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REVIEW

Immunology of COVID-19 and disease-modifying therapies: The good, the bad and the unknown

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Objective: The outbreak of the SARS-CoV-2 pandemic, caused by a previously unknown infectious agent, posed unprecedented challenges to healthcare systems and unmasked their vulnerability and limitations worldwide. Patients with long-term immunomodulatory/suppressive therapies, as well as their physicians, were and are concerned about balancing the risk of infection and effects of disease-modifying therapy. Over the last few months, knowledge regarding SARS-CoV-2 has been growing tremendously, and the first experiences of infections in patients with multiple sclerosis (MS) have been reported.
Methods: This review summarizes the currently still limited knowledge about SARS-CoV-2 immunology and the commonly agreed modes of action of approved drugs in immune-mediated diseases of the central nervous system (MS and neuromyelitis optica spectrum disorder). Specifically, we discuss whether immunosuppressive/immunomodulatory drugs may increase the risk of SARS-CoV-2 infection and, conversely, may decrease the severity of a COVID-19 disease course.
Results: At present, it can be recommended in general that none of those therapies with a definite indication needs to be stopped per se. A possibly increased risk of infection for most medications is accompanied by the possibility to reduce the severity of COVID-19.
Conclusions: Despite the knowledge gain over the last few months, current evidence remains limited, and, thus, further clinical vigilance and systematic documentation is essential.

KEYWORDS
COVID-19, DMT, immunosuppression, MS, NMOSD, SARS-CoV-2

INTRODUCTION

In December 2019, a new viral disease, COVID-19, initially presenting as pneumonia of unknown etiology, emerged in Wuhan (China) and rapidly spread worldwide. On March 11, 2020 the WHO declared the disease a pandemic [1,2]. The causative agent was promptly identified as a novel enveloped RNA-betacoronavirus, which is referred to as SARS-CoV-2 due to its phylogenetic similarity to the SARS coronavirus [2]. As of August 8, more than 18 902 735 COVID-19 cases have been reported worldwide, of which 709 511 were fatal [3]. The contagiosity of SARS-CoV-2 is reflected in its basic reproduction number, R0, of 1.5–5.7 (for comparisons: measles R0 = 12–18; SARS R0 = 2–5, influenza R0 = 0.9–2.1). Although most patients have a relatively mild or even asymptomatic disease course, several comorbidities, particularly age, seem to determine the risk of severe disease courses, including fatalities [4]. Therefore, the COVID-19 pandemic and the lack of specific therapies evoked concerns among neurologists about whether patients treated with immunomodulating/immunosuppressive therapies for various neurological disorders are exposed to a higher risk of COVID-19-associated complications

and, thus, how to proceed regarding initiation, continuation, postponement or interruption of such disease-modifying therapies. Therefore, we aimed to provide an overview of the underlying immunopathology of COVID-19 and the potential interactions of the modes of action of currently used disease-modifying drugs in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) as prototypic neuroimmunological disorders.

COVID-19

The clinical course of COVID-19 is characterized by three disease phases [5]. The early infection phase represents either no or only mild symptoms, such as fatigue, high body temperature and dry cough, but active SARS-CoV-2 replication and possibly also lymphopenia. With progress of the infection, typical viral pneumonia evolves, which might already reflect systemic inflammation with lymphopenia and elevated transaminases. Computed tomography shows bilateral pneumonic infiltrates, so-called ground-glass opacities. This stage potentially advances into systemic hyper-inflammation, constituting the transition into the most severe disease course. Now, inflammatory cytokines are strongly elevated and this 'cytokine storm' causes viral sepsis and disseminated intravasal coagulation, which may both manifest with multi-organ failure and fatal outcome [5].

Immunopathology of COVID-19

The spike protein of SARS-CoV-2 interacts with the abundant angiotensin-converting enzyme-related carboxypeptidase 2 (ACE2) receptor of the host cell using the cellular serine protease transmembrane protease serine subtype 2 (TMPRSS2) for priming [6]. Other potential entry routes have also been described, including the interaction of viral spike protein and CD147, which is widely expressed along with inflamed tissue and lymphocytes [7]. Once having entered the host cell, viral replication commences, leading to the formation of virus-containing vesicles, which are subsequently released to facilitate viral spread [8].

To date, the exact mechanism of the specific antigen presentation and the humoral and cellular as well as innate immune responses to SARS-CoV-2, are far from being fully elucidated. The cytopathic properties of SARS-CoV-2 probably trigger the innate immune system via damage-associated molecular patterns and pathogen-associated molecular patterns, leading through different pathways, e.g., the nuclear factor-κB pathway, to secretion of inflammatory cytokines, and mounting a type I interferon (IFN) response [9,10]. The closely related SARS-CoV uses the nucleocapsid protein to antagonize IFN-β, which is likely to be a similar escape mechanism also in SARS-CoV-2 [11]. Indeed, a recent report suggests an impaired IFN type I response in the case of SARS-CoV-2, which was associated with a high viral load, while cellular responses to stimulation were preserved [12]. In general, severely affected patients demonstrate a rapid activation of innate immune pathways with significantly elevated levels of circulating cytokines. Interleukin (IL)-1β, IL-1Ra, IL-6, IL-7, IL-10, IP-10 and tumor necrosis factor-α, in particular, have been associated with disease progression to acute respiratory distress syndrome, with this dysfunctional immune response known as a 'cytokine storm' [13,14]. Increased IL-6 serum levels, especially, are correlated with poor clinical outcome [15,16]. The exact cellular source, however, still needs to be determined. Two, not necessarily mutually exclusive, scenarios might provide an explanation: 'primary hypercytokinemia', characterized by a hyper-inflammatory response to primary viral infection by monocytes and resident macrophages, and 'secondary hypercytokinemia', driven by hyper-activated T cells. There is evidence supporting both hypotheses as shown by (i) expansion of highly inflammatory monocytes as well as monocyte-derived macrophage with concomitant loss of tissue-resident macrophages, further associated with disease progression and secretion of IL-6 and IL-1β and (ii) expansion of pro-inflammatory CD4 T cells, although the total number of circulating T cells is reduced [17-19].

The adaptive immune system plays a fundamental role in limiting viral infection. Typically, there is a mild to severe lymphopenia, affecting T cells in particular, as well as natural killer cells, with an increase in neutrophils [15,20]. The reason for the decrease in T cells is not yet fully known; however, inflammation-related migration and activation-induced cell death are a likely explanation. Autopsy studies of the lung showed mononuclear inflammatory infiltrates predominantly consisting of lymphocytes and multinucleated syncytial cells, with atypical enlarged pneumocytes bearing features of viral cytopathic-like changes [21]. In this context, a recent paper described altered phenotypes of immune cells in the peripheral blood: decrease of central memory CD4/CD8 T cells, low frequencies of terminally differentiated CD8 T cells and an overall dramatic reduction of $CD11a^+$ T cells, which migrate to other tissues, including the lung, pointing at least partly to an inflammatory-related migration process [22]. In addition, single-cell RNA sequencing analysis of bronchoalveolar fluid showed an increase of CD8 T cells as well as their clonal expansion [19]. By contrast, an autopsy study examining lymphoid tissue demonstrated extensive cell death of lymphocytes in SARS-CoV-2 infection, implying IL-6 and FAS-FASL (indicating activation-induced cell death) as a potential underlying mechanism [23].

In order to control viral infections, T-cell responses are essential. In the case of SARS-CoV-2, it has been demonstrated that predominantly CD4 central memory as well as CD8 effector memory cells show activity against viral SARS-CoV-2 proteins [24-26]. In congruence, mildly diseased patients harbored an increased expansion of clonal T cells in bronchoalveolar fluid and peripheral blood compared to more severely diseased patients [19,27]. In general, CD8 T cells are more strongly activated compared to CD4 T cells in SARS-CoV-2 [28].

Dysregulation of T-cell responses likely contributes to COVID-19 severity and, in fact, patients experiencing a severe disease course show lower numbers of T-regulatory cells, thus possibly pointing to altered immunosuppressive counter-regulation in severe cases [15,29]. Additionally, expansion of aberrant pro-inflammatory $GM\text{-}CSF^+CD4^+$ and $IL\text{-}6^+CD4^+$ T cells has been observed in critically diseased patients, again supporting severe immune dysregulation [18]. Further, functional studies demonstrated suppressed IFN-γ production by CD4 T cells as well as reduced multifunctionality, while CD8

T cells in severe COVID-19 cases revealed a higher concentration of cytotoxic components as well as subsequent exhaustion markers, which may partly contribute to COVID-19-associated damage. Normalization of lymphocyte counts and cytotoxicity/exhaustion markers is then observed in convalescent patients [30].

