Cellular and humoral vaccination response under immunotherapies — German consensus on vaccination strategies in neurological autoimmune diseases

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Abstract

Background: With the development of highly effective disease-modifying treatments, vaccinations are becoming increasingly important in people with neurological autoimmune diseases. However, questions regarding the safety and efficacy of vaccinations under immunotherapy remain.

Objective: To provide recommendations on types and timing of vaccinations for people with neuroimmunological diseases under different immunotherapies.

Design: Our study presents a German evidence-based expert consensus on vaccination under immunotherapies in neurological autoimmune diseases.

Methods: Based on literature research, a consortium of experts evaluated the quality of evidence, integrated clinical experience, and responded to a questionnaire determining an agreement (>75%) on statements concerning vaccination upon immune therapies in neuroimmunological diseases.

Results: The specific humoral and cellular response to vaccination can be compromised under alemtuzumab, azathioprine, cladribine, cyclophosphamide, CD19/CD20 antibodies (inebilizumab, ocrelizumab, ofatumumab, rituximab, ublituximab), dimethyl fumarate/diroximel fumarate, FcRn inhibitors (efgartigimod, rozanolixizumab), complement C5 inhibitors (eculizumab, ravulizumab, zilucoplan), interleukin-6 receptor antibodies (tocilizumab, satralizumab), intravenous immunoglobulins, long-term steroid administration, methotrexate, mitoxantrone, mycophenolate mofetil, tacrolimus, teriflunomide, tumor necrosis factor-α blockers, and sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, ponesimod, siponimod), as well as after autologous stem cell transplantation. The lymphocyte count can have an influence here. Overall, it is generally advisable to complete vaccination before starting immunotherapy. However, in the case of an active inflammatory disease course with possible irreversible neurological deficits, a delay in therapy initiation until immunization has been completed cannot be justified. The application of live vaccines is contraindicated for most therapies and is only recommended after a strict risk–benefit assessment.

Conclusion: Vaccinations are necessary for individuals on immunotherapy to reduce the risk of infections and the associated risk of worsening neurological autoimmune diseases. However,

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the humoral and cellular vaccination response may be impaired under immunotherapy necessitating close monitoring. Here, we provide applicable recommendations to optimize immunization for individuals receiving immunotherapy due to a neurological autoimmune disease.

Plain language summary

Cell- and antibody-mediated vaccination response under immunotherapies—German consensus on vaccination strategies in neurological autoimmune diseases

Aims and purpose of the research: Based on currently available literature on vaccination in people receiving treatment for a neurological autoimmune disease, a group of experts generated recommendations on how to handle vaccination in people receiving immunotherapy.

Background of the research: Medications used in treating autoimmune diseases may create a risk for patients due to reduced immune defence and impact on vaccination success. Protection against the respective pathogen may be reduced under different immunotherapies despite formally completed immunization. This may result in the need for repeated vaccination or special protective measures against infections.

Methods and research design: Based on a thorough literature search, a consortium of experts generated applicable recommendations and consented on these via a questionnaire.

Results and importance: The vaccination response is evaluated under alemtuzumab, azathioprine, cladribine, cyclophosphamide, CD19/CD20 antibodies (inebilizumab, ocrelizumab, ofatumuab, rituximab, and ublituximab), dimethyl fumarate/diroximel fumarate, FcRn inhibitors (efgartigimod and rozanolixizumab), complement C5 inhibitors (eculizumab, ravulizumab and zilucoplan), interleukin-6 receptor antibodies (tocilizumab, satralizumab), intravenous immunoglobulins, long-term steroid administration, methotrexate, mitoxantrone, mycophenolate mofetil, tacrolimus, teriflunomide, tumor necrosis factor-α blockers and sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, ponesiomd and siponimod), as well as after autologous stem cell transplantation. The white blood cell count can have an influence on the vaccination response. Overall, it is generally advisable to complete vaccination before starting immunotherapy. However, in the case of an active course of the disease with possible irreversible neurological deficits, a delay in the start of therapy until immunization has been completed cannot be justified. The application of live vaccines is contraindicated for most therapies and is only recommended after a strict risk-benefit assessment.

Conclusion: Vaccinations are necessary for individuals receiving immunotherapy to reduce the risk of infections and the associated risk of worsening neurological autoimmune diseases. However, the antibody- and cell-mediated vaccination response may be impaired under immunotherapy, thus necessitating close monitoring.

Keywords: immunotherapies, neuroimmunological diseases, neurological autoimmune diseases, vaccination

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Introduction

Immunotherapies (specifically considered in this work: alemtuzumab, azathioprine, cladribine, cyclophosphamide, CD19/CD20 antibodies (inebilizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab), dimethyl fumarate/diroximel fumarate, FcRn inhibitors (efgartigimod and rozanolixizumab), complement C5 inhibitors (eculizumab, ravulizumab, and zilucoplan), interleukin-6 (IL-6) receptor antibodies (tocilizumab, satralizumab), intravenous immunoglobulins (IVIG), long-term steroid administration, methotrexate (MTX), mitoxantrone, mycophenolate mofetil (MMF), tacrolimus, teriflunomide, tumor necrosis factor-α (TNF-α) blockers, and sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ozanimod, ponesimod, and siponimod), and autologous stem cell transplantation) applied in neurological autoimmune diseases (i.e., multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), autoimmune encephalitis, myasthenia gravis, vasculitis of the central nervous system (CNS), neurosarcoidosis, and immune neuropathies) influence parts of the process leading to immunity after vaccination. Thus, protection against the respective pathogen may be reduced under different immunotherapies despite formally completed immunization. This may result in the need for repeated vaccination or special protective measures against infections.

