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REVIEW ARTICLE

Drugs Used in the Treatment of Multiple Sclerosis During COVID-19 Pandemic: A Critical Viewpoint

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Abstract: Since COVID-19 has emerged as a word public health problem, attention has been focused on how immune-suppressive drugs used for the treatment of autoimmune disorders influence the risk for SARS-CoV-2 infection and the development of acute respiratory distress syndrome (ARDS). Here, we discuss the disease-modifying agents approved for the treatment of multiple sclerosis (MS) within this context. Interferon (IFN)-β1a and -1b, which display antiviral activity, could be protective in the early stage of COVID-19 infection, although SARS-CoV-2 may have developed resistance to IFNs. However, in the hyperinflammation stage, IFNs may become detrimental by facilitating macrophage invasion in the lung and other organs. Glatiramer acetate and its analogues should not interfere with the development of COVID-19 and may be considered safe. Teriflunomide, a first-line oral drug used in the treatment of relapsing-remitting MS (RRMS), may display antiviral activity by depleting cellular nucleotides necessary for viral replication. The other first-line drug, dimethyl fumarate, may afford protection against SARS-CoV-2 by activating the Nrf-2 pathway and reinforcing the cellular defenses against oxidative stress. Concern has been raised regarding the use of second-line treatments for MS during the COVID-19 pandemic. However, this concern is not always justified. For example, fingolimod might be highly beneficial during the hyperinflammatory stage of COVID-19 for a number of mechanisms, including the reinforcement of the endothelial barrier. Caution is suggested for the use of natalizumab, cladribine, alemtuzumab, and ocrelizumab, although MS disease recurrence after discontinuation of these drugs may overcome a potential risk for COVID-19 infection.

Keywords: Disease-modifying therapy, multiple sclerosis, COVID-19 pandemic, Sars-Cov-2, immunomodulation, neuroprotection, cytokine storm, risk-benefit ratio.

1. INTRODUCTION

In late 2019, a novel Coronavirus was shown to cause a cluster of unusual viral pneumonia in Hubei province (China). Being the third highly pathogenic human-infecting Coronavirus after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS- CoV), this double strand-RNA β-coronavirus was named "SARS-CoV-2". Despite its high genomic homology with SARS-CoV (79%), the novel agent has high transmissibility that empowered an accelerated worldwide spread; SARS-CoV-2 associated Coronavirus Disease (COVID-19) was officially declared a pandemic in March 2020 and has infected, to date, more than 50 million people [1, 2].

To infect human cells, SARS-CoV-2 Spike (S) protein first cleaves human proteases (transmembrane protease serine protease 2, cathepsin L and furin) and then binds the angiotensin-converting enzyme 2 (ACE2) to allow the entry into the host's cell [3]. ACE2 is widely expressed across the respiratory tract, including nasal epithelial cells, as well as in endothelium, enterocytes, renal tubules, heart and corneal cells [4]; more recently, neuropilin-1 (NRP1) was discovered to enhance SARS-CoV-2 infectivity, explaining the clinical involvement of organs where ACE2 expression is low, such as olfactory neuronal cells [5, 6].

SARS-CoV-2 stands out from the other highly virulent HCoVs and other respiratory viruses; even if it is primarily a respiratory disease, the spectrum of COVID-19 is extremely

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wide in terms of both clinical manifestations and severity. Also, in its pathogenesis, the host factors seem to weigh more than viral properties in determining the clinical outcomes (though the role of viral load at the time of infection remains to be determined).

Three levels of severity (asymptomatic-mild, moderate, severe) can be distinguished and somehow these correspond to three stages of pathogenesis [7]. After the incubation period, most of the infected patients remain asymptomatic or manifest a flu-like syndrome with fever, loss of smell and taste, myalgia, headache or backache. This is the moment in which innate and adaptive immunity are protective. If the first antiviral immune response does not allow a rapid virus clearance, the infection continues toward the second stage: SARS-CoV-2 reaches the lungs and causes severe interstitial pneumonia with possible hypoxia. About 20% of patients enter the third stage and require intensive management: an exaggerated, auto-aggressive immune response with cytokine overproduction may cause acute respiratory distress syndrome (ARDS), hypercoagulability with multiorgan failure, and peripheral lymphopenia [8-10]. This is a life-threatening critical stage with a mortality rate of 40-50%. Older age, immunosuppression, pre-existing diseases (cardiovascular, neurological, or metabolic disorders, cancer, *etc*.) account for the majority of deaths [11].

From the beginning of the pandemic, concerns were raised regarding the immunomodulatory and immunosuppressive therapies because these treatments may enhance the risk of infection and ARDS and impact the efficacy of future vaccinations [12]. Nowadays, a wide range of DMTs are available to restrain the dysimmune attack against CNS oligodendrocytes that causes disability accumulation in MS. The mechanisms of action of these drugs include immunomodulation and, in some cases, immunosuppression, which increase the risk of infection [12] and may impact vaccination strategies.

Additionally, given that the vast majority of people with MS (pwMS) receive DMTs, it is difficult to specifically assess the possibility that MS dysimmune state itself may (*i*) predispose to SARS-CoV-2 infection and (*ii)* enhance the risk of a severe COVID-19 course [13-15]. In a multicentre retrospective observational cohort study recruiting 347 patients, the risk of severe COVID-19 was greater in untreated MS patients than in patients receiving disease-modifying therapies (DMTs), and the Expanded Disease Scale Score (EDSS) was identified as an independent risk for COVID-19 severity [15]. An increased incidence of COVID-19 infection was found in a cohort of Spanish MS patients, although the outcome of COVID-19 infection was good in these patients [16]. In contrast, no increased risk of COVID-19 infection was observed in patients with MS or neuromyelitis optica spectrum disorders (NMOSD), irrespective of whether these patients received DMTs, in a survey conducted through the Chinese Medical Network for Neuroinflammation [14]. Similarly, 1115 patients affected by neuroinflammatory disorders recruited in the United States showed a risk of suspected COVID-19 similar to the reference population [17].

Since the current COVID-19 pandemic started, both clinicians and pwMS receiving DMTs have faced the problem of balancing a possible enhanced susceptibility to SARS-CoV-2 and the potential damages of an uncontrolled disease. To help with decision-making, national and international advisory boards have developed practical recommendations on therapeutic strategies. So far, several studies have confirmed for MS-DMTs an acceptable level of safety with respect to SARS-CoV-2 infection [15, 18-21]. In addition, although patients with MS are concerned about becoming infected by SARS-CoV-2, they are compliant with continuing DMTs [22].

However, each MS-DMT has distinct biological activities impacting specific components of the immune system; the final, predictable effects on the host's response against the novel Coronavirus are still being evaluated in the clinical and experimental settings, both in people with and without MS. In fact, the ascertainment of an auto aggressive immune dysregulation underlying severe COVID-19 has prompted the possibility that some MS-DMTs may be quickly repurposed to help manage these patients, as happens for other autoimmune diseases' drugs. A second issue should be considered; MS drugs that induce immune tolerance might be protective in the third stage when a dysregulated cytokine storm and systemic hyperinflammation occur.

CNS involvement in SARS-CoV-2 infection should also be considered. SARS-CoV-2 is potentially neurotropic and 25% of patients show symptoms related to CNS dysfunction. Neurological consequences may depend on either pulmonary or systemic disease or on virus invasion into the CNS and binding to ACE2 expressed by astrocytes and neurons [23]. For example, one of the routes of SARS-CoV-2 entry in the CNS is the neural-mucosal interface in olfactory mucosa followed by retrograde transport of the virus from sensory nerve endings to the olfactory bulb [24].

