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Original Research Paper

The risk of infections for multiple sclerosis and neuromyelitis optica spectrum disorder disease-modifying treatments: Eighth European Committee for Treatment and Research in Multiple Sclerosis Focused Workshop Review. April 2021

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Abstract: Over the recent years, the treatment of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) has evolved very rapidly and a large number of disease-modifying treatments (DMTs) are now available. However, most DMTs are associated with adverse events, the most frequent of which being infections. Consideration of all DMT-associated risks facilitates development of risk mitigation strategies. An international focused workshop with expert-led discussions was sponsored by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and was held in April 2021 to review our current knowledge about the risk of infections associated with the use of DMTs for people with MS and NMOSD and corresponding risk mitigation strategies. The workshop addressed DMT-associated infections in specific populations, such as children and pregnant women with MS, or people with MS who have other comorbidities or live in regions with an exceptionally high infection burden. Finally, we reviewed the topic of DMT-associated infectious risks in the context of the current SARS-CoV-2 pandemic. Herein, we summarize available evidence and identify gaps in knowledge which justify further research.

Keywords: Multiple sclerosis, neuromyelitis optica spectrum disorder, disease-modifying treatment, DMT-associated infections, progressive multifocal leukoencephalopathy, coronavirus disease 2019, COVID-19, SARS-CoV-2, risk mitigation strategies

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Introduction

Over the recent years, the treatment of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) have evolved very rapidly and a large number of disease-modifying treatments (DMTs) are now available for people with these conditions.[1–3] The availability of these drugs contributed to improving the natural history of these conditions.[1–3] With the notable exception of first-line injectable DMTs, all DMTs result in some degree of immune impairment, and a corresponding increased risk of adverse events (AEs), mainly infections, compared with untreated patients or the general population.[4,5] It is important to note that MS per se can also imply a higher risk of infections compared to the general population.[4] Although serious DMT-associated infections are relatively rare, they are potentially lethal, or, on some occasions, can aggravate the underlying neurological condition. For these reasons, understanding the risks associated with the drugs currently being used for MS and NMOSD is important, as is early detection procedures and risk mitigation strategies.

Given the importance of the topic, an ECTRIMS Focused Workshop was held in April 2021 to review infections associated with currently available drugs for MS and NMOSD. DMT-associated risks may depend on the specific population that receives the treatment; accordingly, strategies of prevention and management of infections in specific MS populations were also discussed. Finally, given the exceptional and challenging times we are experiencing in the context of Coronavirus Disease-19 (COVID-19) due to SARS-CoV-2 infection, the management of DMT-treated MS and NMOSD patients during the current COVID pandemic was also discussed. This manuscript summarizes the discussions during this workshop, and identifies gaps in knowledge which justify further research. Vaccines in people with MS and NMOSD on DMTs will be summarized in a separate review.

Infections associated with disease-modifying treatments

Understanding the mechanism of action (MoA) of the MS and NMOSD drugs is crucial for understanding the type of immunity impairment correlated with a specific treatment. Table 1 shows the leading medications for MS and NMOSD (except for injectables) and the associated risks of infection observed in the main clinical trials. Below we describe the main infectious risks associated with the main drugs available for MS and NMOSD. Table 2 shows some recommendations related to risk mitigation strategies in relation to infections that can occur in the context of DMT usage. Table 2 also includes DMT-specific considerations related to COVID-19. Table 3 shows the risk of progressive multifocal leukoencephalopathy (PML) associated with the different DMTs. Finally, Table 4 describes COVID-19 outcomes in patients with MS and risk factors of higher severity.

Teriflunomide

Teriflunomide is a dihydroorotate dehydrogenase inhibitor. Dihydroorotate dehydrogenase is a key mitochondrial enzyme in the de novo pyrimidine synthesis that is required by rapidly dividing cells. This means that teriflunomide interferes with the pyrimidine metabolism selectively in activated lymphocytes, and presumably in auto-reactive lymphocytes. Side effects of teriflunomide may include mild to moderate lymphopenia and neutropenia, although these effects were rare—or very rare—in the phase III trials of the drug, and mainly appeared during the first 3 months of treatment.[36] All in all, in the trials, teriflunomide was not associated with an increased risk of infections, which were generally mild for all treatment arms. No clear opportunistic infections were observed either (Table 1).[6–8]

Dimethyl fumarate

Dimethyl fumarate was approved to treat relapsing MS in 2013, after two successful phase III trials, the CONFIRM and DEFINE studies.[9,60] Although the exact MoA of dimethyl fumarate is unknown, it seems to cause immunomodulation by activating the intracellular Nrf2 pathway.[36] Lymphopenia occurs in 37% of patients, but severe lymphopenia (lymphocyte count $<500/mm^3$) only occurs in 8% of them.

In the phase III trials, the incidence of infections was similar in dimethyl fumarate and placebo arms (Table 1). However, the 9-year follow-up ENDORSE study[10] showed that prolonged periods of severe lymphopenia due to dimethyl fumarate treatment were associated with an increased risk of serious and opportunistic infections.[36] To date, nine cases of PML have been reported, mainly in the context of persistent (for more than 6 months) moderate–severe lymphopenia (Table 3). Other opportunistic infections associated with dimethyl fumarate treatment, within and outside the central nervous system (CNS), have also been reported,[10,57] in particular Varicella-Zoster virus (VZV) (within and outside CNS), followed by Herpes Simplex virus (HSV) (within and outside CNS), cytomegalovirus (outside CNS), *Cryptosporidium* species (outside CNS), *Mycobacterium tuberculosis* (outside CNS), and *Candida* species (outside CNS).[57]

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Table 1. Infections reported in phase III (and main phase II) clinical trials of disease-modifying treatments currently in use for MS and NMOSD.

DMT	Name of trial (reference)	Trial population	% of patients with infection		Infections described in active arm (% patients affected)	Increased infection risk in active arm with respect to control arm
			Active arm	Control arm		
- Teriflunomide	TEMSO study (O'Connor et al.[6])	RMS (with or without progression) $N=1088$	TFL 7 and 14 mg: similar to placebo	Placebo: not specified	Nasopharyngitis,[a] UTI,[a] influenza[a]	No increased risk
- Teriflunomide	TENERE study (Vermersch et al.[7])	RMS (with or without progression) $N=324$	TFL 7 mg: 64.5% TFL 14 mg: 49.1%	IFNb-1a: 46.5%	Nasopharyngitis (23%), TB (1 case, <1%)	No increased risk
- Teriflunomide	TOWER study (Confavreux et al.[8])	RMS (with or without progression) $N=1169$	TFL 7 mg: 48% TFL 14 mg: 44%	Placebo: 51%	Nasopharyngitis (12%),[b] URTI (9%),[b] UTI (8%)[b]	No increased risk
- Dimethyl fumarate	CONFIRM study (Fox et al.[9])	RRMS $N=1430$	BG-12 BD: 56% BG-12 TDS: 56%	GA: 50% Placebo: 50%	Nasopharyngitis (17%),[b] UTI (13%),[b] URTI (12%)[b]	No increased risk
- Dimethyl fumarate	DEFINE study (Gold et al.[10])	RRMS $N=1237$	BG-12 BD: 64% BG-12 TDS: 68%	Placebo: 65%	Nasopharyngitis,[a] URTI,[a] UTI,[a] influenza[a]	No increased risk
- S1P receptor modulator: fingolimod	TRANSFORMS study (Cohen et al.[11])	RRMS $N=1292$	FTY pooled (1.25 and 0.5 mg): 51%–53%[c]	IFNb-1a: 51%–53%[c]	Nasopharyngitis (21%),[b] URTI (8%),[b] influenza (7%),[b] UTI (6%),[b] herpes viral infections (FTY 1.25 mg: 5.5%; FTY 0.5 mg: 2.1%)	No increased risk except for herpes viral infection in FTY 1.25 mg arm
- S1P receptor modulator: fingolimod	FREEDOMS study (Kappos et al.[12])	RRMS $N=1272$	FTY pooled (1.25 mg and 0.5 mg): 69%	Placebo: 72%	Nasopharyngitis (27%),[b] URTI (18%), influenza (11%),[b] LRTI (11%),[b] herpes viral infections (7%),[b] UTI (6%)[b]	No increased risk except for LRTI, especially for FTY 1.25 mg arm

(Continued)

Table 1. (Continued)