With regard to humoral immune responses, protective antibodies can be generated in response to SARS-CoV-2 infection [31,32]. Seroconversion typically occurred 7–14 days after onset of disease symptoms [33,34], and convalescent plasma therapy in patients with severe COVID-19 seemed to positively impact on the disease outcome [35]. However, it should be borne in mind that an increased immunoglobulin G (IgG) response, which is reflected in high antibody titers, is likely to be associated with a more severe disease course [36]. This may also indicate a potential pathogenic IgG response, as known from other virus infections, via antibody-dependent amplification, or be explained by a delayed but highly inflammatory response [37,38]. However, there is currently no evidence in terms of antibody-dependent amplification [39].

In summary, severely affected COVID-19 patients exhibit features of severe immune dysregulation as reflected by (i) hypercytokinemia due to a potentially delayed (hyper-) inflammatory response of the innate immune system and (ii) reduced numbers of total T cells, of which the remaining are partly hyperactivated and may display exhaustion. Antibody production likely contributes to recovery and there is no evidence to date that antibodies are involved in exacerbating pathogenesis.

DISEASE-MODIFYING THERAPIES

In MS and NMOSD, immunomodulatory and immunosuppressive therapies are widely used to improve the course of the disease. The SARS-CoV-2 pandemic poses two important questions to neurologists regarding disease-modifying therapies: (i) Is the risk of infection with SARS-CoV-2 increased? and (ii) Is the risk of a severe COVID-19 course higher, or might it even be lower? As the first question has already been addressed extensively in the literature and study findings have been just recently excellently compiled [40], the present review focuses on question (ii), that is, on the potential mechanisms of action of disease-modifying therapies and the immunopathology of SARS-CoV-2 (Figure 1).

Interferon β

Interferon β, belonging to type I IFNs, is a long-established therapy in MS. Its mode of action is suggested to be manifold, involving

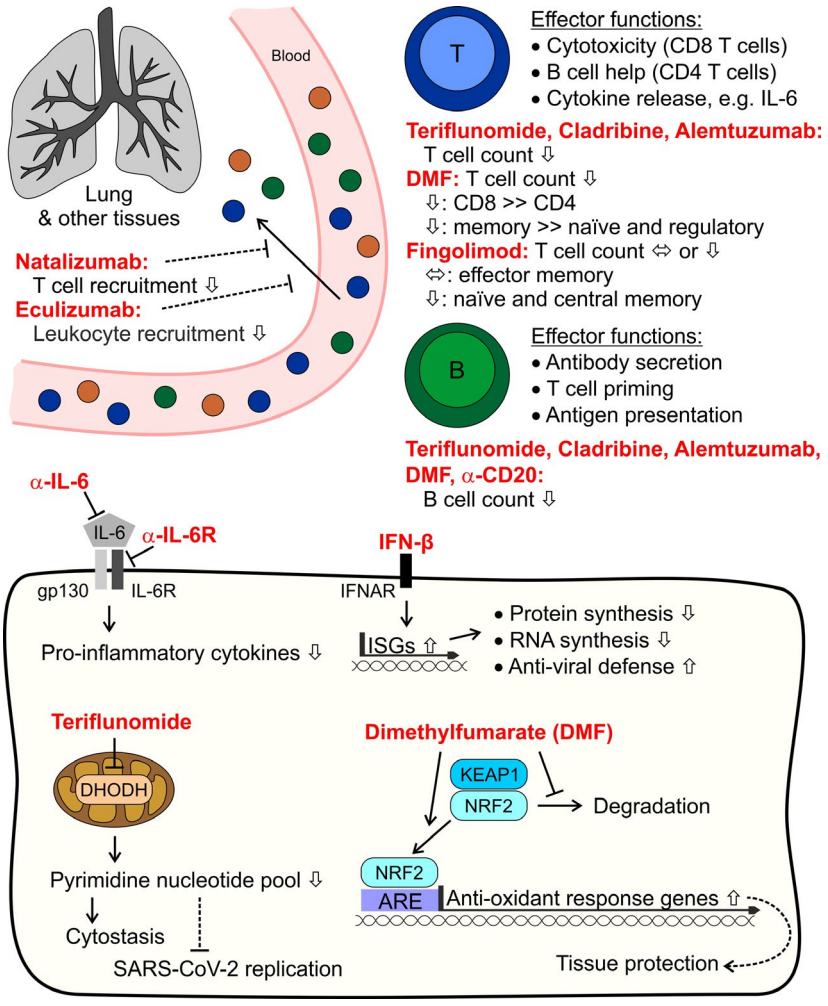

FIGURE 1 Potential effects of disease-modifying therapies on SARS-CoV-2 infection. Disease-modifying therapies can potentially impact on SARS-CoV-2 infection in a manifold way. Dashed lines represent questionable/putative pathways influencing SARS-CoV-2-related replication, leukocyte recruitment or tissue damage. Brown circles represent monocytes. DHODH, dihydroorotate dehydrogenase; DMF, dimethyl fumarate; IFN, interferon; IFNAR, interferon-α/β receptor; IL, interleukin; IL-6R, interleukin-6 receptor; ISG, interferon-stimulated gene; KEAP, Kelch-like ECH-associated protein, antioxidant response element

decreased levels of co-stimulation, reduction of pro-inflammatory cytokine release, inhibition of transmigration of immune cells across the blood–brain barrier and enhancement of T-cell regulatory function (for review see Kieseier [41]). IFNs were originally discovered to have an ability to 'interfere' with viruses [42]. The IFN pathways are triggered by pattern recognition receptors through recognition of viral components [43]. IFN-β leads, in an autocrine and paracrine manner, to a cascade of signaling pathways by binding to the IFN-α/β receptor (IFNAR) complex, leading to downstream cascade via the JAK-STAT pathway and finally to the induction of IFN-stimulated genes (ISGs). To date, more than a hundred ISGs have been identified; mostly, they interfere with viral infection by inhibiting cell entry and by downregulation of protein and RNA synthesis [44]. So far, only few data are available providing mechanistic insights into the interaction of SARS-CoV-2 and IFN-β. However, there is evidence regarding the closely related SARS and MERS, for which IFN-β was proposed as a possible treatment. For both SARS and MERS, *in vitro* data described IFN-β as the most potent inhibitor among IFNs [45,46]. However, data in humans are inconsistent, mostly due to different study designs, combination of therapies and heterogeneous patient cohorts, and do not permit a final conclusion on IFN-β efficacy [47-49].

Interestingly, SARS-CoV has developed mechanisms to antagonize IFN responses on multiple levels [11,50,51]. Whether these mechanisms are conserved in SARS-CoV-2 remains to be elucidated as well. Some data show suppressed IFN responses in COVID-19 patients; other data highlight that SARS-CoV-2 is more susceptible to treatment with IFN-β [12,52,53]. Generally, phase III trials on IFN-β did not reveal an elevated risk of infections [54-56]. The MS patients with SARS-CoV-2 infection and IFN-β treatment that have been reported to date experienced a mild disease course [57]. To our knowledge, of the published larger cohorts with a positive SARS-CoV-2 PCR, seven patients were on IFN-β treatment, one needed hospitalization and none required intensive care unit (ICU) treatment or died [58-62]. Therefore, there is no evidence to date that IFN-β exacerbates SARS-CoV-2 infection. The MS community might provide valuable insights, analyzing susceptibility to SARS-CoV-2 and outcome in MS patients on IFN treatment. In our view, IFN-β possesses the potential ability to strengthen the viral defense mechanism, thereby reducing the risk of severe infection.

Summary

1. Risk of SARS-CoV-2 infection: no increased risk, support of viral defence appears possible.
2. Risk of aggravated COVID-19 disease course: not to be expected.

Glatiramer acetate

Glatiramer acetate (GA) is composed of randomly sized synthetic peptides consisting of four amino acids (tyrosine, alanine, lysine and glutamic acid). Initially explored to mimic myelin basic protein and, therefore, to be used to induce experimental autoimmune encephalomyelitis, it was later shown that GA effectively reduces relapse rate in MS patients [63]. The exact mechanism of action is still unclear, however, altering T-cell response to myelin proteins and initiating a shift from Th1 to Th2 induction of T-regulatory cells and modulation of B-cell responses are supposed mechanisms of action (for review see Rommer *et al*. [64]). So far, available data indicate that GA therapy is hardly susceptible to infections [65,66]. Therefore, it is unlikely that GA significantly influences the immune response to SARS-CoV-2. To our knowledge, of the published larger cohorts with a positive SARS-CoV-2 PCR test, 13 patients were on GA treatment, one needed hospitalization, one required ICU treatment and one patient died [58-62].

