during the SARS-CoV-2 pandemic. (Bowen et al., 2020; Berger and Brandstadter, 2020) we found 140 patients on GA who were infected with SARS-CoV-2. Among them, 2 (1.4%) patients died: a 71-year-old man with secondary progressive MS (SPMS), history of obesity, and venous thromboembolism in treatment with anti-coagulants (Parrotta et al., 2020) and a 64-year-old man with relapsing-remitting MS (RRMS), an expanded disability status scale (EDSS) score of 2 without known comorbidities. (Sormani et al., 2020)

Two studies (Dalla Costa et al., 2020; Nesbitt et al., 2020) reported 84 suspicious patients (suspected to have COVID-19) on either Interferon or GA, not further specified.

### 3.1.3. Dimethyl fumarate (DMF)

The therapeutic mechanism of DMF in MS is not fully elucidated. A significant portion of patients treated with DMF experience variable lymphopenia (with CD8 T cells being affected more than CD4 T cells and memory cells more than naive T cells and B cells). (Mehta et al., 2019) Although there was little difference in infection risk between DMF and placebo during clinical trials, DMF can induce grade 3 lymphopenia in 5–7% of the patients. Moreover, severe opportunistic infections have been reported in few patients treated with DMF. (Berger and Brandstadter, 2020; Mehta et al., 2019)

In vitro studies showed that DMF blocks pro-inflammatory cytokine production and can inhibit macrophage function, which results in suppressing inflammation (Berger and Brandstadter, 2020). These immunomodulatory effects could be potentially beneficial in the context of the COVID-19 cytokine storm. (Berger and Brandstadter, 2020) (Fig. 2)

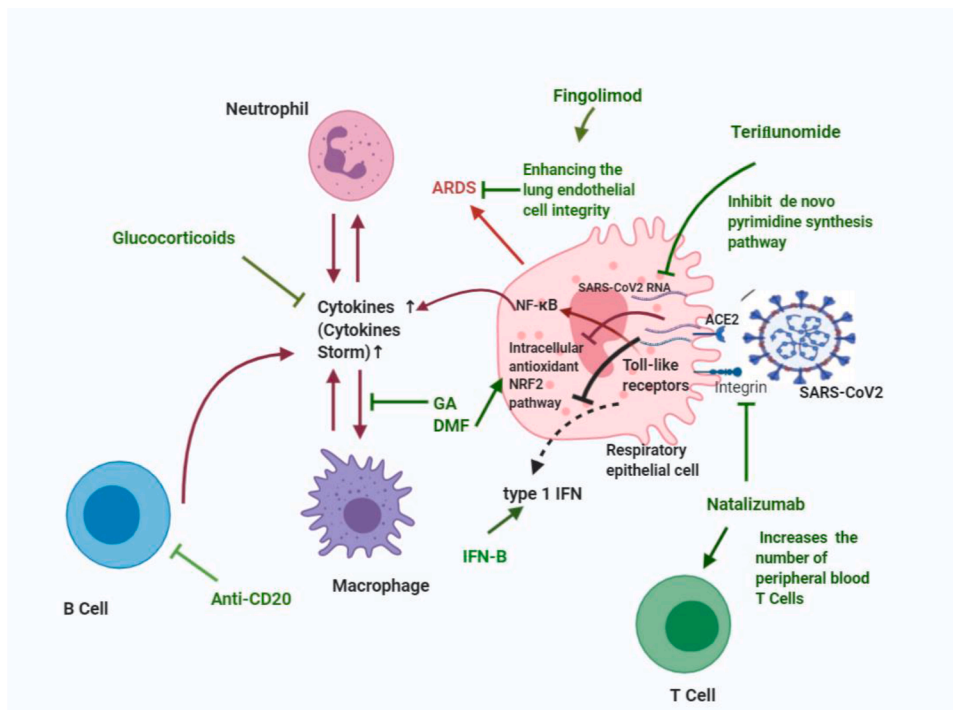
Current studies did not report an increased risk of severe outcome COVID-19 in patients on DMF; however, the presence or absence of lymphopenia did not evaluate in the course of disease in these patients.

