




Vaccination and immunotherapies in neuroimmunological diseases

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Abstract | Neuroimmunological diseases and their treatment compromise the immune system, thereby increasing the risk of infections and serious illness. Consequently, vaccinations to protect against infections are an important part of the clinical management of these diseases. However, the wide variety of immunotherapies that are currently used to treat neuroimmunological disease — particularly multiple sclerosis and neuromyelitis optica spectrum disorders — can also impair immunological responses to vaccinations. In this Review, we discuss what is known about the effects of various immunotherapies on immunological responses to vaccines and what these effects mean for the safe and effective use of vaccines in patients with a neuroimmunological disease. The success of vaccination in patients receiving immunotherapy largely depends on the specific mode of action of the immunotherapy. To minimize the risk of infection when using immunotherapy, assessment of immune status and exclusion of underlying chronic infections before initiation of therapy are essential. Selection of the required vaccinations and leaving appropriate time intervals between vaccination and administration of immunotherapy can help to safeguard patients. We also discuss the rapidly evolving knowledge of how immunotherapies affect responses to SARS-CoV-2 vaccines and how these effects should influence the management of patients on these therapies during the COVID-19 pandemic.

A variety of neuroimmunological diseases can affect the CNS, PNS and the neuromuscular junction, and the pharmacological arsenal for the treatment of these diseases is growing (TABLE 1). The most common of these diseases is multiple sclerosis (MS), a chronic immune-mediated disease of the CNS that leads to demyelination, axonal damage and reduction of synapses^{1,2}. Pathogenesis of MS involves components of the adaptive immune system, including B cells and T cells, and of the CNS-resident innate immune system, including microglia³. On the basis of these mechanisms, various immunosuppressive therapies have been developed for MS, and more than 15 disease-modifying therapies (DMTs) are currently available.

Similarly, three immunosuppressive therapies have now been approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD), which is a primarily antibody-mediated inflammatory CNS disease. In addition, various immunotherapies are used off-label for the treatment of other neuroimmunological diseases for which no therapies are approved such as myelin oligodendrocyte glycoprotein antibody-associated disease, autoantibody-mediated encephalitides, Guillain-Barré syndrome (GBS) and its variants, chronic inflammatory demyelinating polyneuropathy, myasthenic disorders, and inflammatory myopathies (TABLE 1).

Advances in immunotherapy and the development of targeted therapies on the basis of pathophysiological pathways have greatly improved the management of neuroimmunological diseases but immunotherapies carry the risk of serious infections. Therefore, effective prophylaxis of infections is critical for people undergoing immunotherapy for neuroimmunological diseases^{4,5}, but the effects of these therapies on immune function can also compromise responses to vaccinations. Given that perturbations of the immune system are causative in neuroimmunological diseases and that immunotherapies drastically alter immune function, multiple levels of complexity exist for patients and physicians in relation to the use of vaccinations^{6,7} (BOX 1). A full understanding of the effects of immunotherapies on vaccination responses is needed to ensure maximum protection from infection alongside therapeutic benefits.

In this Review, we first discuss the fundamentals of vaccine immunology before considering in detail how immunotherapies with different modes of action influence responses to vaccines and what these interactions mean for the clinical use and timing of vaccinations in relation to immunotherapies. We focus on MS and NMOSD, as a broad range of licenced DMTs are available for these diseases, yet the same therapies

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Key points

- Vaccination against infection is an essential part of the management of neuroimmunological diseases.
- All indicated vaccinations should be administered before initiation of immunotherapy whenever possible; appropriate intervals between vaccination and treatment vary with treatment and vaccination.
- Inactivated vaccines are considered safe in neuroimmunological diseases but live vaccines are generally contraindicated during immunotherapy.
- Vaccination responses during immunotherapy can be diminished or abrogated, depending on the treatment and vaccination; antibody titre testing to monitor responses can be considered where appropriate.
- Vaccinations must be avoided during relapses or exacerbations of neuroimmunological diseases.
- Vaccination against SARS-CoV-2 is recommended for patients with neuroimmunological disease but some immunotherapies limit the immune response; therefore, timing should be considered carefully.

are commonly used in various other neuroimmunological diseases (TABLE 1). We also consider the current and rapidly evolving knowledge about SARS-CoV-2 vaccines and their use in people with and receiving treatment for neuroimmunological diseases.

Vaccines and immunological responses

Vaccinations provide active immunization, meaning that an antigen is administered to elicit an antibody and cellular response. This mechanism is in contrast with passive immunization, which is achieved through direct administration of hyperimmune globulins or monoclonal antibodies that provide immediate but short-lasting immunity. Active immunization with vaccines provides longer-lasting protection.

Established forms of vaccines include live attenuated pathogens, inactivated whole pathogens, purified proteins or polysaccharides, and genetically engineered antigens. Various vaccine types are commonly used for a wide variety of diseases and elicit various responses with varying durability (Supplementary Table 1). Novel types of vaccines, such as DNA-based and RNA-based vaccines, are emerging, and this process has been accelerated by the COVID-19 pandemic^{8–10} — nucleoside-modified mRNA-based vaccines against SARS-CoV-2 (REFS^{11–15}) are the first of this type to be approved for use in humans.

Our understanding of how immunity develops after vaccination has evolved over the past two centuries. During the past five decades, research has focused on

adaptive immune responses to infectious agents and the capacity of these responses to produce tailored, specific and long-lasting immune effects^{7,16}. Adaptive immune responses involve clonal selection of T cells and antibody production by B cells to respond to antigens. However, the innate immune system is also involved in the response to infection. This response is generally directed against common structures of antigens and does not depend on clonal selection processes and therefore the immune system is immediately available to react. Macrophages, dendritic cells and mast cells bind to pathogens via Toll-like receptors, leading to chemokine and cytokine activation by various intracellular pathways. This innate immune response triggers adaptive immune responses¹⁷. In the past 5 years, insight into vaccine immunology has blurred the boundaries between innate and adaptive immune responses and altered the classical view of vaccine-induced immunity.

For example, evidence has emerged that the innate immune function is altered as a result of Bacille Calmette–Guérin (BCG) immunization against tuberculosis, that BCG vaccination provides protection from reinfection that is independent of T cells and B cells¹⁸, and that overall mortality is reduced after BCG vaccination¹⁹. Together, these findings suggest a previously unknown process in which haematopoietic stem cells and multipotent progenitor cells are reprogrammed, leading to ‘innate immune memory’ or ‘trained immunity’²⁰. These changes could be driven by epigenetic reprogramming, metabolomic rewiring and/or alterations in gene expression signatures^{18,21}. Micronutrients and nano-biologicals that were originally designed to reduce transplant rejection via modulation of bone marrow cells are currently under investigation for their ability to augment innate immune responses to vaccines¹⁸. These insights into the role of innate immune responses to vaccination are important in the context of neuroimmunological disease because some immunotherapies alter components of the innate immune system and could therefore influence the innate immune response to vaccination.

Immune responses to vaccines can be enhanced by the use of adjuvants (such as oil-in-water emulsions, aluminium, Toll-like receptor agonists and virosomes; Supplementary Table 2), which can reduce the dose of antigen needed to achieve protection or can amplify protection in immunocompromised individuals^{22,23}. Concerns have been raised about the possibility that such adjuvants can evoke an autoimmune or inflammatory syndrome²⁴. One well-documented example is the development of narcolepsy in children with a genetic predisposition who received a pandemic influenza vaccine that contained AS03 adjuvant but not in children who received a vaccine that contained MF57 adjuvant^{24,25}. However, all adjuvants seem to generate a comparable inflammatory response in the first few hours after vaccination²², and licenced vaccine adjuvants have generally been proven safe and effective in immunocompromised and non-immunocompromised individuals²⁶.