Summary

1. Risk of SARS-CoV-2 infection: no increased risk.
2. Risk of aggravated COVID-19 disease course: not to be expected.

Sphingosine-1-phosphate receptor modulator

Fingolimod resembles the sphingolipid sphingosine 1-phosphate (S1P), which exerts its effects via G-protein-coupled receptors. At least five receptor subtypes exist, and fingolimod binds to four of them, while siponimod selectively binds to S1P1/5, with S1P1 being the most implicated in exerting its immunomodulatory effects [67]. By binding to S1PR, fingolimod/siponimod induce internalization and thereby inhibit the egress of lymphocytes (for review see Chun *et al*. [68]). Preferentially $CCR7^+$ naive T cells and T central memory cells (preferably CD4 over CD8) are retained, while T memory effector cells are spared [69]. However, recently activated T cells might overcome retention by downregulation of CCR7, which is in line with evidence showing the ability to mount an immune response against novel antigens in fingolimod-treated patients [70,71]. Given the fact that T memory effector cells are spared, the clearance of infections by this T-cell subset is in general not severely impaired [72,73]. However, phase III clinical trials have shown that fingolimod was associated with higher frequency of lower respiratory tract infections and cases of herpes infections [74,75]. Furthermore, studies revealed that antiviral activity against herpes virus is diminished by fingolimod treatment, thereby bearing a slightly increased risk of herpes virus reactivation [76]. The reason for this impaired control against herpes virus is still a matter of debate; however, failure of recruitment of lymphocytes from the naive and the T-central memory subtype might be implicated. In general, patients receiving fingolimod treatment are able to mount an immune response in response to vaccination, leading to seroprotection; however, response rates are reduced compared to placebo [77].

Interestingly, preclinical evidence exists that modulating S1P during influenza virus infection ameliorated lung pathology by

reducing infiltration and activation of inflammatory cells. Also, S1P has been shown to enhance endothelial barrier function [78,79]. However, reduction of lung permeability might have a dose-dependent effect and could also worsen ventilator-induced lung injury [80]. Furthermore, the fact that, in clinical studies, a higher frequency of dyspnea and decreased lung function in patients receiving fingolimod was reported should be considered, although the underlying mechanism remains unclear [74].

To date, seven case reports of COVID-19 infection in fingolimod-treated MS patients have been reported, with two patients requiring ICU treatment. These patients were rapidly stabilized and discharged. In all but one of the seven cases, fingolimod treatment was stopped due to concerns regarding immunosuppression. Lymphocyte counts of MS patients rapidly increased after fingolimod treatment was discontinued. In the most severe case, high levels of IL-6 were reported and intubation was necessary. If discontinuation of fingolimod increased the risk of acute respiratory distress syndrome, or if fingolimod effect *per se* is attributable to this course, remains unknown [81-85]. Notably, two patients remained completely asymptomatic during COVID-19 infection [86]. To our knowledge, of the published larger cohorts with a positive SARS-CoV-2 PCR, 24 patients were on S1P-modulating treatment, three needed hospitalization, two required ICU treatment and one patient died [58-62].

It remains to be seen whether the immunomodulatory properties and potential effects on the lung will influence SARS-CoV-2 infections. In our view, a potential higher risk for infection can be assumed, and beneficial effects counter-regulating the hyperinflammatory response are conceivable.

Summary

1. Risk of SARS-CoV-2 infection: a higher risk is not excluded.
2. Risk of aggravated COVID-19 disease course: the potential beneficial effect on SARS-CoV-2-associated hyperinflammation versus drug-related pulmonary adverse effects remains to be clarified.

Teriflunomide

Teriflunomide has been reported to interrupt DNA synthesis in rapidly dividing cells by a non-competitive reversible inhibition of the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which is highly expressed in lymphocytes, leading to cytostasis (for review see Bar-Or *et al*.) [87]. Inhibition of DHODH interferes with pyrimidine synthesis and thereby also with viral replication, explaining its potential antiviral effects [88]. In fact, *in vitro* experiments showed that inhibiting DHODH delays SARS-CoV-2 replication due to pyrimidine depletion [89].

T and B cells are both susceptible to DHODH inhibition, although to different extents. In particular, the interplay between the two cell types seems to be affected the most [90,91]. Compared to dimethyl fumarate (DMF), teriflunomide reduces lymphocyte counts to lesser extents [92]. In phase III clinical trials, no increased incidence of infections was observed compared to placebo [93,94].

Similarly, vaccine responses do not seem to be substantially altered in teriflunomide-treated patients [95,96]. All case reports, to our knowledge, on patients with teriflunomide treatment who have SARS-CoV-2 infection have reported that they had a rather mild disease course [97-99]. Of the published larger cohorts with a positive SARS-CoV-2 PCR, eight patients were on teriflunomide treatment, one needed hospitalization, none required ICU treatment and one patient died [58-62].

Whether the proposed dual mechanism of antiviral activity and mild immunomodulation will hold true in the case of SARS-CoV-2 regarding susceptibility and disease course remains to be seen.

Summary

1. Risk of SARS-CoV-2 infection: no increased risk to be expected with normal lymphocyte count, viral replication may even be restricted by mode of action.
2. Risk of aggravated COVID-19 disease course: not to be expected; inhibitory effects on SARS-CoV-2 viral replication and hyperinflammatory responses in SARS to be discussed.

Dimethyl fumarate

Dimethyl fumarate is a second-generation ester of fumarate, exerting its disease-modifying effects on multiple levels. A prominent pathway is described for the activation and stabilization of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and acting as agonist on the hydroxycarboxylic acid receptor 2 (HCA_2) [100,101]. Via this pathway, antioxidant proteins are upregulated, leading to a cytoprotective effect of DMF [102]. Whether these cytoprotective effects may also play a role in acute severe lung injury in COVID-19 patients is unknown; nevertheless, experimental evidence exists that restoring the Nrf2 pathway protects patients from lung injury by reestablishing alveolar macrophage function and enhancement of antioxidant gene expression [103-105]. However, DMF also reduces the number of lymphocytes, presumably via apoptosis, with CD8 T cells being predominantly affected [106-108]. Within these subsets, memory T cells seem to be more susceptible compared to regulatory or naïve subsets [109]. Given these facts and the evidence showing reduced T-regulatory cells and predominance of the effector memory CD8 or central memory CD4 subtype in the role of severe SARS-CoV-2 infection, it is tempting to speculate that DMF contributes to a balanced response to SARS-CoV-2 in DMF-treated patients and inhibits a hyperinflammatory response [24,25,110]. However, severe lymphopenia, although rare, could impair an antiviral response, thereby reducing viral clearance, prolonging the infectious state and ultimately leading to a more severe disease course. DMF-associated lymphopenia seems to be dose-dependent and anecdotal progressive multifocal leukoencephalopathy was reported in

patients with prolonged absolute lymphopenia [111-113]. In phase III clinical trials, reported infections were similar among treatment and placebo groups [114,115]. So far, case series on COVID-19-infected MS patients receiving DMF treatment report on rather mild disease courses and no need for intensive care treatment [116]. Of the published larger cohorts with a positive SARS-CoV-2 PCR, 27 patients were on DMF treatment, three needed hospitalization, one required ICU treatment and one patient died [58-62].

Similarly to T cells, circulating mature and differentiated B cells are reduced on DMF treatment, and B cell responses are altered in an anti-inflammatory manner [117]. However, immune responses to vaccinations do not seem to be significantly impacted by DMF [118]. In our view, severe decreased lymphocyte count might increase infectious risk, however, the anti-inflammatory and anti-oxidative properties might influence SARS-COV-2 infection in a beneficial way.

Summary

1. Risk of SARS-CoV-2 infection: a higher risk in patients with lymphopenia is not excluded.
2. Risk of aggravated COVID-19 disease course: beneficial effects on hyperinflammatory responses due to anti-inflammatory and anti-oxidative properties of DMF to be discussed.

Cladribine

Cladribine is a prodrug, depending on phosphorylation by deoxycytidine kinase, which is imported into cells, where it acts as purine nucleoside analogue leading to interferences with DNA synthesis, finally resulting in cell death [119]. The level of deoxycytidine kinase and the counteracting cytosolic 5′-nucleotidases (5-NT) determines the relative cell-specific toxicity [120]. Cladribine causes a long-lasting lymphocyte depletion, predominantly affecting B cells, particularly memory B cells, and a moderate reduction of T cells, particularly central and naïve T cells compared to effector T cells, within the first 2 years [121-124]. Grade IV lymphopenia is rare and has been described in a subset of patients. In those patients, an increased rate of infection is to be assumed. The effects on the innate immune system are less pronounced and affect mainly neutrophil granulocytes and natural killer cells [125]. Patients on cladribine treatment have a mildly elevated risk of infections, and more herpes virus infections were noticed in phase III clinical trials [126-128]. Safety data on clinical trials and follow-up studies confirmed that most common viral infections, except herpes zoster, were not significantly increased compared to the placebo group [129]. To date, the impact on vaccination response has not yet been published. With regard to cladribine and infectious risks, one has consider that, due to its recent approval, there are fewer long-term data on safety in comparison to the extensive experience with other therapeutic agents.