A vaccination response requires a complex interaction of antigen-presenting cells, cytotoxic and memory T cells and B cells. For some vaccine types (polysaccharide vaccines), there is evidence that an intact complement system is important for the formation of antibodies after vaccination. Most of the studies on vaccinations in people receiving immunotherapy refer to antibody concentrations and compare these either with previously defined criteria for seroprotection or with control groups. Even though immunity through most vaccines could be shown to correlate with antibody levels, antibody levels are only surrogates for the actual protection provided by vaccination.[1–8] Correlates of protection vary between pathogens and large-scale studies on true protection against infection in people with autoimmune diseases are lacking. Cell-mediated (especially CD8 T cells) immune response is also necessary and measurable for certain germs.[9]

Overall, for the scope of this work, we have chosen to use antibody levels and vaccine-specific T cell responses as approximates for the effectiveness of vaccinations.

Modes of vaccines

Various modes of action of vaccines have been established to date. A distinction must be made between live vaccines and inactivated vaccines. Live vaccines contain viruses or bacteria capable of reproduction in an attenuated form.[10,11] This is brought about by growing the virus in nonhuman cell culture, which leads to a reduced ability to multiply in human cells.[11] After application, specific immunity is triggered without causing disease.[10,11] Live vaccines include the combined mumps-measles-rubella vaccine as well as yellow fever, rotavirus, and some varicella vaccines. By binding the structural pathogen components to antigen-presenting cells, the antigen is presented to T cell receptors.[10,11] This generates antigen-specific CD4+ or CD8+ effector cells as well as long-lived memory T lymphocytes.[10,11] At the same time, the natural adjuvant of the pathogen components induces the release of T cell-attracting and -stimulating chemokines and cytokines.[10,11] With the help of T helper cells, memory B cells and plasma cells are activated and expanded, which release antigen-specific antibodies.[10,11]

Inactivated vaccines contain inactivated pathogens or components of the pathogen. These include inactivated whole particle vaccines (e.g., polio, hepatitis A, rabies, tick-borne encephalitis (TBE), influenza, SARS-CoV-2, cholera, and some varicella vaccines). They induce an immune response with CD4+ T effector and memory T cells, as well as memory B cells and antibody-producing B cells.[10,11] Protein vaccines contain inactivated toxins (diphtheria toxoid, pertussis toxoid, tetanus toxoid) or immunogenic proteins (hemagglutinin from *Bordetella pertussis*, spike protein from SARS-CoV-2), which act as antigens on antigen-presenting cells to trigger a vaccine-specific T cell response and antibody production.[10,11] As these cannot trigger an immune response on their own, they are enriched with immunogenicity-enhancing components (adjuvants).[10,11] Some bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) have an outer capsule of polysaccharides. In polysaccharide vaccines (e.g., PPSV23 against *S. pneumoniae*),

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direct stimulation of B lymphocytes is induced by human leukocyte antigen-independent mediated antigen presentation, namely via B cell receptors or C3-binding type 2 complement receptors.[10,11] By coupling with carrier proteins (e.g., tetanus toxoid or diphtheria toxoid (cross-reacting material 197)), additional activation of bystander T cells (against the carrier protein, not against the polysaccharide) can enhance the B cell immune response against the polysaccharide. This can increase the affinity and longevity of the antibodies and memory B cells.[10,11] These so-called "conjugate vaccines" include, for example, the pneumococcal conjugate vaccine (PCV) against serotype 7, 10, or 13 (PCV-7, PCV-10, PCV-13); and meningococcal vaccines against serogroups C (Men C) and ACWY (Men ACWY).[12]

Messenger RNA (mRNA) vaccines (e.g., for SARS-CoV-2), a type of inactivated vaccine, have another mechanism of action. These contain mRNA, often packaged in liposomal fat envelopes, which cause translation of the antigen after cellular uptake by antigen-presenting cells, among others.[12,13] These then lead to a T and B cell-mediated immune response with CD4+ and CD8+ effector cells, as well as T and B memory cells and antibody production by plasma cells. Finally, vector vaccines use a modified viral vector (adenovirus) as a carrier of viral DNA, which is transcribed into mRNA after cellular uptake, resulting in antigen production and a subsequent immune response.[14] Protection against the Ebola virus is derived from a vector vaccine, while a vector vaccine developed for SARS-CoV-2 is no longer available.

Vaccinations and disease activity

Although it is improving, vaccination hesitancy is still an issue in people with neurological autoimmune diseases, especially in people with MS (pwMS), and depends greatly on the vaccination education of patients.[15–19] For many years, there has been concern that in autoimmune diseases such as MS, stimulation of the immune system, for example, through vaccination, could be accompanied by an activation of the disease (flare-ups). However, the available evidence clearly speaks against a connection between vaccinations and the initial manifestation of MS.[20–26] Furthermore, several studies have not found a significantly increased relapse rate 8–12 weeks after vaccination in general and specifically for vaccination against hepatitis B, tetanus, influenza, tuberculosis, TBE, rabies, SARS-CoV-2, influenza, yellow fever, diphtheria, or pneumococcus.[22,26–45] Overall, the suspicion that there was a connection between vaccination and MS, as suggested in individual case reports, could not be substantiated by larger studies.[46]

In the case of NMOSD or MOGAD, individual case reports observed relapses after vaccination, particularly in patients without immunotherapy.[47–58] A recent study describes the occurrence of NMOSD relapses after vaccination against meningococcal disease before starting therapy with eculizumab in 9 out of 45 people with aquaporin-4 (AQP-4) antibody-positive NMOSD.[59] As this disease is highly active prior to therapy, it is not possible to estimate with certainty the proportion of relapses actually related to meningococcal vaccination prior to the start of therapy. In this case, overlapping low-dose antibiotic prophylaxis could be used to postpone vaccination until the immunotherapy is fully effective.