A common concern with vaccines is the possibility of inducing neuroimmunological disease or worsening of existing neuroimmunological disease. Large cohort

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Table 1 | Neuroimmunological diseases and immunotherapies approved or commonly used for their treatment

Site of disease	Disease	Pathophysiology	Approved immunotherapies	Other commonly used immunotherapies
CNS	Multiple sclerosis	Chronic immune-mediated disease leading to demyelination, axonal damage and reduction of synapses following the loss of immune tolerance against CNS antigens	Alemtuzumab, azathioprine, IFN β , cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, glatirameroids, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, siponimod, teriflunomide	Cyclophosphamide, glucocorticosteroids ^a , high-dose IVIg, plasma exchange ^a , rituximab, stem cell transplantation
	NMOSD	Primarily antibody-mediated inflammatory CNS disease directed against neuronal surface molecules that triggers activation of the classical complement cascade to cause granulocyte, eosinophil and lymphocyte infiltration, culminating in injury to astrocytes and then oligodendrocytes, followed by demyelination and neuronal loss	Eculizumab, inebilizumab, sartralizumab	Azathioprine, glucocorticosteroids ^a , mycophenolate mofetil, plasma exchange ^a , rituximab, tocilizumab
	MOGAD	Primarily antibody-mediated inflammatory CNS disease directed against neuronal surface molecules, characterized by the coexistence of perivenous and confluent primary demyelination with partial axonal preservation and reactive gliosis in the white and grey matter, with a particular abundance of intracortical demyelinating lesions	None	Azathioprine, glucocorticosteroids ^a , plasma exchange ^a , rituximab
	Autoantibody-mediated encephalitides	Auto-antibodies against neuronal surface molecules	None	Cyclophosphamide, glucocorticosteroids ^a , high-dose IVIg ^a , plasma exchange ^a , rituximab
PNS	GBS (and variants)	Acute peripheral neuropathy mediated by molecular mimicry, antiganglioside antibodies, involvement of cellular and humoral immune mechanisms, and probably complement activation	High-dose IVIg ^a , high-dose SCIg, plasma exchange ^a	
	CIDP (and variants)	Acquired, immune-mediated chronic inflammatory demyelinating polyneuropathy that affects peripheral nerves and nerve roots, mediated by cellular and humoral mechanisms (T cell activation, immunoglobulin and complement deposition on myelinated nerve fibres)	Glucocorticosteroids ^b , high-dose IVIg ^b , high-dose SCIg, plasma exchange ^b	Azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab
Neuro-muscular junction	Myasthenia gravis	Auto-antibodies against components of the postsynaptic membrane lead to impairment of neuromuscular transmission by complement-mediated damage	Azathioprine, eculizumab, glucocorticosteroids, high-dose glucocorticosteroids ^a	Cyclophosphamide, high-dose IVIg ^a , mycophenolate mofetil, plasma exchange ^a , rituximab
	Lambert–Eaton syndrome	Auto-antibodies to the presynaptic voltage-gated calcium channel	Treatment of underlying cancer	Azathioprine, glucocorticosteroids, high-dose IVIg ^b , plasma exchange ^b
Muscle	Polymyositis	T cell-mediated cytotoxic process directed against unidentified muscle antigens	Glucocorticosteroids ^b	Azathioprine, cyclophosphamide, high-dose IVIg, mycophenolate mofetil, rituximab
	Dermato-myositis	Humoral-mediated autoimmune disease in which antigen-specific antibodies are deposited in the microvasculature	Glucocorticosteroids ^b	Azathioprine, cyclophosphamide, high-dose IVIg, mycophenolate mofetil, rituximab
	Inclusion body myositis	Features of inflammatory and degenerative processes, such as inflammatory infiltrates, but also myonuclear degeneration and protein aggregates	None	High-dose IVIg
	Immune-mediated necrotizing myopathies	A group of inflammatory myopathies associated with anti-SRP or anti-HMGCR myositis-specific auto-antibodies	Glucocorticosteroids ^b	Azathioprine, cyclophosphamide, high-dose IVIg, mycophenolate mofetil, rituximab

HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain–Barré syndrome; IVIg, intravenous immunoglobulins; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; SCIg, subcutaneous immunoglobulins; SRP, signal recognition particle. ^aRelapse treatment. ^bInduction therapy.

Box 1 | Interactions between neuroimmunological disease, infections, vaccinations and disease-modifying therapy

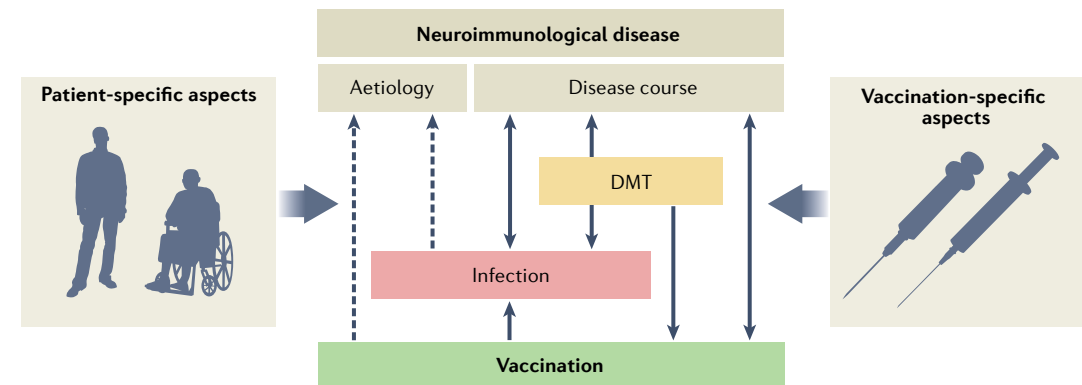
In neuroimmunological diseases, infection, vaccination and disease-modifying therapies (DMTs) all interact with the disease and with each other (Figure), and these interactions need to be managed to minimize the risk of infection and maximize the benefits of vaccination. The course of a neuroimmunological disease influences the risk of infection in the patient (for example, silent aspiration and pneumonia or urinary tract infections) and can also influence the efficacy of vaccination (for example, previous therapies).

Conversely, the disease course can be affected by infections and vaccinations owing to activation of the immune system — for instance, by the Toll-like receptor pathway. For example, myasthenic crisis can occur after infections and multiple sclerosis relapses can follow infection of the upper respiratory tract or pneumonia. Vaccinations that prevent infections have been shown to stabilize the course of neuroimmunological diseases.

DMTs not only alter the course of the disease but, by altering immune function, also increase the risk of infection and affect the efficacy of vaccinations. Vaccinations reduce the risk of infection associated with disease or therapy and can also influence the course of disease (for instance, multiple sclerosis relapses can occur after yellow fever vaccination owing to mild immune activation); these interactions need to be managed carefully. Finally, the effects of infections and vaccinations on immune function could contribute to the aetiology of some neuroimmunological diseases, though such effects remain uncertain (indicated by dashed lines in the figure). For example, increasing evidence indicates that the Epstein–Barr virus can contribute to the pathogenesis of multiple sclerosis^{227,228} and *Campylobacter jejuni* infection is thought to trigger Guillain–Barré syndrome as a result of molecular mimicry³⁰.

The effects of vaccination depend on various additional aspects, including the vaccination type (live attenuated, inactivated, conjugate, virus-like particle, recombinant, toxoid or RNA/DNA based), additives (preservatives, stabilizers, adjuvants and manufacturing residuals) and the vaccination history of the patient (whether they are receiving a primary vaccination, revaccination or booster vaccination).

The effects of all of these factors and their interactions can also be influenced by a variety of patient-specific characteristics, including age, sex, comorbidities, immune status, co-medication and drug interactions, use of complementary and alternative medicines, and social issues.



studies, meta-analyses and prospective trials have provided convergent evidence that vaccination has no correlation with induction of MS^{27–29}. However, GBS can occur in rare cases after active vaccinations against influenza, yellow fever, rabies, hepatitis A and B, measles, tetanus, and others^{30–32}. The estimated risk of GBS is 1 per million people with the influenza vaccination compared with 17 per million people after influenza infection³².

Immunotherapy and vaccination response

The effects of immunotherapy on the immune system are only partially understood and the effects on vaccine responses also remain unclear. Responses to vaccination vary with different therapies and relate to the drug’s mode of action (Supplementary Table 3). The following sections consider how immunotherapies with various modes of action influence vaccine responses.

Depletion and cytotoxicity of immune cells

Vaccination responses primarily depend on adaptive immunity. Multiple immunotherapies reduce levels of B cells or T cells and therefore carry the risk of reduced

vaccine efficacy. However, responses to vaccination vary between these types of drugs.

Ocrelizumab. Ocrelizumab is an anti-CD20 humanized monoclonal antibody that depletes CD20⁺ B cells. Ocrelizumab is widely used for the treatment of relapsing–remitting MS and is the first treatment to be licenced for use in primary progressive MS.