We found 314 patients on DMF infected with SARS-CoV-2. One (0.3%) of these patients died from complications of COVID-19. He was a 68-year-old man with SPMS, EDSS of 6.0, and past medical history of cerebrovascular disease and hypertension, both known negative prognostic factors for COVID-19. (Sormani et al., 2020)

### 3.1.4. Teriflunomide

Teriflunomide, an active metabolite of leflunomide, selectively and reversibly inhibits dihydro-orotate dehydrogenase, an essential mitochondrial enzyme in the de novo pyrimidine synthesis pathway. (Maghzi et al., 2020; Ciardi et al., 2020) Through this mechanism, Teriflunomide reduces immune activation without significant immunosuppression. This function may be potentially beneficial in SARS-CoV-2 infection and may prevent an excessive/fulminant host immune response. (Maghzi et al., 2020; Ciardi et al., 2020) Moreover, Teriflunomide may affect the replication of SARS-CoV-2 inside the infected cell. (Laroni et al., 2020) (Fig. 2)

Past studies have suggested a possible effect of Teriflunomide against several viruses, including respiratory syncytial virus (RSV), Ebola, cytomegalovirus, Epstein-Barr, and picornavirus. (Maghzi et al., 2020)



**Fig. 2.** SARS-CoV-2 inhibits the antiviral type 1 IFN molecules' production by the infected cells and the intracellular antioxidant NRF2 pathway. GA causes a shift from a pro-inflammatory to an anti-inflammatory response. DMF blocks pro-inflammatory cytokine production and can inhibit macrophage function. Teriflunomide may affect the replication of SARS-CoV-2 inside the infected cell. Fingolimod enhancing lung endothelial cell integrity. Natalizumab as an antibody against  $\alpha$ 4-integrin might be protective toward the infection. Anti-CD20 monoclonal antibodies moderately reduced immune response by peripheral B cell reduction, which might play a favorable role in COVID-19. Designed with <https://biorender.com/>.

ARDS: Acute respiratory distress syndrome, GA: Glatiramer acetate, DMF: Dimethyl fumarate, IFN: Interferon beta. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Accordingly, Teriflunomide could be useful against SARS-CoV-2 through dual antiviral and immunomodulatory actions. (Maghzi et al., 2020; Berger and Brandstadter, 2020)

On the other hand, Teriflunomide could reduce leukocyte count by approximately 15%, and upper respiratory tract infections and influenza are more common among patients taking Teriflunomide. (Berger and Brandstadter, 2020) Overall serious infections resulting in increased morbidity and mortality have not been reported. (Berger and Brandstadter, 2020).

In this study, we found 132 patients on Teriflunomide and COVID-19. There have been reports of the benign course of COVID-19 in many of these patients. (Maghzi et al., 2020) However, one (0.7%) died. This patient was a 55-year-old woman with SPMS, EDSS of 7.5, and an additional diagnosis of myotonic dystrophy, which confers its own cardiac risks. (Bowen et al., 2020)

Of note, in one study, patients who contracted COVID-19 while on treatment with Teriflunomide developed antibody levels following seroconversion like those detected in immunocompetent patients. (Bollo et al., 2020) This observation should be taken into account because it can mimic the vaccination outcome in patients treated with Teriflunomide.

### 3.1.5. Fingolimod

Fingolimod is a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction by blocking trafficking to the target organ. It reduces the total mean circulating lymphocyte count by 73% from baseline and preferentially sequesters the naive and central memory lymphocytes rather than effector memory T cells. (Berger and Brandstadter, 2020; Mehta et al., 2019; Giovannoni et al., 2020) Fingolimod is associated with an increased risk of mild infections, mainly involving the lower respiratory tract, and increased risk for Herpes virus infections/reactivations (Berger and Brandstadter, 2020). Accordingly, there are some concerns about the increased risk of SARS-CoV-2 infection in these patients. COVID-19 was reported in 257 patients on Fingolimod. Most patients had a relatively benign disease course despite lymphopenia and showed complete recovery. Only one Fingolimod (0.3%) patient died. She was a 42-year-old woman with RRMS and EDSS: 6.0. She had severe cognitive impairment, a history of struma treated with radioiodine, and refused Intensive Care Unit (ICU) admission. (Loonstra et al., 2020)

On the other hand, blunting the immune response and potential of sphingosine-1-phosphate enhancing the lung endothelial cell integrity may be the possible explanations that make Fingolimod a potential therapy to control the severe respiratory disease. (Fig. 2) Gomez-Mayordomo V et al. (Gomez-Mayordomo et al., 2020) reported a case of clinical exacerbation of SARS-CoV-2 infection after Fingolimod withdrawal in a 57-year-old man with RRMS and EDSS 6.0. The patient showed hyper-inflammation syndrome one week after Fingolimod withdrawal, and he progressively improved following steroid therapy.