DMT	Name of trial (reference)	Trial population	% of patients with infection		Infections described in active arm (% patients affected)	Increased infection risk in active arm with respect to control arm
			Active arm	Control arm		
- S1P receptor modulator: fingolimod	FREEDOMS II study (Calabresi et al.[13])	RRMS $N=1083$	FTY 1.25 mg: 73% FTY 0.5 mg: 74%	Placebo: 72%	URTI (25%),[b] nasopharyngitis (24%),[b] sinusitis (14%),[b] influenza (9%),[b] LRTI (12%),[b] herpes viral infections (9%),[b] UTI (14%)[b]	No increased risk except for herpes viral infections, especially for FTY 1.25 mg arm
- S1P receptor modulator: fingolimod	INFORMS study (Lublin et al.[14])	PPMS $N=970$	FTY 0.5 mg: similar to previous studies with FTY[c]	Placebo: similar to previous studies with FTY[c]	Nasopharyngitis (23%), UTI (15%), URTI (11%), influenza (9%), LRTI (7%), herpes viral (VZV) infection (3%)	No increased risk
- S1P receptor modulator: siponimod	EXPAND study (Kappos et al.[15])	SPMS $N=1651$	BAF312: 49%	Placebo: 49%	Nasopharyngitis (14%), UTI (12%), herpes viral infections (5%), including VZV reactivations (2%)	No increased risk except for VZV reactivations
- S1P receptor modulator: ozanimod	SUNBEAM study (Comi et al.[16])	RMS $N=1346$	Ozanimod 0.5 and 1.0 mg: similar to IFNb-1a (range: 26.7–18.9%)	IFNb-1a: similar to ozanimod (range: 26.7%–18.9%)	Nasopharyngitis (7%–10%), URTI (7%–9%), UTI (2%–4%)	No increased risk
- S1P receptor modulator: ozanimod	RADIANCE study (Cohen et al.[17])	RMS $N=1695$	Ozanimod 0.5 and 1.0 mg: similar to IFNb-1a	IFNb-1a: similar to ozanimod	Nasopharyngitis (13%–16%), UTI (4%–5%)	No increased risk (except for slightly higher risk of nasopharyngitis in ozanimod groups, i.e., 0.5 and 1.0 mg)
- S1P receptor modulator: ponesimod	OPTIMUM (Kappos et al.[18])	RMS (with or without progression) $N=1133$	Ponesimod: similar to teriflunomide	Teriflunomide: similar to ponesimod	Nasopharyngitis (19%), URTI (11%)	No clearly increased risk

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Table 1. (Continued)

DMT	Name of trial (reference)	Trial population	% of patients with infection		Infections described in active arm (% patients affected)	Increased infection risk in active arm with respect to control arm
			Active arm	Control arm		
- Cladribine	CLARITY study (Giovannoni et al.[19])	RRMS $N=1326$	CLA 3.5 mg: 48% CLA 5.25 mg: 49%	Placebo: 43%	Nasopharyngitis (14%)[b], URTI (12%)[b], herpes viral infections, mainly VZV (2%)[b], TBC reactivation (one case, <1%)[b]	Slightly increased risk of overall infection rate, and serious infectious AE
Monoclonal antibodies						
- Anti-α4 integrin: natalizumab	AFFIRM study (Polman et al.[20])	RRMS $N=942$	NTZ: 79%	Placebo: 79%	UTI (20%), LRTI (17%), GE (11%), Vaginitis (10%), Tonsilitis (7%)	No increased risk
- Anti-α4 integrin: natalizumab	SENTINEL study (Rudick et al.[21])	RRMS $N=1171$	NTZ + IFNb-1a: 83%	IFNb-1a: 81%	Nasopharyngitis (39%), URTI (15%), influenza (17%) UTI (<1%), PML (2 cases: 1 during and 1 after trial)	No increased risk, except for JCV-PML cases
- Anti-CD52: alemtuzumab	CARE-MS I (Cohen et al.[22])	Treatment naïve RRMS $N=581$	ALZ: 67%	IFNb-1a: 45%	Nasopharyngitis (20%), UTI (17%), herpes viral infections (16%), including herpes simplex virus (13%) and VZV (4%),[d] URTI (15%), disseminated TB (1 case)	Increased risk of: overall rate of infections, all individual types of infections, especially herpes viral infections, and serious infectious AE
- Anti-CD52: alemtuzumab	CARE-MS II (Coles et al.[23])	Previously treated RRMS $N=840$	ALZ 12 mg: 77% ALZ 24 mg: 83%	IFNb-1a: 66%	Nasopharyngitis (30%),[b] UTI (22%),[b] URTI (17%),[b] herpes viral infections (16%),[b] including herpes simplex virus (9%)[b] and VZV (6%),[b,e], sinusitis (13%),[b] influenza (10%)[b]	Increased risk (in both ALZ arms, which behaved similarly) of: overall rate of infections, all individual types of infections, especially herpes viral infections, and serious infectious AE

(Continued)

Table 1. (Continued)

DMT	Name of trial (reference)	Trial population	% of patients with infection		Infections described in active arm (% patients affected)	Increased infection risk in active arm with respect to control arm
			Active arm	Control arm		
- Anti-CD20: rituximab	HERMES study, phase II (Hauser et al.[24])	RRMS $N=104$	RTX: 70%	Placebo: 71%	Nasopharyngitis (20%), URTI (19%), UTI (15%), sinusitis (13%), influenza (6%); no opportunistic infections reported	Increased risk of UTI (15% vs 9%) and sinusitis (13% vs 9%); no increased risk of infection-related AE
- Anti-CD20: rituximab	OLYMPUS study, phase II-III (Hawker et al.[25])	PPMS $N=439$	RTX: 68%	Placebo: 65%	LRTI (pneumonia, bronchitis), UTI, pyelonephritis (1 case), cellulitis (2 cases), diverticulitis (1 case), meningitis (1 case), E. coli bacteriemia (1 case), influenza (1 case)	Increased risk of infection-related serious AE (4% vs $<1\%$)
- Anti-CD20: rituximab	RIN-1 study, phase II/III (Tahara et al.[26])	NMOSD $N=38$	RTX: not specified (possibly $\geqslant 58\%$)[a]	Placebo: not specified (possibly $\geqslant 52\%$)[a]	Nasopharyngitis (37%), URTI (21%)	Possibly increased risk of URTI (21% vs 5%), although low numbers
- Anti-CD20: ocrelizumab	OPERA I and II studies (Hauser et al.[27])	RMS $N=821$ (OPERA I) $N=835$ (OPERA II)	OCR: 59% (pooled OPERA I and II)	IFNb-1a: 53% (pooled OPERA I and II)	Nasopharyngitis (15%), URTI (15%), UTI (12%), herpes viral infections (6%), including VZV (2%) and oral herpes (3%) infections; no opportunistic infections reported	Slightly increased risk of nasopharyngitis (15% vs 10%), URTI (15% vs 11%), and herpes virus infections (6% vs 3%)
- Anti-CD19: inebilizumab	N-Momentum study, phase II/III (Cree et al.[28])	NMOSD $N=230$	IBZ: not specified[a]	Placebo: not specified[a]	UTI (12%), nasopharyngitis (7%), URTI (3%), herpes virus infection, mainly oral herpes (1%); no opportunistic infections reported	Slightly increased risk of UTI (12% vs 9%)
- Anti-IL6: satralizumab	SAkuraStar study, phase III (Traboulsee et al.[29])	NMOSD $N=168$	STZ: 54%	Placebo: 44%	UTI (17.5%), URTI (15.9%), nasopharyngitis (14.3%); no opportunistic infections reported	No clearly increased risk

(Continued)

Table 1. (Continued)

DMT	Name of trial (reference)	Trial population	% of patients with infection		Infections described in active arm (% patients affected)	Increased infection risk in active arm with respect to control arm
			Active arm	Control arm		
- Anti-IL6: satralizumab	SAkuraSky study, phase III (Yamamura et al.[30])	NMOSD $N=83$	STZ + IS[f]: 68%	IS: 62%	Nasopharyngitis (24%), URTI (24%), UTI (17%); no opportunistic infections reported	No increased risk
- Anti-IL6: tocilizumab	TANGO study, phase II (Zhang et al.[31])	NMOSD $N=118$	TCZ: 66%	AZA: 73%	URTI (29%), UTI (29%); no opportunistic infections reported	No increased risk
- Anti-C5: eculizumab	PREVENT study, phase III (Pittock et al.[32])	NMOSD $N=143$	ECZ (±IS): not specified[a]	Placebo (±IS): not specified[a]	Upper respiratory tract infection (29%), nasopharyngitis (21%), UTI (14%); 1 patient in the ECZ group who was also receiving azathioprine died during the open-label extension study due to a pulmonary empyema	Increased risk of URTI (29% vs 13%). NB: due to the known higher risk of infections by capsulate bacteria associated with ECZ, all patients had been vaccinated against *Neisseria meningitidis* before study initiation

DMT: disease-modifying treatment; RMS: relapsing multiple sclerosis; TFL: teriflunomide; UTI: urinary tract infection; TB: tuberculosis; URTI: upper respiratory tract infection; RRMS: relapsing remitting multiple sclerosis; BG-12 BD: dimethyl fumarate twice daily; BG-12 TDS: dimethyl fumarate thrice daily; GA: glatiramer acetate; FTY: fingolimod; LRTI: lower respiratory tract infection; PPMS: primary progressive multiple sclerosis; VZV: Varicella-Zoster virus; BAF312: siponimod; CLA: cladribine; AE: adverse event; NTZ: natalizumab; PML: progressive multifocal leukoencephalopathy; JCV-PML: JC virus-associated progressive multifocal leukoencephalopathy; ALZ: alemtuzumab; NMOSD: neuromyelitis optica spectrum disorder; OCR: ocrelizumab; IBZ: inebilizumab; STZ: satralizumab; IS: immunosuppressant; TCZ: tocilizumab; AZA: azathioprine; ECZ: eculizumab; S1P: sphingosine 1-phosphate; IFNb: interferon beta; TBC: tuberculosis; SPMS: secondary progressive multiple sclerosis; GE: gastroenteritis; RTX: rituximab; NB: nota bene (latin).