The effects of ocrelizumab on humoral responses to selected vaccines were assessed in a phase IIIb controlled prospective multicentre study³³. In 68 patients with relapsing–remitting MS who were receiving ocrelizumab treatment, immune responses to vaccination at 12 weeks after initiation of treatment were compared with those in 34 patients receiving IFNβ or no treatment³³. At 4 and 8 weeks after the tetanus toxoid booster vaccine, geometric mean levels of IgG and the proportion of patients with a positive response were lower among patients treated with ocrelizumab than among control participants. However, all patients who exhibited a response were seroprotected at 4 and 8 weeks after vaccination. Similarly, at 4 and 8 weeks after vaccination with the pneumococcal

polysaccharide vaccine directed against 23 pneumococcal serotypes (23-PPV) and the additional pneumococcal conjugate vaccine directed against 13 pneumococcal serotypes (13-PCV), geometric mean levels of specific antibodies were lower among the ocrelizumab recipients than among control participants. The proportion of individuals who exhibited a positive vaccination response to 23-PPV was lower in the ocrelizumab group than in the control group, and additional vaccination with 13-PCV did not markedly increase the response to the 12 serotypes that it has in common with the 23-PPV vaccine.

At 4 weeks after vaccination against five strains of influenza (seasons 2015–2016 and 2016–2017), 55.6–80% of individuals who received ocrelizumab and 75–97% of control participants developed seroprotective antibody titres³³. After vaccination with the keyhole limpet haemocyanin neoantigen (KLH) — an antigen to which previous immune reaction is not suspected — responses were lower in patients receiving ocrelizumab than in control participants. Repeated KLH administration elicited a boosting effect only in the control group³³. After all tested vaccines, humoral responses were diminished in patients receiving ocrelizumab compared with patients not receiving B cell depleting treatment at all investigated time points. Nonetheless, patients receiving ocrelizumab were able to mount humoral responses to various vaccines and to neoantigen³³.

Though specific studies have not been done to determine the appropriate timing of vaccination relative to ocrelizumab treatment, we recommend that inactivated vaccines should be administered >4 weeks before ocrelizumab treatment to allow adequate time for the immune response to develop. Seasonal influenza vaccination during ongoing treatment is recommended, though the humoral response could be attenuated.

Rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes CD20⁺ B cells. The effects of rituximab on vaccine response have been studied in patients receiving the antibody for NMOSD³⁴. In this study, antibody responses against the H1N1 influenza vaccine were lower among patients receiving rituximab than among people with MS who were receiving treatment with IFN β or azathioprine. However, antibody titres against hepatitis B virus surface antigen, measles and tetanus were not affected by treatment with rituximab, IFN β or azathioprine.

Rituximab is also commonly used in rheumatoid arthritis and its effects on vaccine responses have been investigated in this population. Assessment of responses to tetanus toxoid, 23-PPV and KLH and of delayed-type hypersensitivity (DTH) to *Candida albicans* showed that treatment with rituximab combined with methotrexate produced markedly reduced responses to neoantigens and T cell-independent antigens than those with methotrexate treatment alone. Recall responses to T cell-dependent tetanus toxoid antigen and DTH responses were not affected to the same extent³⁵.

In another small study of patients with rheumatoid arthritis, influenza vaccine and PPVs were administered to 11 patients at 6 months after rituximab treatment

(post-rituximab group), to 8 patients at 6 days before rituximab treatment (pre-rituximab group) and to 10 patients who did not receive rituximab (control group). Six days after vaccination, influenza-specific B cell responses were lower in the post-rituximab group than in the other groups and, on day 21, influenza-specific IgG production was undetectable in 55% of individuals in the post-rituximab group. Similarly, 23-PPV-specific IgG production was lower in the post-rituximab group than in the other groups. Thus, rituximab seems to compromise cellular and humoral vaccine responses in patients with rheumatoid arthritis³⁶. On the basis of these studies, primary immunizations should be given before rituximab therapy is initiated where possible to ensure that an adequate immune response can develop.

Ofatumumab. Ofatumumab is a human anti-CD20 monoclonal antibody that was approved for the treatment of MS in 2020 in the USA and in 2021 in the EU and Australia³⁷. The efficacy and safety of protective vaccines in people receiving ofatumumab have not been specifically studied to date. However, given that its mechanism of B cell depletion is the same as that of ocrelizumab and rituximab, the immune response to vaccination is likely to be impaired in a similar way.

Inebilizumab. Inebilizumab is an anti-CD19 monoclonal antibody that depletes CD19⁺ B cells (a broader population than CD20⁺ B cells) and is approved for the treatment of NMOSD. In the phase III trial of inebilizumab, antitetanus toxoid IgG levels were measured to assess the effect of inebilizumab on vaccine-generated antibody titres and these levels were not decreased at the end of the study³⁸. However, the safety of immunization with live or live attenuated vaccines after inebilizumab therapy has not been studied, and administration of such vaccines is not recommended during treatment and until B cell repletion is achieved owing to the risk of vaccine-related infection.

Alemtuzumab. Alemtuzumab is an anti-CD52 monoclonal antibody that depletes CD52⁺ T cells and B cells. In a pilot case–control study that involved 24 patients with MS, the effects of alemtuzumab treatment on the ability to mount antibody responses to diphtheria, tetanus and poliomyelitis vaccine, *Haemophilus influenzae* type b and meningococcal group C vaccine, and pneumococcal polysaccharide vaccine were assessed³⁹. Results were compared with historical control data. Vaccine responses to T cell-dependent recall antigens (tetanus, diphtheria and poliomyelitis), T cell-dependent novel antigen (meningococcus C) and T cell-independent antigens (pneumococcal) were normal. Follow-up of 5 patients showed that responses to vaccination were not diminished within 6 months of alemtuzumab treatment³⁹. Furthermore, in 20 patients, the persistence of antibodies to mumps, rubella, varicella zoster virus (VZV) and the Epstein–Barr virus were measured before alemtuzumab treatment and at 1 month and 9–11 months after alemtuzumab treatment. Serum antibodies against these common viruses remained detectable after treatment. In conclusion, though vaccine

Delayed-type hypersensitivity (DHT). A cell-mediated overreaction to foreign antigens that leads to inflammation and tissue damage.

Recall antigens
Antigens to which healthy people are generally expected to have previously been exposed to such as tetanus, streptococcus, candida or tuberculosis.

responses seem to be maintained after alemtuzumab therapy, we advocate a 6-month interval between the previous treatment course and vaccination to ensure an adequate immune response.

Cladribine. Cladribine is a synthetic analogue of deoxyadenosine that is incorporated into DNA, leading to apoptosis and depletion of B cells and T cells, including non-proliferating cells^{40,41}. No dedicated studies, other than in the context of SARS-CoV-2 vaccination, have been conducted to examine vaccination responses during oral cladribine treatment^{42,43}. Whether oral cladribine affects immunological memory acquired from previous vaccinations has also not been assessed but patients who are treated with cladribine seem to be capable of mounting an intact cellular response to SARS-CoV-2 mRNA vaccines^{44,45}. Live attenuated vaccines should be administered at least 4–6 weeks before cladribine treatment to avoid the risk of infection. On the basis of the little evidence available, inactivated vaccines seem to be safe during cladribine therapy, but immunization should be completed before therapy whenever possible.

Inhibition of immune cell proliferation

Drug-induced inhibition of immune cell proliferation is expected to reduce the expansion of immune cells that normally follows vaccination, resulting in attenuated vaccine responses. Drugs with this mechanism of action have variable effects on immune cell proliferation, leading to different levels of protection after vaccination.

Teriflunomide. Teriflunomide inhibits pyrimidine synthesis and inhibits the proliferation of rapidly dividing cells such as activated T cells. In one study, the effects of teriflunomide on the immune response to the 2011–2012 seasonal influenza vaccine was investigated⁴⁶. The study involved patients with MS who were receiving 7 mg or 14 mg teriflunomide or IFN β -1b. Antibody responses did not differ significantly between the groups except the response to the influenza A (H3N2) antigen — the antibody response was significantly lower in patients receiving 14 mg teriflunomide than in patients receiving the lower dose of teriflunomide or IFN β -1b⁴⁶.