The risk of aggressive rebound of MS activity with Fingolimod's discontinuation (Delbue et al., 2007; Berger and Brandstadter, 2020) should be carefully weighed when considering treatment discontinuation due to the risk of infections. The ultimate decision should be individualized through discussion between physician and patient.

The other concern about patients on Fingolimod is the effect of vaccination and immunoglobulin response. Bollo L et al. (Bollo et al., 2020) reported a 34-year-old female with RRMS, EDSS 2.5 on Fingolimod, who had a reduced immunoglobulin response (IgG serum response) to SARS-CoV-2 as compared to immunocompetent controls. (Bollo et al., 2020)

### 3.1.6. Natalizumab

Natalizumab is a humanized monoclonal antibody against  $\alpha$ 4-integrin indicated for the treatment of MS and Crohn's disease. By inhibiting the binding to VCAM and MADCAM, it prevents the migration

of lymphocytes through the brain and guts endothelial microvasculature. The impairment of CNS immune surveillance caused by Natalizumab may contribute to opportunistic infections. (Giovannoni et al., 2020; Luna et al., 2019) A registry-based cohort study performed by Luna G et al. (Luna et al., 2019) showed no significant increase in the general risk of infection with Natalizumab compared to platform therapies.

Until now, 233 patients on Natalizumab with SARS-CoV-2 infection were reported. Three (1.2%) of these patients died. These patients were aged 60-year-old, 51-year-old, and 52-year-old, and two had other underlying comorbidities (coronary artery disease, hypertension, and obesity). (Table 1) Aguirre C et al. (2020) suggested that Natalizumab treatment could even be helpful in the COVID-19 pandemic context. Based on the recent studies showing that SARS-CoV-2 may use integrin to enter the human cells, Natalizumab as an antibody against  $\alpha$ 4-integrin might be protective toward the infection. (Fig. 2)

### 3.1.7. Alemtuzumab

Alemtuzumab is a fully-humanized IgG1 directed against CD52 and used to treat chronic lymphocytic leukemia (CLL) and MS. It acts via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In addition, it activates pro-apoptotic pathways on CD52 expressing cells. (Berger and Brandstadter, 2020) Alemtuzumab reduces T and B-lymphocytes count for many months following administration. The incidence of infection in the early months after treatment with Alemtuzumab is high, given the profound lymphopenia (Amor et al., 2020), but the rate of severe infection was <3%. (Amor et al., 2020) Considering significant infectious risks with Alemtuzumab - particularly in the first two years of treatment - the risk of COVID-19 may be higher in these patients. (Giovannoni et al., 2020)

We found 37 reported patients on Alemtuzumab and COVID-19. Most of them had a benign course and recovered completely. None of them died. (Guevara et al., 2020) However, there is insufficient evidence from the published cases to indicate whether patients at the beginning of the treatment are at greater risk.

Following the initial depletion, Alemtuzumab produces a lymphocyte reconstitution from a new lineage. This lymphocyte reconstitution, including changes in composition, phenotype, and lymphocytes' function, may cause a potential resistance of this new lineage to the virus or blunts the cytokine storm associated with life-threatening complications of SARS-CoV-2 infection. (Matfas-Guiu et al., 2020)

### 3.1.8. Cladribine

Oral Cladribine, a purine nucleoside analog prodrug, interferes with cellular metabolism and inhibits DNA repair, which causes apoptosis, especially in lymphocytes. (Berger and Brandstadter, 2020; Giovannoni et al., 2020) The effect of Cladribine is mainly on CD4+ and CD8+ T cells, and also B cells. Accordingly, transient lymphopenia (most often mild to moderate) is a common adverse event. The effect on innate immune cells such as neutrophils, monocytes, and NK cells are minor. (Berger and Brandstadter, 2020; Giovannoni et al., 2020) Due to the lymphopenia, the risk of infection with SARS-CoV-2 may be increased in patients on Cladribine.

Ninety-one MS patients on Cladribine infected with COVID-19 have been reported to date. Jack et al. (2020), from Merck KGaA Global Patient Safety Database, reported that as of June 29, approximately 19,000 patients with relapsing MS had been treated with Cladribine. From them, 18 patients had confirmed COVID-19, and twenty-eight patients were suspected of infection. However, the cases reported in the Merck Global Patient Safety Database may overlap with other published reports; thus, it is difficult to ascertain the precise number of cases affected by COVID. Regardless, no fatal cases of COVID-19 in patients on Cladribine have been reported. The findings collected so far do not support an increased risk for severe outcomes in patients with RRMS treated with Cladribine and who acquire COVID-19.

