Infectious issues of therapeutic monoclonal antibodies in multiple sclerosis and neuromyelitis optica spectrum disorders

Asako Tagawa

Department of Neurology, Hiratsuka City Hospital, Hiratsuka City, Kanagawa, Japan

Correspondence
Asako Tagawa, MD, PhD, Department of Neurology, Hiratsuka City Hospital, 1-19-1 Minamihiara, Hiratsuka City, Kanagawa, 254-0065, Japan. Email: atagawa@hiratsuka-city-hospital.com

Abstract

Various effective monoclonal antibodies (mAbs) have been approved for both multiple sclerosis (MS) and anti-aquaporin-4-seropositive neuromyelitis optica spectrum disorders worldwide, including in Japan. As these newer mAbs have distinct modes of action that effectively suppress the recurrence of inflammation and slow disability progression, they can modulate and interfere with the protective immune response against pathogens, resulting in various infectious complications. Among various mAbs, natalizumab (NTZ) has the highest risk of causing progressive multifocal leukoencephalopathy (PML), a rare but fatal opportunistic brain infection caused by John Cunningham polyomavirus. Switching from NTZ to B-cell-depleting mAbs, such as ocrelizumab, is also a possible risk factor for PML development. Alemtuzumab carries the risk of reactivation of varicella-zoster virus (VZV); therefore, prophylactic acyclovir treatment is required. NTZ has also been associated with VZV reactivation. Eculizumab can cause severe meningococcal infection due to Neisseria meningitidis, and vaccination prior to treatment induction is required. Attention to the reactivation of hepatitis B or Mycobacterium tuberculosis is also needed during mAb therapy. Additionally, in the era of severe acute respiratory syndrome coronavirus 2 infection (COVID-19), the risk for of developing severe COVID-19 may be associated with some mAbs, such as B-cell-depleting agents. Thorough understanding and mitigation strategies for infectious risks are essential.

KEYWORDS
COVID-19, infections, multiple sclerosis, neuromyelitis optica spectrum disorders, progressive multifocal leukoencephalopathy, therapeutic monoclonal antibodies

1 INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are autoimmune-mediated inflammatory and degenerative diseases that affect the central nervous system (CNS).\textsuperscript{1,2} MS begins with a relapsing–remitting course termed relapsing remitting MS (RRMS), followed by insidious worsening disability without clinically apparent relapses, known as secondary progressive MS.\textsuperscript{3} NMOSD are characterized by recurrent optic neuritis, acute myelitis, and brain syndromes. They are divided into anti-aquaporin-4 (AQP-4)-seropositive NMOSD (seropositive NMOSD) and anti-AQP4-seronegative NMOSD (seronegative NMOSD).\textsuperscript{4}

In the last 15 y, new disease-modifying drugs (DMDs) have become available for MS, which has prompted a change in treatment algorithms.\textsuperscript{5,6} Additionally, since 2019 three monoclonal antibodies (mAbs) have been approved for seropositive NMOSD worldwide,
including in Japan. mAbs used to treat MS and seropositive NMOSD and their action mechanisms are shown in Table 1. Some drugs such as ocrelizumab (OCR) and alemtuzumab (ATZ) have not been approved in Japan. Rituximab (RTX) is widely used for MS and NMOSD in Western countries, and in 2022 it has been approved for NMOSD, including in Japan.

Compared with the first-generation DMDs for MS (interferon beta and glatiramer acetate) and conventional immunosuppressive drugs for NMOSD, these newer mAbs are more effective in preventing the recurrence of inflammation and reducing disability progression. These mAbs have distinct immunological action mechanisms that can modulate and interfere with the protective immune response against various pathogens, resulting in various infectious complications (Table 1). Some complications, such as progressive multifocal leukoencephalopathy (PML) and reactivation of the herpes virus or hepatitis viruses, can be life-threatening. Additionally, since the beginning of 2020 we have been experiencing a pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19). The risk of developing COVID-19 may increase under immunosuppressive treatments. Recently, several groups of MS experts have published clinically relevant, evidence-based recommendations of general screening for viral, bacterial, and fungal infections, and vaccination before starting or switching DMDs, including mAbs, as well as mitigation and surveillance strategies for infectious complications during DMDs treatment. These recommendations could also be applied to NMOSD treatments.7–10

Here, I review particularly important infectious complications associated with treating MS and NMOSD with antimonalocinal agents.

2 | VIRAL INFECTIONS

2.1 Progressive multifocal leukoencephalopathy

PML is a rare but fatal opportunistic brain infection caused by the John Cunningham polyomavirus (JCV). The development of PML is associated with cell-mediated immune system impairment.11 For the last two decades, PML has been known as an opportunistic infection of pharmacological immunosuppressive conditions in patients treated with mAbs for MS and other autoimmune diseases.

Natalizumab (NTZ), a humanized anti-α4β1-integrin mAb,12 was the first mAb approved for RRMS in 2004. NTZ effectively reduced the clinical relapse rate and disability progression.9 Among the approved mAbs for MS and NMOSD, the incidence of PML is the highest with NTZ.14,15 In 2005, the first two NTZ-associated PML (NTZ-PML) cases were reported in patients with MS taking NTZ in combination with interferon-β.16,17 which prompted a transient market withdrawal. As of February 2022, there were 884 confirmed PML cases among 251,119 patients exposed to NTZ (Biogen, Cambridge, MA, USA, data on file).18

Patients with NTZ-PML are not systemically immunosuppressed, and inadequate immune surveillance is the major explanation for the mechanism.19 PML risk increased with previous immunosuppressant exposure (more than 2 y before NTZ treatment) and the presence of serum anti-JCV antibodies.20 Among patients who were anti-JCV antibody-negative at baseline in the AFIRM12 and STRATIFY-1 trials, 97% remained negative or below an index threshold of 1.5 over 18 mo.22

The clinical stage of NTZ-PML and characteristic magnetic resonance imaging (MRI) findings are presented in Table 2. In NTZ-PML, favorable prognostic outcomes are expected when PML is diagnosed in the early asymptomatic period.23 Generally, the survival rate of NTZ-PML is better than that of most other PML.24 In addition, Dong-Si et al23 reported that mortality in symptomatic patients was 24.6%, whereas that in asymptomatic patients was 3.3%. Brain MRI is a vital tool for PML diagnosis.19 Moreover, NTZ-PML can be diagnosed using routine MRI scans before any neurological symptoms develop.25–28 Nonenhancing punctate patterns on T2-weighted/FLAIR images of the cerebral subcortical U-fiber region are observed in presymptomatic or asymptomatic NTZ-PML.29,30 However, a confirmed diagnosis may be difficult when MRI changes suggestive of PML are observed, but CSF JCV-PCR results are negative during the same period.19 In 2016, the European Medical Agency confirmed initial recommendations for the early diagnosis of PML aimed at minimizing CNS injury and avoiding severe disability.31 They also stratified the risk of PML by the index value of the serum anti-JCV antibodies. Major et al advocated a protocol for surveillance in patients with NTZ-treated MS, and emphasized the need for more frequent MRI scans in patients with a higher anti-JCV antibody index and longer duration of treatment.19,32 The protocol for the surveillance of NTZ-PML is summarized in Table 3. Currently, there are no effective drugs for the treatment of NTZ-PML. Mefloquine and mirtazapine are used to treat PML under clinical settings in Japan, although their effectiveness has not been proven. In a recent study, the efficacy of filgrastim, a granulocyte-colony stimulating factor, for treating NTZ-PML has been reported; 17 patients survived 2 y after the onset of PML.33

The correlation between CSF JCV viral load and outcome has also been described; a higher JCV-DNA copy number in CSF at diagnosis resulted in worse outcomes.34,35 Generally, the CSF JCV-DNA load at PML diagnosis tends to be low in NTZ-PML patients.24