Whether or not MS or other neuroinflammatory disorders may facilitate the access of SARS-CoV-2 in the CNS and this may exacerbate MS pathology is unclear at present. In a single case of a COVID-19 affected patient with progressive MS, there was no evidence for MS exacerbation, and no SARS-CoV-2 RNA was found in brain MS lesions [25].

However, those MS drugs that cross the blood-brain barrier (BBB) and also act in the CNS might have a direct impact on neuro-COVID.

We will therefore summarize the present evidence regarding MS-DMTs during SARS-CoV-2 pandemic, analyzing their effects on innate and adaptive immunity and discussing their repositioning potential. Also, we will describe neuroprotective and pro-cognitive effects of some of these molecules, which may provide added benefits to COVID-19 patients, given the high frequency of neurological involvement [26]. We will focus exclusively on drugs that are specifically indicated for the treatment of MS.

2. FIRST-LINE DRUGS

2.1. Interferons

Type-I interferons (IFNs-I) are a family of cytokines, mainly represented by IFN-α and IFN-β, which play a key role in orchestrating the anti-viral response. They are primar-

ily produced by plasmacytoid dendritic cells (pDCs), which are cellular elements of the innate immune system, as a result of the interaction between pathogen-associated molecular patterns (PAMPS) with pattern recognition receptors (PRRs) expressed by pDCs. IFNs-I exert their effects by interacting with membrane receptors, activating the JAK/STAT pathway, and regulating the expression of interferon-stimulated genes (ISGs) in target cells [27]. IFNs-I are used in the treatment of viral infections and MS. Subcutaneous and intramuscular formulations of IFN-β1a and subcutaneous formulations of IFN-β1b are used in the treatment of MS. Specific ISGs involved in the anti-viral activity of IFNs are downregulated in B cells of MS patients, and this contributes to beneficial effects of IFNs in MS (reviewed by Severa *et al*., 2020) [28].

Upon the arrival of the SARS-CoV-2 pandemic, IFN therapy is under the spotlight. So far, a number of clinical trials have been designed to test the efficacy of numerous IFN-α and IFN-β formulations alone or in combination with other antiviral drugs in the treatment of COVID-19 (*e.g*., ClinicalTrials.gov Identifier: NCT04293887; NCT04320238; NCT04254874; NCT04315948). First results have been released and seem encouraging, as recently reviewed by Schreiber (2020) [29]. However, the timing of IFN-I administration still remains a critical question. Despite *in vitro* evidence for anti-viral activity of IFN-β1a against already-established SARS-CoV-2 infections in cultured cells [30-32], it has been suggested that IFN-I therapy would be effective when administered in the very early phases of host infection and, in contrast, might be detrimental if administered at later stages [33]. This hypothesis is strengthened by previous data obtained with the related betacoronaviruses, SARS-CoV and MERS-CoV, and partly supported by emerging clinical data on IFN-I kinetics of response in SARS-CoV-2-infected patients. In a similar way to SARS-CoV and MERS-CoV infection [34], in SARS-CoV-2-infected subjects, an early peripheral IFN-I response is thought to be predictive of a mild to moderate disease outcome, while a delayed peripheral increase of IFNs-I is considered a hallmark of severe evolution [35]. Accordingly, blood analysis has shown that low levels of IFNs-I in peripheral immune cells correlate with disease severity [36, 37]. In addition, a differential IFN-I response between lung resident and peripheral immune cells may occur. This could explain the low peripheral response in patients developing heavy respiratory symptoms. Neutralizing autoantibodies against IFNs-I were detected in patients with life-threatening COVID-19 pneumonia, while they were absent in mild-SARS-CoV-2 infected or in asymptomatic patients. Patients with anti-IFN-I antibodies had low to undetectable IFN-α levels in blood plasma during the acute phase of lung disease [38]. Zhang *et al*. (2020) found an association between rare genetic variants of type-3 toll-like receptors (TLR3) and IFN-I signaling pathways and life-threatening COVID-19 pneumonia. Patients with these variants, which are predicted to induce loss of function, showed low serum levels of IFN-I [39]. This further supports the hypothesis that a defective IFN-I response may lead to severe COVID-19 [40]. However, studies on post-mortem lungs of severely diseased subjects have provided contrasting results with evidence of low [41] or increased IFN-I expression [42]. On the other hand, analysis of bronco-alveolar lavage fluid (BALF) from severely diseased subjects showed the presence of aberrant T cell and macrophage responses and increased ISGs, which account for an abnormal cytokine and chemokine release [43, 44]. Taken together, these data support the hypothesis that the effects of IFN-I administration are detrimental in the late stages of COVID-19 disease. Another concern related to IFN-I therapy for COVID-19 patients is that the gene encoding ACE2 is an ISG [45, 46]. However, recent findings demonstrate that a newly identified truncated form of ACE2, called deltaACE2 (dACE2), and not ACE2, is an ISG. Because dACE2 does not bind to SARS-CoV-2 spike protein [47], treatment with IFN-β in MS should not cause an amplification of viral spread. These considerations lay the ground for a discussion on the safety of IFN-β treatment in pwMS during COVID-19 outbreak and, in particular, on the efficacy of IFN-β in SARS-CoV-2-infected MS patients. In recent years, the use of IFN-β for pwMS has been gradually reduced due to the introduction of more effective DMTs. However, IFN-β is still the first-line drug in MS. Since the beginning of the COVID-19 pandemic, international guidelines have suggested to start or continue IFN-β treatment in pwMS [48, 49]. Subsequent studies on MS patients affected by SARS-CoV-2 have suggested that, in general, DMTs should not increase the risk to develop a severe COVID-19 infection, and MS patients under IFN-β therapy are in the "no-risk" group [15]. In Italy, the first European country where the pandemic spread at the beginning of 2020, a task force of neurologists was soon set up to monitor MS patients [19, 21]. Studies are ongoing and data will be released in the near future. Based on the emerging complexity of the SARS-CoV-2-induced IFN-I response, several scenarios might occur in the case of MS patients infected by SARS-CoV-2. It is likely that MS patients who at the moment of SARS-CoV-2 infection are under treatment with IFN-β are protected against SARS-CoV-2. The ongoing IFN-I activity could have a preconditioning role, thus counteracting viral replication and diffusion. Accordingly: (i) there is evidence for low risk of infections in MS patients treated with IFN-β [14]; (ii) *in vitro* data demonstrate an anti-SARS-CoV-2 efficacy of IFN-β pretreatment in cultured cells [31, 32]; and, (iii) an early, rather than late, IFN-I administration during SARS-CoV-2 infection might be beneficial [33]. Hence, the development of a rapid, severe COVID-19 infection in pwMS under IFN-β treatment is expected to be a rare event. A different scenario may occur when pwMS contract SARS-CoV-2 when they are newly diagnosed or treated with other DMTs, *i.e*., when the supposed positive preconditioning effect of IFN-β is absent. In these cases, neurologists could evaluate a switch to IFN-β, considering the potential beneficial effects of IFN-β against the virus and the early therapeutic window to successfully treat SARS-CoV-2 infection with IFN-β. Nevertheless, in these subjects, some critical features of SARS-CoV-2 biology could complicate the picture and should be considered. It has been hypothesized that SARS-CoV-2, like other betacoronaviruses, has evolved developing the ability to escape IFN-mediated immune response, which could also explain the dysregulated IFN expression pattern observed in severely affected subjects [33]. This aspect of SARS-CoV-2 biology has just started to be unraveled. It has been shown that specific SARS-CoV-2 proteins, including ORF6, which