[a]The exact number of cases (and %) are not specified.

[b]Pooled active arms.

[c]No more information provided.

[d]VZV infection includes: 12 cases (3% of patients) of VZV reactivation (herpes zoster) and 1 case (<1%) of VZV primoinfection (varicella).

[e]VZV infection includes: 38 cases (6% of patients) of VZV reactivation (herpes zoster) and 2 cases (<1%) of VZV primoinfection (varicella).

[f]IS could include oral glucocorticoids, azathioprine, mycophenolate mofetil, azathioprine plus glucocorticoids, or mycophenolate mofetil plus glucocorticoids.

Table 2. Risk mitigation strategies for DMT-related infections: recommendations.

Main potential infection risks	Risk minimization strategies	
	Before starting DMT	During DMT
All DMTs		
Influenza	• Annual vaccination	• Annual vaccination
Measles, rubella, mumps	• Ab screening; vaccination if negative IgG	–
HIV	• Antigen p24 detection: referral to specialized unit of positive	–
Streptococcus pneumoniae	• Consider vaccination[33] (conjugate vaccine PCV13 and/or polysaccharide PPSV23 pneumococcal vaccine)[b] especially if immunosuppression is planned	–
Clostridium tetani	• Vaccination (tetanus, generally with Diphtheria (dT) or with Diphtheria and *Bordetella pertussis (dTpa)*)[b]	–
Teriflunomide		
SARS-CoV-2	• COVID-19 vaccine	• No association with SARS-CoV-2 infection or severe COVID-19[34,35] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or vaccine booster (if/when indicated by regulatory agencies) • COVID-19 vaccine expected to trigger a satisfactory humoral and cellular immune response[34]
Tuberculosis	• Tuberculin skin test or IGRA • Thorax X-ray in patients with positive results; TB treatment if positive	• Thorax X-ray monitoring
Dimethyl fumarate		
JCV-PML	• Screening anti-JCV IgG and index (not mandatory but relevant)	–
SARS-CoV-2	• COVID-19 vaccine	• Risk of severe COVID-19 is small in patients with mild (counts above 800/mm^3) lymphopenia[36] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or vaccine booster (if/when indicated by regulatory agencies) • COVID-19 vaccine expected to trigger a satisfactory humoral and cellular immune response, especially if there is no lymphopenia[37,38]
Cryptococcus	–	• Low threshold of suspicion when finding meningeal signs[a] • Consider *Cryptococcus* especially if age >50 years and prolonged treatment • Monitoring of lymphopenia
Tuberculosis	• Tuberculin skin test or IGRA • Thorax X-ray in patients with positive results • TB treatment if positive	• Thorax X-ray monitoring
S1P receptor modulators: fingolimod, siponimod, ozanimod, and ponesimod		
JCV-PML	• Screening anti-JCV IgG and index for patients on natalizumab	• No specific anti-PML monitoring strategy unless patient has switched from NTZ due to JCV seroconversion: in that case, increased MRI monitoring during the first (6–12) months (more data are needed)
HSV	–	• Prophylaxis with acyclovir 200 mg bd if grade IV lymphopenia

(Continued)

Table 2. (Continued)

Main potential infection risks	Risk minimization strategies	
	Before starting DMT	During DMT
VZV	• VZV Ab screening; vaccination if negative IgG	• Monitoring of lymphopenia
HPV	• Screening (Pap smear test) • Referral to specialized unit if positive; vaccination	• Increased HPV screening program
SARS-CoV-2	• COVID-19 vaccine	• No association with SARS-CoV-2 infection or severe COVID-19[34] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or vaccine booster (if/when indicated by regulatory agencies) • FTY treatment may imply reduced cellular and humoral responses to COVID-19 vaccine;[39] patients should be advised to reinforce anti-COVID protective measures
Cryptococcus	–	• Low threshold of suspicion when finding meningeal signs • Consider *Cryptococcus* especially if age >50 years and prolonged treatment • Monitoring of lymphopenia
Candida	–	• Monitoring of mucocutaneous candidiasis • Monitoring of lymphopenia
Tuberculosis	• Tuberculin skin test or IGRA • Thorax X-ray in patients with positive results • TB treatment if positive	• Thorax X-ray monitoring
Cladribine		
HSV	–	• Prophylaxis with acyclovir 200 mg bd if grade IV lymphopenia
VZV	• VZV Ab screening; vaccination if negative IgG	• Monitoring of lymphopenia
SARS-CoV-2	• COVID-19 vaccine • If patient not yet on cladribine, the start of the drug may be delayed 2–4 weeks after complete vaccination	• Possibly increased risk of infection and reinfection for SARS-CoV-2 • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies) • Cladribine is associated with a reduced cellular response to COVID-19 vaccine if administered before immune reconstitution;[36] therefore, COVID-19 vaccine/booster needs to be administered preferably after immune reconstitution
Tuberculosis	• Tuberculin skin test or IGRA • Thorax X-ray in patients with positive results • TB treatment if positive	• Thorax X-ray monitoring
Nocardia spp.	–	• Monitoring of lymphopenia
Natalizumab		
JCV-PML	• Screening anti-JCV IgG and index for patients on natalizumab	• Increased MRI surveillance • Monitoring of anti-JCV antibodies and index for patients on natalizumab • Extended dosage (6 weeks for natalizumab) • Switch to a low-PML risk drug
HSV	–	• Prophylaxis with acyclovir 200 mg bd if grade IV lymphopenia

(Continued)

Table 2. (Continued)

Main potential infection risks	Risk minimization strategies	
	Before starting DMT	During DMT
VZV	• VZV Ab screening; vaccination if negative IgG	• Monitoring of lymphopenia (if present)
SARS-CoV-2	• COVID-19 vaccine	• No increased risk of SARS-CoV2 infection or severe COVID-19[34] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies) • COVID-19 vaccine expected to trigger a satisfactory humoral and cellular immune response[37]
Cryptococcus	–	• Low threshold of suspicion when finding meningeal signs • Consider *Cryptococcus* especially if age >50 years and prolonged treatment • Monitoring of lymphopenia (if present)
Candida	–	• Monitoring of mucocutaneous candidiasis • Monitoring of lymphopenia (if present)
Alemtuzumab		
HSV	–	• Prophylaxis with acyclovir 200 mg bd if grade IV lymphopenia or during 28 days after each alemtuzumab course
VZV	• VZV Ab screening; vaccination if negative IgG	• Monitoring of lymphopenia
HPV	• Screening (Pap smear test) • Referral to specialized unit if positive; vaccination	• Increased HPV screening program
HAV, HBV, HCV	• Ab/Ag screening (anti-HAV IgG, HBsAg, anti-HBs, anti-HBc, anti-HCV Ab) • Vaccination against HAV and HBV if seronegative • Referral to specialized unit if positive	–
CMV	• –	• Monitoring of viral load every 3 months or more frequently (suggested)
SARS-CoV-2	• COVID-19 vaccine • If patient not yet on ALZ, the start of the drug may be delayed 2–4 weeks after complete vaccination	• Possibly increased risk of infection and reinfection for SARS-CoV-2, and severe COVID-19; susceptibility may be greatest during the first 6 months after an alemtuzumab cycle[36] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or vaccine booster (if/when indicated by regulatory agencies) preferably after immune reconstitution: although COVID-19 vaccine is expected to trigger a satisfactory humoral and cellular immune response, vaccine response is likely best when administered at least 6 months after the last alemtuzumab dose[37]
Candida	–	• Monitoring of mucocutaneous candidiasis • Monitoring of lymphopenia
Tuberculosis	• Tuberculin skin test or IGRA • Thorax X-ray in patients with positive results • TB treatment if positive	• Thorax X-ray monitoring