In almost all cases of NTZ-PML, immune reconstitution inflammatory syndrome (IRIS) occurs to some degree upon discontinuation of NTZ, within days to weeks after plasma exchange (PLEX), which is often used to accelerate the clearance of active drugs.36 On MRI examination, contrast-enhancing lesions are the most common earliest signs of IRIS following NTZ-PML.37 In a histological study, abundant perivascular and parenchymal CD8-positive T-cell infiltration was observed in patients with IRIS following NTZ-PML.38 The incidence of PML-IRIS among patients treated with NTZ was higher than in other patients with PML.39 PLEX and immunoabsorption have been used to rapidly remove NTZ, which results in restored lymphocyte trafficking into the CNS. Paradoxically, the effective removal of NTZ and restoration of cellular immunity can worsen the neurological deficit. Tan et al40 reported that early-onset PML-IRIS resulted in worse survival and neurological outcomes in 28 patients with NTZ-PML. From an examination of 372 NTZ-PML cases, Dong-Si et al23 reported...
| Drug            | Indications | Modes of action                                                                 | Infectious complications                                                                 | Recommended evaluations before treatment induction                                      |
|-----------------|-------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| **MS**          |             |                                                                                  |                                                                                          |                                                                                          |
| Natalizumab (NTZ) | RRMS       | Binds to the α4 integrin subunit of α4β1 integrin. And blocks leukocytes migration via the BBB into the CNS. | PML. Herpes virus reactivation                                                             | Serum JCV titers and brain MRI. Exclusion of active and latent infections (including HIV, HBV, HCV). Tuberculosis test. Herpes viral infections (the history of infections and anti-VZV IgG titer). |
| Alemtuzumab (ATZ) | RRMS       | Directs against CD52, expressed at high levels on T cells and B cells, and depletes them | PML (not reported in MS patients). Listeria-associated infections. Herpes virus including CMV reactivation. Hepatitis B reactivation. *Mycobacterium tuberculosis* infection. Others: upper respiratory infections | Exclusion of active and latent infections (including HIV, HBV, HCV). Herpes viral infections. *—if negative, vaccination might be recommended. Tuberculosis test. Chest radiography. |
| Ocrelizumab (OCR) | RRMS     | Depletes circulating immature and mature B cells, but spares CD20-negative plasma cells. Antibody-dependent cellular cytotoxicity | PML (almost carry-over; previously treated with NTZ or fingolimod). Herpes virus reactivation. Hepatitis B reactivation. COVID-19? | Exclusion of active and latent infections (including HIV, HBV, HCV). |
| Ofatumumab (OFAB) | RRMS     | Depletes circulating CD-20-positive B cells. Complement-dependent cellular cytotoxicity | COVID-19?                                                                                   | Exclusion of active and latent infections (including HIV, HBV, HCV). Blood examinations (CBC, blood biochemistry). |
| **Seropositive NMOSD** |             |                                                                                  |                                                                                          |                                                                                          |
| Eculizumab (ECZ) | Relapse prevention | Inhibits the terminal complement protein C5 and prevents the cleavage into C5a and C5b | Meningococcal infection (*Neisseria Meningitis*). Other encapsulated bacteria. | Exclusion of active and latent infections (including HIV, HBV, HCV). Blood examinations (CBC, blood biochemistry). |
| Satralizumab (SAT) | Relapse prevention | Binds to membrane-bound and soluble IL-6 receptors, and blocks the IL-6 signaling pathways | Bacterial pneumonia. *Mycobacterium tuberculosis* infection. Atypical mycobacteriosis. Hepatitis B reactivation. | Exclusion of active and latent infections (including HIV, HBV, HCV). Blood examinations (CBC, blood biochemistry). Tuberculosis test. Herpes virus infections. *—Chest radiography. |
| Inebilizumab (INEB) | Relapse prevention | Binds and depletes CD19-positive B cells, including plasma blasts | Pneumonia                                                                                   | Exclusion of active and latent infections (including HIV, HBV, HCV). Blood examinations (CBC, blood biochemistry). |
| Rituximab (RTX)   | NMOSD (approved) | Binds and depletes CD20-positive B cells                                      | PML (very rare in MS and NMOSD). COVID-19?. Hepatitis B (rare in rheumatoid diseases). Hepatitis C reactivation. | Exclusion of active and latent infections (including HIV, HBV, HCV). Blood examinations (CBC, blood biochemistry). Brain MRI. |

MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; RRMS, relapse-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PML, progressive multifocal leukoencephalopathy; CMV, cytomegalovirus; COVID-19, severe acute respiratory syndrome coronavirus 2 infection; JCV, John Cunningham virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; VZV, varicella zoster virus; CNS, central nervous system; BBB, blood–brain barrier.

*Taking history of previous infections and evaluation of anti-VZV IgG titers.
**Table 2** Clinical stage and MRI findings of NTZ-PML (modified citation from reference 19)

| Stage               | Symptoms                                      | JCV-DNA detection in CSF | MRI findings                                                                 |
|---------------------|-----------------------------------------------|--------------------------|------------------------------------------------------------------------------|
| Presymptomatic PML  | No obvious symptoms                           |                          | Small and solitary subcortical lesions on DWI and FLAIR images               |
|                     |                                               |                          | (FLAIR image is more sensitive than T2 image)                               |
|                     |                                               |                          | (DWI image could be useful for distinguishing between PML lesions and MS relapse) |
|                     |                                               |                          | Punctate pattern of cerebral subcortical region, brainstem and cerebellum    |
|                     |                                               |                          | May be associated with Gd-enhancement                                         |
| Symptomatic PML     | Cognitive impairments                         | May be low levels in NTZ-PML (25-1,000,000 copies/mL) | Enlarging subcortical lesions on FLAIR and T2 images                         |
|                     | Aphasia                                        |                          | T1 image presents low signal intensity                                         |
|                     | Visual disturbance                             |                          | Gd-enhancement is considered rare                                              |
|                     | Hemiparesis                                    |                          | Observed no mass effect                                                        |
| Symptomatic PML     | Punctate pattern of cerebral subcortical region, brainstem and cerebellum |                          |                                                                               |
|                     | May be associated with Gd-enhancement          |                          |                                                                               |
| PML with IRIS       | Worsening of speech and disability            | Vary but may be declining levels (Not detection to >20,000 copies/mL)        | Enlargement of the lesions and mass effects                                   |
|                     | Fever, Headache                               |                          | Contrast enhancement is often recognized                                       |
| Post-PML            | Residual disability                           | Often undetectable       | No contrast enhancement and no mass effects                                   |
|                     | Progressive cognitive impairiments, etc.      | But may be still detectable |                                                                               |
|                     |                                               |                          | Brain atrophy progression                                                     |

PML, progressive multifocal leukoencephalopathy; NTZ, natalizumab; NTZ-PML, natalizumab-associated progressive multifocal leukoencephalopathy; PML JCV, John Cunningham polyomavirus; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; MS, multiple sclerosis; Gd, gadolinium.

**Table 3** Protocol for PML surveillance in patients with NTZ-treated MS (modified citation from reference 19)

| PML risk (/1000)* | Recommended frequency for anti-JCV antibody titer monitoring | Recommended frequency for MRI | Remarks (about MRI sequence) |
|-------------------|-------------------------------------------------------------|-------------------------------|-------------------------------|
| Anti-JCV negative | Every 6 mo                                                  | Annually                      | Conventional sequences<sup>ab</sup> |
| Anti-JCV positive, no prior immunosuppressant | | | |
| · Anti-JCV titer index <0.9 | | | |
| Treatment duration 1–72 mo | 0.6–1.0 | Every 6 mo | Annually | Conventional sequences<sup>b</sup> |
| · Anti-JCV antibody titer 0.9–1.5 | | | |
| Treatment duration 1–36 | 0.8–1.0 | Every 6 mo | Annually | Conventional sequences<sup>b</sup> |
| Treatment duration 37–72 mo | 2–3 | Further test is not required | Every 3–4 mo | DWI image is recommended |
| · Anti-JCV antibody index >1.5 | | | |
| Treatment duration 1–24 mo | 0.2–0.9 | Further test is not required | Annually | Conventional sequences<sup>b</sup> |
| Treatment duration 25–72 mo | 3–10 | Further test is not required | Every 3–4 mo | DWI image is recommended |
| Anti-JCV antibody positive, prior immunosuppressant | | | |
| Treatment duration 1–24 mo | 0.3–0.4 | Further test is not required<sup>cd</sup> | Annually | Conventional sequences<sup>b</sup> |
| Treatment duration 25–72 mo | 4–8 | Further test is not required<sup>cd</sup> | Every 3–4 mo | DWI image is recommended |

The patients with anti-JCV index >0.9 should receive MRI scans annually in the first 24 or 36 mo after induction, then every 3–4 mo afterwards. Frequency of anti-JCV antibodies and MRI evaluations should be increased as appropriate.