Summary

1. Risk of SARS-CoV-2 infection: a higher risk is possible, especially in patients with prolonged lymphopenia.
2. Risk of aggravated COVID-19 disease course: may not be increased because of no impairment of viral immunity in general.

Natalizumab

Natalizumab is a monoclonal antibody targeting α4-integrin [130]. By blocking α4-integrin on activated T cells, B cells and myeloid cells, adhesion to endothelium via vascular cell adhesion molecule 1 (VCAM-1) is prevented, thereby leading to a reduction of blood–brain barrier transmigration [131-134]. Similarly, it reduces leukocyte trafficking into the intestinal endothelium by inhibiting α4β7-integrin interaction with mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) [135]. In general, patients treated with natalizumab have no increased risk of infections, with a notable exception for progressive multifocal leukoencephalopathy, reflecting its strong effect on interfering with central nervous system immunosurveillance [65,136]. The contribution of the very late antigen-4 (VLA-4)/VCAM-1 or α4β7/VCAM-1 axis during viral lung infection is not fully elucidated; so far, there is experimental evidence suggesting a potentially decreased leukocyte recruitment on inhibition [137,138]. However, it is questionable whether this effect might play a role in SARS-CoV-2 infection. In phase III clinical trials, a slightly elevated risk of infections was noticed [139,140]. Assessing the vaccination response to influenza, there was no difference for patients under natalizumab treatment [141]. All in all, there seems to be little evidence for a substantial impact of natalizumab treatment on immune responses during SARS-CoV-2 infection. However, one might consider that SARS-CoV-2 potentially possesses a neuroinvasive ability, which could have deleterious consequences during natalizumab treatment. So far, we are aware of just two case reports with a mild COVID-19 infection during natalizumab treatment [142,143]. Of the published larger cohorts with a positive SARS-CoV-2 PCR, 10 patients were on natalizumab treatment, one needed hospitalization, one required ICU treatment and one patient deceased [58-62].

Summary

1. Risk of SARS-CoV-2 infection: a higher risk is unlikely.
2. Risk of aggravated COVID-19 disease course: appears unlikely, however, it may be speculated that SARS-CoV-2-associated neurological complications could be aggravated due to natalizumab-related decreased central nervous system immunosurveillance.

Alemtuzumab

Alemtuzumab is a monoclonal antibody depleting $CD52^+$ cells by antibody-dependent cell-mediated cytolysis and

complement-dependent cytolysis. Although CD52 is highly expressed on B and T cells, the molecular function is poorly understood [144]. Cell depletion by alemtuzumab is profound and affects more than 95% of CD4 T cells, at least 80% of CD8 T cells and more than 85% of CD19 B cells [145]. Lymphocyte recovery is slow, with B cells repopulating after 7 months, CD8 T cells at approximately 20 months, and CD4 T cells at approximately 32 months after a single course [146].

Reportedly in phase III trials, infection rates during alemtuzumab treatment were significantly increased overall; they were, however, mostly mild to moderate, including herpes virus, influenza virus and fungal infections, as well as infections of the respiratory tract and urinary tract [147,148]. Pooled analyses of phase III trials and follow-up periods confirmed an increased infection risk, especially within the first 2 years after treatment initiation [149,150]. In a pilot study that investigated vaccination responses in MS patients treated with alemtuzumab in general, it was shown that the patients triggered an antibody response; however, a trend towards lower seroconversions was observed in a study investigating vaccination responses in alemtuzumab-treated kidney transplant patients in comparison to other immunosuppressant agents [151,152]. The fact that most infections do not cause life-threatening disease might be attributable to only minor effects of alemtuzumab to the innate as compared to the adaptive immune system. This is also evident in a rapid repopulation of natural killer cells, which is even faster compared to cladribine [123,153]. In light of these profound alterations within distinct immunological compartments, anti-viral cellular immune responses are likely to be impaired. However, to date, we are aware of six case reports on patients who received alemtuzumab and experienced a mild COVID-19 disease course [154-157]. Of the published larger cohorts with a positive SARS-CoV-2 PCR, one patient received alemtuzumab treatment without reported complications [58-62]

Summary

1. Risk of SARS-CoV-2 infection: a high risk is possible, especially within the first 2 years.
2. Risk of aggravated COVID-19 disease course: harmful effects cannot be excluded, however, consistent with a general view on effects of immunosuppressants in hyperinflammatory syndrome, it may be speculated that alemtuzumab has anti-inflammatory properties for this condition.

Anti-CD20 monoclonal antibodies

Anti-CD20 monoclonal antibodies deplete $CD20^+$ B cells via antibody-dependent cellular cytotoxicity or a complement-dependent mechanism (for review see Barun and Bar-Or [158]). A minor fraction of T cells expresses CD20 as well, and they are similarly depleted, although their exact function is incompletely understood [159]. Anti-CD20-depleting agents also affect non-CD20-expressing T cells and experimentally dampen CD8 T-cell responses; however, it was shown that myelin-specific T cells are more reduced compared to influenza-specific CD8 T cells [160,161] A nationwide cohort study found that patients with CD20-depleting treatment have a general higher risk of infections, while in phase III clinical trials for ocrelizumab there was no significant overall infection rate; however, upper respiratory tract infections were more common in the ocrelizumab group compared to placebo [65,162,163]. However, CD20 depletion does not seem to increase the risk of influenza infection; nevertheless, there is experimental evidence that T-cell responses are diminished by CD20 depletion at least in lymphocytic choriomeningitis (LCMV) infection [164,165]. The influence of CD20-depleting agents on macrophages is less clear; it putatively polarization of macrophages in a less pro-inflammatory way, and single reports implied a beneficial effect in macrophage activation syndrome [166,167]. It remains to be shown if this modulated response will be beneficial or deleterious in the case of SARS-CoV-2. Immune responses to vaccination are diminished in patients on CD20-depleting agents compared to untreated or IFN-β-treated patients, although a protective response can still be mounted [168]. Although prolonged rituximab treatment potentially leads to hypogammaglobulinemia, two patients with agammaglobulinemia and SARS-CoV-2 infection did not experience a severe disease course. [169,170]. To date, the MS patients treated with CD20-depleting agents and with confirmed SARS-CoV-2 infection recovered mostly without serious complications [171-175]. Of the published larger cohorts with a positive SARS-CoV-2 PCR, 32 patients received a CD20-depleting agent, seven needed hospitalization, four required ICU treatment and three died [58-62]. Nevertheless, whether an antibody-specific response will be mounted in CD20-treated patients or in response to a future anti-SARS-CoV-2 vaccination is an important matter of current debate [176].

Summary

1. Risk of SARS-CoV-2 infection: a higher risk is not excluded.
2. Risk of aggravated COVID-19 disease course: anti-inflammatory effects, e.g., reduced antibody production, may decrease the severity of hyperinflammatory immune reactions. However, effects on the production of protective antibodies, be they in response to COVID-19 disease or to a potential future anti-SARS-CoV-2 vaccination, are as yet completely unknown.

Complement inhibition

Eculizumab is a terminal complement inhibitor. By binding with high affinity to complement factor C5, it compromises cleavage of C5 into C5a and C5b and thereby inhibits complement-mediated cell lysis [177]. Besides forming the membrane attack complex via C5b,

C5a is a potent chemoattractant involved in the recruitment of leukocytes [178].

The complement system plays a role in viral immune defense, however, mostly in pathways prior to terminal complex formation (for review see Stoermer and Morrison [179]). Nevertheless, patients on eculizumab treatment have been reported to have higher rates of viral and bacterial infections, with invasive Neisseria being the most life-threatening [180]. So far, the role of C5 in viral immunopathogenesis is poorly understood. Experimental evidence in a model for influenza and MERS-CoV-2 infection showed that blockade of the C5 axis leads to reduced alveolar macrophage and neutrophil infiltration, resulting in alleviation of tissue damage [181,182], while knockout of C3 aggravated disease [183]. To date, four patients with severe COVID-19 have been treated with eculizumab and did show a marked clinical improvement after infusion [184].