(Continued)

Table 2. (Continued)

Main potential infection risks	Risk minimization strategies	
	Before starting DMT	During DMT
Listeria monocytogenes	–	• Free *Listeria* diet and/or cotrimoxazole 960 mg three times per week for 1 month after each cycle of alemtuzumab
Nocardia spp.	–	• Monitoring of lymphopenia
Anti-CD20 therapies: rituximab and ocrelizumab		
JCV-PML	• Screening anti-JCV IgG and index (not mandatory but recommended, given that later hypogammaglobulinemia can interfere with testing)	–
HSV	–	• Prophylaxis with acyclovir 200 mg bd if grade IV lymphopenia
VZV	• VZV Ab screening • Vaccination if negative IgG	• Monitoring of lymphopenia
HAV, HBV, HCV	• Ab/Ag screening (anti-HAV IgG, HBsAg, anti-HBs, anti-HBc, anti-HCV Ab) • Vaccination against HAV and HBV if seronegative; referral to specialized unit if positive	–
SARS-CoV-2	• COVID-19 vaccine • If patient not yet on anti-CD20, the start of the DMT may be delayed 4 weeks after complete vaccination	• Increased risk of infection and reinfection for SARS-CoV-2 and severe COVID-19[40–44] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies) • Anti-CD20 drugs are associated with a reduced humoral response to COVID-19 vaccine,[45] at least up to 4 months after the second vaccine dose.[46] Instead, the cellular response to COVID-19 vaccine seems to be preserved.[46,47] • To optimize chances of developing a humoral response, COVID-19 vaccine/booster should be administered at least 6 months (and preferably 9 months) after the last anti-CD20 drug infusion, and at least 4 weeks before the next one • Consider prophylaxis with SARS-CoV-2 neutralizing antibodies[48] for contacts of COVID-19-positive subjects if no optimal vaccine response has been achieved • For anti-CD20 drugs: ○ check IgG/M/A before each infusion; ○ if hypogammaglobulinemia exists, consider IVIG; ○ consider extended dosage; however, caution must be advised regarding extended dosing in NMOSD patients (risk of severe/disabling attacks)
Candida	–	• Monitoring of mucocutaneous candidiasis • Monitoring of lymphopenia

(Continued)

Table 2. (Continued)

Main potential infection risks	Risk minimization strategies	
	Before starting DMT	During DMT
Anti-CD19 drugs: inebilizumab		
SARS-CoV-2	• COVID-19 vaccine • If patient not yet on anti-CD19, the start of the DMT may be delayed 4 weeks after complete vaccination	• Possibly increased risk of infection and reinfection for SARS-CoV-2 and severe COVID-19, given its mechanism of action[49] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies) • COVID-19/booster needs to be administered preferably at least 6 months after the last anti-CD19 infusion • For anti-CD19 drugs: ○ check IgG/M/A before each infusion; ○ if hypogammaglobulinemia exists, consider IVIG; ○ consider extended dosage; however, caution must be advised regarding extended dosing in NMOSD patients (risk of severe/disabling attacks)
Candida	–	• Monitoring of mucocutaneous candidiasis • Monitoring of lymphopenia
Anti-IL-6 receptor: satralizumab and tocilizumab		
SARS-CoV-2	• COVID-19 vaccine	• A priori, no increased risk of SARS-CoV2 infection or severe COVID-19[49] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies) • In selected cases (high IL-6 levels and respiratory insufficiency), tocilizumab might be beneficial to treat COVID-associated inflammatory syndrome[50,51]
Anti-C5 drugs: eculizumab		
SARS-CoV-2	• COVID-19 vaccine	• A priori, no increased risk of SARS-CoV-2 infection or severe COVID-19[52,53] • Recommendation of COVID-19 vaccine (if vaccination not done before DMT onset) or booster (if/when indicated by regulatory agencies)
Neisseria meningitidis	• *Vaccination against Neisseria meningitides (serogroup B (MenB) and quadrivalent conjugate vaccine (MACWY135))*[b]	–
Haemophilus influenzae	• Vaccination against *Haemophilus influenzae*[c]	–

DMT: disease-modifying treatment; Ab: antibody; IgG: immunoglobulin G; HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 19; IGRA: interferon-gamma release assay; TB: tuberculosis; JCV-PML: JC virus-associated progressive multifocal leukoencephalopathy; PML: progressive multifocal leukoencephalopathy; NTZ: natalizumab; JCV: JC virus; MRI: magnetic resonance imaging; HSV: herpes simplex virus; VZV: Varicella-Zoster virus; HPV: human papillomavirus; FTY: fingolimod; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; CMV: cytomegalovirus; ALZ: alemtuzumab; IVIG: intravenous immunoglobulin; NMOSD: neuromyelitis optica spectrum disorder; IL-6: interleukin 6; S1P: sphingosine 1-phosphate.

[a]First cases of cryptococcosis with dimethyl fumarate have been recently reported.[54]

[b]Following general guidelines applicable in each country.

[c]*Haemophilus influenzae* type b can cause many different kinds of infections. These infections usually affect children under 5 years of age, but can also affect adults.[55]

Table 3. DMT-associated PML.

Drug	Frequency figures in the literature	References
Teriflunomide	No cases described	–
Dimethyl fumarate	• Rare cases described (i.e. nine so far) • Cases described mainly in the context of persistent (>6 months) moderate-severe lymphopenia • Rare cases reported in patients with normal blood lymphocyte counts • Prior natalizumab use: risk factor for DMT-associated PML	Diebold et al.[56] Kim et al.[57]
S1P receptor modulators	• Fingolimod: low incidence (between 0.069[58] and ~0.12[59] per 1000 patients exposed) • Siponimod: no cases described • Ozanimod: no cases described • Ponesimod: no cases described	Roy et al.[58] Berger et al.[59]
Cladribine	No cases described in MS, but some PML cases described in patients with hematological conditions	Otero-Romero et al.[33] Gold et al.[60]
Natalizumab	• Overall prevalence: 4.2/1000 treated patients • Prevalence in people with >24 m on natalizumab and prior immunosuppressant exposure: 1/70 • Cumulative PML probability over 6 years: 1.7%	Schwab et al.[61] Major et al.[5]
Alemtuzumab	• One case described	Gerevini et al.[62]
Anti-CD20 therapies	• One case described	Patel et al.[63]
Anti-CD19 drugs	• No cases described	–
Anti-IL-6 receptor drugs	• No cases described	–
Anti-C5 drugs	• No cases described	–

DMT: disease-modifying treatment; PML: progressive multifocal leukoencephalopathy; S1P: sphingosine 1-phosphate; MS: multiple sclerosis; IL-6: interleukin 6.

Sphingosine 1-phosphate receptor modulators

In 2010, oral fingolimod, a sphingosine 1-phosphate (S1P) receptor modulator, was approved to treat relapsing-remitting multiple sclerosis (RRMS).[64] More recently, other S1P-modulators, including siponimod, ozanimod, and ponesimod, have also been approved for the treatment of MS.[65,66] S1P is a phospholipid involved in the regulation of immune cell response, cardiac rate, smooth muscle tone, and endothelial barrier function.[64] There are five different subtypes of S1P receptors, expressed in other cells: T and B lymphocytes mainly express S1P1 and S1P3 receptor subtypes, and, to a lesser extent, S1P4. Both S1P1 and S1P3 are expressed in many other cells, whereas S1P4 is only expressed in lymphoid tissue and airway smooth muscle cells.[64] S1P5 is expressed in the CNS tissue, in oligodendrocytes.[67]

All S1P modulators approved or under investigation for treating MS bind to the S1P1 receptors on immune cells, as part of their clinical MoA, responsible for the desired clinical effects, and commonly also bind to some other receptors. Such non-S1P1 receptor binding and the ubiquity of the S1P1 receptor explain many of the AE associated with S1P modulators.[64] However, the infection-related AE associated with S1P modulators appear in the context of their MoA: through the binding to S1P1 receptors on immune cells.[64] The binding of S1P modulators to S1P1 receptors prevents lymphocytes from egressing from lymph nodes because the complex S1P-modulator-plus-S1P1-receptor is internalized and the receptor is degraded permanently. This means that the receptor, which is needed for lymphocyte egress from lymph nodes, is not available for signaling. This results in the sequestration of lymphocytes in secondary lymphoid organs and, subsequently, sustained lymphopenia.[64] However, the lymphopenia, which reduces the inflammatory activity and is associated with the beneficial clinical effects of S1P modulators, also results in a growing risk of infections in patients exposed to these therapies.[64] On the other hand, the actual lymphocyte levels in blood have not shown a correlation with the infectious risk.[68]

S1P modulators have been associated with specific infectious risks, mainly viral and fungal infections (Table 1). Concerning viral, and particularly herpetic infections, both VZV primary infection and reactivation have been observed in fingolimod-treated patients who showed a reduced number of VZV-specific T-cells in the blood and signs of subclinical

reactivation in the saliva.[69] Primary herpetic infections, which have been described in the context of fingolimod, siponimod, ponesimod, and ozanimod treatment, may be particularly harmful, leading to a disseminated, lethal disease. Concerning fungal infections, cryptococcal infections stand out for their frequency and severity and include primary cutaneous, pulmonary, and disseminated cryptococcosis, as well as cryptococcal meningoencephalitis. Infections with *Mycobacterium leprae* and *Mycobacterium tuberculosis* have also been described in patients treated with fingolimod, who developed leprosy[33] and tuberculous meningitis,[70] respectively. Finally, fingolimod treatment has been also associated with rare PML cases[58,59] (Table 3).