<sup>a</sup>For patients with prior immunosuppressive treatment, no significant difference was observed in median index between non-PML and PML patients<sup>26</sup>. PML, progressive multifocal leukoencephalopathy; NTZ, natalizumab; MS, multiple sclerosis; JCV, John Cunningham polyomavirus; DWI, diffusion-weighted image.

<sup>b</sup>For patients with prior immunosuppressive treatment, no significant difference was observed in median index between non-PML and PML patients<sup>26</sup>. PML, progressive multifocal leukoencephalopathy; NTZ, natalizumab; MS, multiple sclerosis; JCV, John Cunningham polyomavirus; DWI, diffusion-weighted image.

<sup>c</sup>For patients with prior immunosuppressive treatment, no significant difference was observed in median index between non-PML and PML patients<sup>26</sup>. PML, progressive multifocal leukoencephalopathy; NTZ, natalizumab; MS, multiple sclerosis; JCV, John Cunningham polyomavirus; DWI, diffusion-weighted image.

<sup>d</sup>Fluid-attenuated inversion recovery and T2-weighted images.
that more than 80% of asymptomatic patients with PML were treated with PLEX, and 66.7% of them developed IRIS. Recently, it has been suggested that there is no evidence for the beneficial effects of PLEX in NTZ-PML. Intravenous pulse corticosteroid therapy can lead to favorable functional outcomes. However, early corticosteroid use had no effect on the subsequent progression of IRIS in early-PML-IRIS. The efficacy of maraviroc, a C-C chemokine receptor type 5 blocker, on PML or PML-IRIS associated with immunosuppressive agents including NTZ, has not yet been proven.

Today, emerging evidence suggests that extended interval dosing (EID) NTZ (infusion every 6 wk) might decrease the risk of PML among patients who were positive for JCV antibodies and had received prior immunosuppressants compared to standard interval dosing (SID) (every 4 wk). NTZ effectiveness was maintained when switched to EID from SID after more than 1-y treatment. However, it should be noted that the risk of PML cannot be completely eliminated with EID, and vigilance is required even under this regimen.

Compared to NTZ, the risk of PML was lower with other mAbs. Nevertheless, anti-CD-20 mAbs that selectively deplete B-cells, such as RTX and OCR, may be associated with PML development. B-cell depletion reduces antibody production, modulates antigen presentation, and diminishes the proinflammatory reaction of the T-cell, which may increase the risk of PML. However, the relationship between RTX and PML remains unclear. Although the onset of PML has been described in RTX-treated patients with rheumatoid arthritis, ANCA-associated vasculitis, and systemic lupus erythematosus (SLE), the incidence was only 1/30,000. RTX-induced PML in patients with MS is very rare. Although the study sample was small, no patients developed PML on a clinical trial of RTX for NMOSD in Japan (RIN-1 study).

To date, 10 cases of confirmed PML after treatment with OCR for MS have been reported. Nine out of 10 cases had carryover PML: eight patients had previously been treated with NTZ, and one with fingolimod. In all eight cases, the duration of NTZ treatment prior to OCR was 22–120 mo. The interval between the last NTZ and the first OCR infusion was 43–98 d, and the onset of PML was within 6 mo of the last NTZ infusion. All patients had tested positive for serum JCV antibodies and had clinical worsening symptoms or MRI findings compatible with PML before OCR initiation. Notably, one patient reported by Patel et al developed PML under OCR monotherapy. The PML of all 10 of the above-referenced cases was nonfatal. The switch from NTZ to B-cell depleting therapy should be performed with extreme caution after adequate clinical and MRI evaluation. Regarding ofatumumab (OFAB), the onset of PML has not been reported during administration for MS and NMOSD. Regarding inebilizumab (INEB), there has been one death due to CNS lesions in the open-label extension of the N-MOmentum study, in which the possibility of PML could not be ruled out.

ATZ is an mAb against CD52 that depletes B and T cells. To date, no cases of PML have been reported after ATZ administration for MS, although they have been reported in patients with lymphocytic leukemia or post-organ transplantation underlying conditions known to predispose to PML. Berger et al classified ATZ based on PML risk as Class III.

As mentioned previously, the anti-JCV antibody index is commonly used to evaluate the risk of developing PML. However, since OCR/RTX and ATZ deplete B-lymphocytes from peripheral circulation, monitoring the anti-JCV index might not be reliable for predicting the risk of PML. In fact, the anti-JCV antibody index was reduced after ATZ and RTX/OCR treatment.

### 2.1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

The first case of SARS-CoV-2 infection (COVID-19) was reported in Wuhan, China, in December 2019. After its rapid spread within China, outbreaks have occurred in almost all countries worldwide. The global mean mortality of COVID-19 is estimated to be 3%, but mortality increases with age, obesity, and comorbidities, such as diabetes, chronic heart disease, severe asthma, and immunosuppressive conditions. Current evidence shows that simply having MS does not increase the risk of developing COVID-19. In the first worldwide meta-analysis of 101,462 MS patients from 1029 articles, the rate of hospitalization and intensive care unit (ICU) admission was low among patients with MS; 4 out of 570 suspected/confirmed COVID-19 patients died, which was lower than the rate in the healthy population. Moreno-Torres et al reported that among 5641 Spanish patients with MS from February to May 2020, 219 patients (3.9%) developed COVID-19, and this incidence was not greater than that in the general Spanish population. They also reported no association between the risk of onset or severity of COVID-19 and the use of specific DMDs. Similarly, COVID-19 clinical outcomes were not associated with exposure to different DMDs in a population-based MD cohort in Austria.

However, there have been reports that treatment with B-cell mAbs, especially RTX, may increase the severity of the COVID-19 clinical course. From their analysis, Safavi et al reported that being on B-cell mAbs was associated with a 2.6-fold increase in the risk of developing COVID-19 compared to treatment with NTZ and fingolimod. In a large cohort of patients with MS and COVID-19 from 28 countries, Simpson-Yap et al reported that RTX was associated with a higher risk of hospitalization, ICU admission, and the need for artificial ventilation, while OCR was associated with hospitalization and ICU admission. Smith et al examined 1439 patients with MS on DMDs, of whom 230 had COVID-19. They reported that, whereas no mAbs (NTZ, OCR, and RTX) were found to be significantly associated with an increased risk for the onset of infection, RTX was associated with increased severity. Salter et al also reported that RTX, but not OCR, was associated with hospitalization. As of September 25, 2021, the Novartis Safety Database recorded 90 confirmed COVID-19 cases receiving OFAB. Most cases (80 patients) were nonserious. From an analysis of the ALITHIOS (open-label, ongoing extension phase 3b trial of OFAB) study, 245 out of 1703 patients (14.3%) receiving OFAB developed COVID-19. Most cases were of mild (44.1%) or moderate (46.5%) severity, and 9% had a severe/life-threatening course (9.8%). These data did not suggest any evidence of
an increased risk of severe or fatal infection compared to hospitalization and fatality rates, as reported in the literature for the general and MS populations.\textsuperscript{68}

Recently, the immune response to SARS-CoV-2 in patients with MS treated with anti-CD20 mAb has been reported.\textsuperscript{69,70} Thornton et al\textsuperscript{71} reported two OCR-treated patients with MS and mild COVID-19 who were negative for IgG against SARS-CoV-2 virus even at 9–12 wk postinfection. Conte et al\textsuperscript{69} analyzed 24 patients with MS infected with COVID-19; only four out of 15 patients using OCR developed antibodies against SARS-CoV-2, while eight out of nine on other DMDs developed antibodies. Similar case reports and cohort studies demonstrating the attenuation of antibody responses following COVID-19 infection during OCR treatment have been published.\textsuperscript{72,73} Florez-Gonzalez et al\textsuperscript{74} reported an OFAB-treated woman with MS with asymptomatic COVID-19 who was fully depleted of CD-19-positive B cells in the blood but mounted a successful humoral response to the virus through IgG and IgM antibodies. Adamic et al\textsuperscript{75} analyzed four OFAB-administrated MS cases with mild COVID-19. Three out of four patients showed fully depleted CD-19-positive B cells. The total serum IgG and IgM levels were normal in all four patients. However, three out of four patients were negative for serum SARS-CoV-2 IgG at the onset of COVID-19, and two patients were still negative 6 mo after the onset, indicating a diminished humoral response to the virus. In contrast, T-cell immunity against SARS-CoV-2 was observed in three out of four patients in the interferon-γ EPISpot assay. Recovery from COVID-19 infection without the development of a humoral immune response to the virus suggests that T-cell-mediated responses may adequately contribute to protection against SARS-CoV-2.\textsuperscript{76}