Apart from individual case reports, no increased disease activity or triggering of myasthenia gravis is described after vaccination against influenza, hepatitis B, human papillomavirus (HPV), Japanese encephalitis and tuberculosis, diphtheria, tetanus, pneumococci, meningococcal disease, or SARS-CoV-2.[60,61] A yellow fever vaccination is contraindicated in case of thymus dysfunction (myasthenia and/or presence of a thymoma or condition after thymectomy) due to the association with the increased risk of yellow fever vaccine-associated visceral disease.[62–66]

With regard to autoimmune encephalitis, there are also only individual case reports that suggest a connection between vaccination against SARS-CoV-2 (whole particle vaccine against SARS-CoV-2), Japanese encephalitis, tetanus/diphtheria/pertussis/poliomyelitis, yellow fever and HPV, and the first manifestation of anti-N-methyl-d-aspartate (NMDA) receptor or anti-metabolic glutamate receptor 5 (mGluR5) encephalitis.[67–69] In large observational studies, these cases were very rare making any impact negligible.[67–69] In an observation of 121 people with autoimmune encephalitis (86 anti-NMDAR, 15 anti-GABAbR, 15 anti-LG1/Caspr2, 3 anti-AMPAR, 1 anti-mGluR5, and 2 anti-GFAP), 1 person experienced disease activity within 30 days after SARS-CoV-2 vaccination and 3 people

within 120 days after vaccination, 2 of whom were untreated.[70]

Although the incidence of Guillain–Barré syndrome (GBS) is slightly increased after SARS-CoV-2, herpes zoster[71,72] and influenza vaccination (but still significantly less frequent than after either infection),[73–83] there is no direct correlation between vaccination and increased disease activity or incidence of other chronic immune neuropathies. In a large study of 1.8 million vaccinations against HPV, there was no increased incidence of GBS or chronic inflammatory demyelinating polyneuropathy (CIDP).[84] In three studies of people with CIDP, 1.5% of 411, 1% of 268, and 5 of 24 patients developed GBS after influenza vaccination (timing not specified).[85–87]

In regards to an effect of vaccination on disease activity, 4% of 311 GBS patients and 8% of 65 CIDP patients experienced an exacerbation of the disease after vaccination (the specific vaccination was not reported). About 0% of 162 GBS patients, 3% of 188 CIDP patients, and 4% of 53 patients with multifocal motor neuropathy (MMN), as well as 5% (13 CIDP and 3 MMN patients) of 307 patients (260 CIDP, 47 MMN) experienced an exacerbation of the disease after vaccination against SARS-COV-2 (mRNA and vector).[88,89]

Very few reports of CNS vasculitis after vaccination were found in three international spontaneous reporting systems (<1% of vasculitis reports), of which 40% were reported in association with immunization against HPV.[90] CNS vasculitis was reported in 1 out of 158 cases of vasculitis after application of SARS-CoV-2 mRNA vaccine.[91] To date, no causal connection between vaccination (specifically against influenza, hepatitis B, tuberculosis, meningococcal C, hepatitis A, HPV, rotavirus, diphtheria, pertussis, tetanus, typhoid, yellow fever, anthrax, mumps/measles/rubella (MMR)) and vasculitis could be established.[92,93] To our knowledge, other potential consequences of vaccination have not yet been investigated with sufficient power.

Overall, for most neurological autoimmune diseases (MS, myasthenia gravis, autoimmune encephalitides, immune neuropathies, NMOSD, MOGAD) clear evidence of increased disease activity after infections is reported.[58,85,86,94–102] There are indications that immunotherapy can positively influence infection-triggered disease activity.[96] The least amount of data can be found on neurosarcoidosis and CNS vasculitis. However, vaccinations in sarcoidosis are generally considered safe.[103]

Vaccination under immunosuppression

In addition to questions concerning the stimulation of the immune system by vaccination and the extent of the humoral and cellular vaccination response under immunotherapy, the safety of live vaccines remains relevant. Vaccination with a live vaccine under immunotherapy is associated with a risk of triggering the respective infection.[104–107] The extent and quality of immunosuppression depend on the medication administered. This article assesses the available evidence regarding the safety of live vaccine application under different immunotherapies.

As described above, a humoral and cellular vaccination response requires a complex interplay of various cells and messengers. Disease-modulating therapies in MS and other neurological autoimmune diseases influence parts of this process, so that the measurable vaccination response may be reduced under different immunotherapies despite completed immunization, which may be associated with reduced protection against the respective infection. This may necessitate repeated vaccinations or special protection against infections. In the following, the current evidence on the cellular and humoral vaccination response under the various disease-modifying drugs (alemtuzumab; azathioprine; cladribine; cyclophosphamide; the CD19/CD20 antibodies inebilizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab; dimethyl fumarate/diroximel fumarate; the FcRn inhibitors efgartigimod and rozanolixizumab; the complement C5 inhibitors eculizumab, ravulizumab, and zilucoplan; MTX; mitoxantrone; MMF; tacrolimus; teriflunomide; the TNF-α blockers infliximab, etanercept, dalimumab, and the S1P modulators fingolimod, ozanimod, ponesimod, and siponimod), as well as after autologous stem cell transplantation will be summarized and consensus recommendations defined; an overview is shown in Figure 1. This work aims to provide recommendations for physicians involved in the treatment of people with neuroimmunological illnesses under immunotherapies. Cooperation of these physicians, mainly involving general practitioners performing

Figure 1. Influence of respective therapy on vaccination response after inactivated vaccinations in relation to time since last therapy administration. Dark green: normal titer; light green: reduced but sufficient vaccination response; orange: anticipated slightly reduced vaccination response, check titer after complete vaccination if necessary based on an individual risk analysis; purple: anticipated reduced vaccination response (vaccination should be sought 4–6 weeks before initiating therapy).
aHSCT, autologous hematopoietic stem cell transplantation; CBC, complete blood count; FcRn, neonatal Fc receptor; IVaCD20, intravenously administered CD20 antibodies; IVIG, intravenous immunoglobulins.

the vaccination and a neurologist evaluating the patient's specific risk and benefit of the vaccination, is key for safe, patient-centered care.