Treatment of S1P-modulator-associated infections starts with the suspension of the drug, although this may mean an increased risk of disease rebound afterwards. However, a post hoc analysis that evaluated discontinuation from fingolimod from the phase III placebo-controlled trials FREEDOMS and FREEDOMS II reported no difference in severe relapse rates or Gd-enhancing lesion volume on magnetic resonance imaging (MRI) between those who discontinued fingolimod and those who stopped placebo; a severe relapse rate of 4.0% was reported in FREEDOMS and 3.5% in FREEDOMS II after stopping fingolimod, compared to rates of 4.4% and 4.1%, respectively, for placebo, and there was no difference in Gd-enhancing lesion volume among those who discontinued placebo and fingolimod.[71]

Cladribine

Cladribine is a chlorinated deoxyadenosine purine nucleoside analogue, whose activated form accumulates in lymphocytes and, since it inhibits DNA synthesis and repair, leads to cellular apoptosis of highly dividing cells, such as B- and T-cells. It has a strong impact on B lymphocytes with a 6-month recovery time and a less profound but persistent effect on CD4+ T-cells. Lymphopenia therefore occurs mainly during the first months after dosing. The effect of cladribine on the innate immune system is relatively limited; accordingly, neutropenia and pancytopenia are rare.[19]

In the phase III trial CLARITY, cladribine-treated patients showed an increased incidence of VZV infection compared with placebo, which correlated with severe lymphopenia (lymphocyte count below 500/mm^3). Reactivation of latent tuberculosis occurred in the context of pancytopenia. Apart from these infections, cladribine was not associated with an increased risk of severe infections (Table 1).[19]

Natalizumab

Natalizumab was the first monoclonal antibody to be approved for use in relapsing MS, initiating an era of genuinely high-efficacy drugs.[20,72,73] This monoclonal antibody against the α4 integrins blocks the entry of inflammatory cells into the brain, drastically reducing the inflammatory activity within the CNS, and a corresponding important decrease in rate of clinical relapses.[20,21] Shortly after approval, clinicians reported cases of developing PML,[74–76] which has influenced use of natalizumab in MS patients.[5] PML is an infectious demyelinating disease of the CNS caused by reactivation of the JC virus (JCV), which mainly affects patients with compromised immune systems.[5,77] Of note, PML has also been associated with the use of other DMTs apart from natalizumab (Table 3).

The risk of natalizumab-associated PML is associated with JCV antibody positivity and high anti-JCV antibody index score, longer duration of natalizumab exposure, and exposure to prior immunosuppressive treatments.[5] Primary JCV infection is usually asymptomatic and common in childhood in the general population. After transmission, the virus causes a chronic asymptomatic infection in the kidney. In approximately 50% of the population JC virions can be detected in urine.[78,79] JCV may eventually escape to blood and infect lymphoid tissue and bone marrow by infecting CD34+ stem cells. Natalizumab forces migration of these cells to peripheral blood, where CD34+ cells differentiate to CD19+ and CD20+ (i.e. pre-B and B) cells. Importantly, all JCV strains isolated from asymptomatic individuals are of an archetypal non-pathogenic genetic variant, whereas all JCV isolated from patients with PML are of a different type (i.e. prototype variant), with significant DNA rearrangements. Such viral rearrangements may occur within the infected lymphoid cells, that is, CD34+, CD19+, or CD20+.[5] Moreover, natalizumab upregulates DNA transcription factor SpiB and miRNA-126.[80] This accelerates JCV multiplication, generating free virions and infected B-cells which can penetrate the blood–brain barrier and infect oligodendrocytes. In addition, natalizumab blocks the passage of T-cells through the blood–brain barrier, reducing natural clearance of JCV from the brain by CD4+ and CD8+ T-cells.[5]

The diagnosis of natalizumab-associated PML is based on MRI and laboratory findings, ideally at the pre-symptomatic stage of the infection when prognosis is better.[5] During the pre-symptomatic stage, PML may be detected as a new lesion on surveillance MRI, which is generally small and hyperintense on

diffusion-weighted imaging (DWI).[5] The MRI protocol to diagnose PML includes T2-weighted/fluid-attenuated inversion recovery (FLAIR) sequences and DWI is also recommended.[81] The MRI features that are considered most helpful to diagnose natalizumab-associated PML are: the location in subcortical regions (with involvement of U-fibers), T1 hypointensity, DWI hyperintensity, and the presence of punctate T2-hyperintense lesions[82,83] Peripheral gadolinium enhancement and lesion growth are compatible with the diagnosis,[84] although diagnosis should ideally be made before any growth is observed. Detection of JCV DNA in the cerebrospinal fluid (CSF) and/or the detection of JCV protein in the brain (through biopsy or autopsy) is required to confirm the diagnosis.[85,86] Persistently negative JCV polymerase chain reaction (PCR) in the CSF can be observed in some patients with early PML disease.[87] Such early detection and rapid suspension of natalizumab will probably limit the replication of the virus which results in lower viral copies and absence of JCV DNA detection with common PCR tests. In negative cases, PCR should be optimized for detection of low JC viral load. The sensitivity of various laboratories may vary and, if suspicion is high, then an effort to use a lab that can detect low levels (e.g. <10 copies) should be considered. Anti-JCV antibodies in the CSF can support the diagnosis, especially when JCV PCR in the CSF is repeatedly negative.[87] In the blood, rapidly increasing anti-JCV antibody titers also support the diagnosis.[4] Once symptomatic, the clinical features of PML mimic those of a brain tumor.

Treatment of PML requires early and accurate diagnosis. Due to the absence of an effective JCV-directed antiviral therapy, immune reconstitution is crucial to combat PML. Plasma exchange therapy speeds removal of natalizumab to facilitate trafficking of immune cells to control the CNS infection, although it can accelerate immune reconstitution inflammatory syndrome (IRIS) leading to irreversible neurological symptoms. Corticosteroid treatment may reduce severe symptoms when they occur. Some patients have been reported to have improved after mefloquine and mirtazapine, but the supporting evidence for their use is weak.[88–90] New agents that increase cellular immune response against JCV may be promising for treatment of natalizumab-associated PML,[85] including infusion of BK virus-specific T-cells, a treatment based on the genetic similarity between the BK and JC viruses,[91,92] checkpoint inhibitors such as pembrolizumab, an anti-PD1 drug,[93] and interleukin (IL)-15 superagonist therapies.[94] However, boosting/regenerating lymphocytes against JCV may be effective mostly for conditions with lymphocyte depletion (e.g. for patients developing PML on dimethyl fumarate) and data about their usefulness in natalizumab-associated PML are lacking.

Importantly, natalizumab has also been associated with other infections, not only JCV-associated PML, such as meningovasculitis[95] or retinitis,[96] both in the context of VZV infection and herpes simplex encephalitis.[97] Table 2 shows the main risk mitigation strategies in relation to PML (and other infectious risks)

CD52 lymphodepleting therapy

CD52 is expressed on T- and B-lymphocytes, which are thought to mediate MS inflammation, and it is a crucial target of lymphodepleting therapies. Alemtuzumab is a humanized monoclonal antibody against the CD52 complex. It, therefore, depletes circulating CD52+ T- and B-lymphocytes, causing a significant halt in MS inflammatory activity, with significant clinical improvement. Upon its administration, full recovery of the B-cell population requires from 3 to 6 months. At the same time, at least 1 year is necessary for T-cells to reach a level equal to the lower limit of normality (LLN).[98,99] Of note, following immune reconstitution after alemtuzumab, the percentage of CD4+ Treg subtype increases; alemtuzumab does not deplete innate immune cells.[22,100]

Regarding AE, in the phase II and phase III trials, alemtuzumab-treated patients had a higher rate of mild-to-moderate infections compared with interferon beta (IFNb)-treated patients, most commonly affecting the upper respiratory tract (Table 1).[98–100] Herpes infections were increased several fold mainly secondary to T-cell lymphopenia. Acalculous cholecystitis appeared as an uncommon, but potentially life-threatening infection associated with alemtuzumab treatment. Long-term data indicate that the risk of infections does not increase over time or as a consequence of multiple alemtuzumab treatment courses.[99]

The most common infections associated with alemtuzumab treatment are herpetic infections, including infections for HSV and cytomegalovirus, and certain bacterial infections which tend to occur in the context of T-cell immunosuppression, such as *Listeria monocytogenes* or *Mycobacterium tuberculosis.*[101]

Anti-CD20 therapies

The most commonly prescribed anti-CD20 therapies used for MS are ocrelizumab and rituximab.