Interestingly, one reported by Florez-Gonzalez et al,\textsuperscript{74} who showed the presence of CD19-positive B cells and SARS-CoV-2 IgG after COVID-19 onset, was administered OFAB 24 d prior to COVID-19, but had a gap of 28 wk of OFAB application beforehand due to low IgM levels. The link between the time to last infusion or the number of doses of B-cell-depleting mAbs and COVID-19 risk is a problem that needed to be investigated. Reducing the frequency of dosing or adjusting it according to the monitoring of B-cell repopulation kinetics may allow maintenance of efficacy while limiting the risk of infection.\textsuperscript{77} However, the safety and efficacy of EID of B-cell-depleting mAbs have not been established yet. If people with MS take DMDs, especially B-cell-depleting mAbs and test positive for COVID-19, they should immediately contact their healthcare provider to discuss potential treatment options.\textsuperscript{57}

The use of ATZ, which depletes both B cells and T cells, did not seem to cause a severe COVID-19 course.\textsuperscript{63,78} However, the number of patients with MS treated with ATZ who developed COVID-19 is too low to draw meaningful conclusions. NTZ does not increase the risk of developing severe COVID-19 and stopping NTZ treatment or delaying its induction is not recommended.\textsuperscript{79}

Emerging research has been published demonstrating attenuation of the vaccine response following COVID-19 vaccination in various patients with MS/NMOSD treated with DMDs, especially CD-20 depleting agents. As of March 2022, mainly mRNA (Moderna, Pfizer-BionNTech, New York, NY, USA\textsuperscript{90,81} and adenovirus-based (Johnson & Johnson, New Brunswick, NJ, USA)\textsuperscript{82} COVID-19 vaccines have been used worldwide. Some reports have demonstrated an attenuated immune response against SARS-CoV-2 in patients treated with OCR following exposure to both vaccines. Biguat et al\textsuperscript{83} reported that in vaccinated patients with MS, the median IgG index was lower in patients treated with CD-20-depleting agents and S1PR modulators than in patients receiving other DMDs, with exposure to both Pfizer and Moderna vaccines. Achiron et al\textsuperscript{84} demonstrated attenuated IgG production only in 22.7% of all Pfizer-vaccinated patients with MS treated with OCR. Guerrieri et al\textsuperscript{85} also found that the serological response was recognized in only 37.5% of all vaccinated patients with MS under OCR treatment. The response was greater (62.5%) in patients treated with fingolimod.

The Multiple Sclerosis International Federation (MSIF) published an expert consensus recommendation for vaccines.\textsuperscript{57} The MSIF has prompted global COVID-19 advice for people with MS, including a description of the timing of COVID-19 vaccination in relation to DMDs (Table 4).

The relationship between mAbs used for serositive NMOSD and the risk of COVID-19 is unclear. Interestingly, a survey of 192 neurologists who saw patients with NMO from the USA and Canada found that 52% of these patients had been treated with RTX and 11% with eculizumab (ECZ) before the COVID-19 pandemic. Among them, 74% of neurologists differed in the dose for RTX, and 90% of neurologists changed the dosing interval for RTX.\textsuperscript{86} Although INEB has not been reported to increase the risk of COVID-19,\textsuperscript{87} the risk of COVID-19 could be inferred from its similar mechanism of action to other B-cell-depleting agents, such as RTX and OCR.

Tocilizumab (TOC) (not approved for NMOSD) and satralizumab (SAT) bind to membrane-bound and soluble IL-6 receptors and inhibit the IL-6 signaling pathway that involved inflammation.\textsuperscript{88,89} To date, the relationship between SAT and COVID-19 remains unknown. In COVID-19, IL-6 is an important proinflammatory cytokine and is a biomarker for the COVID-19 severity.\textsuperscript{90} IL-6R mAbs have been used for COVID-19 treatment in the early acute phase, and its efficacy for mitigating the severity and mortality has been reported.\textsuperscript{91} However, impairment of IL-6 signaling may result in normalization of C-reactive protein levels and body temperature, even in the presence of systemic infections, and may delay diagnosis. The effect of the long-term use of an IL-6R mAbs on the risk of COVID-19 is an important problem to be resolved.

Regarding ECZ, an anti-C5 mAb approved for serositive NMOSD, there has been one case report of a patient with NMOSD who developed COVID-19 during a year-long treatment with ECZ.\textsuperscript{85} The patient showed a mild clinical course without suspension of ECZ. In the USA and Canada, ATI and ECZ are approved for the treatment of MS and NMOSD. In the study, 52% of the patients were using ATI or ECZ before the COVID-19 pandemic. The participants were asked to continue taking their disease-modifying drugs during the COVID-19 pandemic.
TABLE 4  Summary of recommendations for timing DMTs and the COVID-19 vaccines.(citation from global COVID-19 advice for people with MS published by MSIF[49])

| Drugs         | For the patients about to start treatment | For the patients already taking treatment |
|---------------|------------------------------------------|-----------------------------------------|
| Natalizumab   | Do not delay starting for COVID-19 vaccine injection | No adjustments to the drug are needed |
| Alemtuzumab   | Consider getting fully vaccinated at least 4 wk before starting | Consider getting vaccinated at least 24 wk after the last ATZ dose When possible, resume ATZ at least 4 wk after getting fully vaccinated^a |
| Ocrelizumab   | Consider getting vaccinated two to 4 wk before starting | Consider getting vaccinated at least 12 wk after the last OCR/RTX dose When possible, resume OCR/RTX at least 4 wk after getting fully vaccinated^a |
| Rituximab     | Consider getting fully vaccinated at least 2 wk before starting | There is no data to currently guide timing of the vaccine in relation to the last OFAB dose Consider getting vaccinated 4 wk after your last dose of OFAB When possible, resume OFAB injections 4 wk after getting fully vaccinated^a |

DMTs, disease-modifying therapies; MS, multiple sclerosis; COVID-19, severe acute respiratory syndrome coronavirus 2 infection; ATZ, alemtuzumab; OCR, ocrelizumab; RTX, rituximab; OFAB, ofatumumab. ^aVaccinated the single dose of the J&J or the second dose of other types of vaccines.

decisions regarding NMOSD during the COVID-19 pandemic era should be individualized according to the risk of disease relapse, age, and individual comorbidities.

2.2  Hepatitis B and C infections

Chronic and resolved hepatitis B virus (HBV) is associated with potentially fatal viral reactivation during the use of immunosuppressants, particularly, anti-CD20 mAbs. When the drugs are administered, lymphocyte function is suppressed, and many effector pathways, including the production of viral inhibitory cytokines, are inhibited. This permits increased viral replication and viral protein expression on the hepatocyte surface. After the drugs are discontinued, immune system reconstitution occurs, and cytotoxic T cells recognize viral peptide-expressing hepatocytes. HBV infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg), and in most infected patients, detectable serum HBV-DNA can be as low as 10 IU/mL or as high as several billion IU/mL. The antibody to hepatitis core antigen (anti-HBc Ab) is an accurate and reliable marker of current and previous infections.

HBV reactivation has been reported in patients with cancer treated with RTX-containing immunosuppressants. In contrast, in rheumatological patients, although the risk of HBV reactivation under RTX has been less studied, it is probably lower. Data on OCR and the risk of HBV reactivation are limited. In phase III trials of HBsAg-negative/anti-HBc Ab-positive patients with MS and undetectable HBV DNA, no cases of HBV infection were reported. A single case report of HBV reactivation has been described in patients with MS who were HBsAg-negative/anti-HBc Ab-positive and undergoing OCR treatment. To date, there have been no cases of HBV infection during OFAB treatment. The Food and Drug Administration (FDA) has warned of the risk of HBV infection during OFAB treatment.