Regarding immune responses and antibody formation to SARS-CoV-



2, Celius EG (Celius, 2020) reported adequate immune response with detectable antibodies three months after infection in a 35-year-old female with RRMS on Cladribine.

### 3.1.9. Anti-CD20 monoclonal antibodies (Ocrelizumab and Rituximab)

Therapy with anti-CD20 monoclonal antibodies, such as Ocrelizumab and Rituximab, has demonstrated high efficacy in reducing MS relapses by targeting B cells. Moreover, these agents reduce pro-inflammatory B-cell cytokines. (Berger and Brandstadter, 2020) A higher risk of infection was reported with Rituximab than with platform MS DMTs (IFN- $\beta$  and GA) (Luna et al., 2019), although infection rates were only slightly higher with Ocrelizumab than interferon  $\beta$ -1a. (Berger and Brandstadter, 2020; Luna et al., 2019) Hypo-gammaglobulinemia may be observed in the patients who had prolonged use of anti-CD20 therapies but is rarely associated with severe infection. (Berger and Brandstadter, 2020; Giovannoni et al., 2020) In this pandemic, it was shown that a direct role of B cells in SARS-CoV-2 infection is less likely. Soresina et al. (2020) reported two cases of COVID-19 with pneumonia and lymphopenia in patients with X-linked agammaglobulinemia, both of whom recovered.

There are several reports of COVID-19 in patients receiving anti-CD20 monoclonal antibodies.

The Roche/Genentech global safety databases include over 160,000 MS patients worldwide treated with Ocrelizumab. As of April 30, 2020, 100 COVID-19 cases (74 confirmed) were reported from these patients. Twenty-six patients from the confirmed group were reported as either hospitalized at the time of report ( $n = 12$ ) (four classified as critical) or previously hospitalized ( $n = 14$ ). (Suwanwongse and Shabarek, 2020)

We found reports of 306 MS patients with COVID-19 on Ocrelizumab. (Table 1) However, our results are likely to have some overlaps with the Roche safety database report. (Suwanwongse and Shabarek, 2020) Three (0.9%) patients died due to complications of COVID-19. One of them was a 66-year-old man with SPMS and a history of prostatic cancer. (Parrotta et al., 2020) The other patient was a 59-year-old man with SPMS and EDSS of 5.5, with a history of chronic obstructive pulmonary disease (COPD) and refused ICU admission. (Loonstra et al., 2020) The third one was a 50-year-old woman with SPMS and EDSS of 6, without any significant comorbidity. (Sormani et al., 2020)

In the Rituximab group, we found 113 patients with MS and 20 patients with NMO/DMT infected with SARS-CoV-2. Among these patients, nine patients died or were admitted to ICU due to complications of COVID-19. (Tables 1 and 2)

Sormani et al. (2020) found that after adjusting for age, sex, and progressive MS course, anti-CD20 therapy (Ocrelizumab or Rituximab) was significantly associated with an increased risk of severe COVID-19 course.

In another study from Iran, it was demonstrated that the risk of SARS-CoV-2 infection among patients on B-cell-depleting therapy was higher than patients on other DMT (Safavi et al., 2020; Sahraian et al., 2020b). Although the use of the drug was not associated with increased odds of hospitalization. (Sahraian et al., 2020b)

However, most patients, especially those without underlying comorbidities, had a complete recovery, and other studies did not have similar findings. (Louapre et al., 2020a) In published case reports, the number of B cells does not seem to impact the prognosis. (Table 1) It was even suggested that a moderately reduced immune response due to a lack of peripheral B cells in the patients on anti-CD20 monoclonal antibodies might play a favorable role in these patients. The lack of a significant increase of IL-6 (that might be released by the peripheral B cells) seems to support this hypothesis. (Novi et al., 2020) (Fig. 2)

Another relevant consideration for anti-CD20 monoclonal antibodies is their effect on vaccination since they are partially blunt antibody responses to vaccines. Anti-CD20 monoclonal antibody therapy is not expected to affect responses of the innate immune system, which are critical for initial viral control. (Berger and Brandstadter, 2020; Giovannoni et al., 2020) It also remains to be seen how this class of

therapies will impact the vaccine response to some of the candidate vaccines with novel mechanisms, particularly those that express mRNA to generate an immune response.