Methods

In this original study, a German evidence-based expert consensus on vaccination under immunotherapies in neurological autoimmune diseases is established. First, a literature search was conducted (by author M.S.) up to June 2024 on studies in PubMed, the national guidelines of Germany's Robert Koch Institute (RKI) and the Standing Committee on Vaccination (STIKO), as well as the respective technical information (summary of product characteristics) and international and national vaccination recommendations of the professional associations the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), and the European Academy of Neurology (EAN) and the disease-related German Competence Network Multiple Sclerosis. The therapies were selected according to their use in the following neuroimmunological diseases: MS, NMOSD, MOGAD, autoimmune encephalitides, myasthenia gravis, CNS vasculitides, neurosarcoidosis, and immune neuropathies. The search included combinations of the disease name (and/or acronym), therapy (using the active ingredient, agent name, and common abbreviation as search terms), and the term "vaccination" or "vaccine." Where results were lacking for neuroimmnunological diseases research on rheumatic, malignant (for autologous hematopoietic stem cell transplantation (aHSCT)), and other autoimmune diseases was analyzed, preferably consulting national or international guidelines and professional associations on these diseases. Results in German or English were considered. An overview of the selected reports and the screening process can be found in the Supplemental Figure 1 and Supplemental Table 1. After the initial compilation, the group of authors, all of whom are specialized in the treatment of neuroimmunological diseases, assessed the quality of the evidence separately and independently. On this basis and based on clinical experience, the individual recommendations were agreed upon by means of an online questionnaire (originally conducted in German using www.empirio.de; a translation is provided as Supplemental Methods). The percentage of agreement is stated after the respective recommendation. A recommendation was accepted as consensus if approval had reached >75%; a summary of all treatment-specific recommendations can be found in Supplemental Table 2.

Results of the literature review and recommendations

Vaccinations can reduce the risk of infections and the associated possible progression of neuroimmunological diseases; an up-to-date, complete vaccination status in accordance with the guidelines of the STIKO is recommended.

Overall, the induction of disease activity after vaccination in people with neurological autoimmune diseases cannot be completely ruled out due to the lack of large studies and the availability of mainly only individual case reports. With clear evidence of the triggering of relapse events and disease activity after infection and the risk of the infection itself in all of these diseases (MS, NMOSD, MOGAD, autoimmune encephalitides, myasthenia gravis, CNS vasculitides, neurosarcoidosis, and immune neuropathies), the protection provided by vaccination certainly outweighs the risks.

Therefore, from a safety perspective, vaccinations with inactivated vaccines can generally be recommended for people with a neurological autoimmune disease, regardless of the therapy. Overall, our consensus-based recommendations are inclined toward recently published consensus recommendation of the EAN and ECTRIMS for pwMS.[40]

Diverging recommendations can be found for yellow fever vaccination in MS. An expert consensus of the RKI advises against vaccination in pwMS undergoing treatment with glatiramer acetate or interferons despite the absence of contraindications to live vaccinations.[106] A current consensus recommendation of the EAN and ECTRIMS does not describe a clear risk of relapse activity after yellow fever vaccination based on the studies also cited above.[31,36,40,42,106] The application of yellow fever vaccination in pwMS should therefore always be decided on a case-by-case basis after a strict benefit–risk assessment.

Under immunosuppressive therapy, vaccination with a live vaccine can trigger the corresponding infectious disease due to attenuated but replicable viruses.[104–107] For this reason, vaccination with a

live vaccine is still contraindicated under immunosuppressive therapy. Due to this precautionary measure, the number of vaccinated people is likely to remain too low to ever be able to make statistically justified reliable statements as to whether activation of the underlying disease is to be feared. Under immunotherapy, vaccination with a live vaccine can be considered in individual cases if there is sufficient cellular immunity and after a strict risk–benefit assessment (including the situational risk of infection).[10,106] Completion of immunization with live vaccines before starting immunosuppressive therapy is generally recommended. The extent and quality of immunosuppression depends on the medication and dosage administered. A graphical representation of the recommended intervals between therapy and vaccination with a live vaccine can be found in Figure 2 and is described further in the course of the text.

Immunization with inactivated vaccines, on the other hand, can also take place during the administration of immunotherapy. For people with neurological autoimmune diseases and especially those undergoing treatment with immunosuppressants, a recommendation should be made for seasonal influenza vaccination, pneumococcal and herpes zoster vaccination and other vaccinations.[108] The general vaccination recommendations applicable in each case should be followed. To optimize the humoral and cellular vaccination response, the immunization should be completed 4–6 weeks before the start of immunotherapy. However, if there is high disease activity (multiple relapses in a very short time, rapid progression of symptoms, and/or high paraclinical activity) and a clinically urgent indication to start immunotherapy promptly, a delayed start of therapy to complete the recommended immunization cannot be justified and the start of therapy should precede completion of the vaccination series.