Regarding ATZ, no cases of HBV reactivation during treatment for MS have been reported, while hematological patients have a high risk of reactivation. At present, NTZ is not considered to be associated with a high risk of HBV reactivation, although a fatal case of reactivation from the carrier state has been reported. The relationship between anti-IL6R agents and the risk of HBV reactivation is yet to be elucidated. However, reactivation of resolved HBV may occur in patients with treated with TOC. The Japan Society of Hepatology has listed both SAT and TOC as drugs that could cause HBV reactivation.

Screening for HBsAg and anti-HBc Ab is mandatory before starting mAbs. The Japan Society of Hepatology has published guidelines for strategies to combat HBV infection following treatment with immunosuppressive agents and chemotherapy (Figure 1). In principle, when HBsAg is positive, patients and doctors should consult specialized physicians.

HCV reactivation is uncommon. However, Grebely et al reported that HCV-RNA recurrence was observed in 19% patients after adequate treatment for hepatitis. RTX is the most commonly used agent to precede reactivation. The authors reported a female patient with RRMS who developed HCV reactivation during treatment with fingolimod. She had been previously treated for hepatitis C and remained an undetectable HCV-RNA state for more than 4 y. The clinical manifestations of HCV reactivation may vary from asymptomatic to markedly increase aminotransferase levels, and severe hepatic failure may occur. If patients have a previous history of HCV treatment, HCV-RNA should be regularly evaluated after starting immunosuppressive treatments.

2.3  Herpes viruses

Herpes simplex (HSV) 1 and 2, varicella-zoster virus (VZV), and cytomegalovirus (CMV) are the most common herpes viruses that require treatment. Disseminated VZV infections can be life-threatening in immunocompromised individuals. Among the mAbs used for MS and
NMOSD, ATZ is associated with an increased incidence of severe VZV infection. In a randomized controlled phase III trial, the incidence of HSV and herpes zoster infections was more than 4-fold in patients with ATZ compared with that in patients with interferon β1-treated patients. Consequently, the FDA product label recommended prophylaxis with acyclovir from the start of ATZ treatment until CD4-positive lymphocytes are recovered to at least 200 cells/μL, with a minimum duration of prophylaxis of 2 mo, even if CD4-positive lymphocytes resolve earlier. While CMV frequently occurs in patients with ATZ with hematologic diseases, it rarely occurs in patients with MS. Although herpetic infections during NTZ treatment are rare, ~14 cases have been reported of VZV-associated CNS infections or acute retinal necrosis (ARN) during NTZ treatment. Among the 14 cases of ARN, nine resulted in visual impairment or blindness. Herpes simplex encephalitis has also been reported. Herpetic infection might occur in patients both with and without prior immunosuppressive drug use, irrespective of the length of NTZ treatment. Temporary suspension or discontinuation of NTZ should be considered when patients develop a severe herpetic infection.

Although herpetic infections during NTZ treatment are rare, ~14 cases have been reported of VZV-associated CNS infections or acute retinal necrosis (ARN) during NTZ treatment. Among the 14 cases of ARN, nine resulted in visual impairment or blindness. Herpes simplex encephalitis has also been reported. Herpetic infection might occur in patients both with and without prior immunosuppressive drug use, irrespective of the length of NTZ treatment. Temporary suspension or discontinuation of NTZ should be considered when patients develop a severe herpetic infection.

The association between anti-CD20 mAbs and herpetic infections remains unclear. In clinical trials, OCR was associated with increased herpetic infections compared to no treatment (4.7% vs. 3.3%) and IFNβ (5.9% vs. 3.4%). Herpetic infection during RTX therapy has been reportedly lower than that during NTZ and fingolimod therapy.

Before starting mAb treatment, VZV-IgG and HSV-IgG should be evaluated in all patients. Vaccination is recommended in some cases. Patients who are VZV-IgG seronegative and do not have a history of prior varicella infection or vaccination should receive a varicella live-attenuated vaccine (BIKEN in Japan) before starting mAbs. Although the Shingrix (not a live recombinant vaccine) is not indicated to prevent primary varicella infection, it is more effective than the live vaccine in preventing VZV reactivation. In Japan, the Shingrix vaccination of patients with MS before and during mAbs is not generally used. However, it may be recommended for patients who receive low-dose immunosuppressive therapy in addition to mAbs.

3 | BACTERIAL INFECTION

3.1 | Mycobacterium tuberculosis

Mycobacterium tuberculosis (TB) infection in adults usually occurs due to the reactivation of the latent foci of bacteria. TB remains among the top 10 causes of death worldwide. In Japan, both mortality and
morbidity are gradually decreasing, but morbidity trends in younger age groups are increasing slightly. Strategies for latent TB infection (LTBI) are becoming important in the era of widespread biological agents. A medical history, physical examination, and chest radiography are needed to diagnose LTBI. In addition, an interferon-γ-release assay (IGRA) should be performed. QuantiFERON-TB Gold (QFT) and T-SPOT.TB (T-SPOT) are the main assays used. The T-SPOT assay, performed with sorted lymphocytes from the blood, can more accurately distinguish between positive and negative results than QFT.\textsuperscript{127}

ATZ can prompt TB infection because it selectively targets cell surface CD52 to deplete circulating T and B cells, leading to a distinctive pattern of cellular repopulation. TB reactivation occurred in only two of more than 900 cases in an ATZ randomized large-scale phase III trials for MS.\textsuperscript{112,113} However, ATZ is associated with high rates of TB infection in patients with hematological malignancies.\textsuperscript{128,129}

Anti-B-cell agents, including OCR and RTX, are not considered to increase the risk of TB infections.\textsuperscript{123,124,130} Even in TB-endemic countries, anti-B-cell-depleting agents may be safely chosen.\textsuperscript{131}

NTZ may have an influence on the immune control over TB, because it blocks α4-integrin and prevents lymphocyte migration to organs. Nevertheless, TB infection was not observed in randomized control trials,\textsuperscript{12,13} and TB reactivation among latent infections did not occur in the postmarketing experience.\textsuperscript{132} However, notably, Dahdaleh et al\textsuperscript{133} reported two female Irish and Turkish patients who developed apparent TB infection during NTZ treatment.

Anti-IL-6R mAbs might be associated with TB infection, as the blockade of IL-6 signaling may suppress protective immunity against mycobacteria.\textsuperscript{134} In some studies,\textsuperscript{106,135} screening before TOC initiation and prophylactic treatment for LTBI under the use of TOC has been emphasized. Naturally, in the package inserts of TOC and SAT, careful medical history, evaluation of chest radiographs, and IGRA or tuberculin reaction tests are strongly recommended.

### 3.2 Other bacterial infections

ECZ inhibits the terminal complement protein C5, prevents its cleavage into C5a and C5b, and increases the risk of encapsulated bacterial infection, particularly meningococcal infection caused by Neisseria meningitidis. Meningococcal disease develops rapidly and causes meningocencephalitis, bacteremia, and pneumonia. In fulminant cases, disseminated intravascular coagulation and adrenal insufficiency occur, and mortality is 10%–15%, even with appropriate antibiotic therapy. In Japan, meningococcal vaccination with Menactra (MenACWY), which is effective against serotypes A, C, W, and Y, is highly recommended before the induction of ECZ. The Advising Committee on Immunization Practice recommends serogroup B meningococcal vaccine (MenB)\textsuperscript{136} in addition to MenACWY, because serogroup B meningococcal infection is more common in the USA than in Japan. MenB is not produced or approved in Japan. In ECZ-treated NMOSD, meningococcal infection has not been reported in either large clinical trials\textsuperscript{137,138} or postmarketing studies. However, from 2008 to 2016, 16 cases of meningococcal infection were reported after MenACWY (88%) and MenB (75%) in the USA.\textsuperscript{139} Even after vaccination prior to ECZ induction, strict observation is indispensable to avoid overlooking infection during treatment. If patients treated with ECZ present with a high fever, they must immediately consult medical doctors. Prompt examination, including blood culture test, and immediate initiation of antibiotic therapy are essential.