Ocrelizumab was approved for both relapsing MS and primary progressive multiple sclerosis (PPMS) in 2017. Rituximab is used as an off-label therapy for MS and NMOSD in several countries. CD20+ cells play key immunological functions, including antigen presentation, cytokine production, and are precursors of antibody-producing plasma cells. Anti-CD20 drugs exert a profound effect on the B-cell repertoire by eliminating most B-cells between the early stages of development up to the plasma cell stage. This causes prolonged B-cell lymphopenia, which may lead to hypogammaglobulinemia.[36]

In the main MS trials with anti-CD20 agents there was, overall, a slightly increased risk of infections in the anti-CD20-treated arms with respect to placebo, although not in all trials (Table 1). This effect was mainly present for rituximab trials[24,25] rather than the ocrelizumab ones,[27,102] where the percentages of infections were very similar between arms. A large nationwide registry linkage study performed in Sweden showed that rituximab was associated with a 1.7-fold increase in risk of serious infections compared to IFNb and glatiramer treatment, and also an increased use of antibiotics, but not herpes antivirals.[103] Finally, the use of anti-CD20 drugs has been recently associated with the development of babesiosis, a parasitic infection caused by *Babesia microti* and transmitted by deer ticks.[104]

In other conditions different from MS and in pediatric populations, anti-CD20 drugs have also been associated with increased rate of severe infections.[105,106] Risk factors for rituximab-associated infections include low IgG levels after rituximab treatment.[107,108]

New NMOSD treatments: anti-CD19, anti-IL-6 receptor, and anti-C5 drugs

New monoclonal antibodies have been recently developed for NMOSD treatment. Randomized, controlled trials with anti-CD19, anti-IL-6 receptor, and anti-C5 agents are efficacious in reducing relapses, with benefits demonstrated exclusively in AQP4 IgG-positive patients. The new treatments were generally safe, and there was no demonstrated risk of infections associated with any of these drugs (Table 1), although compared to pivotal studies conducted with MS patients, these recent studies in NMOSD had small samples and probably lacked power to detect rare infectious side effects. Also, patients participating in the eculizumab trial had to be vaccinated against *Neisseria meningitidis* before starting the trial.

Anti-CD19: inebilizumab. Inebilizumab is a humanized IgG1 kappa monoclonal antibody that targets CD19 and has been approved by the Food and Drug Administration (FDA) to treat NMOSD. CD19 is expressed on a broad spectrum of B-cells, including plasmablasts, the main producers of the pathogenic IgG antibodies against aquaporin 4 (AQP4-IgG). This ultimately leads to B-cell depletion and, therefore, B-cell lymphopenia.[109]

In the phase II/III clinical trial N-MOmentum,[28] none of the AE observed, including infections, reached a prevalence higher than 20%. Also, in on no occasion, there seemed to be a higher frequency of infections in the treatment than in the placebo arm. Although 2% of treated patients presented a grade III neutropenia and 13% had IgG hypogammaglobulinemia during the open-label period, there was no associated increased risk of infections in the medium term.[109]

IL-6-receptor inhibitors: satralizumab and tocilizumab. IL-6 is a cytokine that has a key role in inflammation and immunomodulation. It promotes T-cell differentiation into inflammatory T-helper 17 (Th17), survival of B-cells, and production of anti-AQP4-IgG by plasma cells. Satralizumab is a humanized monoclonal IgG2 antibody against the IL-6 receptor, both the membrane and the soluble subtypes, acting as an antagonist of IL-6. Its half-life is longer than that of tocilizumab, since the former has been designed to dissociate from the IL-6 receptor in certain environments (i.e. in a pH-dependent manner), leading to its recycling and return to blood in its active form. This drug has been approved by the FDA and European Medicines Agency (EMA) for the treatment of AQP4-seropositive NMOSD.

During the phase III controlled trials, SAkuraStar (satralizumab monotherapy vs placebo)[29] and SAkuraSky (satralizumab as add-on immunotherapy vs placebo),[30] common infections were observed in both treatment arms (see Table 1), with no clear increased infectious risk among those treated with satralizumab. Nonetheless, leukopenia was observed in 14.6% of the patients treated with satralizumab in the SAkuraSky trial; however, this was not significantly higher than the placebo arm.[30]

Tocilizumab is a humanized monoclonal IgG1 antibody that also blocks the IL-6 receptor. In NMOSD, it is administered off-label, based in part on the phase II TANGO study which reported that tocilizumab was superior to azathioprine.[31] In the trial, no clearly

increased risk of infections was observed in the tocilizumab versus the active comparator arm.

Anti-C5: eculizumab. Eculizumab antagonizes the complement molecule C5, which is recruited following complement activation triggered by the binding of anti-AQP4-IgG to AQP4 on astrocytes.[32] Eculizumab was the first drug approved by the FDA and EMA for NMOSD, based on the positive results of the phase III PREVENT study of eculizumab versus placebo.[32]

During the clinical trial, in general, no clear increased risk of infections was observed in the active arm compared to placebo. However, based on its use in hematological conditions, it is evident that there is an increased risk of encapsulated bacterial infections associated with complement inhibiting drugs. Furthermore, patients had been vaccinated against *Neisseria meningitidis* before study initiation, and no *N. meningitidis* infections were reported in the phase III studies, although one case of serogroup B *N. meningitidis* infection occurred in the phase II study, for which a vaccine became available in the interval between the phase II and III studies. During the open-label extension, one patient treated with eculizumab and azathioprine died of pulmonary empyema.

Autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) has been proposed as a treatment for people with highly active relapsing MS that either do not respond to first-line and second-line, high-efficacy drugs, or for whom second-line therapies are contraindicated.[110,111] Evidence from non-randomized studies suggests that AHSCT may be an effective treatment approach especially for younger and less disabled patients with relapsing forms of the disease.[112] However, AHSCT may also imply a higher risk of severe infections than other high-efficacy approaches, or first-line DMTs.[113] Infectious risks are the highest immediately after AHSCT, but are subsequently reduced and around 18–24 months after treatment they are similar to MS patients on regular DMTs.[113] During the first 6 months after AHSCT, there may be differences in infection risks between different AHSCT conditioning regimens, but these differences tend to disappear afterwards.[113] The most common infections are those caused by herpes virus (especially VZV). Bacterial sepsis and other viral and bacterial infections can also be observed.[113]

Prevention and management of infections in specific MS populations

Children with MS

Pediatric MS is rare, particularly in pre-puberty.[114] Therefore, due to the limited number of reported cases, it is difficult to assess a causal relationship between the use of immunosuppressive or immunomodulatory treatments and the development of infections.[115]

Four main issues arise when trying to evaluate such a relationship. First, there is no consensus on the correct dosage to be used in terms of efficacy and safety. Drug dosages that are safe may not be adequately efficacious. For example, in the PARADIGMS trial (fingolimod vs IFNb-1a), only 10/215 children were less than 40 kg (nine patients in the fingolimod group), it was not possible to evaluate the effect of dose and age on the risk of infections.[116] Second, AE in children may not be limited to or be similar to those observed in adult patients. For instance, B-cell depletion therapies used in children, such as rituximab, are perhaps more commonly associated with neutropenia than in adults.[117] Also some literature suggests rituximab-associated hypogammaglobulinemia and other immunological changes may be more common in children.[118,119] Of note, children may be more likely to become JCV positive than their adult counterparts.[120] Third, given the longer disease duration of pediatric-onset MS and NMOSD than adult-onset conditions, children who finally receive a high-efficacy drug may have been exposed to more drugs than their adult counterparts, and it is unknown to what extent previous DMTs affect the infection risks associated with subsequent DMTs. Fourth, it is difficult to control the environmental risks to which children may be exposed, given that their lives necessarily entail high levels of socialization such as attending school and sports. In any case, risks of infection should be considered when using immunotherapies, as we do with adult patients.