In a single-centre, randomized, placebo-controlled study, antibody responses to rabies vaccine were assessed in 46 healthy individuals who received teriflunomide or placebo⁴⁷. Geometric mean antibody titres were lower in people who received teriflunomide. However, antibody levels after vaccination were above the threshold for seroprotection in all participants. In addition, the proportion of individuals with DTH reactions to various recall antigens (tuberculin, *Candida albicans* and trichophyton antigens) was similar in both groups and cellular responses to recall antigens did not differ substantially. Overall, teriflunomide therapy does not seem to have a clinically relevant impact on vaccine response^{48,49}.

Azathioprine. Azathioprine inhibits purine synthesis to impair cell proliferation. In a small study of patients receiving azathioprine for neuroimmunological disease, antibody responses to influenza vaccination were not hampered and treatment did not influence pre-existing

antibody titres to hepatitis B, measles or tetanus³⁴. On the basis of this evidence, immunization with inactivated vaccines during azathioprine treatment for neuroimmunological diseases seems to induce protection as in patients receiving azathioprine for other underlying diseases.

Cyclophosphamide and mitoxantrone. Cyclophosphamide and mitoxantrone are classical cytostatic drugs that disrupt DNA synthesis and structure. Immune responses after vaccination in patients receiving these drugs for neuroimmunological disease have not been systematically studied, but these drugs impair immune responses and are expected to have a more sustained detrimental impact on vaccination efficacy than other cells that inhibit proliferation. Therefore, vaccines should be administered at least 2 weeks before treatment with these drugs when possible and live and live attenuated vaccines must be avoided for at least 3 months after treatment.

Mycophenolate mofetil. Mycophenolate mofetil depletes guanosine nucleotides in T cells and B cells, thereby preventing their proliferation. Antibody responses with mycophenolate mofetil have been studied in patients with NMOSD³⁴. In this study, antibody responses to influenza vaccination were significantly lower among patients receiving mycophenolate mofetil than among patients receiving IFN β and among healthy control participants³⁴. Given that treatment with mycophenolate mofetil impairs vaccine immunogenicity, additional vaccine doses are generally advisable (for example, in the case of SARS-CoV-2 vaccination) or should be recommended according to quantifiable antibody responses (for example, in the case of hepatitis A or B vaccination).

Impairment of immune cell migration

Several immunotherapies prevent invasion of the CNS by immune cells from the periphery. With these drugs, the response to vaccination would be expected to be maintained. However, the effects on vaccination responses differ between drugs of this type. Those that influence the egress of lymphocytes from the lymphatic tissue seem to impair vaccine responses to a greater extent than those that specifically target the trafficking of immune cells across the blood–brain barrier.

Natalizumab. Natalizumab is a humanized monoclonal antibody that binds to α 4 β 1 integrin on lymphocytes, thereby blocking interactions with cell adhesion molecules that are essential for the lymphocytes to cross the blood–brain barrier. The effects of natalizumab on responses to vaccines have been investigated in several studies.

In a single-centre, randomized, placebo-controlled study, 17 patients who were receiving natalizumab for relapsing–remitting MS and 10 healthy control participants received trivalent influenza A/B vaccine³⁰. Influenza-specific IgG levels were measured up to 12 weeks after vaccination. In both groups, anti-influenza B IgG levels increased substantially after vaccination.

Initial increases in levels of anti-influenza A IgG were smaller in both groups; a substantial increase at 4 weeks was seen only in the natalizumab group. IgG titres did not differ significantly between natalizumab-treated individuals and healthy control participants at any time point. Overall, vaccination against influenza in patients receiving natalizumab produced an equivalent humoral immune response to that achieved in healthy individuals.

In a randomized, multicentre, open-label trial⁵¹, the effects of natalizumab on responses to tetanus toxoid (a recall antigen) and KLH were investigated in patients with relapsing–remitting MS. Both vaccines were administered to patients who were natalizumab naive receiving no treatment and to patients receiving natalizumab at 6 months after treatment. An adequate response was defined as at least a twofold increase in specific serum IgG levels 28 days after vaccination. The responses to both antigens were adequate and similar in the two groups, indicating that natalizumab does not affect responses to the tested vaccinations in a clinically meaningful way. Consequently, no special measures need to be taken with the use of inactivated vaccines in the context of natalizumab treatment but live attenuated vaccines must be avoided.

Fingolimod. Fingolimod is a non-selective sphingosine 1 phosphate (S1P) receptor modulator that prevents lymphocyte egress from lymph nodes. In a blinded, randomized, multicentre, controlled study, the effects of fingolimod on responses to seasonal influenza and tetanus booster vaccinations were assessed in patients with MS who were receiving fingolimod or placebo⁵². At 6 weeks after vaccination, responses were lower in patients receiving fingolimod than in those receiving placebo.

In another study, 11 patients with MS received 2 doses of the attenuated live vaccine against VZV before commencing fingolimod treatment. VZV seroconversion was achieved when fingolimod treatment started 26–76 days after the second vaccine dose⁵³. Retesting for VZV IgG after a mean latency of 2.42 years from initiation of therapy revealed a global reduction of antibody titres in all patients and the disappearance of antibodies in 7 patients. After cessation of fingolimod, antibodies reoccurred in 2 of these 7 patients.

Overall, the evidence indicates that fingolimod therapy decreases vaccination-induced humoral immune responses. Therefore, testing for antibody responses, additional booster vaccines or other measures to prevent infections should be considered in the context of fingolimod therapy.

Ozanimod and ponesimod. Ozanimod and ponesimod are second-generation S1P receptor modulators that are more selective than fingolimod — ozanimod is selective for the S1P1 and S1P5 receptors and ponesimod is selective for the S1P1 receptor. The efficacy and safety of vaccines in people receiving these drugs have not been studied to date. However, given the similar mechanism of action to fingolimod, the immune response to vaccination is likely to be compromised in the same way.

Siponimod. Siponimod is a second-generation S1P receptor modulator that is selective for the S1P1 and S1P5 receptors. The effects of siponimod on vaccine responses have been investigated in a double-blind, placebo-controlled, parallel-group study in which 120 healthy adults received T cell-dependent (influenza) and T cell-independent (23-PPV) vaccinations⁵⁴. Participants were randomly assigned to four groups and underwent either 7 weeks of treatment with 2 mg siponimod daily or placebo. Those who received siponimod were assigned to one of three treatment groups: preceding siponimod, in which siponimod treatment was stopped 7 days before immunization; concomitant siponimod, in which siponimod treatment was continued throughout; and interrupted siponimod, in which treatment with siponimod was stopped 10 days before immunization and restarted 14 days after.

At 4 weeks after vaccination, mean titres of influenza antibodies were similar in the placebo group, the preceding siponimod group and the interrupted siponimod group but were lower in the concomitant siponimod group. However, the proportion of participants in whom seroprotective levels were achieved was similar in all groups for most antigens. For one of the two influenza B virus strains, the seroprotective threshold was not met in the interrupted siponimod and concomitant siponimod groups. 23-PPV vaccination induced a twofold or greater increase in IgG concentrations compared with baseline in 90–100% of participants. Overall, this study provides evidence that siponimod has a limited effect on the efficacy of vaccinations with neoantigens. However, the success of vaccination was not tested in patients with MS. As with other S1P receptor modulators, responses to vaccination might be hampered, and testing for antibody responses, additional booster vaccines or other measures to prevent infections might be necessary.

Pleiotropic therapies

β -Interferons. IFN β -1a and IFN β -1b are cytokines with immunomodulatory effects. In a small trial that involved 33 healthy control participants and 26 patients receiving IFN β -1a or IFN β -1b for MS, antibody and cellular responses to seasonal influenza vaccine were comparable between the two groups⁵⁵.

Similar findings were produced by a prospective, non-randomized, open-label study in which 85 patients receiving IFN β -1a for MS and 77 patients with MS who were receiving no treatment were administered influenza vaccine against various strains⁵⁶. No significant differences in immune responses were detected between the groups, demonstrating that patients with MS mount an appropriate immune response to influenza vaccine even if they are receiving high-dose, high-frequency IFN β -1a treatment. Interferons do not seem to attenuate humoral or cellular responses to vaccines and no special measures have to be considered when vaccinations are performed.

Glatiramer acetate. Glatiramer acetate consists of peptides that resemble myelin basic protein and have immunomodulatory effects. Humoral immune responses to protective vaccines in patients treated with glatiramer acetate have mainly been studied in trials

with seasonal influenza vaccines. In general, antibody responses were reduced in patients receiving glatiramer acetate compared with those in patients treated with IFN β ^{57–59}. The same was true in a small study of tick-borne encephalitis vaccination⁶⁰. In general, the evidence suggests that live and inactivated vaccines are safe for patients receiving glatiramer acetate therapy but immune responses are inadequate.