Furthermore, only recently, it was shown in an experimental model that the N protein of SARS-CoV-2 possesses the ability to bind and potentiate via mannose-binding lectin (MBL), leading to an auto-activation of MASP-2 (lectin pathway) and subsequent uncontrolled complement activation. The authors support their suggestion by showing high levels of C5a in the serum of patients with severe but not mild COVID-19 and tested an anti-C5a antibody successfully in two patients [185]. Whether this mechanism is causal for high C5a in the serum has yet to be proven; however, safe administration of anti-C5a reveals an exciting target. In phase III clinical trials testing eculizumab compared to placebo, the overall infection rate was similar; however, upper respiratory tract infections were more common in the eculizumab treatment group [186].

It remains to be seen whether blockade of C5 by eculizumab ameliorates rather than aggravates COVID-19 disease by reducing inflammation and leukocyte recruitment.

Summary

1. Risk of SARS-CoV-2 infection: data on possible protection against infection based on experimental studies are limited, thus, a higher risk is not to be excluded yet.
2. Risk of aggravated COVID-19 disease course: potentially beneficial effects have been reported in a very few patients.

Anti-interleukin-6 receptor monoclonal antibodies

Interleukin-6 acts via the IL-6 receptor (IL-6R) and a transmembrane protein, namely gp130. IL-6R is expressed on hepatocytes, lymphocytes and monocytes; gp130 is expressed ubiquitously. IL-6 can also act by forming a complex with soluble IL-6 receptor, further binding to gp130 on cells which putatively do not express the transmembrane IL-6R (trans-signaling pathway); for review see Kang *et al*. [187]. Given the fact that anti-IL-6R antibodies are approved for cytokine release syndrome and that severe COVID-19 patients show elevated IL-6 serum levels, anti-IL-6R treatment was proposed as a possible treatment option in COVID-19 [15,188,189]. Indeed, a recent meta-analysis suggests a beneficial effect of anti-IL-6 treatment in severe SARS-CoV-2 infection [190]. One question that has to be addressed is the difference between IL-6 versus IL-6R blockade with regard to the efficacy of SARS-CoV-2 treatment because patients treated with anti-IL6 receptor antibody were reported to have an increased risk of infection [191]. However, to date, we are only aware of one patient undergoing IL-6R antibody treatment, who developed a mild form of COVID-19 [192]. In phase III clinical trials, infections did not differ between treatment and placebo groups [193,194]. Vaccination studies did not reveal an inhibited response to influenza or pneumococcal vaccines [195,196].

Summary

1. Risk of SARS-CoV-2 infection: a higher risk is not excluded.
2. Risk of aggravated COVID-19 disease course: the approved indication for conditions with cytokine release syndrome and promising reports of anti-IL-6R-treated severe COVID-19 cases indicate the likelihood of beneficial effects in SARS-CoV-2-caused hyperinflammatory responses.

CONCLUSION

The outbreak of the SARS-CoV-2 pandemic not only posed unprecedented challenges for society and the healthcare system worldwide, but also for respective medical disciplines. In particular, neurologists treating patients with immunosuppressive/immunomodulatory therapies have to balance the risk of a SARS-CoV-2 infection and its course against a possible neurological disease progression. Although there are genetic similarities, and hence overlaps with other coronaviruses, experiences of the effects of the SARS-CoV and MERS-CoV pandemics on neurological autoimmune disorders are extremely limited. It is thus all the more important to understand the immunological basis of both the viral disease and potential interactions of the drugs used. Although data are limited, current insights are increasing rapidly and preliminary recommendations are available [197].

In general, it can be said that, with the current knowledge, all approved disease-modifying therapies should be continued unaltered. The benefits in terms of prevention of further MS or NMOSD disease progression likely outweigh the risk of infection for nearly all therapies. However, in the need to switch therapies, the potentially increased risk of infection for the now new therapy (see Table 1) must be taken into consideration. It should also be noted that therapies such as alemtuzumab, CD20 antibodies and cladribine are therapies with long-term efficacy due to long-term immunosuppressive effects. Decrease or depletion of immune cells lasts at least several months, thus, individual benefit–risk evaluations, weighing up the risk of further MS/NMOSD disease activity versus potentially increased drug-related SARS-CoV-2 infections, are of paramount importance. On the

TABLE 1 Disease-modifying therapies and impact on COVID-19

Drug	Mode of action	Risk of viral infection	Impact on COVID-19 disease severity	Other considerations
Interferon	Lymphocyte activation/migration ↓	None	Potentially beneficial	
Glatiramer acetate	Th1→Th2 shift; Tregs ↑	None	Unlikely	
Sphingosine-1-P	Lymphocyte egress ↓	Probably	Potentially beneficial/deleterious	Lymphocyte count
Teriflunomide	Lymphocyte proliferation ↓	None/low	Potentially beneficial	Lymphocyte count
Dimethylfumarate	Antioxidative response ↑, Th1 → Th2 shift, macrophage activation ↓	Probably	Potentially beneficial	Lymphocyte count
Cladribine	Lymphocyte replication ↓	Probably	Potentially beneficial/deleterious	Lymphocyte count, effects lasting for years
Natalizumab	Blockade of α4-integrin	Unlikely	Unlikely	Potential severe neuroinvasion
Alemtuzumab	CD52+ depletion	Increased risk	Potentially deleterious	Effects lasting for years
Anti-CD20 mAb	CD20+ cell depletion	Probably	Potentially beneficial/deleterious	Effects lasting for months
Complement inhibition	Blockade of C5 cleavage	Uncertain	Potentially beneficial/deleterious	
Anti-IL-6 and Anti-IL-6R mAb	Inhibition of IL-6	Probably	Potentially beneficial	

Abbreviations: IL, interleukin; IL-6R, interleukin-6 receptor; mAb, monoclonal antibody; Sphingosine-1-P, sphingosine-1-phosphate receptor modulator; TH, T helper cell.

(beneficial) contrary, it seems that many or probably most of the discussed drugs exhibit the possibility to limit or even decrease the severity of COVID-19 disease course due to their various anti-inflammatory effects. Specifically, there is a growing number of case reports/series of patients with severe SARS-CoV-2-associated hyperimmunity and cytokine release syndrome that are efficiently treated with immunosuppressive therapies that are established for the treatment of MS, NMOSD and myasthenia gravis.

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CONFLICT OF INTEREST

T.Z. has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. I.W. has nothing to declare. P.S.R. has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis or neuromyelitis optica spectrum disorders: Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and received research grants from Biogen, Merck, Roche. T.B. has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for MS: Almirall, Bayer, Biogen, Biologix, Bionorica, Celgene, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, TG Pharmaceuticals, TEVA-ratiopharm and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, Merck, Novartis, Roche and Sanofi/Genzyme) and for participation in clinical trials in MS sponsored by Alexion, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, and TEVA.

AUTHOR CONTRIBUTIONS

Tobias Zrzavy: Conceptualization; Data Curation; Formal analysis; Writing-original draft. **Isabella Wimmer:** Conceptualization; Data Curation; Formal analysis; Visualization, Writing-review editing. **Paulus S. Rommer:** Conceptualization; Data curation; Formal Analysis; Supervision; Writing-review editing. **Thomas Berger:** Conceptualization; Data curation; Formal Analysis; Supervision; Writing-original draft; Writing-review editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

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REFERENCES

1. Wu F, Yu B, Chen Y, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579:265-269.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733.
3. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed August 8, 2020.
4. Guan W-J, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.

5. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39:405-407.
6. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271.e8-280.e8.
7. Wang K, Chen W, Zhou YS, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *BioRxiv*. 2020. https://www.biorxiv.org/content/10.1101/2020.03.14.988345v1.abstract. Accessed August 10, 2020.
8. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal*. 2020;10:102-108.
9. Schifanella L, Anderson JL, Galli M, et al. Massive viral replication and cytopathic effects in early COVID-19 pneumonia. arXiv preprint arXiv:2005.00004; 2020.
10. Chu H, Chan JF, Yuen TT, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. *Lancet Microbe*. 2020;1:e14-e23.
11. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. *J Virol*. 2007;81:548-557.
12. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. *MedRxiv*. 2020;369:718-724.
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
14. Yang Y, Shen C, Li J, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. *MedRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.02.20029975v1. Accessed August 10, 2020.
15. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investig*. 2020;130:2620-2629.
16. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180:934-943.
17. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discovery*. 2020;6:1-18.
18. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *National Sci Rev*. 2020;76:998-1002.
19. Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med*. 2020;26:1-3.
20. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. 2020;55:102763.
21. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420-422.
22. Anft M, Paniskaki K, Blazquez-Navarro A, et al. COVID-19 progression is potentially driven by T cell immunopathogenesis. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.04.28.20083089v2. Accessed August 10, 2020.
23. Feng Z, Diao B, Wang R, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.27.20045427v1. Accessed August 10, 2020.
24. Dong C, Ni L, Ye F, et al. Characterization of anti-viral immunity in recovered individuals infected by SARS-CoV-2. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.17.20036640v1. Accessed August 10, 2020.
25. Braun J, Loyal L, Frentsch M, et al. SARSCoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature*. 2020. https://doi.org/10.1038/s41586-020-2598-9
26. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome. *Sci Immunol*. 2020;548:eabd2071.
27. Huang L, Shi Y, Gong B, et al. Blood single cell immune profiling reveals the interferon-MAPK pathway mediated adaptive immune response for COVID-19. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.15.20033472v1. Accessed August 10, 2020.
28. Yang X, Dai T, Zhou X, et al. Analysis of adaptive immune cell populations and phenotypes in the patients infected by SARS-CoV-2. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.23.20040675v2. Accessed August 10, 2020.
29. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020;7115:762-768.
30. Zheng H-Y, Zhang M, Yang CX, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol*. 2020;17:1-3.
31. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. *Nat Commun*. 2020;11:4704.
32. Bao L, Deng W, Gao H, et al. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. *BioRxiv*. 2020. https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.full?fbclid=IwAR0bNmFCEwxzjiyMnK8ZPq7CUauOkJJeQ-ye6HQdFPcto4TVl9Vov7sPVzA/. Accessed August 10, 2020.
33. Haveri A, Smura T, Kuivanen S, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. *Eurosurveillance*. 2020;25:2000266.
34. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020;581:1-5.
35. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci*. 2020;117:9490-9496.
36. Zhang B, Zhou X, Zhu C, et al. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. *Front Mol Biosci*. 2020;7:157.
37. Liu L, Wei Q, Lin Q, et al. Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. 2019;4:e123158.
38. Wan Y, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J Virol*. 2020;94:e02015-19.
39. Gao Q, Bao L, Mao H, et al. Rapid development of an inactivated vaccine for SARS-CoV-2. *bioRxiv*. 2020. https://www.biorxiv.org/content/10.1101/2020.04.17.046375v1.abstract. Accessed August 10, 2020.
40. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e761.
41. Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. *CNS Drugs*. 2011;25:491-502.
42. Isaacs A, Lindenmann J. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci*. 1957;147:258-267.
43. Xu L-G, Wang Y-Y, Han K-J, Li L-Y, Zhai Z, Shu H-B. VISA is an adapter protein required for virus-triggered IFN-β signaling. *Mol Cell*. 2005;19:727-740.
44. Schoggins JW. Interferon-stimulated genes: what do they all do? *Ann Rev Vir*. 2019;6:567-584.

45. Scagnolari C, Vicenzi E, Bellomi F, et al. Increased sensitivity of SARS-coronavirus to a combination of human type I and type II interferons. *Antivir Ther*. 2004;9:1003-1011.
46. Hart BJ, Dyall J, Postnikova E, et al. Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol*. 2014;95:571.
47. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3:e343.
48. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11:1-14.
49. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42-46.
50. Narayanan K, Huang C, Lokugamage K, et al. Severe acute respiratory syndrome coronavirus nsp1 suppresses host gene expression, including that of type I interferon, in infected cells. *J Virol*. 2008;82:4471-4479.
51. Sun L, Xing Y, Chen X, et al. Coronavirus papain-like proteases negatively regulate antiviral innate immune response through disruption of STING-mediated signaling. *PLoS ONE*. 2012;7:e30802.
52. Lokugamage KG, Hage A, Vries M, et al. Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV. *J Virol*. 2020;JVI.01410-20. https://doi.org/10.1128/JVI.01410-20
53. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C, Antiviral Activities of Type I Interferons to SARS-CoV-2 Infection. *Antiviral Res*. 2020;179:104811.
54. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655.
55. Ebers GC. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352:1498-1504.
56. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol*. 1996;39:285-294.
57. Barzegar M, Mirmosayyeb O, Ghajarzadeh M, et al. Characteristics of COVID-19 disease in multiple sclerosis patients. *Mult Scler Relat Disord*. 2020;45:102276.
58. Crescenzo F, Marastoni D, Bovo C, Calabrese M. Frequency and severity of COVID-19 in multiple sclerosis: a short single-site report from northern Italy. *Mult Scler Relat Disord*. 2020;44:102372.
59. Bowen JD, Brink J, Brown TR, et al. COVID-19 in MS: initial observations from the Pacific Northwest. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e783.
60. Loonstra FC, Hoitsma E, van Kempen ZLE, Killestein J, Mostert JP. COVID-19 in multiple sclerosis: the Dutch experience. *Mult Scler J*. 2020;26:1256-1260.
61. Parrotta E, Kister I, Charvet L, et al. COVID-19 outcomes in MS: observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. *Neurol Neuroimmunol Neuroinflam*. 2020;7:e835.
62. Sormani MP. An Italian programme for COVID-19 infection in multiple sclerosis. *Lancet Neurol*. 2020;19:481-482.
63. Johnson K, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology*. 1995;45:1268-1276.
64. Rommer PS, Milo R, Han MH, et al. Immunological aspects of modern MS therapeutics. *Front Immunol*. 2019;10:1564.
65. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurol*. 2020;77:184-191.
66. Wijnands JMA, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. *J Neurol Neurosurg Psychiatry*. 2018;89:1050-1056.
67. Gergely P, Nuesslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol*. 2012;167:1035-1047.
68. Chun J, Hartung H-P. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol*. 2010;33:91.
69. Mehling M, Brinkmann V, Antel J, et al. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. *Neurology*. 2008;71:1261-1267.
70. Pham TH, Okada T, Matloubian M, Lo CG, Cyster JG. S1P1 receptor signaling overrides retention mediated by Gαi-coupled receptors to promote T cell egress. *Immunity*. 2008;28:122-133.
71. Mehling M, Hilbert P, Fritz S, et al. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. *Ann Neurol*. 2011;69:408-413.
72. Sallusto F, Geginat J, Lanzavecchia A. Central memory and effector memory T cell subsets: function, generation, and maintenance. *Annu Rev Immunol*. 2004;22:745-763.
73. Pinschewer DD, Ochsenbein AF, Odermatt B, Brinkmann V, Hengartner H, Zinkernagel RM. FTY720 immunosuppression impairs effector T cell peripheral homing without affecting induction, expansion, and memory. *J Immunol*. 2000;164:5761-5770.
74. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362:387-401.
75. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:545-556.
76. Ricklin ME, Lorscheider J, Waschbisch A, et al. T-cell response against varicella-zoster virus in fingolimod-treated MS patients. *Neurology*. 2013;81:174-181.
77. Kappos L, Mehling M, Arroyo R, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. *Neurology*. 2015;4:872-879.
78. Walsh KB, Teijaro JR, Wilker PR, et al. Suppression of cytokine storm with a sphingosine analog provides protection against pathogenic influenza virus. *Proc Natl Acad Sci*. 2011;108:12018-12023.
79. Camp S, Bittman R, Chiang ET, et al. Synthetic analogs of FTY720 [2-amino-2-(2-[4-octylphenyl] ethyl)-1, 3-propanediol] differentially regulate pulmonary vascular permeability in vivo and in vitro. *J Pharmacol Exp Ther*. 2009;331:54-64.
80. Müller HC, Hocke AC, Hellwig K, et al. The Sphingosine-1 Phosphate receptor agonist FTY720 dose dependently affected endothelial integrity in vitro and aggravated ventilator-induced lung injury in mice. *Pulm Pharmacol Ther*. 2011;24:377-385.
81. Barzegar M, Mirmosayyeb O, Nehzat N, et al. COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e753.
82. Foerch C, Friedauer L, Bauer B, Wolf T, Adam EH. Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. *Mult Scler Relat Disord*. 2020;42:102180.
83. Valencia-Sanchez C, Wingerchuk DM. A fine balance: immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. *Mult Scler Relat Disord*. 2020;42:102182.
84. Luca B, Guerra T, Bavaro DF, et al. Seroconversion and indolent course of COVID-19 in patients with multiple sclerosis treated with fingolimod and teriflunomide. *J Neurol Sci*. 2020;416:117011.
85. Gomez-Mayordomo V, Montero-Escribano P, Matías-Guiu JA, González-García N, Porta-Etessam J, Matías-Guiu J. Clinical exacerbation of SARS-CoV2 infection after fingolimod withdrawal. *J Med Virol*. 2020;1-4. https://doi.org/10.1002/jmv.26279