Concerning SARS-CoV-2 infection, in general, for children with MS, the benefits of continuing treatment will outweigh the risks of stopping an MS therapy because of concerns over COVID-19. When discussing the risk of DMTs in the context of the COVID-19 epidemics, a number of specific pediatric considerations need to be considered: (1) by contrast to adults, children with COVID-19 typically presented with only mild acute infection but perhaps had a higher risk of a secondary inflammatory syndrome; notably, although, children may have worse outcomes

with variants (e.g. DELTA variant); (2) children with MS typically have very low levels of disabilities (most have unlimited mobility with normal bulbar function) and lower rates of comorbidities, and hence, the risk of respiratory infections is lower; (3) MS in children is more inflammatory, and hence, any alteration in treatment has a higher risk of relapse compared to adults.

Because of the rarity of pediatric MS, international collaborative cohort studies and phase IV clinical studies are needed to provide new insights to improve the clinical management of pediatric MS patients.

Pregnant women with MS

Pregnancy induces unique changes in the maternal immune system. Schematically, while the first trimester is proinflammatory, the second and early third trimester are more "tolerogenic," before a late reactivation of the immune system before childbirth.[121] This tolerogenic state induces a higher susceptibility to infections, particularly urinary tract infections and mild respiratory infections. A specific concern during pregnancy is that seemingly benign or asymptomatic infections in the mother can cause severe pregnancy-related complications (spontaneous abortion and preterm labor/delivery), or induce malformation or death due to vertical transmission to the fetus.

The specific influence of DMTs on infection risk during pregnancy for women, or for the neonate following childbirth, is only partly known. Data from kidney-transplanted women suggest that in utero exposure to immunosuppressants increases the risk of infection in the neonatal period and early childhood.[122] Data specific to MS are scant, but two small recent studies suggest an increased risk of infections in the first weeks of life for neonates exposed to natalizumab during third trimester,[123] and an increased risk of severe infection in pregnant women treated with rituximab.[124]

Risk mitigation strategies for infections during pregnancy include dietary measures and vaccination to avoid vertical transmission or neonatal infection. Women with MS conceiving while on a DMT should be advised to apply hygiene and dietary measures strictly, especially in the case of lymphopenia or hypogammaglobulinemia. Finally, the potential need for vaccination against VZV and Rubeola of women with MS of childbearing age should be anticipated early in the disease to allow proper vaccination before DMT onset. Of importance it is the advice to postpone vaccinations with Bacillus Calmette–Guérin (BCG) or live attenuated vaccines within the first 4 weeks of life in neonates with reduced B-cells or with exposure to other, non-anti-CD20 monoclonal antibodies during the last trimester of pregnancy: disseminated lethal tuberculosis was reported in a baby following BCG vaccination, whose mother was treated with infliximab during pregnancy.[125]

People with MS and other comorbidities

Age is associated with "immunosenescence,"[126] a global decrease in immune system efficiency, leading to an increased susceptibility to infections and reduced vaccination response. In MS, immunosenescence may contribute to the reduced inflammatory disease activity and the well-documented reduction in attacks and MRI activity with aging. While another aspect of immunosenescence is "Inflammaging," a low-grade proinflammatory state that might contributes to progressive neurodegeneration.[127,128]

Immunosenescence induces changes in lymphocyte populations (inversion of CD8+/CD4+ ratio, decrease in B-cell precursor population, and functional modification of innate immunity), which somewhat reflect changes induced by DMTs. Hence, DMTs might carry an increased risk of infections in older patients, as illustrated by dimethyl fumarate for which a higher age is a risk factor for treatment-induced lymphopenia, and longer lymphocyte repopulation after drug cessation.[129] Indeed, age is a key risk factor of PML both under dimethyl fumarate[130] and natalizumab,[131] and older patients with MS are at increased risk of infection-related hospitalization, compared to younger patients with MS, or to people of a similar age within the general population.[132]

Comorbidities, in particular cardiometabolic comorbidities, are more frequent in people with MS than in the general population and increase in frequency with age, and they contribute to an increase in mortality and morbidity.[133,134] As patients older than 55 years, or with significant comorbidities where largely excluded from phases II to III studies, data are lacking to specifically guide prescription in older patients with MS. In rheumatoid arthritis, a composite score integrating age and comorbidities has been developed to assess the risk of severe infection in patients treated by biotherapies,[135] and the development of a similar score would be of particular interest for counseling older patients with MS.

Altogether, the DMT risk/benefit profile shifts with increasing age. It is recommended that treatment initiation after the age of 60 years should be considered

only when a recent disease-specific activity has been radiologically documented. In patients already treated, the pertinence of DMT continuation should be regularly re-evaluated, integrating newly diagnosed comorbidities. Older patients should be closely monitored for lymphopenia, PML, and VZV reactivation.

People with MS in high infection burden region

Latin America. The prevalence of MS in Latin America is low, probably thanks to a combination of genetic and environmental protective factors. A minor latitudinal gradient in MS frequency seems to exist between different Latin American countries, which could be explained by regional-specific ethnic and environmental factors.[136–139]

In Latin American countries, there is a general increase in opportunistic infections in the context of DMT use, including tuberculosis. This has led local expert panels to issue some recommendations for screening of infections in MS patients planning to start a DMT.[136,140,141] For instance, with respect to latent tuberculosis, which is highly prevalent in Latin America (17%),[142] current consensus recommendations include (1) screening of latent tuberculosis for all patients who are to start a DMT; (2) if screening is positive, patients should undergo specific anti-tuberculous treatment and start DMT only 4–8 weeks after treatment initiation; (3) if screening is negative, patients need to be checked annually for tuberculosis and receive antibiotics if positive. Other opportunistic infections should also be checked when treating patients with DMTs in Latin America, such as paracoccidioidomycosis, caused by *Paracoccidioides brasiliensis*, an endemic fungus in Latin America, which mainly affects the lungs.[143,144] Its treatment, which usually includes itraconazole, has been described in detail.[145]

In summary, post-marketing data and real-world evidence available in the Latin American population do not differ from results of international clinical trials. However, before starting DMTs and during DMT treatment, patients should be screened for infections that are common in Latin American countries.

India. MS is considered as an orphan disease in India, because of its low prevalence.[123] Accordingly, the management of MS is not prioritized. Since "off-label" therapies like classical immunosuppressants are more affordable than on-label DMTs, these are often used as first-line treatment for MS. According to the Mangalore Demyelinating Disease Registry (MANNDIR), IFNb and glatiramer acetate are the first line in female patients with childbearing potential, while dimethyl fumarate is the preferred choice if there are no childbearing issues. Generic azathioprine and mycophenolate mofetil are also considered as first-line drugs. Rituximab and (generic) fingolimod are used as second-line treatments.[146–148]

Patients are screened for latent tuberculosis, and other chronic infections such as hepatitis B and C, and HIV, by inquiring about weight loss, fever, cough, past family history of or contact with tuberculosis as well as serologies, hemogram derangements (e.g. lymphopenia), chest X-ray, and abdominal ultrasound. Once a patient starts on the DMT, blood and urine tests are repeated every 3 months.

In summary, it is important to explain the risks of infection associated with the different DMTs, and monitor for them and prevent them when possible. This is especially relevant in India and other Asian countries with a high infection risk burden.

Management of MS and NMOSD patients during a (COVID) pandemic

Since November 2019, the rapid emergence of the COVID-19 pandemic has challenged the care of patients with MS and NMOSD. The surge of SARS-CoV-2 infected patients into hospital during the spring of 2020 has, in most regions, led to an increased difficulty for patients with MS to access healthcare facilities,[149] sometimes leading to discontinuation of DMTs and rehabilitation therapies, generating disease worsening in some patients.

Patients with MS were rapidly identified as being possibly at higher risk of a severe COVID-19 due to their disability and exposure to DMTs. Before data were available about effects of DMTs on the course of COVID-19, patients and MS specialists faced a dilemma regarding DMT continuation when exposed or ill with COVID-19. While immunosuppression was globally considered as a risk factor for severe infections, some postulated that DMTs could mitigate the "cytokine storm" or hyperinflammatory state responsible for the high mortality risk in severe COVID-19 forms.

COVID-19 outcomes in patients with MS

Data about factors influencing the outcome of COVID-19 infections in patients with MS are now available from multiple national registries, detailed in

Table 4. Registries analyzed the relationship between demographical data, comorbidities, MS type, treatment, and disease course. Due to their declarative and retrospective design, registries carry inherent sampling bias, and direct comparison of outcomes in between them is not entirely valid as local policies influence case identification (such as PCR-test availability or screening program) and outcomes (different intensive care unit (ICU)/hospital-admission criteria). However, accurate data regarding individual risk factors predictive of disease course can be obtained from internal analysis.