Dimethyl fumarate. Dimethyl fumarate is a prodrug that is metabolized to monomethyl fumarate, which has immunomodulatory effects through the Nrf2 pathway. The drug is approved for the treatment of relapsing–remitting MS and, in some regions, psoriasis. In one study, immune responses to vaccination with tetanus/diphtheria, pneumococcus (polyvalent) and meningococcus (groups A, C, W-135 and Y) antigens were compared in 38 patients receiving dimethyl fumarate and 33 patients receiving non-pegylated interferon⁶¹. Response rates were comparable between the two groups, ranging between 53% for meningococcal serogroup C and 95% for pneumococcal serotype 8. Overall, immune responses to vaccination seem to be maintained in patients treated with dimethyl fumarate^{61,62} so no special measures are needed.

Diroximel fumarate. Diroximel fumarate is a novel oral fumarate. No studies have been conducted to investigate the effects of vaccination during diroximel fumarate treatment to date. However, the response to vaccination is expected to be maintained as with dimethyl fumarate therapy.

Tocilizumab. Tocilizumab is a monoclonal antibody to the IL-6 receptor that is approved for the treatment of NMOSD and has been granted emergency use authorization to prevent severe COVID-19. By binding to soluble and membrane-bound IL-6 receptors, tocilizumab reduces the pro-inflammatory effects of IL-6. The efficacy and safety of vaccines have not been studied in patients receiving tocilizumab for NMOSD or any other neuroimmunological disease. In a study of patients with various other autoimmune inflammatory diseases, antibody responses to pneumococcal polysaccharide vaccination were suppressed in people receiving tocilizumab in comparison with those in people receiving rituximab⁶³. However, a different study showed that responses to hepatitis B vaccination were stronger in people receiving tocilizumab than in people receiving rituximab in autoimmune diseases⁶⁴. Studies in patients with rheumatoid arthritis have shown that antibody responses to pneumococcal polysaccharide, conjugate and influenza vaccines are not reduced in patients receiving tocilizumab compared with those in untreated patients^{65,66}. Overall, antibody responses to vaccination seem to be maintained in patients treated with tocilizumab therapy so no special measures need to be taken.

Satralizumab. Satralizumab is a humanized monoclonal antibody to the IL-6 receptor that is approved for the treatment of NMOSD in some countries. The efficacy and safety of vaccines with satralizumab treatment

have not been studied. Given that this antibody has the same immunological target as tocilizumab, the expected effects on vaccine efficacy are similar. Thus, immunization can be performed in patients who are treated with satralizumab.

Ecilizumab. Ecilizumab is a C5 complement inhibitor that was originally used for the treatment of haemolytic–uraemic syndrome and paroxysmal nocturnal haemoglobinuria but has been adopted for the treatment of some neuroimmunological diseases. Ecilizumab has been approved for the treatment of treatment-refractory acetylcholine receptor antibody-positive myasthenia gravis and of aquaporin 4 antibody-positive NMOSD^{67,68}. Few studies have been conducted to investigate the effects of ecilizumab on immune responses to vaccination and none have been conducted in patients with neurological diseases. One methodological difficulty is that commonly used antibody test systems require the presence of complement and therefore rabbit serum is typically used as a complement source to enable the analysis of serum from complement-inhibited patients⁶⁹.

One retrospective study involving 23 patients with paroxysmal nocturnal haemoglobinuria investigated the effects of ecilizumab on serological responses after vaccination with various meningococcal vaccines⁷⁰. Vaccinations had been administered before treatment initiation for 78% of patients and 43% had been vaccinated more than once owing to chronic ecilizumab treatment. No meningococcal infections were observed but overall serological responses differed for the meningococcal subgroups. The protective effects of novel vaccines against meningococcal serogroup B still require assessment. A similar study has been conducted in patients receiving ecilizumab for cold agglutinin disease⁷¹. In this study, levels of protective antibodies varied for different meningococcal serogroups but declined early or were absent with ecilizumab treatment. Based on these findings, we recommend repeated serological analysis for patients receiving chronic ecilizumab treatment in addition to revaccination every 3 years and, dependent on serological analysis, early booster vaccinations as recommended for adults with asplenia.

Glucocorticosteroids. Glucocorticosteroids bind to the glucocorticoid receptor and have dose-dependent immunosuppressive effects. Patients with various underlying diseases receiving relatively low doses of glucocorticosteroids (<20 mg prednisolone daily or equivalent in adults) seem to achieve adequate immune responses to vaccination^{72,73}. Among patients receiving glucocorticosteroid therapy for neuromuscular diseases, immune responses to seasonal influenza vaccination were comparable to those among patients who were not receiving glucocorticosteroid therapy⁷⁴. A meta-analysis showed that antibody responses can be reduced in children receiving low-dose glucocorticosteroids for rheumatoid arthritis but these individuals could still develop seroprotection⁷⁵ and glucocorticosteroids had no detrimental effect on established antibody responses in this study.

Higher doses of glucocorticosteroids do impair antibody formation although protective effects might be maintained⁷⁵. In a study of patients with rheumatoid arthritis, antibody responses to pneumococcal polysaccharide or conjugate vaccine were reduced among adults receiving prednisolone at doses above 7.5 mg daily⁶³. Similarly, after influenza vaccination in patients with systemic lupus erythematosus, only 53.9% of patients receiving ≥ 20 mg prednisolone daily developed protective antibodies compared with 72% of untreated patients and healthy control participants⁷⁶. By contrast, a study of patients receiving < 20 mg prednisolone daily for systemic lupus erythematosus showed no impairment of immune response to the hepatitis B vaccine⁷⁷. Taken together, the evidence shows that inactivated and live vaccines are safe for patients receiving low-dose systemic glucocorticosteroids; however, for patients receiving higher doses of glucocorticosteroids, live vaccines should be avoided and antibody responses to inactivated vaccines can be impaired.

High-dose intravenous immunoglobulin. High-dose intravenous immunoglobulins (IVIg) are antibodies that are pooled from healthy donors and that have various effects on the immune system, including inhibition of the complement system, effects on macrophages and T cells, and modulation of cytokine networks^{78,79}. Immune responses to vaccination after treatment with IVIg for neuroimmunological diseases have not been studied. In some cases, such as for hepatitis B vaccine, IVIg administered in the days after vaccination could neutralize the vaccine antigen and therefore limit the immune response. Therefore, if IVIg is given within 4 weeks after vaccination, revaccination can be considered at 4 weeks after IVIg therapy to ensure a complete immune response.

Plasma exchange. Plasma exchange is effective in antibody-mediated neurological diseases, such as GBS, and in the treatment of acute exacerbation of neuroimmunological diseases, in which it can yield rapid clinical improvements^{80–82}. The response to vaccines administered during plasma exchange for neuroimmunological diseases has not been studied systematically. In general, responses to vaccinations administered 2–4 weeks before the treatment period and during treatment are likely to be compromised as vaccine antigens are likely to be removed during plasma exchange^{82,83}, and passive vaccination with immunoglobulins is not useful in this period as the treatment removes the antibodies. After completion of plasma exchange, cellular immune response mechanisms are maintained and the production of cytokines and immunoglobulins is expected to normalize within days⁸³. Therefore, vaccination does not necessarily need to be delayed by more than 1–2 weeks, but studies of the immune response to vaccination after plasma exchange are needed to determine the best approach.

Stem cell transplantation

Stem cell transplantation, in particular autologous haematopoietic stem cell transplantation, is a potential treatment option for some patients with MS or NMOSD⁸⁴. Given the extremity of the procedure, vaccination in this

situation is a complex medical issue with various influencing factors. The cellular immune response to previous vaccination might be compromised by stem cell transplantation; therefore, baseline vaccination might need to be repeated after transplantation and reconstitution of the immune system. Vaccinations should be administered according to stem cell transplantation guidelines. Generally, guidelines advise immunization no earlier than 3–6 months after stem cell transplantation, depending on individual immune reconstitution^{85,86}. Basic vaccinations include pneumococcus, tetanus, diphtheria, pertussis, poliomyelitis, *Haemophilus influenzae* and annual influenza^{26,84}. Live attenuated vaccines, such as measles, mumps, rubella or VZV, are recommended only for patients in whom antibodies are not detectable after complete immune reconstitution^{84,87}.