were already studied in the context of SARS-CoV infection, inhibit IFN-β promoter activation, while other viral proteins induce IFN-β responses [32]. In addition, a recent study has shown that IFN-I evasion by SARS-CoV-2 involves multiple molecular mechanisms, which include ORF6 [50]. Moreover, SARS-CoV-2-related nonstructural protein 6 (nsp6) and 13 (nsp13) inhibit IFN-I signaling more efficiently than nonstructural proteins of SARS-CoV and MERS-CoV [49]. In contrast to previous findings, the same study shows that SARS-CoV-2 is resistant to IFN-I treatment [50]. Although this point needs further clarifications, it is reasonable to hypothesize that these mechanisms of IFN-I escape by SARS-CoV-2 could be potentiated in a context of low or incomplete IFN-I responses, such as those elicited by other DMTs, which show other immunomodulatory activities and lower anti-viral action. Thus, in these patients, a replacement or the initiation of IFN-β therapy should be carefully evaluated according to general patient conditions, MS disease stage and course, and SARS-CoV-2 infection-related symptoms. Another option for pwMS would be to use IFN-βas an add-on treatment.

2.2. Glatiramer Acetate

Glatiramer acetate (GA) is a non-biological complex drug used as first-line subcutaneous therapy for relapsing-remitting MS (RRMS). GA and FOGAs, follow-on GA products, are composed by a heterogenous mixture of peptides formed by 4 amino acids (alanine, lysine, glutamate, tyrosine), which are enriched in epitopes of the myelin basic protein. These peptides and their cleavage products are processed by antigen-presenting cells, and this drives the immune response towards Th2 and Treg at the expense of Th1 and Th17 [51]. GA also interacts with leukocyte Ig-like receptors B (LRBs), expressed by myeloid cells, and, therefore, regulates maturation of myeloid lineage and B cells [52].

GA may act in the CNS by enhancing the production of brain-derived neurotrophic factor (BDNF) in astrocytes and microglia and the production of anti-inflammatory cytokines [53, 54]. Preclinical studies showed that GA prolonged the lifespan of mice modeling Huntington's disease [55], suggesting a direct neuroprotective action of GA in the CNS. Neuroprotection might be mediated by BDNF acting through TrkB [56, 57]. Of note, GA is one of the safest disease-modifying drugs used in MS and lacks teratogenic effects in pregnancy. Hence, it can be concluded that GA and FOGAs could be safely administered to MS patients during the SARS-CoV-2 pandemic and could be maintained during SARS-CoV-2 infection, even though immune tolerance induced by these drugs could delay viral clearance. GA and FOGAs should have a limited impact on SARS-CoV-2 vaccination, although this remains to be determined [58].

2.3. Teriflunomide

Teriflunomide (HMR-1726) is a first-line oral agent for the treatment of RRMS with immunosuppressive and anti-inflammatory activities. It is generally well-tolerated, safe and, in contrast to other DMTs, has low risk of both lymphopenia and infections [59], despite some concerns about the possible reactivation of tuberculosis [60]. Teriflunomide is the active metabolite of the anti-rheumatic drug leflunomide, acting as a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH). Such inhibition results in the blockade of *de novo* pyrimidine synthesis in T and B lymphocytes with the consequently reduced proliferation of target cells. This effect is specific for highly proliferative T and B cells because resting T cells do not use DHODH to synthetize pyrimidines but recycle them from degraded DNA and RNA [61]. Thus, teriflunomide is not expected to interfere with mechanisms of innate immunity.

Several DHODH-independent mechanisms of action have been proposed for teriflunomide, such as the reduced release of IL6, IL8 and MCP-1 from LPS-activated PBMCs [62] and increased release of IL-10 from *in vitro* activated microglia [63]. The latter effect suggests a potential neuroprotective action of teriflunomide, knowing that the drug crosses the blood-brain barrier (BBB) [64]. In addition, former studies with leflunomide in animal models of MS suggested that teriflunomide promotes polarization of T cells from a Th1 to a Th2 phenotype [65, 66]. Moreover, being structurally similar to kynurenines, teriflunomide was initially predicted to activate the aryl hydrocarbon receptor (AHR), which is involved in mechanisms of immune suppression and tolerance, but this was demonstrated in *in vitro* experiments only for its prodrug leflunomide [67]. In contrast, an *in vivo* study showed that teriflunomide activates AHR, which, however, was demonstrated to account for teriflunomide metabolism and not for immunomodulatory effects [68].

Relevant to our discussion regarding the use of teriflunomide in pwMS during the COVD-19 pandemic, some data demonstrate a broad anti-viral action of teriflunomide, which may explain the preserved immune response to influenza virus vaccination [69] and a reduced risk of infections in pwMS [59]. In addition to some studies showing inhibition of BK virus and herpes simplex virus type 1 [70, 71], teriflunomide was found effective against the Epstein-Barr virus (EBV), which is increasingly recognized to play a role in the pathogenesis of MS [72]. Teriflunomide was reported to inhibit the proliferation of EBV-transformed cells and the growth of EBV-induced lymphomas in *in vivo* models [72]. Of note, *in vitro* experiments showed that teriflunomide was able to inhibit the lytic phase of EBV replication in B cells, thus preventing the early phases of lytic reactivation of the virus [73]. Gilli and colleagues (2017) showed that teriflunomide attenuated the death rate of BKH cells infected with Theiler's virus. Such antiviral property was further demonstrated in Theiler's encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) model, which serves as a model of both murine infection and progressive MS. Viral load in necropsy spinal cords of teriflunomide-treated mice was almost undetectable compared to vehicle-treated controls, suggesting an efficient viral clearance [74]. Finally, it has been shown that a group of selective DHODH inhibitors are effective against infection by several RNA viruses, namely influenza A virus, Zika virus, Ebola virus, and, more importantly, SARS-CoV-2 [75]. Noteworthy, teriflunomide is among these identified compounds. Similar to the other identified DHODH inhibitors, teriflunomide was shown to efficiently reduce viral copies in the supernatant of SARS-

CoV-2-infected Vero E6 cells, even at low multiplicity of infection (MOI). Moreover, the study shows that DHODH inhibitors are able to decrease peripheral cytokine levels in the late phase of the murine model of influenza A virus infection. Even if teriflunomide is not tested in these *in vivo* experiments, these data raise the possibility that teriflunomide and other DHODH inhibitors could be effective to restrain the cytokine storm phase of COVID-19. Despite the lack of animal testing models of COVID-19, which at the moment are not yet available, these results are of great importance for two main reasons: (i) they encourage the experimental use of teriflunomide in patients affected by COVID-19 and, (ii) they suggest that teriflunomide may protect pwMS against the development of severe COVID-19.

Therefore, the above-described anti-viral activity of teriflunomide is supportive of its safety and efficacy in pwMS against SARS-CoV-2 infection. According to initial guidelines and recent studies [14, 48], pwMS treated with teriflunomide are in the "low-risk" category to develop severe COVID-19, and several cases of teriflunomide-treated patients who developed a mild COVID-19 have been reported to date. The case of an MS patient under treatment with teriflunomide and high doses of corticosteroids who developed a mild COVID-19 has been described [76]. Moreover, two different case series have provided evidence for a self-limiting SARS-CoV-2 infection in MS patients treated with teriflunomide, supporting the idea that the drug should not be discontinued [77, 78]. More recently, it has been described a case of a teriflunomide-treated MS patient, who developed a mild COVID-19 pneumonia and who showed no major changes in the percentages of immune activation before and after infection [79]. Should this be confirmed in further studies, one can conclude that teriflunomide does not impair protective immunity and may exert efficient anti-viral effects against SARS-CoV-2.