If immunity is not yet present, a live vaccination against varicella zoster virus (VZV) is recommended before treatment with fingolimod, siponimod, ponesimod, cladribine, ozanimod, alemtuzumab, or CD19/CD20 antibodies.[106,109–117] The STIKO recommends this even before any immunotherapy if the VZV titer is negative.[118] In 99% of people who grew up in Germany before the VZV vaccine introduction in 2004, contact to VZV is presumed and thus titer control is not deemed necessary.[108] In an immunosuppressed state, immunisation against VZV can be performed with the inactivated vaccine, licensed to prevent herpes zoster (Shingrix®; Glaxo Smith Kline GmBH & Co. KG), as an off-label application.[108,119,120] In this case, titer control should be performed.[108] Vaccination to prevent herpes zoster through administration of an inactivated vaccine (Shingrix®; Glaxo Smith Kline GmBH & Co. KG) is recommended by the STIKO for people adults under immunosuppression.[108]

In the event of a lack of vaccination protection, measured by vaccination titers, despite a sufficient number of vaccination doses or in the case of clear contraindications against attempting vaccination, risk reduction should take place, for example, vaccination of close relatives. However, the measurable titers can also remain negative, especially with CD20 antibodies, but protection against infections can also be provided by T cell responses.[121] Administration of a higher number of vaccinations than normal is not recommended. In addition, we recommend increased vigilance for symptoms under any immunosuppression so that if necessary, early antiviral or antibiotic treatment can be initiated in the event of an infection.

Specifics of neuromyelitis optica spectrum diseases, MOG-associated disease

NMOSD and MOGAD should be considered in a more differentiated way in some cases, since relapses after vaccination are described in case reports, particularly without immunotherapy, but controlled studies are insufficient.[47–58] In the context of the SARS-CoV-2 pandemic and vaccination with the vector vaccine, cases of an initial manifestation of MOGAD after vaccination have been reported.[58] Complement activation is an essential component in the pathogenesis of NMOSD, but is also observed to some extent in MOGAD. The complement C5-neutralizing antibodies eculizumab and ravulizumab are approved not only for myasthenia gravis but also for AQP4 antibody-positive NMOSD. Vaccinations—in particular polysaccharide vaccinations (pneumococci and meningococci)[122,123] and possibly vector vaccinations[124,125]—can in turn induce activation of the complement system, so that a potential increased relapse rate in NMOSD/MOGAD could be explained by this.[126–130] The latter appears particularly relevant in the case of mandatory meningococcal