Comparison of therapies

In several studies, the effects of various immunotherapies on immune responses to seasonal influenza vaccines have been investigated and compared. In one such study⁵⁸, vaccine-specific antibody responses to the pandemic H1N1 swine flu 2009 vaccine and the seasonal H1N1 and H3N2 influenza 2010 vaccine were analysed in 289 patients with MS who were receiving DMT (IFN β , glatiramer acetate, natalizumab or mitoxantrone) and 251 healthy control participants. Overall, patients receiving DMT had lower antibody protection rates after H1N1 2009 vaccination compared with control participants (27.4% versus 43.5%). Protection was not influenced by IFN β but was lowered by all other DMTs included. A similar pattern was seen with the 2010 influenza vaccine.

In a similar study, antibody responses and seroprotection rates after vaccination with the 2012–2013 seasonal influenza vaccine (H1N1, H3N2) in 90 patients receiving various DMTs for MS (fingolimod, glatiramer acetate, IFN β , natalizumab or no treatment) were compared with those in 62 healthy control participants⁵⁹. At 3, 6 and 12 months after vaccination, protection rates among patients receiving IFN β and glatiramer acetate did not differ significantly from those among control participants. By contrast, patients receiving fingolimod had reduced protection at all time points and natalizumab recipients had diminished protection at 3 and 6 months. Among patients with MS who were not receiving DMT, protection rates did not differ from those among control participants.

In a prospective, multicentre, non-randomized observational study of 108 patients with MS, antibody responses and seroprotection to trivalent seasonal influenza vaccination (H1N1, H3N2, B) were analysed. Patients were receiving various DMTs, including IFN β , glatiramer acetate, natalizumab and fingolimod⁵⁷. Vaccination elicited robust immune responses in patients receiving IFN β and glatiramer acetate. Among patients receiving natalizumab and fingolimod, response rates were low, particularly for H3N2. Overall, a longer disease duration was associated with an increased risk of insufficient immune response to vaccination.

Finally, in another prospective, multicentre, non-randomized observational study, the immunogenicity

of a tick-borne encephalitis vaccine was analysed in 20 patients with MS who were receiving IFN β , glatiramer acetate, fingolimod or natalizumab⁶⁰. Vaccination led to protective antibody titres in 77.8% of participants. Patients who were receiving IFN β or glatiramer acetate developed sufficient antibody titres, whereas patients receiving fingolimod had low antibody titres.

Practicalities of immunization

Several working groups have published guidelines for the vaccination of patients with neuroimmunological diseases — mainly MS — and of immunocompromised individuals^{88–91}. Implementation of these guidelines in day-to-day clinical practice is vital.

Before initiation of immunotherapy for neuroimmunological diseases, or when switching between therapies, several infection-related aspects need to be considered (TABLE 2). Regulatory authorities, such as the FDA and EMA, request specific screening to exclude latent infections, such as tuberculosis, and detect the absence of immune protection, including undetectable VZV antibodies, before initiating treatment with some immunotherapies. In addition, some immunotherapies cannot be initiated until after vaccination if immune protection is lacking.

When determining the appropriate timing of protective vaccination, the biological half-lives and pharmacodynamics of individual immunotherapies should be considered (TABLE 3). Special attention is required when live attenuated vaccines are being considered for patients receiving immunotherapies as inappropriate use of these vaccines can lead to severe adverse effects or deterioration of the underlying disease.

Measurement of immune responses to vaccines is not routinely recommended, but correlates of protection can be assessed for, among others, hepatitis A, hepatitis B, measles, tetanus, tick-borne encephalitis, rabies and VZV^{92–96}. Importantly, immune protection can be primarily cell mediated, and therefore antibody titres might not always be the best surrogate marker for vaccine-induced protection.

SARS-CoV-2 in neuroimmunological diseases

Vaccination against SARS-CoV-2 is generally recommended for people with neuroimmunological disease. Indeed, in some countries, this group has been prioritized for vaccination. Overall, the risk of SARS-CoV-2 infection does not seem to be higher among patients with MS than among the general population^{97,98} but the risk of severe COVID-19 does seem to be increased in patients receiving treatment with specific immunotherapies for neuroimmunological disease^{99–103}. Early data suggest that treatment with monoclonal antibodies that deplete B cells carries an increased risk of serious illness^{99,100,104–109}. Patients with MS or NMOSD who are receiving anti-CD20 therapy have lower antibody responses after SARS-CoV-2 infection than patients receiving other DMTs or no DMT^{110–113}. However, in a Swedish cohort of patients with MS, rituximab treatment did not increase the risk of hospitalization above that with other DMTs and neither the timing of rituximab infusion nor the cumulative lifetime dose influenced

COVID-19 severity¹¹⁴. Impaired antibody responses to SARS-CoV-2 infection in patients receiving fingolimod for MS has also been observed^{113,115}. By contrast, treatment with IFN β for MS does not seem to increase the risk of severe COVID-19 (REF.¹¹⁶).

In this context, vaccination against SARS-CoV-2 is important to reduce the risk of SARS-CoV-2 infection and, more importantly, minimize the severity of COVID-19 in patients with MS and other neuroimmunological diseases¹¹⁷. Data on SARS-CoV-2 vaccination in these patients and the effects of immunotherapies on responses to SARS-CoV-2 vaccinations are accumulating rapidly. A regularly curated literature hub is likely to help all relevant stakeholders stay abreast of new developments¹¹⁸.

SARS-CoV-2 vaccines

Internationally, a large number of SARS-CoV-2 vaccines have been approved and the number is likely to continue increasing^{13,119–124}; the WHO maintains a regularly updated website that provides an overview of the licenced vaccines and candidate vaccines¹⁴. Approved vaccines are of various types. Among them are novel nucleoside-modified mRNA vaccines^{11–15}, which consist of delivery vehicles, such as lipid nanoparticles, that encapsulate nucleoside-modified mRNA that encodes the SARS-CoV-2 spike glycoprotein^{8,125–127}. The mRNA-based vaccines produced by BioNTech (BNT162b2) and Moderna (mRNA-1273) do not lead to intracellular virus replication and can therefore be considered non-live vaccines^{128–130}.

Other types of approved SARS-CoV-2 vaccines are recombinant viral vector vaccines (ChAdOx1 COVID-19 vaccine^{131,132}, Ad26.COVS.133,134, Gam-COVID-Vac/Sputnik V^{135,136} and Ad5-nCoV^{137,138}), inactivated whole-cell COVID-19 vaccines (CoronaVac/Sinovac COVID-19 vaccine, BIBP COVID-19 vaccine, WIBP-CorV, Covaxin and others^{135,137,138}), and subunit vaccines, in which COVID-19 proteins are used as antigens (EpiVacCorona¹²⁴, ZF2001, MVC COVID-19 vaccine, Soberana 02 (REFS^{139,140}), NVX-CoV2373 (REFS^{141,142}) and CoV2 preS dTM¹⁴³). In general, SARS-CoV-2 vaccines seem to be safe and do not lead to specific adverse events in people with neuroimmunological disease^{117,135,144–150}.

Immunological responses

The immune response to SARS-CoV-2 vaccinations is not yet fully understood, but knowledge is rapidly accumulating. Evidence suggests that a balanced humoral and T helper type 1 cellular immune response are critical for protection against SARS-CoV-2 (REF.¹⁵). Quantitative testing for immune responses to SARS-CoV-2 vaccination generally involves measurement of antibodies against the SARS-CoV-2 spike protein. However, the clinical correlates of this antibody response are yet to be defined^{151–153}. Measurement of specific cellular vaccine responses is not routinely available, and whether T cell responses alone will translate into protection against SARS-CoV-2 remains unclear¹⁵⁴. BNT162b2 vaccination protects against SARS-CoV-2 (REF.¹⁵⁵) and induces a specific T cell response¹⁵⁶ that lasts at least 6 months in healthy adults¹⁵⁷.