2.4. Dimethyl Fumarate

Dimethyl fumarate (DMF) is a first-line oral drug in RRMS, with greater efficacy in terms of annualized relapse rate, with respect to the other first-line drugs. DMF is converted into the active metabolite, monomethyl fumarate (MMF). Plasma MMF levels are highly variable, and the terminal half-life of MMF is about 12 hours. The final metabolite, fumarate, is processed through the citric acid cycle to generate carbon dioxide, with no involvement of the cytochrome system [80-82].

The mechanism of action of DMF in MS is complex. Fumarate derived from DMF is substrate for cysteine "succination" of glycolytic enzymes, such as glyceraldehyde 3-phosphate dehydrogenase, in immune cells [83]. DMF activates the antioxidant nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2) pathway by causing an initial depletion of the intracellular pool of reduced glutathione (GSH). This releases Nrf-2 from binding to Keap-1, which commits Nrf-2 to degradation *via* the ubiquitin-proteasomal pathway [84]. Released Nrf-2 translocates into the cell nucleus and drives the expression of genes that are protective against oxidative damage. Through this mechanism, DMF causes the expansion of $FoxP3^+$ T_{reg} cells, promoting immune tolerance [85]. Interestingly, the Nrf-2 pathway was found to be suppressed in lung biopsies from SARS-CoV-2 infected patients, and drugs that activate the Nrf-2 pathway, such as 4-octyl-itaconate or DMF, were found to potently inhibit replication of SARS-CoV-2 and other pathogenic viruses through IFN-I-independent mechanisms [86]. DMF and MMF also activate type-2 hydroxycarboxylic acid receptors (HCAR2), and mice with genetic deletion of HCAR2 are resistant to DMF-induced protection against experimental autoimmune encephalomyelitis [87]. DMF might be safe and even beneficial in SARS-CoV-2 infected patients with mild lymphopenia [58]. Caution is recommended for patients with severe lymphopenia because of the blood lymphocyte lowering effect of DMF [57]. Interestingly, DMF has been shown to improve pulmonary fibrosis in mouse models of pulmonary arterial hypertension [88]. Thus, DMF might lower the risk of pulmonary fibrosis in patients recovering from severe SARS-CoV-2 infection.

DMF may also act in the CNS by restraining inflammatory activation of glial cells, reducing inducible nitric oxide synthase expression, and enhancing antioxidant defenses in response to an initial GSH depletion [89]. In addition, HCAR2 activation by DMF/MMF may drive microglial cells toward an anti-inflammatory phenotype [87] and restrain glutamate release from excitatory nerve endings [90]. In principle, these mechanisms might confer protection against SARS-CoV-2-induced CNS inflammation.

3. SECOND-LINE DRUGS

3.1. Natalizumab

Natalizumab (NTZ) is a recombinant, humanized monoclonal antibody (IgG4k) directed against the α4 (CD49d) subunit of membrane integrins. Integrin α4β1 (Very Late Antigen-4 or VLA4) is expressed on the surface of T, B lymphocytes, NK cells, monocytes, eosinophils and neutrophils. NTZ inhibits cellular transit in the CNS and intestine by preventing the binding of the integrins α4β1 and α4β7 with the respective endothelial receptors, vascular-cell adhesion molecule 1 (VCAM-1) and mucosal addressin-cell adhesion molecule 1 (MAdCAM-1). The α4β1 and VCAM-1 binding is also involved in the homing and persistence of hematopoietic stem cells and plasma cells in the bone marrow, causing an increase in circulating CD34+ hematopoietic stem cells. NTZ promotes, already after the first 4 weeks of treatment, a significant increase in blood counts of $CD4^+$ and $CD8^+$ T lymphocytes, $CD56^+$ NK cells and, more significantly, in immature circulating $CD19^+CD10^+$ B lymphocytes. Moreover, NTZ inhibits the retention of memory B-lymphocytes and marginal zone lymphocytes in the spleen [91-93]. In relation to infections, although some cases of herpetic infections have been reported, the main risk of treatment with NTZ is progressive multifocal leukoencephalopathy (PML), with JCV seropositivity, progressive drug exposure and previous therapy with immune suppressant drugs being main alerting factors [94-96].

It is likely safe to continue ongoing therapy with NTZ, and it may also be administered in MS patients in a setting with minimal risks of SARS-CoV-2 infection when the individual's risk of PML is acceptable. VLA4 is expressed in the

virally inflamed lung, and, thus, NTZ may limit monocyte and T cell penetration in the lung parenchyma. On one side, control of immune cell migration could be protective in the 3rd stage of SARS-CoV-2 infection, characterized by hyper-inflammation and respiratory failure, but, on the other side, this may limit viral clearance from the respiratory system, particularly in the early phases of infection. NTZ inhibits trans-endothelial migration of immune cells across the BBB, but the drug does not act directly on the CNS and probably does not exert immune defense against SARS-CoV-2. NTZ reduces lymphocyte trafficking also in the gut, and could potentiate viral shedding, considering that SARS-CoV-2 can infect the gastrointestinal tract [97, 58].

There are few specific descriptions in the literature regarding COVID-19 infection in people treated with NTZ. Rimmer and collaborators reported a fatal case of SARS-CoV-2 infection in a 51-year-old woman with adverse comorbidities, like obesity, hypertension and significant disability, while on NTZ therapy. Ten days after the dosing, she had fever and cough with a confirmed positive SARS-CoV-2 RT-PCR; a severe respiratory distress syndrome occurred in a context of a cytokine storm followed by multi-organ failure, even if the authors do not consider NTZ to be the cause of the deadly course [98].

The group of Parrotta analyzed a cohort of 72 patients with COVID-19 and MS and they reported four patients on natalizumab treatment, that is 5.4% of the sample, including the death of a 60-year-old African American male with severe comorbidities and a pulmonary embolism concomitant with deep vein thrombosis. COVID-19 in the other three cases did not require hospitalization considering that risk factors for hospitalization are age, the progressive subtype of MS, and the level of disability without a specific risk signal related to the MS DMTs [20]. Favorable outcomes were also reported in the Danish national study where, among 86 patients with MS and COVD-19 compatible symptoms, three cases treated with NTZ did not require hospitalization [99]. The severity of SARS-CoV-2 infection in 232 MS patients was analyzed in Italy, and 10.8% of patients were under treatment with NTZ. Hospitalization was required only in one of these cases, and the final outcome is actually unknown [19]. Finally, Aguirre *et al*. and Boriello *et al*. reported the cases of two mildly disabled male patients, with EDSS of 1.5 and aged 29 and 18, respectively, who developed COVID-19 shortly after NTZ dosing, both with positive nasopharyngeal swab and antibody production against SARS-Cov-2 in the first case. These cases had a favorable course, without cytokine storm, within ten days from the onset of symptoms, and NTZ was not interrupted (extended interval dosing) [100, 101].

The extensive French experience, where 16.4% of the 347 cases in the COVID registry were under NTZ, confirms a favorable evolution of these patients [15].

In the light of current data, NTZ therapy does not appear to add a specific risk profile in the context of SARS-CoV-2 infection since the drug is not a cell-depleting agent. There is no evidence that the drug should be discontinued, exposing the patient to the risk of MS aggravation. Nevertheless, caution is required considering the possibility that the drug could limit viral clearance.