All studies about COVID-19 outcomes in patients with MS confirmed that the risk factors for severe COVID infection identified in the general population (male sex, older age, cardiovascular comorbidities, and obesity) were also valid for patients with MS. Regarding MS-specific actors, a higher disability was identified as predictive of poorer outcomes, while a negative influence of having a diagnosis of progressive MS was suggested.[40,41] However, this later finding was possibly confounded by the older age and more severe disability of those with progressive MS. Table 2 shows the main details of the influence of DMTs on the course of COVID-19 and the main risk mitigation strategies.

Immunization strategies

COVID-19 vaccines currently appear to be the primary way to limit severe infection at an individual level and achieve pandemic control at a population level. COVID-19 vaccines are safe in patients with MS, including during pregnancy and breastfeeding. Immune-mediated side effects occur, but severe symptoms following vaccination are exceptional, and there is no apparent excess of CNS demyelinating events following vaccination. COVID-19 vaccination is highly recommended for patients with MS. As the frequency and duration of natural immunization after a COVID-19 infection is unknown especially in the case of DMT use, patients with a history of COVID-19 infection, symptomatic or asymptomatic, should also be vaccinated.

Regarding vaccine efficacy, the immune response is considered unaltered for patients under IFNb, glatiramer acetate, teriflunomide, natalizumab, and dimethyl fumarate with normal lymphocyte counts. Concerning dimethyl fumarate with associated lymphopenia, specific data about vaccine efficacy are lacking, but the response might be attenuated. However, treatment discontinuation is not guaranteed to improve vaccine response as the normalization of lymphocyte counts can take months after discontinuation. Altogether vaccines are highly recommended without any treatment modification.

S1P modulators attenuate the humoral immune response to COVID-19 vaccine measured by antibodies levels according to case reports and small series (3.8% of 26 patients seroconverted),[39] but another recent study identifies a seroconversion in 10 out of 16 patients treated with fingolimod after vaccination.[152] The VELOCE study identified an attenuated response to the vaccine in patients treated with ocrelizumab, particularly towards neoantigens.[153] Other B-cell depleting therapies (alemtuzumab and cladribine) also induce a transient decreased efficacy of vaccines in the 4–6 months following treatment.[154] A small study about 23 patients treated with cladribine vaccinated with COVID-19 vaccine at least 4 months after the previous cycle (interquartile range (IQR) = 6.1–9.4) shows that patients developed protective humoral immunity.[39] A potential limitation of the reported studies is that they only focused on humoral response, while cellular immunity might contribute to the vaccine-induced protection against COVID-19. In addition, clinical infection after vaccination (vaccine failure) has not been reported in these studies.

Whenever possible, a complete vaccination regime should be performed at least 1 month before the onset of an anti-CD20 therapy, fingolimod, cladribine, or alemtuzumab. For patients treated with S1P modulators, given the high risk of disease rebound, treatment discontinuation to allow vaccination is not recommended. For patients already on treatment with pulsed therapies, whenever possible the postponement of the next rituximab/ocrelizumab infusion is recommended to allow a 1-month gap between vaccination and the administration of the anti-CD20 drug. In the case of ofatumumab, the timing may be more complex. In the United States, it is advised to vaccinate 1 week before the monthly injection.

Lessons learned from critical COVID-19: new pathophysiological insights

Despite their relevance, the aforementioned risk factors for severe COVID-19 do not account for all critical cases of SARS-CoV-2 infection. The course of the disease exhibits a huge interindividual clinical variability in each demographic category: most patients treated with anti-CD20 therapies experience a mild disease course, while some healthy individuals unpredictably develop a life-threatening infection. An exciting hypothesis postulates that patients with an acute SARS-CoV-2 infection might exhibit altered responses in the type I interferon pathway. The COVID human genetic

Table 4. COVID-19 outcomes in patients with MS and risk factors of higher severity.

First author, year (reference)	Country	Population	Outcomes	Risk factors of worse outcomes	DMT-related outcomes
Louapre et al.[150]	France, Luxembourg, Switzerland	*n* = 347 patients; 42.1% confirmed COVID-19; 81.3% relapsing; 81.8% under DMT	21% hospitalization	**Age, male sex, comorbidities (cardiopathy, obesity)**, progressive MS, EDSS	No influence of DMT on infection outcomes
Arrambide et al.[41]	Spain	*n* = 326 patients; 47.2% confirmed COVID-19; 80.7% relapsing MS	21.3% severe COVID-19; 3% critical COVID-19; 2.1% death	**Age**, male sex, MS duration, EDSS, MS course, one comorbidity	Higher severity: pulsed immunosuppressive therapy (anti-CD20, cladribine, alemtuzumab); rituximab; no impact of recent corticosteroid use
Salter et al.[44]	North America (USA, Canada) CoviMS Registry	*n* = 1626 patients; 82.7% confirmed COVID-19; 82.7% relapsing MS	12.3% hospitalization; 4.8% ICU or ventilation; 3.3% death	Older age, male sex, comorbidities, EDSS	Higher disease severity Pulsed immunosuppressant: alemtuzumab, cladribine, **anti-CD20** (stronger association for **rituximab**). Recent corticosteroid use Decreased severity: natalizumab, dimethyl fumarate
Sen et al.[151]	Turkey	*n* = 309 patients; 100% COVID-19; 89.6% relapsing MS; 91.6% under DMT	27.5% hospitalization; 2.9% ICU; 1% death	Older age, **progressive MS phenotype**, high EDSS and **high MSSS**	No significant associations were found between any DMTs and COVID-19 severity
Simpson-Yap et al.[40]	28 countries (MS-Base)	*n* = 2340 patients; 71.9% confirmed COVID-19; 87.9% under DMT	20.9% hospitalization; 5.4% ICU; 4.1% ventilation; 3.2% death	Older age, male sex, progressive MS, EDSS, obesity, comorbidities	Higher risk of disease severity: anti-CD20 (stronger association for rituximab)
Sormani et al.[42]	Italy (Musc-19)	*n* = 844 patients; 33.1% confirmed COVID-19; 80.1% relapsing MS; 82% under DMT	10.9% pneumonia or hospitalization; 5.2% ICU or death	**Age, male sex, higher EDSS**, longer MS duration, comorbidities, progressive MS	Higher severity: **Recent pulsed methyl prednisone and anti-CD20 therapy** vs all other therapies
Sormani et al.[43]	COVISEP + Musc-19: France, Italy, Luxembourg, Switzerland	*n* = 1787 patients; 100% confirmed COVID-19 Italian subcohort: *n* = 1066 patients, 86.2% relapsing MS, 86% under DMT French subcohort: *n* = 721 patients, 78.7% relapsing MS, 77.9% under DMT	For Italy and France, respectively: 11.5% and 12.8% hospitalization; 2.5% and 2.7% ICU or death	**Age, male sex, EDSS, and comorbidities, anti-CD20 therapies, recent corticosteroid use**	Higher severity: **Recent methyl prednisone**, **anti-CD20 therapies** (stronger association for rituximab). Decreased risk: beta-**interferon**

COVID-19: coronavirus disease 19; MS: multiple sclerosis; DMT: disease-modifying treatment; ICU: intensive care unit; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score.
Bold denotes the significant association still present in a multivariate analysis; *n* is the number of suspected or confirmed cases of COVID.

analyzed genomes from 987 patients with COVID worldwide, and identified genetic inborn errors in type I interferon pathway in 3.5%.[155] Interestingly, disturbance through pre-existing anti-type I interferon antibodies was identified in 10% of patients, mostly males (94%) of older age (>65 years), and their presence was associated with poor outcomes.[156] While still preliminary, those findings are of particular interest as they pave the way for possible therapeutic interventions. Studying their prevalence among patients with MS, especially in the case of previous treatment with interferons, would be of particular interest.

Conclusion

The advent of new, highly effective DMTs for MS and NMOSD has been a turning point in the management of patients with inflammatory demyelinating conditions. However, greater efficacy is accompanied by new risks, including developing severe infections, adding complexity to an already complex treatment scenario. Risk mitigation strategies must reduce risks and should be updated regularly as new information becomes available. Furthermore, in those circumstances where there are additional specific risks due to environmental or demographic circumstances, that is, pediatric and pregnant populations, concomitant diagnosis of other conditions (comorbidities), or presence of endemic infections, risk mitigation strategies should be carefully tailored to cover all those extra risks as well. Finally, the COVID-19 pandemic declared by the WHO in March 2020 has challenged all our treatment protocols, even measuring our health systems up. The pandemic has underscored the importance of assessing benefit–risk in relation to choice of DMT at an individual level, and to define, as accurately as possible, the impairment to the immune system that DMTs may cause, in order to apply mitigation strategies accordingly.

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