Table 2 | Recommended infection screening and vaccination before immunotherapy

Drug	FDA and/or EMA requirements		Additional recommendations
	Infection screening	Vaccination	
Alemtuzumab	Annual HPV and Pap smears		Screen for HBV, HCV, HIV, TB, syphilis and VZV; pneumococcal vaccination (regional recommendations); annual influenza vaccination (optional); VZV vaccination if seronegative; avoid attenuated live vaccines (obligatory)
Azathioprine		Live vaccines contraindicated; immune response should be controlled by means of titre determination	Screen for HBV, HCV, HIV, TB and VZV; VZV vaccination if seronegative; pneumococcal vaccination (regional recommendations); annual influenza vaccination (optional); avoid attenuated live vaccines up to 3 months after treatment (obligatory)
Cladribine	Screen for HBV and HCV	VZV if antibody negative	Screen for HBV, HCV, HIV, TB and VZV; VZV vaccination if seronegative; annual influenza vaccination (optional); avoid attenuated live vaccines
Cyclophosphamide	Exclude acute infection; screen for HBV, HCV and TB	Live vaccines contraindicated	Screen for HBV, HCV, HIV, TB, syphilis and VZV; consider antimicrobial and antifungal prophylaxis
Dimethyl fumarate, diroximel fumarate			Screen for HBV, HCV, HIV and TB (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Eculizumab	Exclude acute infection	Immunizations before initiation according to current guidelines; meningococcal vaccine (serogroups A, C, Y, W-135 and B), consider bridging with antibiotic prophylaxis; <i>Haemophilus influenzae</i> and pneumococcal vaccine (age <18 years)	Screen for HBV, HCV, HIV, TB, syphilis and VZV; pneumococcal (regional recommendations); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Fingolimod	VZV antibody screening	VZV if antibody negative	Screen for HBV, HCV, HIV and VZV; VZV vaccination if seronegative; HBV and HPV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Glatirameroids			Annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Glucocorticosteroids	Exclude acute infection		Avoid attenuated live vaccines (obligatory)
IFN β			Annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Inebilizumab	Exclude acute infection; screen for HBV, TB; quantify serum immunoglobulins	Live attenuated or live vaccines not recommended during treatment or until B cell repletion; complete required vaccinations ≥ 4 weeks before initiation	Check vaccination status before initiation; screen for HBV, HCV, HIV, TB and VZV; seasonal influenza vaccination (optional); avoid attenuated live vaccines (obligatory); test for quantitative serum immunoglobulins
Mitoxantrone	Exclude acute infection	Live vaccines contraindicated; delay vaccination for 3 months after treatment	Screen for HBV, HCV, HIV and TB (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Mycophenolate mofetil		Live vaccines contraindicated	Screen for HBV, HCV, HIV, TB and VZV; VZV vaccination if seronegative; pneumococcal vaccination (regional recommendations); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory); screen for hypogammaglobulinaemia during treatment
Natalizumab			Screen for HBV, HCV, HIV, JCV, TB and VZV (optional); VZV vaccination if seronegative; annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Ocrelizumab	Screen for HBV and HCV		Check vaccination status before initiation; screen for HBV, HCV, HIV, TB and VZV; pneumococcal vaccination (regional recommendations); VZV vaccination if seronegative; HBV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)

Table 2 (cont.) | Recommended infection screening and vaccination before immunotherapy

Drug	FDA and/or EMA requirements		Additional recommendations
	Infection screening	Vaccination	
Ofatumumab	Screen for HBV; quantify serum immunoglobulins	Live attenuated or live vaccines not recommended during treatment or until B cell repletion; complete required vaccinations ≥4 weeks before initiation	Check vaccination status before initiation; screen for HBV, HCV, HIV, TB and VZV; pneumococcal vaccination (regional recommendations); VZV vaccination if seronegative; HBV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Ozanimod	VZV antibody screening	VZV if antibody negative	Screen for HBV, HCV, HIV and VZV; VZV vaccination if seronegative; HBV and HPV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Ponesimod	VZV antibody screening	VZV if antibody negative	Screen for HBV, HCV, HIV and VZV; VZV vaccination if seronegative; HBV and HPV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Rituximab			Screen for HBV, HCV, HIV, TB, syphilis and VZV; VZV vaccination if seronegative; pneumococcal vaccination (regional recommendations); HBV vaccination (optional); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Satralizumab	Exclude acute infection; screen for HBV and TB	Immunizations before initiation according to current guidelines	Screen for HBV, HCV, HIV, TB, syphilis and VZV; pneumococcal (regional recommendations); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)
Siponimod	Contraindicated history of PML or cryptococcal meningitis; screen for VZV	VZV if antibody negative; delay treatment initiation until 4 weeks after vaccination	Screen for HBV, HCV, HIV and VZV; VZV vaccination if seronegative; annual influenza vaccination (optional); avoid attenuated live vaccines up to 4 weeks after treatment (obligatory)
Teriflunomide			Screen for HBV, HCV, HIV and TB (optional); annual influenza vaccination (optional); avoid attenuated live vaccines
Tocilizumab	Exclude acute infection; screen for HBV and TB	Immunizations before initiation according to current guidelines	Screen for HBV, HCV, HIV, TB, syphilis and VZV; pneumococcal vaccine vaccination (regional recommendations); annual influenza vaccination (optional); avoid attenuated live vaccines (obligatory)

Information based on REFS^{5,90,220,221}. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis; VZV, varicella zoster virus.

Follow-up studies have shown that antibody responses to SARS-CoV-2 vaccines wane after several months^{132,158–165}, and booster vaccination is required to restore these responses. COVID-19-associated mortality is lower among people who have received two vaccine doses and a booster than among people who have received only two doses of vaccine¹⁶⁶. Of note, heterologous booster vaccination using mRNA or Ad26.COVS showed similar or higher immunogenicity compared to homologous booster vaccine¹⁶⁷.

The extent of protection against severe COVID-19 provided by SARS-CoV-2 vaccines is partly determined by the responsible viral variant. For the delta variant (lineage B.1.617.2), many approved vaccines have proven sufficient to protect against severe disease^{160,162,168–172} and booster doses prevent hospitalization and death with the delta variant for 97–99% of adults in all age groups for at least 10 weeks after the booster dose^{166,173}. However, a greater antibody response is required for protection

against the omicron variant (lineage B.1.1.529) owing to its diminished susceptibility to the vaccine-induced antibody response^{174–176}. Booster vaccination with BNT162 has been shown to elicit a sufficient neutralizing antibody response against the omicron variant¹⁷⁷ and could mitigate the reduction in vaccine effectiveness against this variant^{178–184}. Booster vaccination after SARS-CoV2 infection is also recommended for durable protection against reinfection¹⁸⁵.

SARS-CoV-2 vaccines and immunotherapy

Studies to date suggest that B cell depletion and other immunosuppressive therapy — particularly S1P1 receptor modulation with fingolimod — reduces antibody responses to SARS-CoV-2 vaccination whereas immunomodulatory therapies and IVIg or plasma exchange do not substantially influence vaccine responses^{4,6,186–190}. One study has also suggested that siponimod treatment in patients with secondary progressive MS

reduces the humoral response to SARS-CoV-2 vaccination in comparison with that in healthy control participants¹⁹¹.

In a small study conducted in Israel, the BNT162b2 vaccine was administered to 93 patients with MS who were receiving cladribine, fingolimod, ocrelizumab or no treatment. Antibody responses to the vaccine among patients receiving cladribine were comparable to those among untreated patients¹⁸⁸. By contrast, the majority of patients receiving fingolimod did not develop sufficient antibody responses, and protective antibody titres were reached in only 22.7% of patients receiving ocrelizumab¹⁸⁸. However, no relevant safety signal was detected; in particular, relapse activity was not increased¹⁹².