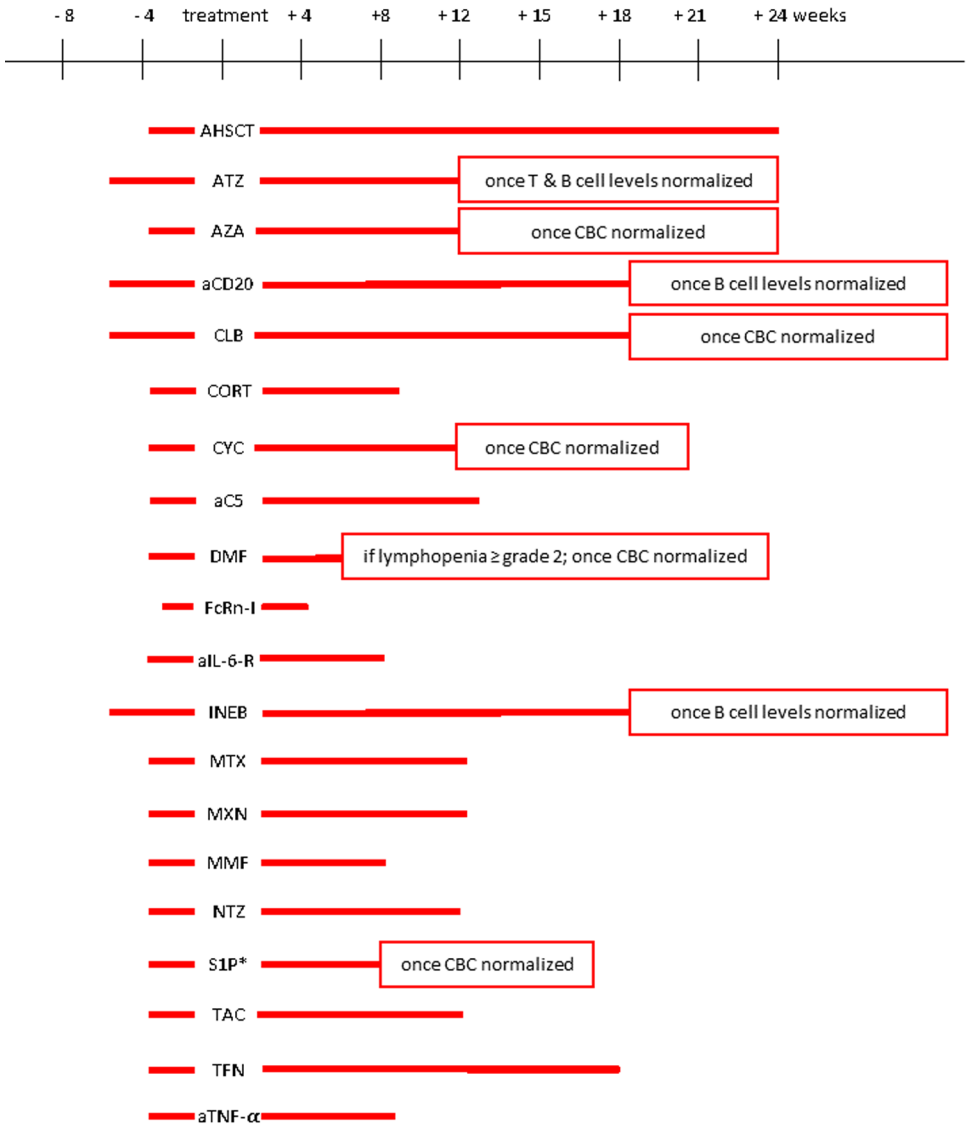

Figure 2. Recommended interval between therapy and application of a live vaccine. Administration of a live vaccine only after strict risk–benefit assessment, possibly depending on the respective dosage and cellular immunity. Red: Administration of a live vaccine contraindicated; boxes span reported repopulation, measurement of lymphocytes, and a risk–benefit analysis take precedence over absolute time as repopulation varies greatly between individuals.
*Distances between live vaccinations and different S1P modulators vary—see recommendations in the text.
aC5, anti-complement C5; aCD20, anti-CD20; aHSCT, autologous hematopoietic stem cell transplantation; aIL-6-R, anti-IL-6 receptor; aTNF-α, anti-TNF-alpha; ATZ, alemtuzumab; AZA, azathioprine; CBC, complete blood count; CLB, cladribine; CORT, glucocorticoids; CYC, cyclophosphamide; DMF, dimethyl fumarate; FcRn-I, FcRn inhibitors; INEB, inebilizumab; MMF, mycophenolate mofetil; MTX, methotrexate; MXN, mitoxantrone; NTZ, natalizumab; S1P, S1P modulators; TAC, tacrolimus; TFN, teriflunomide.

vaccination prior to therapy with eculizumab, ravulizumab, or zilucoplan and has also been described.[59] A reduction of this risk through concomitant oral glucocorticoid therapy may be useful, but must be weighed against the negative effects of steroids (and other prior therapies) on vaccination success. Another option that requires documented consultation is prophylactic antibiotic shielding until complete immunization at a time after disease stabilization under immunotherapy through complement inhibition.[47]

In NMOSD, severe relapses with incomplete remission in particular lead to relevant clinical impairments, thus prompt initiation of immunotherapy is recommended—especially in AQP4 antibody-positive NMOSD.[131–133] It is therefore recommended that immunotherapy and bridging treatment with oral steroid therapy be started immediately.[134,135] An urgent, prompt start can also influence the feasibility of other vaccinations; glucocorticoid therapy or prior immunotherapy can in turn influence seroconversion after vaccination (see below).

In NMOSD prompt complement inhibition is often needed. In such circumstance vaccination under complement inhibition and antibiotic prophylaxis is recommended. A recent German consensus recommends vaccination prior to initiation of complement inhibition in myasthenia gravis, as some antibiotics can aggravate symptoms of the underlying autoimmune disease.[136]

Consensus—general

1. The administration of inactivated vaccines is safe in most cases of neuroimmunological diseases and should follow the recommendations for nondiseased. (100%)
2. If there is an urgent indication for therapy, it must be individually considered whether waiting until complete immunization is justifiable. (97%)
3. Live vaccinations are generally contraindicated under immunotherapies. An interval should be maintained before the start of therapy and after discontinuation of therapy as shown in Figure 2. (97%)
4. Vaccination against yellow fever is contraindicated for people with myasthenia gravis. (93%)
5. A completion of the immune status (inactivated vaccines) according to STIKO should be sought before starting immunotherapy, especially with alemtuzumab, anti-CD19/CD20 antibodies, S1P receptor modulators, or cladribine, if clinically justifiable. (100%)
6. Before treatment with alemtuzumab, anti-CD19/CD20 antibodies, cladribine, or S1P modulators (obligatory before fingolimod, ponesimod, or siponimod; recommended before ozanimod), seronegative people must be fully immunized against the VZV. (100%)
7. Pre- and co-therapies can influence the humoral and cellular vaccination response. (100%)

Vaccination under specific immunotherapy

The following paragraphs list the studies that have been carried out on humoral and cellular vaccination responses in people with neuroimmunological diseases under the respective immunotherapy. From this, clinically applicable recommendations are formulated with regard to the expected vaccination response. The therapeutic agents are arranged alphabetically below and the agreed consensus is found at the end of each paragraph. An overview of the expected vaccination response in relation to the interval between therapy termination and vaccination can be found in Figure 1. If medication is administered in intervals, Figure 1 can help identify the optimal time point for a vaccination (green or orange). It also gives an overview of expected vaccination response and as such can help identify risk groups.

In addition, the humoral and cellular vaccination response after vaccination can be influenced by previous immunotherapy, in particular by long-term depletion of immune cells or a high number of previous immunotherapies. A control of vaccination titers under immunotherapy would be desirable in principle, but is not always possible and feasible for all vaccines and is often not financed. A patient-specific risk analysis including past-medical history (e.g., previous infection, other risk-increasing chronic illnesses), exposure to certain germs (e.g., through occupation or geographic prevalence), or specificities of immunotherapy (e.g., complement-inhibitors) should be applied to evaluate value of titer measurement.

Autologous hematopoietic stem cell transplantation

In aHSCT, high-dose chemotherapy leads to an ablation of existing immune cells, including memory cells. Subsequent transplantation of previously acquired hematopoietic stem cells leads to a repopulation of immune cells.