ATZ is associated with listeriosis caused by Listeria monocytogenes. The estimated prevalence of listeriosis after ATZ treatment is ~0.26%. Mazzitelli et al\textsuperscript{140} reported one case and reviewed eight previous case reports; in some cases, the symptoms developed within a few days after ATZ infusion.\textsuperscript{140} Therefore, maintaining dietary precautions for listeria from 2 wk before the start to at least 1 mo after ATZ therapy is recommended.

Chronic use of anti-IL-6R mAbs can result in bacterial infections, such as bacterial pneumonia.\textsuperscript{106} Evaluation of chest radiography is recommended when patients develop minor symptoms, even if white blood cells or C-reactive protein levels are not elevated in blood test results.

### 4 CONCLUSION

Newer mAbs for MS and NMOSD are quite effective in attenuating relapse rates and preventing disability progression, and many patients worldwide benefit from these drugs. However, each drug has a characteristic mode of action that can modulate and interfere with patient’s protective immune responses. As mentioned above, each mAb may increase the risk of different infections. As NTZ increases the risk of PML, regular monitoring of MRI and serum anti-JCV titers is essential. COVID-19 has been pandemic for about three-and-a-half years. Its infectious risks in relation to differential mAbs have been actively discussed worldwide, and strategies for mitigating the infectious risk under mAb therapy are currently being published.

Although I mentioned particularly important infectious complications, each mAb can cause several infections by other pathogens. Before starting mAbs, a profound understanding of the risks and benefits of each drug, taking into consideration the personal condition of each patient, is needed.

### DISCLOSURE OF ETHICAL STATEMENTS

Approval of the Research Protocol: N/A.
Informed Consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

### CONFLICT OF INTEREST

None declared.

### REFERENCES

1. Lassmann H. Multiple sclerosis pathology. Cold Spring Harb Perspect Med. 2018;8:8. https://doi.org/10.1101/cshperspect.a028936
2. Weinschenk BG, Wingerchuk DM. Neuromyelitis Spectrum disorders. Mayo Clin Proc. 2017;92:663–79.
3. Cree BAC, Arnold DL, Chataway J, Chitnis T, Fox RJ, Pozo Ramajo A, et al. Secondary progressive multiple sclerosis: new insights. Neurology. 2021;97:378–88.
4. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. Curr Opin Neurol. 2019;32:385–94.
5. Pardo G, Jones DE. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J Neurol. 2017;264:2351–74.
6. Freedman MS, Selchen D, Prat A, Giacomini PS. Managing multiple sclerosis: treatment initiation, modification, and sequencing. Can J Neurol Sci. 2018;45:489–503.
7. Farez MF, Correale J, Armstrong MJ, Rae-Grant A, Gloss D, Donley D, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology. Neurology. 2019;93:584–94.
8. Moiola L, Barcella V, Benatti S, Capobianco M, Capra R, Cinque P, et al. The risk of infection in patients with multiple sclerosis treated with disease-modifying therapies: a Delphi consensus statement. Mult Scler. 2021;27:331–46.
9. Papeix C, Donze C, Lebrun-Frenay C, French Group for Recommendations in Multiple Sclerosis iSFdISEP, Co C, Group of evaluators C, Lebrun-Frénay C, Papeix C, et al. Infections and multiple sclerosis: recommendations from the French Multiple Sclerosis Society. Rev Neurol. 2021;177:980–94.
10. Otero-Romero S, Sánchez-Montalvá A, Vidal-Jordan A. Assessing and mitigating risk of infection in patients with multiple sclerosis on disease modifying treatment. Expert Rev Clin Immunol. 2021;17:285–300.
11. Jelicć I, Jelicć I, Kempf C, Largey F, Schippling S, et al. Mechanisms of immune escape in central nervous system infection with neurotropic JC virus variant. Ann Neurol. 2016;79:404–18.
12. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, et al. The risk of infection in patients with multiple sclerosis treated with natalizumab. N Engl J Med. 2006;354:899–910.
13. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911–23.
14. Berger JR. Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord. 2017;12:59–63.
15. Williamson EML, Berger JR. Diagnosis and treatment of progressive multifocal leukoencephalopathy associated with multiple sclerosis therapies. Neurotherapeutics. 2017;14:961–73.
16. Kleinschmidt-DeMasters BK. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med. 2005;353:369–74.
17. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med. 2005;353:375–81.
18. https://tys.ms-supportnavi.com/ja-jp/home/risk/risk01.html
19. Major EO, Yousry TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol. 2018;17:467–80.
20. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870–80.
21. Bozic C, Richman S, Plavina T, Natarajan A, Scanlon JV, Subramanyam M, et al. Anti-John Cunningham virus antibody prevalence in multiple sclerosis patients: baseline results of STRATIFY-1. Ann Neurol. 2011;70:742–50.
22. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014;76:802–12.
isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020;9:221–36.

57. The Multiple Sclerosis International Federation. Global COVID-19 advice for people with MS. MSIF_COVID19_en_20220321. https://www.msif.org/resource/global-advice-on-the-coronavirus-and-ms/

58. Moghadasi AN, Mirmosayyeb O, Barzgar M, Sahraei MA, Ghajarzadeh M. The prevalence of COVID-19 infection in patients with multiple sclerosis (MS): a systematic review and meta-analysis. Neurosci. 2021;42:3093–9.

59. Moreno-Torres I, Meca Lallana V, Costa-Fossard L, Orea-Guevara C, Aguirre C, Alba Suarez EM, et al. Risk and outcomes of COVID-19 in patients with multiple sclerosis. Eur J Neurol. 2021:28: 3712–21.

60. Bstgh Q, Assar H, Hegen H, Heschl B, Leutmezer F, Di Pauli F, et al. COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: insights from a nation-wide Austrian registry. PLoS One. 2021;16:e0255316. https://doi.org/10.1371/journal.pone.0255316

61. Barzgar M, Mirmosayyeb O, Ghajarzadeh M, Nehzat N, Vaheb S, Shayannejad V, et al. Characteristics of COVID-19 disease in multiple sclerosis patients. Mult Scler Relat Disord. 2020:45:102276. https://doi.org/10.1016/j.msrd.2020.102276

62. Sormani MP, De Rossi N, Schiavetti I, Carmisciano L, Cordioli C, Moiola L, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann Neurol. 2021;89:780–9.

63. Simpson-Yap S, De Brouwer E, Kalinic T, Rijke N, Hillert JA, Walton C, et al. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. Neurology. 2021;97:e1870–e85.

64. Salter A, Fox RJ, Newsome SD, Halper J, Li DKB, Kanelis P, et al. Outcomes and risk factors associated with SARS-CoV-2 infection in a north American registry of patients with multiple sclerosis. JAMA Neurol. 2021;78:499–708.

65. Safavi F, Nourbakhsh B, Azimi AR. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult Scler Relat Disord. 2020;43:102195. https://doi.org/10.1016/j.msrd.2020.102195

66. Smith TE, Madhavan M, Gratch D, Patel A, Saha V, Sammarco C, et al. Risk of COVID-19 infection and severe disease in MS patients on different disease-modifying therapies. Mult Scler Relat Disord. 2022;60:103735. https://doi.org/10.1016/j.msrd.2022.103735

67. Cross AH, Delgado S, Habel M, Davydovskaya M, Ward BJ, Cree BC, et al. COVID-19 outcomes and vaccination in people with relapsing multiple sclerosis treated with Ofatumumab. Neurol Ther. 2022;11:741–58.

68. Barzgar M, Mirmosayyeb O, Gajarzadeh M, Afshari-Safavi A, Nehzat N, Vaheb S, et al. COVID-19 among patients with multiple sclerosis: a systematic review. Neurol Neuroimmunol Neuroinflamm. 2021;8:e1001. https://doi.org/10.1212/NXI.0000000000001001

69. Conte WL. Attenuation of antibody response to SARS-CoV-2 infection following COVID-19 infection in two MS patients treated with ocrelizumab. Neurol Ther. 2022;11:741–58.