In a larger study, antibody responses to mRNA SARS-CoV-2 vaccines were lower in patients with MS who were receiving treatment with fingolimod or CD20 antibodies than in patients receiving no treatment¹⁹³. In this study, vaccination with mRNA-1273 led to higher antibody levels than vaccination with BNT162b2 (REF.¹⁹³). Moreover, the humoral response was greater with a longer time since the last administration of anti-CD20 treatment and was associated with the number of repopulated B cells at the time of vaccination¹⁹⁴. In patients vaccinated with mRNA-1273, the overall seroconversion rates at day 70 were 39.3% among patients receiving ocrelizumab compared with 100% among untreated patients¹⁹⁵. The seroconversion rate was 26% among patients who were vaccinated less than 12 weeks after

Table 3 | Suggested intervals between immunotherapies and vaccinations

Mechanism of action	Drug	Interval from vaccine to treatment (weeks)		Live vaccine during therapy permitted	Interval from treatment to live vaccine
		Inactivated vaccine	Live vaccine		
Direct depletion or cytotoxicity	Ocrelizumab	>6	>6	No	~18 months + normal B cell count
	Rituximab	>4	>4	No	>12 months + normal B cell count
	Ofatumumab	2–4	>4	No	Not studied; after B cell repletion (~40 weeks)
	Inebilizumab	>4	>4	No	After B cell repletion
	Alemtuzumab	6	6	No	>12 months + normal B cell count
Impairment of cell proliferation	Teriflunomide	2–4 ^a	4	No	>6 months
	Azathioprine	2–4 ^a	4	No	>3 months
	Cladribine	2–4 ^a	4–6	No	4–6 weeks + normal lymphocyte count
	Cyclophosphamide	2–4 ^a	4	No	>3 months
	Mitoxantrone	2–4 ^a	4	No	>3 months
	Mycophenolate mofetil	2–4 ^a	>4–6	No	>2 months
Inhibition of cell migration	Natalizumab	2–4 ^a	4	No	>3 months
	Fingolimod	2–4 ^a	4	No	>2 months
	Ozanimod	4 ^a	>4	No	3 months
	Ponesimod	4 ^a	>4	No	2 weeks
	Siponimod	4	4	No	4 weeks
Pleiotropic effects	IFNβ	0	0	Individual risk assessment	None
	Glatiramer acetate	2–4 ^a	2–4 ^a	Individual risk assessment (avoid YF vaccine)	None
	Dimethyl fumarate	2–4 ^a	4	No (when lymphopenic)	After normalization of lymphocyte count
	Tocilizumab	4 ^a	4	No	Not studied
	Satralizumab	2–4 ^a	4	No	Not studied
	Eculizumab	2–4	4	Not advised	Not studied
	Glucocorticosteroids ^b	0	0	Yes	None
	Glucocorticosteroids ^b for >2 weeks	2–4	4	No	>2 months
	IVIg	2–4 ^a	2–4 ^a	Yes	>3 months (diminished response to measles vaccine up to 1 year)
Plasma exchange	2–4 ^a	2–4 ^a	Not advised	None	

Information based on prescribing information and REFS^{19,73,83,90,222–226}. IVIg, intravenous immunoglobulin; YF, yellow fever. ^aWhere possible, shorter intervals can lead to reduced immune response. If shorter intervals are unavoidable, testing for antibody responses to vaccination and/or additional vaccination might be necessary. ^bEquivalent to <20 mg prednisolone daily.

administration of ocrelizumab and 50% among patients who were vaccinated more than 12 weeks after ocrelizumab treatment¹⁹⁵. Low B cell counts before vaccination were associated with lower seroconversion rates^{195,196}. The same association has also been observed among patients receiving other anti-CD20 therapies for neuroimmunological disease¹⁹⁷. Interestingly, 24.6% of patients with MS who were receiving anti-CD20 therapy developed protective humoral immunity after a booster dose of mRNA SARS-CoV-2 vaccine, whereas only 6.9% of patients who were receiving fingolimod developed an adequate antibody response¹⁹⁸.

Additional studies have corroborated the finding that the humoral immune response to mRNA and ChAdOx1 nCoV-19 vaccines is reduced in patients with MS receiving treatment with either a selective S1P1 receptor modulator or CD20 antibody therapy^{154,199–203}, and similar results have been obtained with an inactivated SARS-CoV-2 vaccination (BBIBP-CorV)^{204,205}. However, the overall antibody response to the ChAdOx1 nCoV-19 vaccine seems to be lower than that to the BNT162b2 vaccine²⁰⁰. However, this study also showed that 7 of 16 participants without detectable humoral immunity after vaccination did have SARS-CoV-2-specific T cell responses²⁰⁰.

Robust T cell responses to SARS-CoV-2 vaccination (predominantly mRNA vaccines) have been observed in other cohorts of patients receiving anti-CD20 therapy for MS in whom humoral immune responses to SARS-CoV-2 vaccination are attenuated^{154,206–208}. In a study of 49 patients with MS who were receiving treatment with ocrelizumab, the antibody response to BNT162b2 was diminished but, of 29 patients without a sufficient antibody response, 26 had SARS-CoV-2-specific T cells; this proportion is comparable to that of healthy control participants²⁰⁷. Similarly, in a study of 20 patients with MS receiving treatment with anti-CD20 therapy, 89% developed spike-specific antibodies and only 50% developed receptor-binding domain-specific antibodies after vaccination with mRNA SARS-CoV-2 vaccination, whereas all healthy control participants developed antibodies²⁰⁶. In this study, patients receiving anti-CD20 therapy had lower specific memory B cell responses to mRNA SARS-CoV-2 vaccination than did healthy control participants but their antigen-specific CD4⁺ T cell and CD8⁺ T cell responses were comparable to those of healthy control participants²⁰⁶. Overall, evidence suggests that antigen-specific CD4⁺ and CD8⁺ T cell responses after vaccination are adequate in patients with MS who are receiving anti-CD20 monoclonal antibodies despite poor spike-specific and receptor-binding domain-specific antibody production^{62,206,207}. Other studies have shown that patients receiving treatment with fingolimod for MS had low humoral and T cell responses to mRNA or vectored SARS-CoV-2 vaccinations^{62,209}.

Studies of patients receiving anti-CD20 therapy for non-neurological disease have demonstrated similar reduced antibody responses to SARS-CoV-2 vaccines^{210,211}. In one comparison of responses in patients receiving anti-CD20 therapy for MS and rheumatoid arthritis, humoral responses to mRNA SARS-CoV-2 vaccination were impaired in both groups compared

with those in healthy control participants but T cell responses were adequate^{212,213}.

Long-term vaccination responses in people with MS have been analysed in one study. The study included 414 patients with MS and 89 healthy control participants and showed that the protective response to SARS-CoV-2 vaccination in untreated patients and in patients treated with cladribine, dimethyl fumarate, natalizumab or teriflunomide was similar to that in healthy people²¹⁴. However, protective antibody titres at the same time point were observed in only 9.5% of patients treated with fingolimod, 22.8% of patients treated with ocrelizumab and 86.4% of patients treated with alemtuzumab²¹⁴.

Owing to the reduced humoral response to SARS-CoV-2 vaccines in patients receiving anti-CD20 therapy, published recommendations advise vaccination against SARS-CoV-2 at least 3 months after the last anti-CD20 treatment and 4–6 weeks before the next anti-CD20 treatment^{194,215,216}. However, evidence suggests that dosing intervals longer than 6 months can improve the humoral vaccine response^{194,217}. In general, SARS-CoV-2 vaccination should be recommended for all patients receiving immunotherapy. Given the risk of infection during the pandemic, the relative timing of vaccination in relation to dosing of immunotherapy is of minor relevance even if the immune response is reduced^{144,215,218,219}.

Conclusion

Prevention of infectious diseases is an important part of the management of neuroimmunological diseases. The course of these diseases can be negatively affected by infections, and patients with these diseases — particularly those treated with disease-modifying immunotherapy — have a higher risk of acquiring infections and of severe illness as a result of these infections than do healthy individuals; therefore, prophylactic vaccinations are crucial.

Immunotherapies used for neuroimmunological diseases affect the immune system in different ways. Their influence on the individual risk of infection varies and they interact with vaccine immunology (Supplementary Table 3). In general, vaccinations are safe in people with underlying neuroimmunological conditions though live attenuated vaccines should be avoided, especially during concomitant immunotherapy. Both humoral and cellular immune responses to vaccination can be hampered by some immunotherapies though protection from infection can be achieved by vaccination in many cases. Nevertheless, improved knowledge of the interplay between autoimmune dysregulation, immunotherapies and immunization with conventional and novel vaccines is required to improve the care of patients with neuroimmunological diseases. The integration of SARS-CoV-2 vaccinations into treatment paradigms for MS and other neuroimmunological diseases is an ongoing challenge, particularly for patients who are already established on immunotherapy. For these patients, the timing of vaccination is important to ensure maximal safety and protection.

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- In this comprehensive study, analysis of over 10 million adults during a 20-year period demonstrated a strong association of Epstein-Barr virus with the development of MS.**
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A.W. and M.L. wrote and edited the manuscript. M.B. edited the manuscript. A.W., M.L. and H.-P.H. performed the literature search. All authors contributed to conceptualization, data interpretation and review.
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