According to current data, a partial or complete loss of previously existing vaccination protection due to aHSCT can be assumed, measured by the frequency of the seroreversion.[137–140] A study of 58 individuals with hematologic malignancies

found seroconversion in 67% of individuals vaccinated after transplantation, with titers increasing with increasing time between vaccination and transplantation. Interestingly, seroconversion persisted in all 24 individuals vaccinated against SARS-CoV-2 (mRNA vaccines) prior to aHSCT.[140] Another study also found higher antibody titers with increasing intervals between mRNA vaccination against SARS-CoV-2 and aHSCT in 192 people with hematologic malignancies.[141] Another study described a seroconversion in 89.2% of 65 people with hematologic malignancies after aHSCT, with significantly lower titers than healthy controls.[142] Furthermore, an influence of CD19+ B cell and immunoglobulin G (IgG) levels was mentioned here. The interval between vaccination and transplantation had an influence on titer levels after allogeneic hematopoietic stem cell transplantation, but not after aHSCT.[142] In a separate study, 61 people were randomized to receive either a vaccination against pneumococci (heptavalent conjugate vaccine PCV7) or placebo prior to aHSCT. After transplantation, all subjects were vaccinated again after 3 and 6 months. A higher titer was detected in the subjects who had been vaccinated before aHSCT; after triple vaccination, seroprotection (concentration $\geqslant$0.35 µg/mL against all seven vaccine serotypes) was achieved in >60% of patients regardless of their previous vaccination status.[143] The following recommendations are based on the guidelines of the German Society for Hematology and Medical Oncology and the recommendations of the STIKO working group on immunodeficiency.[144,145]

Consensus—aHSCT

1. Partial or complete loss of previously existing vaccination protection due to aHSCT is likely. (96,67%)
2. Re-immunization after transplantation is recommended. Seroconversion appears to increase with increasing time between vaccination and aHCST. To optimize the effectiveness of the vaccination, a certain repopulation of immune cells should already exist: (100%)
   (a) An interval of 3 months after aHSCT should be maintained for tetravalent influenza vaccinations, pneumococcal vaccination (PPSV23), VZV vaccination (Shingrix, inactivated vaccine), and SARS-CoV-2 vaccinations. (97%)
   (b) An interval of 6 months after aHSCT should be maintained for inactivated vaccines against tetanus, diphtheria, pertussis, poliomyelitis (inactivated polio vaccine. Salk), *H. influenzae* type B (conjugate vaccine), meningococcus (meningococcus ACWY and B), and hepatitis B. (97%)
   (c) An interval of 24 months must be upheld for live vaccines (measles/mumps/rubella).[146] (93%)

Alemtuzumab

By binding to CD52, which is expressed on both T and B cells, alemtuzumab leads to cell death, and thus a reduction in the number of lymphocytes. Repopulation of B cells takes place within 4–6 months, while repopulation of T cells takes several years.[147]

The evidence regarding seroconversion after vaccination under alemtuzumab is limited. One study (n=20) described a preserved seroprotection compared to previously published data in healthy controls after vaccination against diphtheria, tetanus, poliomyelitis, *H. influenzae* type B, meningococcus C, and pneumococcus (PPSV23) with a median interval of 18 months (1.5–86 months) since the last alemtuzumab administration.[148] Another study (n=12) showed a regular development of antibody-mediated and cell-mediated immunity against SARS-CoV-2 after vaccination with an mRNA vaccine compared to untreated controls.[149] An analysis of the influence of the interval between alemtuzumab administration and vaccination response was not carried out. Nevertheless, the interval was also extended with a mean of 16 months since last application.[149] Another small study described a preserved vaccination response (antibody levels compared to untreated individuals) in 15 individuals with MS treated with alemtuzumab after vaccination with an mRNA vaccine, but without more detailed subanalyses.[150] In another small cohort (n=8), a dependence of seroconversion on the time since the last administration of alemtuzumab was described.[151]

Consensus—Alemtuzumab

1. A reduced humoral and cellular vaccination response under therapy with alemtuzumab

as well as a dependence on the lymphocyte count and repopulation of immune cells is to be expected. (100%)
2. Completion of immunizations as per recommendations of the STIKO is therefore advised 6 weeks prior to the start of therapy; SARS-CoV-2 immunization up to 4 weeks before the start of therapy. If there is an urgent indication for therapy, starting therapy before completing immunizations should be considered. (97%)
3. The VZV status should be checked before therapy. In the absence of an immune response against VZV, vaccination against VZV should be carried out before administration of alemtuzumab and seroconversion should be verified. (97%)
4. Live vaccinations have not been sufficiently studied and vaccination under alemtuzumab therapy is not recommended until the complete blood count normalizes after therapy; in any case, a strict individualized benefit–risk assessment should be applied. (93%)

Azathioprine

Azathioprine is a purine analog that inhibits RNA/DNA synthesis and thereby reduces the proliferation of immune cells. The evidence regarding vaccination under azathioprine therapy is very limited. In 13 individuals with systemic lupus erythematosus (SLE), reduced seroconversion (31% against H1N1, 8% against H3N2, and 23% against influenza B compared to 58% for influenza A and B in untreated individuals), and reduced seroprotection (hemagglutination inhibition titer (HI) ⩾40; 69% vs 92% against H1N1, 62% vs 100% against H3N2, 62% vs 92% against B/Hong Kong) compared to untreated individuals with SLE has been described.[152] A study of six people with NMOSD treated with azathioprine (2 mg/kg/d) showed seroprotection (HI ⩾40) after H1N1 influenza vaccination.[153] A study of five people with NMOSD showed seroconversion (without a more detailed description of the antibody levels) after SARS-CoV-2 vaccination (mRNA or vector vaccine) or infection under azathioprine.[154]

Consensus—Azathioprine

1. Overall, it can be assumed that the vaccination response under azathioprine therapy is at least slightly reduced until a complete repopulation of the immune cells is achieved after discontinuation. (97%)
2. Live vaccination is contraindicated until the lymphocytes normalize. (93%)

CD19/CD20 antibodies

Inebilizumab

By binding to CD19, inebilizumab leads to a broad depletion within the B cell lineage, including pro-B cells and plasmablasts, which are spared by CD20 antibodies. There is very little data on seroconversion or vaccine-specific T cell response with inebilizumab, which was recently approved against AQP4 antibody-positive NMOSD. A single study reports seroconversion in one of four people under inebilizumab after SARS-CoV-2 infection, but not after vaccination.[154] Whether previously existing immunity could also be lost due to depletion of the plasmablasts as a result of the therapy remains to be investigated in respect to the various vaccinations.