Conte WL (2020) reported a 48-year-old female on Ocrelizumab who was infected with SARS-CoV-2. She had an attenuation of a humoral response after infection. Thornton JR et al. (2020) reported two other patients with mild disease and attenuated antibody production.

Iannetta M et al. (2020) reported two patients: a 36-year-old woman with RRMS, EDSS 5.5, and a history of papillary thyroid carcinoma, who was admitted to the hospital due to SARS-CoV-2 infection, but COVID-19 IgG and IgM were undetectable up to 27 days from symptom onset. The other, a 54-year-old with primary progressive MS (PPMS) and EDSS 7 admitted to the hospital due to COVID-19, and IgG became slightly detectable after 28 days from symptom onset. (Iannetta et al., 2020) Further studies are needed to fully characterize the humoral response to SARS-CoV-2 in this group of patients.

Similarly, negative serologic responses were seen in SARS-CoV-2 infected patients treated with Rituximab as well. (Woo et al., 2020; Wurm et al., 2020)

### 3.1.10. Other medications

We found reports of COVID-19 in patients on other types of medications. Siponimod (2 MS patients) (Parrotta et al., 2020), Ponesimod (1 MS patient) (Sormani et al., 2020), Mycophenolate Mofetil (3 MS patients and 4 NMO/DMT patients) (Louapre et al., 2020a; Ciampi et al., 2020a), Cyclophosphamide (1 MS patient), Mitoxantrone (1 MS patient) (Sormani et al., 2020; Louapre et al., 2020a), Methotrexate (2 MS patient) (Louapre et al., 2020a) Azathioprine (12 MS patients and 3 NMO/DMT patients) (Ciampi et al., 2020a; Sahraian et al., 2020b; Crescenzo et al., 2020; Sormani et al., 2020), IVIG (4 MS patients) (Parrotta et al., 2020; Sormani et al., 2020) Hematopoietic Cell Transplant (5 MS patients) (Olivares Gazca et al., 2020; Loonstra et al., 2020) Steroids (2 MS patients and 3 NMO/DMT patients) (Ciampi et al., 2020a; Chaudhry et al., 2020; Fan et al., 2020) one of them died due to COVID-19 complications, (Tables 1 and 2) and Ofatumumab (2 NMO/DMT patients) (Maillart et al., 2020)

Sormani MP et al. (2020) showed that recent use (<1 month) of methylprednisolone was associated with a worse outcome in MS patients with COVID-19.

### 3.1.11. No medication

Overall, 379 MS patients with COVID-19 were reported who did not receive any medications. (Bowen et al., 2020; Louapre et al., 2020a; Parrotta et al., 2020; Barzegar et al., 2020a; Mantero et al., 2020a; Sahraian et al., 2020b; Nesbitt et al., 2020; Chaudhry et al., 2020; Castillo Álvarez et al., 2020; Crescenzo et al., 2020; Sormani et al., 2020; Evangelou et al., 2020; Loonstra et al., 2020). In this group, 14 (3.6%) patients died. The mean age of the patients who died was 64.2 (range:50–84) year-old. Mean EDSS was 7.2 (range 4–9) (EDSS was reported in 12 cases). In addition to being older and having higher disability scores, most of these patients also had underlying comorbidities, which would make them more vulnerable to COVID-19 complications. These comorbidities included: congestive heart disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, cardiomegaly, and obesity.

### 3.1.12. COVID-19 among pediatric-onset MS patients

Only two studies evaluated the COVID-19 in pediatric-onset MS. (Parrotta et al., 2020). In the first, nine patients were reported: one on GA, two on Ocrelizumab, four on Rituximab, one on Natalizumab, and one without medication. Comorbidities in this group were obesity ( $n = 3$ ), type I diabetes ( $n = 1$ ), or both ( $n = 1$ ). Two of these patients with reported comorbidities were hospitalized and required supplemental oxygen but not invasive ventilation. (Parrotta et al., 2020)

The other study from Italy on 26 pediatric-onset MS patients on Natalizumab did not find a higher risk of SARS-Cov-2 infection in these

patients. (Margoni and Gallo, 2020)

Many early studies and guidelines categorized MS DMTs into three groups according to systemic infection risk: **No risk group**: interferon beta and GA, **low-risk group**: Teriflunomide, DMF, Natalizumab, and other medications including Mycophenolate Mofetil, Cyclophosphamide, and Methotrexate, **intermediate to high-risk group**: Fingolimod, Anti-CD20 monoclonal antibodies (Ocrelizumab and Rituximab), Cladribine, and Alemtuzumab. Louapre et al. (2020a) In this review, we found that most of the MS patients with COVID-19 on DMTs reported in the literature were on low-risk or intermediate to high-risk DMTs. (Fig. 3)

With respect to mortality rates, we found that 46 MS patients overall were reported as having died due to COVID-19 complications. Clinical data of 28 of these MS patients was available. The mean age was 60.0 (Range: 42–84); 16 patients were male. In 24 patients, the type of MS was reported. (RRMS:5, SPMS:17, PPMS:2) .