3.2. Sphingosine-1-phosphate Receptor Modulators (Fingolimod and Siponimod)

Fingolimod is a structural analogue of sphingosine and is converted by type-2 sphingosine kinase into the active metabolite, fingolimod phosphate. Fingolimod phosphate acts extracellularly by activating types 1, 3, 4, and 5 sphingosine-1-phosphate receptors ($S1P_{1,3,4,5}Rs$), which are G-protein coupled receptors displaying pleiotropic activities in many cell types, including lymphocytes. Sustained activation of $S1P_1Rs$ causes receptor desensitization and internalization, restraining the egress of CCR7 chemokine receptor-expressing central memory T cells and naïve T cells from secondary lymphoid organs. Of note, internalized $S1P_1Rs$ receptors may signal from the surface of endosomes and trigger the activation of intracellular pathways that are involved in mechanisms of cell proliferation and survival, such as the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K) pathways [102]. Fingolimod can be phosphorylated in the nuclear membrane, and nuclear fingolimod phosphate inhibits histone deacetylase (HDAC), thereby opening chromatin and enhancing gene expression. This and other mechanisms cause increased production of T_{reg} cells, thereby promoting immune tolerance [103]. Finally, unphosphorylated fingolimod is also pharmacologically active and may reinforce the endothelial barrier by activating the c-Abelson (c-Abl) tyrosine kinase (see below). Fingolimod is administered orally at the daily dose of 0.5 mg, has a large volume of distribution, and may also act in the CNS, activating S1PRs present in neurons, astrocytes, oligodendrocytes, and microglia [104, 105].

During the SARS-CoV-2 pandemic, concerns were raised regarding the safe use of fingolimod because of its multifaced impact on the immune system, and, according to the ABN guidance on the use of DMTs in multiple sclerosis, "*fingolimod may be used cautiously at very high rates of SARS-CoV-2 infection, noting that the SmPC advises that there is an increased risk of viral infection"* [48]. These recommendations would have been fully motivated if fingolimod behaved as a classical immune suppressant. In contrast, fingolimod has pleiotropic actions in immune cells and other cell types, including endothelial cells. How fingolimod shapes the risk and affects the various stages of SARS-CoV-2 infection is uncertain, and here we discuss the possibility that the drug may have beneficial effects at least in the "cytokine storm" phase of SARS-CoV-2 infection, in which mechanisms of innate immunity are overactive in the lung and other organs (see below). In addition, interruption of fingolimod treatment may cause a severe rebound of MS activity [106], and this may seriously affect the outcome of SARS-CoV-2 infection.

SARS-CoV-2 interacts with ACE2 on the surface of target cells, and whether or not fingolimod and other MS drugs (with the exception of interferons) regulate ACE2 expression is unknown. ACE2 physiologically converts angiotensin-2 into the vasoprotective $angiotensin_{1\text{-}7}$, and, interestingly, S1P is involved in the pathophysiology of angiotensin-2-induced

hypertension [107]. In addition, $S1P_1Rs$ are upregulated in angiotensin-2-induced heart hypertrophy, and their activation might contribute to cardiac remodeling [108]. The involvement of S1P/S1PRs in cardiovascular responses to angiotensin-2 raises the possibility that fingolimod could affect ACE-2 expression not only in the heart or blood vessels, but also in other organs such as kidneys, gut, and lungs [109,110]. This hypothesis warrants in-depth investigation in both experimental animals and humans.

One aspect of particular relevance is the impact of fingolimod on ARDS, a condition associated with lymphopenia as a result of the sequestration of immune cells into the infected tissues (see Introduction and references therein). Production of pro-inflammatory cytokines (*e.g.*, interleukin-6) and chemokines by lung cells of the innate immune system is the main culprit of ARDS. Cytokine storm may cause hemophagocytic lymph histiocytosis, with a severe condition of pulmonary involvement and progression to multi-organ failure. This is a critical stage characterized by systemic hyper-inflammation, and about 5% of SARS-CoV-2-infected patients require critical care and ventilator support [111]. Fingolimod may restrain ARDS by supporting immune tolerance [112] and limiting the infiltration of autoreactive T lymphocytes in the lung and other organs, as described above. In addition, fingolimod-phosphate is a potent direct activator of protein phosphate 2A, and this reduces IL-6 and IL-8 production in lung epithelial cells [113].

A chiral fingolimod analogue was found to be protective against the H1N1 influenza virus, which in 2009 rapidly infected millions of people and was associated with great mortality. The compound showed greater efficacy than the neuroaminidase inhibitor, oseltamivir, in enhancing the survival of H1N1 infected mice by limiting pulmonary injury caused by immunopathologic damage [114].

Fingolimod-phosphate enhances endothelial barrier function and maintains vascular barrier integrity [115]. Interaction of fingolimod-phosphate with $S1P_1Rs$ may activate the monomeric GTP-binding protein, RAC-1, leading to focal adhesion, rearrangement of adherens junctions, and recruitment of cytoskeletal effectors into the lipid rafts [116]. By analogy with S1P, fingolimod-phosphate might also directly interact with RAC-1, causing dissociation of RAC-1 from the guanosine disphosphate dissociation inhibitor (GDI) of Rho [116]. Fingolimod can also up-regulate the expression of β-catenin and zonula-occludens protein 1 (ZO1), promoting the assembly of adherens junctions [117]. S1P and fingolimod-phosphate can promote both the translocation of vascular endothelial cadherin to the focal contact sites in epithelial cells and assembly of cell junctions, helping to prevent vascular leakage [118] (Fig. **1**). Unphosphorylated fingolimod can also decrease vascular permeability through an $S1P_1R$-independent pathway by increasing the activity of the non-receptor tyrosine kinase, c-Abl [116, 119] (Fig. **1**). Improvement of endothelial barrier could represent a therapeutic strategy to counteract ARDS and related vascular leak, and, therefore, fingolimod may afford protection against SARS-CoV-2-induced acute lung injury. The efficacy of fingolimod in SARS-CoV-2-infected patients is currently under investigation in a clinical trial (https:// clinicaltrials.gov/ct2/show/NCT04280588).

Fingolimod can cross the blood-brain barrier (BBB) and exert a direct neuroprotective activity, restraining excitotoxic neuronal death. There are two major types of N-methyl-D-aspartate (NMDA) receptors: (i) synaptic GluN2A-containing NMDA receptors, which mediate mechanisms of activity-dependent synaptic plasticity and support neuronal survival; (ii) extrasynaptic Glu2B-containing NMDA receptors, which are involved in excitotoxic neuronal death [119]. Fingolimod restrains the activation of GluN2B-containing extrasynaptic NMDA receptors [120] and attenuates NMDA toxicity in cultured neurons [121, 122]. Fingolimod treatment also enhances the production of BDNF [123, 124], which supports neuronal survival and synaptic plasticity. These mechanisms might be valuable in the control of some CNS manifestations of SARS-CoV-2 infection [125].

An important issue is whether fingolimod or other disease-modifying drugs used in the treatment of MS interfere with the efficacy of SARS-CoV-2 immunotherapy. Live-attenuated vaccines are contraindicated during fingolimod treatment, which, for example, should start one month after the second dose of varicella zoster virus vaccination [126]. A randomized trial of influenza vaccination in fingolimod-treated patients showed that most patients mounted immune responses, but response rates were lower than placebo-treated patients [127]. Thus, when a SARS-CoV-2 vaccine becomes available, patients under treatment with fingolimod should carefully check the immune response [58]. Passive immunization (*e.g.*, anti-SARS-CoV-2 monoclonal antibodies) should not be affected by fingolimod treatment.