70. Zabalza A, Arrambide G, Tagliani P, Cardenas-Robledo S, Otero-Zabalza A, et al. Risk assessment of progressive multifocal leukoencephalopathy in multiple sclerosis patients treated with different disease-modifying therapies. J Neuropathol Exp Neurol. 2021:79:1553–60.

71. 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. https://doi.org/10.1016/j.msrd.2020.102341

72. Lucchini M, Blanco A, Del Giacomo P, De Fino C, Nociti V, Mirabella M. Is serological response to SARS-CoV-2 preserved in

41. Landi D, De Rossi N, Zagaglia S, Scarpazza C, Prosperini L, Albanese M, et al. No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. Neurology. 2017;88:1144–52.

42. Bernard-Valnet R, Moisset X, Maubeuge N, Lefebvre M, Ouallet JC, Roumier M, et al. CCR5 blockade in inflammatory PML and PML-IRIS associated with chronic inflammatory Diseases’ treatments. Neuroreport. 2022;9:e1097. https://doi.org/10.1212/MRX.0000000000001097

43. Ryerson LZ, Foley J, Chang J, Kister I, Cutter G, Metzger RR, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology. 2019;93:e1452–e62.

44. Butzkueven H, Kappos L, Spelman T, Trojan J, Wiendl H, Su R, et al. No evidence for loss of natalizumab effectiveness with every-6-week dosing: a propensity score-matched comparison with every-4-week dosing in patients enrolled in the Tysabri observational program (TOP). Ther Adv Neurol Disord. 2021;14:17562864211042458. https://doi.org/10.1177/17562864211042458

45. Foley JF, Defer G, Ryerson LZ, Cohen JA, Arnold DL, Butzkueven H, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. Lancet Neurol. 2022;21:608–19.

46. Comi G, Bar-Or A, Lassmann H, Uccelli A, Hartung HP, Montalban X, et al. Role of B cells in multiple sclerosis and related disorders. Ann Neurol. 2021;89:13–23.

47. Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol. 2018;24:323–31.

48. Tahara M, Oeda T, Okada K, Kiriya T, Ochi K, Maruyama H, et al. Safety and efficacy of rituximab in neumyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2020;19:298–306.

49. Toorop AA, van Lierop ZYG, Strijbis EEM, Teunissen CE, Petzold A, Wattjes MP, et al. Mild progressive multifocal leukoencephalopathy after switching from natalizumab to ocrelizumab. Neurol Neuroimmunol Neuroinflamm. 2021;8:e904.

50. Patel A, Sul J, Gordon ML, Steinklein J, Sanguinetti S, Pramanik B, et al. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with Ocrelizumab monotherapy. JAMA Neurol. 2021;78:736–40.

51. Clifford DB, Gass A, Richert N, Tomatore C, Vermersch P, Hughes R. Cases reported as progressive multifocal leukoencephalopathy in rituximab-treated patients with multiple sclerosis. The 35th Congress of the ECTRIMS. September 2019. https://medically.roche.com/en/search/pdfviewer.209d68d3-80cc-43de-afe7-f9b72601b973.html?cid=aproxp0919nneoctrims2019

52. Cree BC, Bennett JL, Kim HJ, Weinstein BG, Pittscock J, Wingruch DM, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-Momentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 2019;394:1352–63.

53. Cox AL, Thompson SA, Jones JL, Robertson VH, Hale G, Mannheim W, et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur J Immunol. 2005;35:3332–42.

54. Preziosi C, Grimaldi A, Landi D, Nicolletti CG, Brazzini G, Picentini F, et al. Risk assessment of progressive multifocal leukoencephalopathy in multiple sclerosis patients during 1 year of Ocrelizumab treatment. Viruses. 2021;13:1684.10339/v13091684

55. Sgarlata E, Chisari CG, Toscano S, Finocchiario C, Lo Fermo S, Milleforini E, et al. Changes in John Cunningham virus index in multiple sclerosis patients treated with different disease-modifying therapies. Curr Neuropharmacol. 2021;19. https://doi.org/10.2174/1570159X1966621111123202

56. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus
154

TAGAWA

152

151

150

149

148

147

146

145

144

143

142

141

140

139

138

137

136

135

134

133

132

131

130

129

128

127

126

125

124

123

122

121

120

119

118

117

116

115

114

113

112

111

110

109

108

107

106

105

104

103

102

101

100

99

98

97

96

95

94

93

92

91

90

89

88

87

86

85

84

83

82

81

80

79

78

77

76

75

74

73

72

71

70

69

68

67

66

65

64

63

62

61

60

59

58

57

56

55

54

53

52

51

50

49

48

47

46

45

44

43

42

41

40

39

38

37

36

35

34

33

32

31

30

29

28

27

26

25

24

23

22

21

20

19

18

17

16

15

14

13

12

11

10

9

8

7

6

5

4

3

2

1

MS patients on ocrelizumab treatment? A case report. Mult Scler Relat Disord. 2020;44:102323. https://doi.org/10.1016/j.msard.2020.102323

73. Sormani MP, Schiavetti I, Landi D, Carmisciano L, De Rossi N, Cordioli C, et al. SARS-CoV-2 serology after COVID-19 in multiple sclerosis: an international cohort study. Mult Scler. 2021;13524585211035318:1034–40. https://doi.org/10.1177/13524585211035318

74. Flores-Gonzalez RE, Hernandez J, Tomes L, Rammohan K, Delgado S. Development of SARS-CoV-2 IgM and IgG antibodies in a relapsing multiple sclerosis patient on ofatumumab. Mult Scler Relat Disord. 2021;49:102777. https://doi.org/10.1016/j.msard.2021.102777

75. Adamiec I, Rogic D, Penz MG, Braun C, Habeck M. Humoral and cellular immunity in convalescent COVID-19 people with multiple sclerosis treated with ofatumumab. J Neuroimmunol. 2022;362:577788. https://doi.org/10.1016/j.jneuroim.2021.577788

76. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Stralin K, Gorin JB, Olston A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell. 2020;183(158-68):e14.e158-168.e14.

77. Bar-Or A, Calkwood JC, Chognot C, Evershed J, Fox EJ, Herman A, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology. 2020;95:e1999–2008.

78. Sormani MP. Italian study group on C-19ms. An Italian programme for vaccination in multiple sclerosis patients treated with ofatumumab. J Neuroimmunol. 2020;362:577788.

79. Reyes S, Cunningham AL, Kalincik T, Havrdova EK, Isobe N, Parkpoor J, et al. Update on the management of multiple sclerosis during the COVID-19 pandemic and post pandemic: an international consensus statement. J Neuroimmunol. 2021;357:577627. https://doi.org/10.1016/j.jneuroim.2021.577627

80. Polack FP, Thomas SJ, Kitchen N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15.

81. Baden LR, El Sahly HM, Braun C, Habeck M, Myamoto K, Miyamoto K, et al. Reactivation of hepatitis B virus with immune-escape mutations after ocrelizumab treatment for aquaporin-4 neuromyelitis optica: a pilot study. Neurology. 2014;82:1302–6.

82. Hamdy SM, Abdel-Naseer M, Shalaby NM, Nares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.

83. Hamdy SM, Abdel-Naseer M, Shehata HS, Shalaby NM, Hassan A, Elmazny A, et al. Management strategies of patients with Neuro-myelitis Optica Spectrum disorder during the COVID-19 pandemic era. Ther Clin Risk Manag. 2020;16:759–67.

84. Sormani MP, Italian study group on C-19ms. An Italian programme for vaccination in multiple sclerosis patients treated with ofatumumab. J Neuroimmunol. 2020;362:577788.

85. Graf J, Mares J, Barnett M, Aktas O, Albrecht P, Zamvil SS, et al. Targeting B cells to modify MS, NMOSD, and MOGAD: part 2. Neuro Immunol Neuroinflamm. 2021;8:e919. https://doi.org/10.1211/NX1.00000000000000919

86. Rezaei SJ, Vogel AC, Gazdag B, Alakel N, Kumar AR, Mateen FJ. Neuromyelitis optica practice and prescribing changes in the setting of Covid19: a survey of neurologists. J Neuroimmunol. 2020;346:577320. https://doi.org/10.1016/j.jneuroim.2020.577320

87. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. Rev Med Virol. 2020;30:1–9.