Most of the patients in this group had high EDSS and multiple underlying comorbidities. (Table 1) Overall, according to the different reports, we found the mortality rate in MS patients was about 1.8%(the global death-to-case ratio of Covid-19 was reported about 2.1%) (COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2021); however, in the patients on Rituximab (4.0%) and patients without medication (3.6%), the rates were higher. (Fig. 4) The similarity in mortality rate in these two populations(Patients on Rituximab and patients without medication) may be due to independent risk factors, such as age, disability (EDSS), or other underlying co-morbidities. The further possible explanation for this can be the protective effect of other DMTs in the other groups.

In NMOSD patients, we found reports of 37 patients. Of these patients, five died or were admitted to the ICU due to COVID-19 complications, the mean age of these patients was 43.2 years (range:24–68), and 3 were males. Four of these patients were on Rituximab, and most of them had higher EDSS. (Table 2)

### 3.2. Concerns about the effectiveness of the COVID-19 vaccine in MS patients on DMTs

The safety and efficacy of approved vaccines for SARS-CoV-2 in MS patients on treatment with DMTs should be carefully considered. (Ciotti et al., 2020; Baker et al., 2020)

First, live, and attenuated viruses are contraindicated in immunosuppressed patients, and under these circumstances, DNA-RNA vaccines

Prevalence of MS patients with COVID-19 on different DMTs

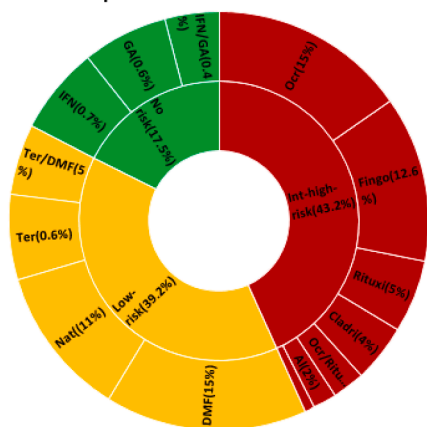


Fig. 3. Prevalence of reported MS patients with COVID-19 on different DMTs, categorized according to the risk of infection. DMF: Dimethyl fumarate, GA: Glatiramer acetate, Ter: Teriflunomide, Nat: Natalizumab, Al: Alemtuzumab, Ocr: Ocrelizumab, Cladri: Cladribine, Rituxi: Rituximab, Fingo: Fingolimod, INF: Interferon beta.

Mortality in MS patients

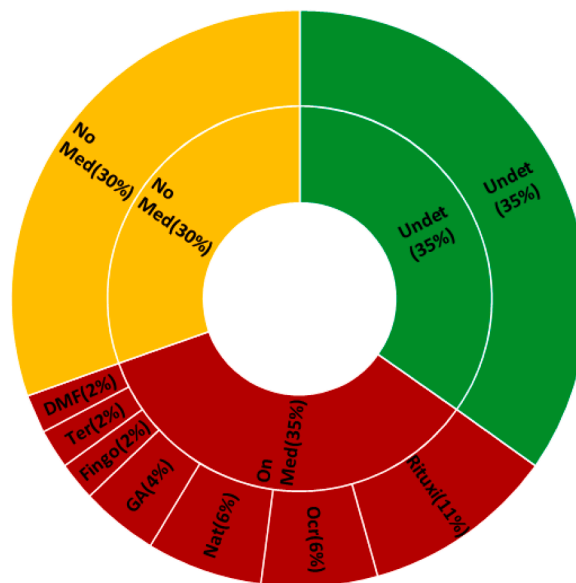


Fig. 4. Prevalence of reported mortality in MS patients with COVID-19 on different DMTs (On Med), without medication (No Med), or undetermined (Undet) groups. (In this chart, we divided the mortality case in each group by the total number of patients who died(46 patients)). DMF: Dimethyl fumarate, GA: Glatiramer acetate, Ter: Teriflunomide, Nat: Natalizumab, Ocr: Ocrelizumab, Rituxi:Rituximab, Fingo:Fingolimod.