Siponimod is a selective $S1P_1R$ and $S1P_5R$ agonist approved for the treatment of relapsing-remitting and secondary progressive MS. Activation of $S1P_5R$ present in oligodendrocytes might support remyelination in MS patients [128, 129]. Knowing that immune regulation and reinforcement of the endothelial barrier by fingolimod are largely mediated by $S1P_1Rs$, it is easy to predict that siponimod may also be beneficial to counteract hyperinflammation in SARS-CoV-2 infected patients. This hypothesis warrants in-depth investigation in experimental animals and humans.

3.3. Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen expressed in particular by B and T cells, which induces rapid depletion of circulating lymphocytes in the bloodstream and a subsequent non-homogeneous blood repopulation for B, CD4 and CD8 T lymphocytes. Interaction between alemtuzumab and CD52 causes antibody-dependent cell-mediated cytolysis, complement-mediated cytolysis, and apoptosis, producing profound blood lymphopenia with a minor impact on the bone marrow progenitors. Alemtuzumab is approved for the treatment of adult patients with RRMS because of its great efficacy; however, the safety profile of alemtuzumab limits its place in therapy to a restricted disease window [130, 131].

The relevance of the drug in the context of SARS-CoV-2 pandemic can be analyzed in the light of symptoms and immune depletion following the initial post-infusion phase, and with reference to the subsequent period of progressive restoration of B and T lymphocyte blood count. Despite pro-

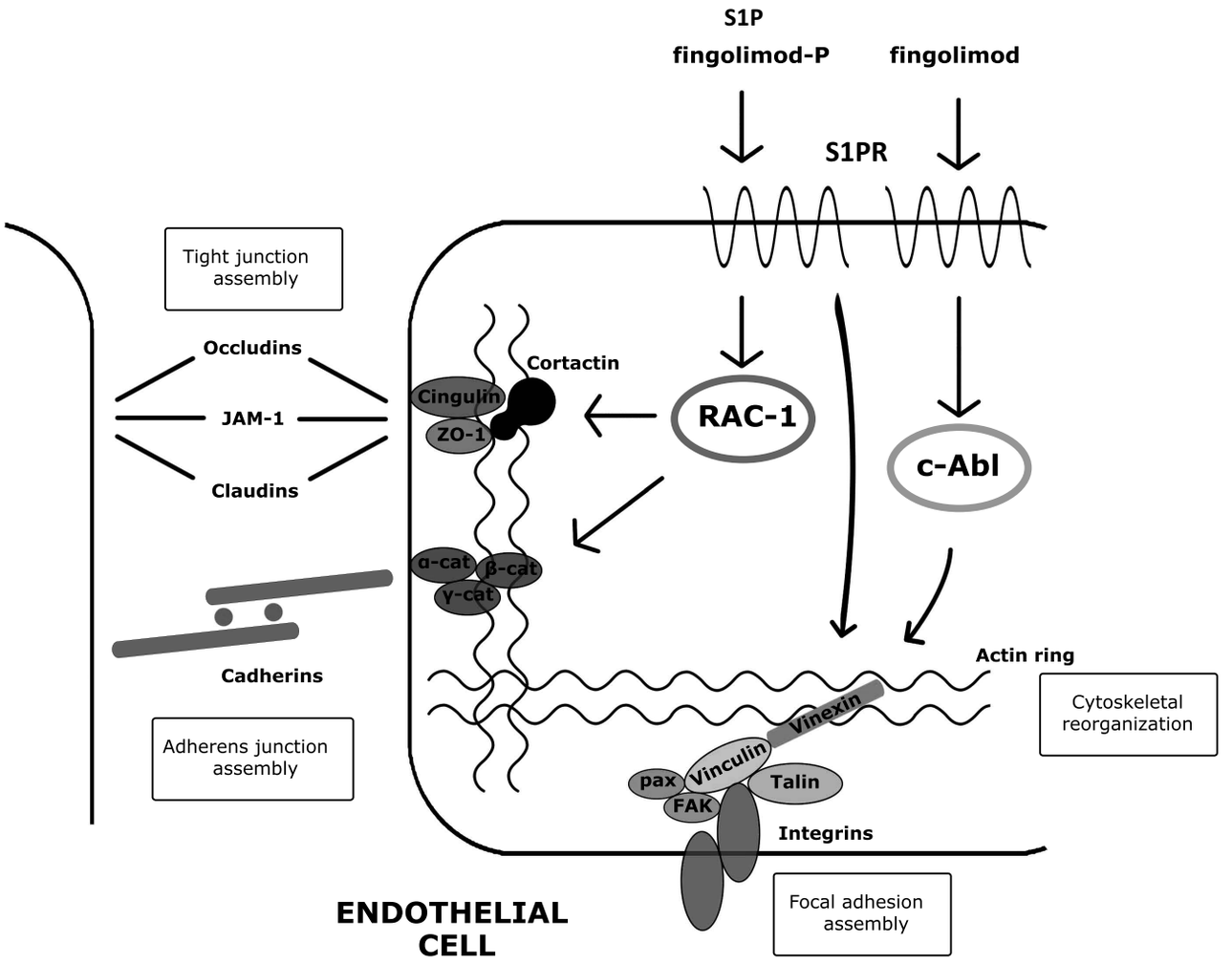

Fig. (1). Regulation of endothelial barrier function by fingolimod. Activation of sphingosine-1-phosphate receptors (S1PRs) by sphingosine-1-phosphate (S1P) and fingolimod-P increases intracellular Ca^{2+} and activates RAC-1 signalling, leading to dynamic actin changes. This in turn increases the amount of actin linked to adherens junction and thigh junction, thereby stabilizing the focal adhesion complex. Unphosphorylated fingolimod may also cause focal adhesion assembly *via* a Gi and lipid raft-coupled signalling, which involves the soluble tyrosine kinase, c-Abl (adapted from ref. [116]). ZO-1, zonula occludens; JAM, junctional adhesion molecule; cat, catenin; pax, paxillin; FAK, focal adhesion kinase; RAC-1, Ras-related C3 botulinum toxin 1; c-Abl, Abelson tyrosine kinase. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

longed depletion of immune cells, could alemtuzumab be beneficial during ARDS or rather facilitate SARS-CoV-2 infection? Because the drug causes sustained lymphopenia, it is a general belief that alemtuzumab should be started only when the infection risk is low. According to the recent study of Loupre and collaborators, in a cohort of 347 analyzed MS patients, no association between DMTs treatment and COVID-19 severity was found [15].

Administration of alemtuzumab results in an infusion-associated reaction, such as pyrexia, headache, malaise, and requires steroid and histamine pretreatment. These symptoms can simulate an infectious picture, a critical aspect in the context of a pandemic, thus requiring a preventive quarantine without risky contacts and a negative nasopharyngeal swab to avoid an acute immunosuppressive treatment in an asymptomatic positive patient.

Recently, Katja Thomas and collaborators analyzed the acute phase course of alemtuzumab administration in 15 patients, using the standard MS dosing protocol. Following the first infusion, there was a marked reduction in lymphocytes, at the limit of detection, and a mild reduction in monocytes and platelets. $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ lymphocytes and NK cells were almost cleared from the blood after the third infusion. One month after the infusion, only lymphocyte depletion persisted. Stimulation of T lymphocytes and APCs demonstrated a clear reduction in cytokine secretion. In summary, alemtuzumab administration impacts both the innate and adaptive components of the immune system [132].