86. Mallucci G, Zito A, Fabbro BD, Bergamaschi R. Asymptomatic SARS-CoV-2 infection in two patients with multiple sclerosis treated with fingolimod. *Mult Scler Relat Disord*. 2020;45:102414.
87. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. *Drugs*. 2014;74:659-674.
88. Hoffmann H-H, Kunz A, Simon VA, Palese P, Shaw ML. Broad-spectrum antiviral that interferes with de novo pyrimidine biosynthesis. *Proc Natl Acad Sci*. 2011;108:5777-5782.
89. Xiong R, Zhang L, Li S, et al. Novel and potent inhibitors targeting DHODH, a rate-limiting enzyme in de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2. *bioRxiv*. 2020. https://www.biorxiv.org/content/10.1101/2020.03.11.983056v1.abstract. Accessed August 10, 2020.
90. Zeyda M, Poglitsch M, Geyeregger R, et al. Disruption of the interaction of T cells with antigen-presenting cells by the active leflunomide metabolite teriflunomide: involvement of impaired integrin activation and immunologic synapse formation. *Arthritis Rheum*. 2005;52:2730-2739.
91. Gandoglia I, Ivaldi F, Laroni A, et al. Teriflunomide treatment reduces B cells in patients with MS. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e403.
92. Miller AE. Oral teriflunomide in the treatment of relapsing forms of multiple sclerosis: clinical evidence and long-term experience. *Ther Adv Neurol Disord*. 2017;10:381-396.
93. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365:1293-1303.
94. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:247-256.
95. Bar-Or A, Freedman MS, Kremenchutzky M, et al. Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. *Neurology*. 2013;81:552-558.
96. Bar-Or A, Wiendl H, Miller B, et al. Randomized study of teriflunomide effects on immune responses to neoantigen and recall antigens. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e70.
97. Ciardi MR, Zingaropoli MA, Pasculli P, et al. The peripheral blood immune cell profile in a teriflunomide-treated multiple sclerosis patient with COVID-19 pneumonia. *J Neuroimmunol*. 2020;346:577323.
98. Maghzi AH, Houtchens MK, Preziosa P, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. *J Neurol*. 2020;1:2790-2796.
99. Möhn N, Saker F, Bonda V, et al. Mild COVID-19 symptoms despite treatment with teriflunomide and high-dose methylprednisolone due to multiple sclerosis relapse. *J Neurol*. 2020;1:2803-2805.
100. Scannevin RH, Chollate S, Jung MY, et al. Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. *J Pharmacol Exp Ther*. 2012;341:274-284.
101. Chen H, Assmann JC, Krenz A, et al. Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. *J Clin Invest*. 2014;124:2188-2192.
102. Linker RA, Lee DH, Ryan S, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain*. 2011;134:678-692.
103. Harvey CJ, Thimmulappa RK, Sethi S, et al. Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. *Sci Transl Med*. 2011;3:78ra32.
104. Ishii Y, Itoh K, Morishima Y, et al. Transcription factor Nrf2 plays a pivotal role in protection against elastase-induced pulmonary inflammation and emphysema. *J Immunol*. 2005;175:6968-6975.
105. Kosmider B, Messier EM, Janssen WJ, et al. Nrf2 protects human alveolar epithelial cells against injury induced by influenza A virus. *Respir Res*. 2012;13:43.
106. Gross CC, Schulte-Mecklenbeck A, Klinsing S, Posevitz-Fejfar A, Wiendl H, Klotz L, Dimethyl fumarate treatment alters circulating T helper cell subsets in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2016;3:e183.
107. Treumer F, Zhu K, Glaser R, Mrowietz U. Dimethylfumarate is a potent inducer of apoptosis in human T cells. *J Invest Dermatol*. 2003;121:1383-1388.
108. Mehta D, Miller C, Arnold DL, et al. Effect of dimethyl fumarate on lymphocytes in RRMS: Implications for clinical practice. *Neurology*. 2019;92:e1724-e1738.
109. Ghadiri M, Rezk A, Li R, et al. Dimethyl fumarate–induced lymphopenia in MS due to differential T-cell subset apoptosis. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e340.
110. Shi Y, Tan M, Chen X, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *medRxiv*. 2020.
111. Wu Q, Wang Q, Mao G, et al. Dimethyl fumarate selectively reduces memory T cells and shifts the balance between Th1/Th17 and Th2 in multiple sclerosis patients. *J Immunol*. 2017;198:3069-3080.
112. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *N Engl J Med*. 2013;368:1658-1659.
113. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med*. 2015;372:1476-1478.
114. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367:1098-1107.
115. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-1097.
116. Mantero V, Abate L, Basilico P, et al. COVID-19 in dimethyl fumarate-treated patients with multiple sclerosis. *J Neurol*. 2020;1-3. https://doi.org/10.1007/s00415-020-10015-1
117. Li R, Rezk A, Ghadiri M, et al. Dimethyl fumarate treatment mediates an anti-inflammatory shift in B cell subsets of patients with multiple sclerosis. *J Immunol*. 2017;198:691-698.
118. von Hehn C, Howard J, Liu S, et al. Immune response to vaccines is maintained in patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm*. 2018;5:e409.
119. Galmarini CM, Mackey JR, Dumontet C. Nucleoside analogues and nucleobases in cancer treatment. *Lancet Oncol*. 2002;3:415-424.
120. Kawasaki H, Carrera CJ, Piro LD, Saven A, Kipps TJ, Carson DA. Relationship of deoxycytidine kinase and cytoplasmic 5'-nucleotidase to the chemotherapeutic efficacy of 2-chlorodeoxyadenosine. *Blood*. 1993;81:597-601.
121. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. *Proc Natl Acad Sci*. 1996;93:1716-1720.
122. Jacobs BM, Ammoscato F, Giovannoni G, Baker D, Schmierer K. Cladribine: mechanisms and mysteries in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018;89:1266-1271.
123. Baker D, Herrod SS, Alvarez-Gonzalez C, Zalewski L, Albor C, Schmierer K. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e360.
124. Stuve O, Soerensen PS, Leist T, et al. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: an extended analysis of surface markers. *Ther Adv Neurol Disord*. 2019;12:1-16.
125. Sellner J, Rommer PS. Immunological consequences of "immune reconstitution therapy" in multiple sclerosis: a systematic review. *Autoimmun Rev*. 2020;19:102492.
126. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:416-426.