will be useful in patients on immunosuppressive agents. (Baker et al., 2020)

Moreover, given some reports about attenuation of the immune response against COVID-19 in patients on DMTs, there are several questions about the efficacy of SARS-CoV-2 vaccine in this group. (Bollo et al., 2020) (Celius, 2020) (Thornton and Harel, 2020) (Iannetta et al., 2020)

In a review article, Ciotti JR et al. (2020) evaluated the immune response to existing vaccines in patients on different DMTs to infer potential results of a vaccine against SARS-CoV-2. They showed that there were adequate immune responses in patients on Interferon-beta. However, a reduced immune response was reported after GA (not statistically significant in some studies), Teriflunomide, Fingolimod, Siponimod, Natalizumab, and anti-CD20 monoclonal antibody treatments. (Ciotti et al., 2020) A recent study by Bar-Or A et al. (2020) provides Class II evidence confirming that the humoral response to non-live vaccines in RRMS patients after Ocrelizumab treatment was attenuated compared with untreated or Interferon-beta treated patients; however, they can still be expected to be protective. (Bar-Or et al., 2020)

A relatively poor vaccine response in patients treated with DMTs, especially in patients treated with anti-CD20 therapies, was predictable. (Ciotti et al., 2020).

For instance, in Rheumatoid Arthritis, it has been shown that following treatment with Rituximab, there is a more markedly blunted seroconversion and titer after vaccination during periods of peripheral B cell depletion and a more significant, but still blunted, vaccine response 6–10 months after infusion. (Baker et al., 2020)

Accordingly, it is possible to create a time-window to vaccinate an individual on the base of differential kinetics of repopulation with pathogenic memory B cells and naive B cells. (Baker et al., 2020)

In anti-CD20 antibodies, the duration of treatment may also have a significant effect. (Ciotti et al., 2020)

At least with Rituximab, it is possible to extend interval dosing or dosing interruption to allow immature B cells to recover (repletion starts to occur within about six months of treatment and is completed within 12 months due to repopulation of the naive cell pool). The required

timing for this to occur for Ocrelizumab is likely to be longer. (Baker et al., 2020) In this case, it seems that there is marked variability in repopulation kinetics between individuals, and the intensity of B cell depletion and repopulation speed relates to the body mass index of the patients. Therefore, dose-adjustment for weight may have some benefit. (Baker et al., 2020) Ultimately, in the case of approved SARS-CoV-2 vaccine, it may be reasonable to consider a treatment interruption or delay to create a window for effective vaccination.

In the other DMTs, such as Cladribine, the medication is rapidly eliminated, allowing CD19 naive B cells to recover within a median of 30 weeks. (Baker et al., 2020) Alemtuzumab markedly depletes memory B cells, but naive B cells rapidly repopulate, and vaccine-related antibody responses can be induced six months after infusion. (Baker et al., 2020)

Besides, serological confirmation of a sufficient response to vaccination may be required in DMT patients after vaccination.

Hopefully, further studies will emerge to help guide treatment strategies to optimize success with vaccination protocols while minimizing treatment interruption risks.

### 3.3. Psychological and neuropsychiatric impact on patients on DMTs during the pandemic

Many studies have assessed the psychological and neuropsychiatric impact of the pandemic on MS patients. (Zhang et al., 2020) Sleep deprivation and a higher rate of depression and anxiety were seen in association with concerns for possible risk of infection, worsening of the underlying diseases, social isolation, difficulties in drug availability, access to health centers, and worries about the economic downturn (Naser Moghadasi, 2020; Salama et al., 2020; Seery et al., 2020; Demir et al., 2020; Rezaeimanesh et al., 2020; Tomczak and Han, 2020; Stojanov et al., 2020). These elements can influence a patient's attitude about continuing their DMTs during the pandemic.