After the post-infusion phase, there is an early progressive restoration of B lymphocyte blood count, and then of the T lymphocytes. In this phase, autoimmune complications may occur [133, 134]. The return of lymphocyte populations

to baseline reference values can be prolonged to three years since the first administration, and this should be seriously considered knowing the negative prognostic value of lymphopenia resulting from SARS-CoV-2 infection [135].

Despite these immunological findings, SARS-CoV-2 infection has been described shortly after alemtuzumab infusion with a favorable evolution. Carandini *et al*. reported the case of a 25-year-old woman who developed infectious symptoms two weeks after the second annual course of alemtuzumab. The nasopharyngeal swab for SARS-CoV-2 was negativized in two weeks, while at the same time, the patient was asymptomatic despite a blood test revealed severe leukopenia with neutropenia and lymphopenia [136].

A similar case was described by Guevara *et al*.; a 35-year-old man became infected with SARS-CoV-2 2.5 months after the second course of alemtuzumab. The paucisymptomatic picture resolved in two weeks with negativization of the second nasopharyngeal swab. The repopulation of B lymphocytes and NK cells had already occurred while T lymphocyte levels were still low [137]. Furthermore, the group of Eva Fernadez Diaz described the cases of two young men who developed COVID-19 one year after alemtuzumab administration and one week after retreatment during the second year, respectively. Both showed severe lymphopenia but a favorable course without respiratory support and the subsequent development of IgG antibody against SARS-CoV-2 [138]. A similar favorable course was described in a 24-year-old woman with no disability, who developed COVID-19 three months after the second course of alemtuzumab. Also, in this case, the infection was verified, a mild lymphopenia was detected and there was the production of anti-SARS-CoV-2 IgG [139].

The response of COVID-19 patients in the most acute phase of immunodepletion appears comforting and, in the light of current data, a similar course is expected in the years following treatment, where the analysis of long-term data demonstrates the progressive reduction in the incidence of infectious risk two years after the last dose of alemtuzumab [140]. Case by case should be analyzed carefully and the choice to start alemtuzumab should be based on individual patient demographics, infection risk and severity of illness. It is advisable to carefully evaluate the risk-to-benefit ratio taking into account the evolution of MS and the risk of a simultaneous infection with SARS-CoV-2 during an acute phase of the pandemic, due to the impairment of cellular and humoral immunity and the evidence of a limited number of published cases.

3.4. Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody targeting CD20 and approved to treat RRMS and PMS. Its action rests on a prolonged depletion of immature and memory B cells. Plasma cells, T and NK lymphocytes, are usually spared, even if in a minority of patients, a global lymphopenia may occur [141]. Cell repopulation takes 6-12 months for the $CD19^{+}$ B cell subset, extending to more than 18 months for memory B lymphocytes. This may cause a reduction in antibody production to viral neoantigens [142]. Moreover, hypogammaglobulinemia is common, deeper for IgG and IgM than for IgA, and may impair the humoral response to microbial exposures.

The first series of reports on the safety of immunomodulatory and immunosuppressive therapies in MS did not detect signals of major detrimental effects for any of the DMTs approved for this condition [19]. Case reports and other series [143-146, 15] agreed on the safety of anti-CD20 in relation to SARS-CoV-2 infection. In one of these reports, it was suggested that anti-CD20-induced selective immunosuppression might also be beneficial for preventing the hyperinflammation state seen in the most severe COVID-19 cases [143], because anti-CD20 antibodies also dampen IL-6 production and secondarily modulate T cell activation [147].

Nonetheless, data from an Iranian cross-sectional survey [148] suggested that B cell depleting agents may enhance the susceptibility to COVID-19 without major effects on recovery. Along the line are results from the New York University MS centre [20]. The largest study available so far, *i.e*. the Italian nationwide observational study that is the continuation of the first published series [19, 21], also confirmed an acceptable level of safety of all DMTs, including anti-CD20 agents. However, the latter treatments may be associated with a slight increase in the risk of severe COVID-19. These results are consistent with the increased frequency of respiratory infections associated with these treatments [12, 149].

We may discuss these results with the lens of SARS-CoV-2 pathobiology and leveraging clinical examples derived from immunocompromised conditions that resemble anti-CD20 effects.

Solid evidence underlines a more pivotal role for T cells in the control of SARS-CoV-2 infection [150-152]; a potent T response is capable to eradicate the virus independently of antibody generation [153], and its reduction and functional exhaustion correlate with clinical deterioration [154]. Moreover, the presence of virus-specific T cells in asymptomatic and convalescent individuals is promising for generating protective immunity [152].

Conversely, in severe cases, SARS-CoV-2 halts the generation of a lasting humoral response by blocking the formation of germinal centres, the anatomo-functional units where activated B cells perform affinity maturation [155]. Also, Woodruf *et al*. highlighted an autoimmune pattern of extrafollicular B cell response in critical COVID-19 cases associated with elevated inflammatory biomarkers and multiorgan failure [156].

A large and comprehensive antibody profiling of COVID-19 patients found that the most severe cases, requiring hospitalization, had significantly lower levels of antibodies targeting common cold viruses (such as Rhinoviruses, Enteroviruses and Influenzavirus). In addition, they pinpointed antibodies targeting SARS-CoV-2 epitopes cross-reacting with common cold Coronaviruses (OC43 and 229E), suggesting their utility in leveraging early humoral response to SARS-CoV-2 [157]. Even if treatment with ocrelizumab does not appear to affect pre-existing humoral immunity [158], the hypogammaglobulinemia frequently induced by B-cell depleting agents may weaken this first, unrefined shield against the virus. The lack of a significant

early antibody response may also delay the diagnosis in these subjects if a serology test is used first [159]. Humoral arm impairment may favor higher viral load and epitope spreading, providing a delayed, dysregulated response and increasing the probability of severe disease [157, 160]. Moreover, given the SARS-CoV-2 quantitative and qualitative effects on lymphocyte populations, the B cell reconstitution phase could be impaired, resulting in an autoimmune-prone asset with detrimental clinical effects.

Looking at reports of patients with congenital absence (X-linked or Autosomal Recessive Agammaglobulinemia; XLA/ARA) or dysfunction (Common Variable Immune Deficiency; CVID) of B cells [161] may help interpret these data.

In XLA/ARA, a loss-of-function mutation of the BTK enzyme stops the B cell maturation process in the bone marrow so that no B cell is found in peripheral blood. Also, the lack of BTK in myeloid cells moderates the inflammatory response of the innate immune system [162]. Patients show low levels of all antibody classes and require polyclonal immunoglobulin infusions to prevent bacterial and viral recurrent infections. SARS-CoV-2 infected XLA/ARA patients exhibited a favourable COVID-19 course, suggesting that T cell-mediated response alone can achieve viral control. The standard immunoglobulin replacement therapy, in these patients, is continued and may have added immunomodulatory effects. Furthermore, BTK deficiency might help prevent hyperinflammation by halting the NLRP3-inflammasome activation associated with severe COVID-19 [162, 163].

Common variable immunodeficiency (CVID) is the most prevalent primary immunodeficiency with heterogeneous genotypes and phenotypes. Its prominent features are hypogammaglobulinemia, leading to recurrent infections, and a "background" immune dysfunction, causing frequent autoimmune and inflammatory complications [164-166]. Autoimmunity in CVID is determined by a reduced frequency of naïve and regulatory T cells, high levels of T helper type 1 (Th1) and T follicular helper (TfH) CD4+ T cells, favoring a multistep failure of B cell tolerance [167]. It is not surprising, therefore, that these non-infective complications can be successfully managed with B cell depleting drugs [168].