127. Leist TP, Comi G, Cree BAC, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurol*. 2014;13:257-267.
128. Cook S, Vermersch P, Comi G, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. *Mult Scler J*. 2011;17:578-593.
129. Cook S, Leist T, Comi G, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. *Mult Scler Relat Disord*. 2019;29:157-167.
130. Sheremata W, Vollmer TL, Stone LA, Willmer-Hulme AJ, Koller M. A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. *Neurology*. 1999;52:1072.
131. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against α 4 β l integrin. *Nature*. 1992;356:63-66.
132. Niino M, Bodner C, Simard ML, et al. Natalizumab effects on immune cell responses in multiple sclerosis. *Ann Neurol*. 2006;59:748-754.
133. Krumbholz M, Meinl I, Kumpfel T, Hohlfeld R, Meinl E. Natalizumab disproportionately increases circulating pre-B and B cells in multiple sclerosis. *Neurology*. 2008;71:1350-1354.
134. Mindur JE, Ito N, Dhib-Jalbut S, Ito K. Early treatment with anti-VLA-4 mAb can prevent the infiltration and/or development of pathogenic CD11b+ CD4+ T cells in the CNS during progressive EAE. *PLoS ONE*. 2014;9:e99068.
135. Berlin C, Berg EL, Briskin MJ, et al. α4β7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell*. 1993;74:185-195.
136. Ransohoff RM. Natalizumab for multiple sclerosis. *N Engl J Med*. 2007;356:2622-2629.
137. Herold S, von Wulffen W, Steinmueller M, et al. Alveolar epithelial cells direct monocyte transepithelial migration upon influenza virus infection: impact of chemokines and adhesion molecules. *J Immunol*. 2006;177:1817-1824.
138. Ou R, Zhang M, Huang L, Flavell RA, Koni PA, Moskophidis D. Regulation of immune response and inflammatory reactions against viral infection by VCAM-1. *J Virol*. 2008;82:2952-2965.
139. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:899-910.
140. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:911-923.
141. Vågberg M, Kumlin U, Svenningsson A. Humoral immune response to influenza vaccine in natalizumab-treated MS patients. *Neurol Res*. 2012;34:730-733.
142. Aguirre C, Meca-Lallana V, Barrios-Blandino A, del Río B, Vivancos J. Covid-19 in a patient with multiple sclerosis treated with natalizumab: may the blockade of integrins have a protective role? *Mult Scler Relat Disord*. 2020;44:102250.
143. Borriello G, Ianniello A. COVID-19 occurring during Natalizumab treatment: a case report in a patient with extended interval dosing approach. *Mult Scler Relat Disord*. 2020;41:102165.
144. Ruck T, Bittner S, Wiendl H, Meuth S. Alemtuzumab in multiple sclerosis: mechanism of action and beyond. *Int J Mol Sci*. 2015;16:16414-16439.
145. Baker D, Herrod SS, Alvarez-Gonzalez C, Giovannoni G, Schmierer K. Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials of alemtuzumab. *JAMA Neurol*. 2017;74:961-969.
146. Hill-Cawthorne GA, Button T, Tuohy O, et al. Long term lymphocyte reconstitution after alemtuzumab treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2012;83:298-304.
147. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012;380:1829-1839.
148. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380:1819-1828.
149. Wray S, Havrdova E, Snydman DR, et al. Infection risk with alemtuzumab decreases over time: pooled analysis of 6-year data from the CAMMS223, CARE-MS I, and CARE-MS II studies and the CAMMS03409 extension study. *Mult Scler J*. 2019;25:1605-1617.
150. Comi G, Alroughani R, Boster AL, et al. Efficacy of alemtuzumab in relapsing-remitting MS patients who received additional courses after the initial two courses: pooled analysis of the CARE-MS, extension, and TOPAZ studies. *Mult Scler J*. 2019;1-11.
151. Silva M Jr, Humar A, James Shapiro AM, et al. Humoral immune response following seasonal influenza vaccine in islet transplant recipients. *Cell Transplant*. 2013;22:469-476.
152. McCarthy CL, Touhy O, Compston DAS, Kumararatne DS, Coles AJ, Jones JL. Immune competence after alemtuzumab treatment of multiple sclerosis. *Neurology*. 2013;81:872-876.
153. Freedman MS, Kaplan JM, Markovic-Plese S. Insights into the mechanisms of the therapeutic efficacy of alemtuzumab in multiple sclerosis. *J Clin Cell Immunol*. 2013;4:872-876.
154. Matías-Guiu J, Montero-Escribano P, Pytel V, et al. Potential COVID-19 infection in patients with severe multiple sclerosis treated with alemtuzumab. *Mult Scler Relat Disord*. 2020;44:102297.
155. Guevara C, Villa E, Cifuentes M, Naves R, de Grazia J. Mild COVID-19 infection in a patient with multiple sclerosis and severe depletion of T-lymphocyte subsets due to alemtuzumab. *Mult Scler Relat Disord*. 2020;44:102314.
156. Carandini T, Pietroboni AM, Sacchi L, et al. Alemtuzumab in multiple sclerosis during the COVID-19 pandemic: a mild uncomplicated infection despite intense immunosuppression. *Mult Scler J*. 2020;26:1268-1269.
157. Fernández-Díaz E, Gracia-Gil J, Garcia-Garcia JG, Palao M, Romero-Sanchez CM, Segura T, COVID-19 and multiple sclerosis: A description of two cases on alemtuzumab. *Mult Scler Relat Disord*. 2020;45:102402.
158. Barun B, Bar-Or A. Treatment of multiple sclerosis with anti-CD20 antibodies. *Clin Immunol*. 2012;142:31-37.
159. Palanichamy A, Jahn S, Nickles D, et al. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *J Immunol*. 2014;193:580-586.
160. Vernengo FF, Beccaria CG, Furlan CLA, et al. CD8+ T Cell Immunity is compromised by Anti-CD20 treatment and rescued by interleukin-17A. *MBio*. 2020;11:e00447-20.
161. Sabatino JJ, Wilson MR, Calabresi PA, Hauser SL, Schneck JP, Zamvil SS. Anti-CD20 therapy depletes activated myelin-specific CD8+ T cells in multiple sclerosis. *Proc Natl Acad Sci*. 2019;116:25800-25807.
162. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376:221-234.
163. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376:209-220.
164. Lykken JM, DiLillo DJ, Weimer ET, et al. Acute and chronic B cell depletion disrupts CD4+ and CD8+ T cell homeostasis and expansion during acute viral infection in mice. *J Immunol*. 2014;193:746-756.
165. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. *N Engl J Med*. 2008;358:676-688.
166. Toubi E, Kessel A, Slobodin G, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:818-820.

167. Bakshi J, Hassan S, D'Cruz D, Chan A. *Rituximab therapy in refractory macrophage activation syndrome secondary to systemic lupus erythematosus*. London, UK: Sage Publications Sage UK; 2013.
168. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. *Neurology*. 2020;95:e1999-e2008.
169. Marcinnò A, Marnetto F, Valentino P, et al. Rituximab-induced hypogammaglobulinemia in patients with neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2018;5:e498.
170. Soresina A, Moratto D, Chiarini M, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. *Pediatr Allergy Immunol*. 2020;315:565-569.
171. Suwanwongse K, Shabarek N. Benign course of COVID-19 in a multiple sclerosis patient treated with Ocrelizumab. *Mult Scler Relat Disord*. 2020;42:102201.
172. Novi G, Mikulska M, Briano F, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? *Mult Scler Relat Disord*. 2020;42:102120.
173. Meca-Lallana V, Aguirre C, Rio B, Cardenoso L, Alarcon T, Vivancos J. COVID-19 in 7 multiple sclerosis patients in treatment with ANTI-CD20 therapies. *Mult Scler Relat Disord*. 2020;44:102306.
174. Ghajarzadeh M, Mirmosayyeb O, Barzegar M, et al. Favorable outcome after COVID-19 infection in a multiple sclerosis patient initiated on ocrelizumab during the pandemic. *Mult Scler Relat Disord*. 2020;43:102222.
175. Woo MS, Steins D, Haubler V. et al. Control of SARS-CoV-2 infection in rituximab-treated neuroimmunological patients. *J Neurol*. 2020;1-3. https://doi.org/10.1007/s00415-020-10046-8
176. Thornton JR, Harel A. Negative SARS-CoV-2 antibody testing following COVID-19 infection in Two MS patients treated with ocrelizumab. *Mult Scler Relat Disord*. 2020;44:102341.
177. Schatz-Jakobsen JA, Zhang Y, Johnson K, Neill A, Sheridan D, Andersen GR. Structural basis for eculizumab-mediated inhibition of the complement terminal pathway. *J Immunol*. 2016;197:337-344.
178. Guo R-F, Ward PA. Role of C5a in inflammatory responses. *Annu Rev Immunol*. 2005;23:821-852.
179. Stoermer KA, Morrison TE. Complement and viral pathogenesis. *Virology*. 2011;411:362-373.
180. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. *Lancet*. 2009;373:759-767.
181. Jiang Y, Zhao G, Song N, et al. Blockade of the C5a–C5aR axis alleviates lung damage in hDPP4-transgenic mice infected with MERS-CoV. *Emerg Microbes Infect*. 2018;7:1-12.
182. Garcia CC, Weston-Davies W, Taveres LP, et al. Complement C5 activation during influenza A infection in mice contributes to neutrophil recruitment and lung injury. *PLoS ONE*. 2013;8:e64443.
183. O'Brien KB, Morrison TE, Dundore DY, Heise MT, Schultz-Cherry S, A protective role for complement C3 protein during pandemic 2009 H1N1 and H5N1 influenza A virus infection. *PLoS ONE*. 2011;6:e17377.
184. Diurno F, Numis FG, Porta G, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci*. 2020;24:4040-4047.
185. Gao T, Hu M, Zhang X, et al. Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. *MedRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.29.20041962v3. Accessed August 10, 2020.
186. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4–positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:614-625.
187. Kang S, Tanaka T, Narazaki M, Kishimoto T, Targeting interleukin-6 signaling in clinic. *Immunity*. 2019;50:1007-1023.
188. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23:943.
189. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun*. 2019;2020:102452.
190. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. *MedRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.30.20048058v1. Accessed August 10, 2020.
191. Machado SH, Xavier RM. Safety of tocilizumab in the treatment of juvenile idiopathic arthritis. *Expert Opin Drug Saf*. 2017;16:493-500.
192. Mihai C, Dobrota R, Schröder M, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. *Ann Rheum Dis*. 2020;79:668-669.
193. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:2114-2124.
194. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2020;19:402-412.
195. Tsuru T, Terao K, Murakami M, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. *Mod Rheumatol*. 2014;24:511-516.
196. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2012;71:2006-2010.
197. Federation, M.S.I.. Global COVID-19 advice for people with MS. http://www.msif.org/wp-content/uploads/2020/05/MSIF-Global-advice-on-COVID-19-for-people-with-MS-_-v2.pdf. Accessed June 6, 2020.

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