Different studies showed that concerns about infection risk were more significant among patients on B-cell depleting therapies. (Seery et al., 2020) Nonetheless, the fear of MS-relapse or worsening MS symptoms motivated most MS patients to continue their DMT despite the pandemic. (Salama et al., 2020; Seery et al., 2020) In some studies, it was even reported that patients were more anxious about the effects of SARS-CoV-2 on their underlying disease rather than the infection itself. (Rezaeimanesh et al., 2020) One study reported the worsening of neurological symptoms due to pandemic-related stress among NMOSD patients. (Tomczak and Han, 2020)

However, a survey carried out among participants of a randomized clinical trial on rehabilitation in progressive MS patients did not confirm significant changes in neuropsychological assessments during the pandemic. (Chiaravalloti et al., 2020) A multi-center study from North America and Europe demonstrated that despite most participants reporting some impact of the virus on their psychological well-being during the pandemic, little changed regarding symptoms of depression and anxiety, and overall quality of life on standardized measures remained mostly unchanged. (Stojanov et al., 2020) Another study from Italy showed that the Beck Depression Inventory and State-Trait Anxiety Inventory scores did not change during pandemic among MS patients. (Capuano et al., 2020)

Despite these encouraging findings, the pandemic's long-term psychological consequences still need to be fully elucidated. Therefore, it continues to appear appropriate to monitor high-risk MS patients, especially those with pre-existing psychiatric disturbances, through the use of anxiety and depression scales and considering therapeutic options such as online support, home exercise programs, and also anti-anxiety and anti-depression medications when needed. (Haji Akhouni et al., 2020)

## 4. Conclusion

In the setting of COVID-19, some early studies have reported a rate of

hospitalization that was higher among MS patients than the general population (Sahraian et al., 2020b), and that MS patients on B-cell-depleting therapy had an increased risk of SARS-CoV-2 infection (Safavi et al., 2020), or a worse clinical course (Sormani et al., 2020), however, other studies could not confirm these observations. (Evangelou et al., 2020) (Loonstra et al., 2020). Furthermore, it appears that most MS patients with COVID-19 do not require hospitalization despite being on DMTs (Parrotta et al., 2020).

Moreover, most current data do not support an increased risk of worse outcomes related to DMTs or even low lymphocyte count (Loonstra et al., 2020), reinforcing the recommendation of not stopping MS treatment despite pandemic risks. (Louapre et al., 2020a; Safavi et al., 2020; Sahraian et al., 2020b; Crescenzo et al., 2020)

We found the risk of mortality of COVID-19 in MS patients overall similar to what was seen in the non-MS population. (Sharifian-Dorche et al., 2020) However, we did see relatively higher mortality among patients on anti-CD20 therapies or patients without medication. Most of the MS patients who died from COVID-19 complications appeared to have had multiple underlying comorbidities and higher EDSS scores.

Different studies showed that other variables such as age, EDSS, cardiac comorbidity, and obesity were independent risk factors for severe COVID-19 and death in MS and NMOSD patients. (Louapre et al., 2020a; Parrotta et al., 2020; Crescenzo et al., 2020)

The overall COVID-19 outcome was favorable in patients with MS and NMOSD receiving DMTs. However, it is still highly recommended that all MS patients undertake personal protective measures to reduce the risk of SARS-CoV-2 infection, particularly when immunocompromised.

Regarding approved COVID-19 vaccines, for patients on DMTs such as Teriflunomide, Fingolimod, Siponimod, and anti-CD20 monoclonal antibodies, attenuation of the post-vaccine immune response is possible.

Finally, among patients with known neuropsychiatric symptoms, careful follow-up of the patients is essential, regardless of the DMTs they are taking.

In conclusion, neurologists should be aware of the potential risks of morbidity and even mortality with COVID-19 in MS and NMOSD patients. Each patient has an individual risk profile, including their underlying comorbidities, disability level, disease activity, age, and therapy. These factors need to be carefully weighed and considered before deciding if any change in therapy is warranted, and every plan should be individualized to that patient's circumstances.

## 5. Limitations

A limitation of this manuscript is that it is likely weighted towards the experiences from certain regions and academic centres that had a large number of cases in the first wave, and were able to publish their experience earlier on, thus, leading to inclusion in this review. Moreover, the articles used in preparation of this review represent raw numbers of COVID-19 cases occurring in patients on specific DMTs, but unfortunately, we do not know the denominator, or overall number of patients on those specific DMTs. Therefore, we cannot deduce what proportions of patients on those individual DMTs actually developed COVID-19 complications to get a more precise risk estimate.

In this review, we tried to gather and summarize the results of all the studies reporting COVID-19 in MS and NMOSD patients since the beginning of the pandemic. We considered both confirmed and suspected patients in this study; accordingly, some suspected patients may have other diagnoses rather than COVID-19. The type of DMT was not reported in some studies, and we reported this group as undetermined. Clinical characteristics were not available for all patients.

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## Declaration of Competing Interest

None.

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