In line with these mechanisms, reported cases of SARS-CoV-2 infected CVID patients describe a severe disease course, with a prominent auto-aggressive cytokine storm syndrome, supposed to be driven by an excessive amount of IL-6 produced by dysfunctional B cells [161].

In summary, patients receiving ocrelizumab may either be framed in the former or latter situation: the B cell repopulation phase and the assets of T and innate cells determine the different quality of response. Both variables suffer from potent endogenous (*i.e.*, genetic) or exogenous (*i.e.*, infectious history, comorbidities, age, *etc.*) influences that can only be settled by studies with very large populations. Pruning the interferences, one could depict two ideal scenarios: (A) during the full depletion phase, if T-cell immunity is conserved, patients may carry an increased infection risk, show a longer viral persistence, but successfully recover without developing life-threatening complications; (B) as B cell depletion occurs, immunological networks acutely deregulated by SARS-CoV-2 may favor the survival of dysfunctional B clones driving the cytokine storm and leading to an unrestrained auto-aggressive state, especially in elderly (due to immunosenescence).

The last, and probably most relevant, concern pertains to vaccination [169]. Live and live-attenuated vaccines are not recommended during B cell depleting therapies. Also, it is plausible that anti-CD20 agents may reduce the efficacy of a vaccine against SARS-CoV-2 in MS patients. Indeed, a recent study confirmed an attenuated humoral response to both T-cell dependent and independent antigens in patients receiving ocrelizumab, an effect shared by other B-depleting agents. Nonetheless, influenza vaccination could offer at least partial seroprotection [137]. Be they complete or partial, the durability of these humoral responses to vaccination has not been evaluated yet and remains an open question [169, 170]. These elements should be taken into account when a SARS-CoV-2 vaccine becomes available; the different repopulation kinetics of memory B cells and naive B cells should be exploited to personalize the timeframe to vaccinate these patients.

3.5. Cladribine

Cladribine is an oral immune reconstitution therapy (IRT) approved for the treatment of RRMS, and administered with annual doses over 2 years. It acts as a deoxyadenosine analogue with a less selective cell depleting effect compared to ocrelizumab, mostly involving $CD20^+$ and $CD19^+$ naïve B cells, with a partial reduction of T cell compartment that reaches 50% for $CD4^+$ and 40% for $CD8^+$ cells [171, 172]. Lymphocyte repopulation times are shorter than with anti-CD20 monoclonal antibodies with a median of 30 weeks after dosing but are longer for T-helper cells [172-174]. The occurrence of severe lymphopenia following cladribine administration results in an increased frequency of infections [175].

In the context of the COVID-19 pandemic, the higher frequency of upper respiratory tract infections seen in cladribine-treated pwMS [175] may deserve some attention. While some of the studies reported below were informative about the safety of anti-CD20 therapies, they were underpowered to fully understand the effects of cladribine due to the more recent approval of this drug and the consequently lower number of treated patients. However, case reports do not suggest additive risk for the frequency and severity of COVID-19 in pwMS receiving cladribine [176-178]; most SARS-CoV-2 infected patients had mild or no symptoms, irrespective of comorbidities and age. A single report on COVID-19 pneumonia with moderate symptoms and concomitant to a profound lymphopenia showed a successful recovery without sequelae [178].

We can hypothesize that the benign infection course is due to: (i) partial preservation of the $CD8^+$T subsets with virus responsiveness [179]; (ii) the dynamic of drug clearance and complete immune reconstitution, which is faster with cladribine than with anti-CD20 antibodies, and less impactful than alemtuzumab; and, (iii) widely-acting drug-induced immunomodulation, which may prevent COVID-19

autoaggressive phenomena through inflammatory cytokine reduction and dendritic cell regulation [180, 181].

The present limited evidence shows preservation of serological response to SARS-CoV-2 [77, 182]. Since there is no published data of vaccination efficacy in cladribine-treated pwMS, these partial results suggest that the drug should not have a strong impact on active immunization strategies against SARS-CoV-2, with the obvious exception of avoiding live and live-attenuated formulations.

In conclusion, even if the number of reports is too small to draw any conclusion, present data depict cladribine as a safe IRT during the pandemic. Anyhow, these patients should be rapidly screened in the case of mild and non-specific symptoms to avoid under-diagnosis favored by the immunosuppressed state. Larger samples and specific studies are needed to clarify a potential use of cladribine against the dysimmune state associated with COVID-19.

CONCLUSION

Age, disability level and a progressive disease are, to date, the most supported risk factors for COVID-19 severity and lethality in pwMS [19]. Thus, the challenges imposed by the current pandemic reinforce the mainstay of preventing MS relapses and progression with drugs, as available data suggest that the therapeutical benefits outweigh the risks of SARS-CoV-2 infection.

Based on published data and, not differently from other microbial exposures, some DMTs may slightly increase the risk for COVID-19 in pwMS, especially if concomitant with other risk factors. However, a limit of present observational evidence is the possibility that severe COVID-19 cases and, particularly, patients' deaths may be under-reported, not only due to publication rules but also the absence of patient agreement. Thus, properly designed, prospective epidemiological studies are awaited to precisely measure the risks-benefit ratio: meanwhile, neurologists maintain their essential role in tailoring case-by-case this "double protection" strategy.

On the other hand, pre-clinical and clinical evidences suggesting beneficial effects of MS-DMTs on SARS-CoV-2 infection are growing, and ongoing clinical trials will clarify their potential use in the treatment of COVID-19. Not only large samples but also correct timing and patients' selection will be fundamental to surgically tackle the viral disease at the right phase with the right drug, thus allowing a definite and unbiased results' interpretation. A remarkable example is the use of IFN-β, which could aid viral clearance if given early after the infection but could be detrimental if administered too late. Conversely, immunomodulant/immunosuppressive effects of highly active MS-DMTs could be useful only in hampering the third hyperinflammatory phase seen in severe cases.

Both acute and chronic postinfectious neurological effects of COVID-19 are a concern that needs to be therapeutically addressed. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), was recently found to prevent clinical deterioration in SARS-CoV-2 infected patients with mild symptoms [183]; its efficacy in COVID-19 suggests a substantial impact of CNS fitness and functionality on disease prognosis. Besides the long-term antidepressant effects, this molecule shows collateral immunomodulant and neuroprotective properties [184]. We described the capacity of drugs developed to primarily act on the immune system (GA, teriflunomide, DMT and fingolimod) to also cause neuroprotection; these joint benefits endorse their maintenance in pwMS during the pandemic and potential testability in moderate COVID-19.

The awaited arrival of vaccines against SARS-CoV-2 will surely help to curtail the growth of the pandemic but will also open issues regarding their safety and protective efficiency in people treated with immunomodulant and immunosuppressive drugs, including pwMS. It is worth saying that, to date, the candidate formulations at the most advanced phases of development are mRNA or replication-incompetent vector vaccines that should be fully compatible with the whole range of MS-DMTs, at least from a safety point-of-view. Further evidence is needed to ascertain definitely the characteristics and duration of the immunological memory after SARS-CoV-2 infection and vaccination, and to inform future COVID-19 prevention strategies for pwMS receiving DMTs.

AUTHORS' CONTRIBUTION

Marika Alborghetti, Gianmarco Bellucci and Antonietta Gentile contributed equally to the manuscript as co-first authors. Ruggero Capra, Marco Salvetti and Diego Centonze contributed equally to the manuscript as co-last authors.

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