88. Group WHOREAF-TW, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA. 2021;326:499–518.

89. Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pnievska B, et al. Trial of Natalizumab in Neuromyelitis Optica Spectrum disorder. N Engl J Med. 2019;381:2114–24.

90. Hamdy SM, Abdel-Naseer M, Shalaby NM, Nares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.

91. Group WHOREAF-TW, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA. 2021;326:499–518.

92. Cabal-Herrera AM, Mateen FJ. COVID-19 in a patient treated with eculizumab for aquaporin-4 neuromyelitis optica. J Neurool. 2021; 268:4479–82.

93. Carrelli J, Demaria O, Vely F, Batista L, Chouaia Benmansor N, Fares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.

94. Carrelli J, Demaria O, Vely F, Batista L, Chouaia Benmansor N, Fares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.

95. Cameli M, Storici F, Caneva G, Fares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.

96. Hamdy SM, Abdel-Naseer M, Shalaby NM, Hassan A, Elmazny A, et al. Management strategies of patients with Neuro-myelitis Optica Spectrum disorder during the COVID-19 pandemic era. Ther Clin Risk Manag. 2020;16:759–67.

97. Seto WK, Chan TS, Hung YY, Wong DK, Fung J, Liu KS, et al. Hepatitis B reactivation during chemotherapy. Ther Adv Cancer. 2021;14:3736–43.

98. Sorgati AO, Petri M, Beretta S, Breda S, Rossi S, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: extending perspective from old to newer drugs. World J Hepatol. 2015;7:344–61.

99. Carrelli J, Demaria O, Vely F, Batista L, Chouaia Benmansor N, Fares J, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2020;588:146–50.
107. The Japan Hepatology Society. Japan Society of Hepatology guidelines for the management of hepatitis B virus infection: 2019 update. Hepatol Res. 2020;50:892–923. https://doi.org/10.1111/hepr.13504

108. Grebely J, Pham ST, Matthews GV, Petoumenos K, Bull RA, Yeung B, et al. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. Hepatology. 2012;55:1058–69.

109. Tagawa A, Ogawa T, Tetsuka S, Otsuka M, Hashimoto R, Kato H, et al. Hepatitis C virus (HCV) reactivation during fingolimod treatment for relapsing and remitting multiple sclerosis. Mult Scler Relat Disord. 2016;9:155–7.

110. Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, et al. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. J Hepatol. 2012;57:1177–85.

111. Vento S, Cainelli F, Longhi MS. Reactivation of replication of hepatitis B and C viruses after immunosuppressive therapy: an unresolved issue. Lancet Oncol. 2002;3:333–40.

112. Cohen JA, Coles AJ, Arnold DL, Canfavreux C, Fox EJ, Hartung HP, 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;380:1819–28.

113. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Canfavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829–39.

114. Brownlee WJ, Chataway J. Opportunistic infections after alemtuzumab: new cases of nocardial infection and cytomegalovirus syndrome. Mult Scler. 2017;23:876–7.

115. Bourre B, Lefaucheur R, Ahtoy P, Travers F, Fetter D, Varicella-zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology. 2013;81:1966–7.

116. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. Clin Infect Dis. 2013;57:849–52.

117. Saraiva VS. Acute retinal necrosis and immune reconstitution inflammatory syndrome in a natalizumab-treated patient with multiple sclerosis. Retin Cases Brief Rep. 2015;9:195–7.

118. Haggström L, Prosperini L, Galgani S, Pozzilli C, Pinnetti C. Extradrenal herpes encephalitis during natalizumab treatment: a case report. Mult Scler Relat Disord. 2016;10:124–6.

119. Good AB, Kumar G, Robinson J. Bilateral acute retinal necrosis in a patient with multiple sclerosis on natalizumab. J Ophthalmic Infect. 2016;6:26.

120. Mulero P, Auger C, Parolin L, Fonseca E, Requena M, Rio J, et al. Reactivation of replication of hepatitis B and C viruses after immunosuppressive therapy: an unresolved issue. Lancet Oncol. 2002;3:333–40.

121. Cohen JA, Coles AJ, Arnold DL, Canfavreux C, Fox EJ, Hartung HP, 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;380:1819–28.

122. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Canfavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829–39.

123. Brownlee WJ, Chataway J. Opportunistic infections after alemtuzumab: new cases of nocardial infection and cytomegalovirus syndrome. Mult Scler. 2017;23:876–7.

124. Bourre B, Lefaucheur R, Ahtoy P, Travers F, Fetter D, Varicella-zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology. 2013;81:1966–7.

125. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. Clin Infect Dis. 2013;57:849–52.

126. Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belonga EA, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep. 2018;67:103–8.

127. Uesugi S, Kohguchi K, Kohguchi Y, Tohyama K. Data analysis of the examination and clinical usefulness of T-SPOT in tuberculosis diagnosis. Igakukensa. 2019;68:358–63. https://doi.org/10.14932/jamt.18-115

128. Au WY, Leung AY, Tse EW, Cheung WW, Shew TK, Kwong YL. High incidence of tuberculosis after alemtuzumab treatment in Hong Kong Chinese patients. Leuk Res. 2008;32:547–51.

129. Kim SJ, Moon JH, Kim H, Kim JS, Hwang YY, Intragumtornchai T, et al. Non-bacterial infections in Asian patients treated with alemtuzumab: a retrospective study of the Asian lymphoma study group. Leuk Lymphoma. 2012;53:1515–24.

130. Liao TL, Lin CH, Chen YM, Chang CL, Chen HH, Chen DY. Different risk of tuberculosis and efficacy of isoniazid prophylaxis in rheumatoid arthritis patients with biologic therapy: a Nationwide retrospective cohort study in Taiwan. PLoS One. 2016;11:e0153217.

131. Akadi A, Akudahniu NJ, Alrehailly A. Risk of tuberculosis reactivation with rituximab therapy. Int J Health Sci. 2017;11:41–4.

132. Mulero P, Camino AB, Neri Crespo MJ, Fernandez-Herranz R, Tellez LN. Latent tuberculosis seems not to reactivate in multiple sclerosis patients on natalizumab. J Neuroimmunol. 2012;243:103–5.

133. Dahdaleh D, Altmann DM, Malik O, Nicholas RS. Breathlessness, night sweats, and weight loss on natalizumab. Lancet. 2012;380:726–7.

134. Appelberg R. Protective role of interferon gamma, tumor necrosis factor alpha and interleukin-6 in mycobacterium tuberculosis and M. avium infections. Immunobiology. 1994;191:520–5.

135. Iba A, Tomio J, Yamana H, Sugiyama T, Yoshiyama T, Kobayashi Y. Tuberculosis screening and management of latent tuberculosis infection prior to biologic treatment in patients with immunemediated inflammatory diseases: a longitudinal population-based analysis using claims data. Health Sci Rep. 2020;3:e216. https://doi.org/10.1002/hsr2.216

136. Centers for Disease Control and Prevention. Meningococcal vaccination: recommendations of the advisory committee on immunization practices, United States, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1–41. https://doi.org/10.15585/mmwr.mr6909a1

137. Pittcock SJ, Lennon VA, McKeon A, Weinschenker BG, Lucchinetti CF, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. Lancet Neurol. 2012;13:564–2.

138. Wingerchuk DM, Fujihara K, Palace J, Berthele A, Levy M, Kim HJ, et al. Long-term safety and efficacy of Eculizumab in Aquaporin-4 IgG-positive NMOSD. Ann Neurol. 2021;89:1088–98.

139. McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High risk for invasive meningococcal disease among patients receiving Eculizumab (Soliris) despite receipt of meningococcal vaccine. MMWR Morb Mortal Wkly Rep. 2017;66:734–7.

140. Mazzitelli M, Barone S, Greco G, Serapide F, Valentino P, et al. Listeria infection after treatment with alemtuzumab: a case report and literature review. Would antibiotic prophylaxis be considered? Infez Med. 2020;28:258–62.

How to cite this article: Tagawa A. Infectious issues of therapeutic monoclonal antibodies in multiple sclerosis and neuromyelitis optica spectrum disorders. Clin Exp Neuroimmunol. 2022;13(3):143–55. https://doi.org/10.1111/cen.12721