Ocrelizumab

The humanized CD20 antibody ocrelizumab causes the complete peripheral depletion of CD20-positive B cells, with repopulation after termination of therapy with a median of 62 weeks (range 27–175 weeks).[155] Reduced seroconversion has been described with ocrelizumab. One study showed that antibody levels against tetanus toxoid in pwMS treated with ocrelizumab ($n = 68$) were reduced by half (54.5% vs 23.9%) compared to those not treated or treated with interferon-beta ($n = 34$), by two-thirds (100% vs 71.6%) against pneumococci (PPSV23), and by 20% (75%–97% vs 55.6%–80%) against influenza vaccines (5 strains).[156] Similarly, the humoral response against keyhole limpet hemocyanin (KLH) as a nonspecific immunostimulant for testing immunocompetence was reduced by half.[156] It should be noted that in this study, the interval between ocrelizumab infusion and vaccination was at least 12 weeks.[156]

With regard to SARS-CoV-2 (mRNA vaccines), there was overall evidence of a greatly reduced antibody-mediated vaccination response (30%–60% seropositivity; $n = 20$ and $n = 22$) compared to healthy controls and untreated individuals with MS, which was also seen in relation to the time

since vaccination and associated B cell count.[150,157] However, some studies showed a comparable to slightly increased specific T cell-mediated vaccination response in anti-CD20-treated individuals compared to healthy controls.[157–160]

Data to date indicate persistent vaccination protection with ocrelizumab when vaccinated before starting therapy.[161–163]

Ofatumumab

The subcutaneously administered CD20 antibody ofatumumab has only been approved for the treatment of relapsing MS since 2020 in the USA (2021 in Europe) and also leads to a depletion of CD20-positive B cells. Recovery of B cells is achieved at a median of 24 weeks.[113] The data available on seroconversion after vaccination with ofatumumab are limited and restricted to the vaccination response to SARS-CoV-2 vaccinations. A seropositivity of 60% (defined by the respective assay used) and a preserved T cell response against SARS-CoV-2 after vaccination in pwMS treated with ofatumumab was detected; absolute antibody levels were significantly lower than in untreated persons or in pwMS receiving ofatumumab who had already received the vaccinations before starting therapy ($n=5$, $n=10$, $n=26$, respectively).[164–166] A recently published study showed a seroprotection (HI $\geqslant$40) in pwMS vaccinated against several influenza A and B strains under ofatumumab comparable to a cohort treated with glatiramer acetate and interferon as well as patients vaccinated $\geqslant$2 weeks prior to ofatumumab initiation. Seroprotection against influenza B Washington strain was lower in those vaccinated under ofatumumab.[167] The rate of seroconversion (here defined as a fourfold increase in HI titer after vaccination if the prevaccination HI titers were $\geqslant$10, or postvaccination HI titers $\geqslant$40 with prevaccination HI titers $<$10) and HI titer change trended to be lower in those vaccinated under ofatumumab but did not reach significance in the limited number of cases ($<$20).[167] To our knowledge, there is no evidence regarding the effect of ofatumumab therapy on the success of other vaccinations.

Rituximab

Rituximab, the first available anti-CD20 antibody, also induces CD20-positive B cell depletion, with a variable repopulation of naïve B cells taking between 12 and 15 months, while memory B cells do not return to baseline levels until more than 25 months.[168] There are only a few studies on the efficacy of vaccinations under therapy with rituximab in people with neurological autoimmune diseases. On the other hand, there are some studies on patients with malignant diseases and rheumatoid arthritis (RA) who were treated with rituximab. Here, a meta-analysis of 38 studies with 905 people under anti-CD20 therapies rituximab or ocrelizumab showed a seroconversion of 44% after pandemic influenza (13 studies with 222 patients), 17% after seasonal influenza (12 studies with 252 patients), 31%–69% after tetanus, diphtheria, and pertussis (12 studies with 309 patients), 73%–77% after *H. influenzae* B (3 studies with 52 patients), 56% after hepatitis B (3 studies with 61 patients), 0–67% after hepatitis A (2 studies with 57 patients), and 0–20% after PPSV23 vaccination (7 studies with 217 patients).[169] A relative risk compared to healthy controls was calculated with a relative risk of 0.22 for lower antibody levels with vaccination within 3 months, 0.44 within 6 months, 0.77 within 6–12 months, and 1.1 at $>$12 months since last rituximab infusion in relation to influenza vaccination. Increased levels tended to be described with longer intervals since the last infusion.[169] The latter observation related to vaccinations against influenza, tetanus, hepatitis A and B, *H. influenzae* B, pertussis, and diphtheria.[169]

A study of 16 people with NMOSD taking rituximab showed seroprotection (HI $\geqslant$40) in 18.8% after vaccination against influenza (H1N1) compared with 100% in healthy controls.[153]

Another study described significantly lower antibody levels against influenza A and B and pneumococci after vaccination in 16 pwMS under rituximab compared to pwMS who were untreated or treated with interferon-beta. In this study, the titer did not correlate with the interval since the last infusion.[170]

After vaccination against SARS-CoV-2 (mRNA vaccine), absolute antibody levels were 20-fold lower in pwMS under rituximab compared to untreated pwMS ($n=25$); seroconversion was exhibited in only 25% of the 19 people with NMOSD or 21 pwMS under rituximab compared to healthy controls.[150,171] Another study described seroconversion in 11% under rituximab ($n=10$) and in 100% without therapy in

people with neuroimmunological diseases (MS, NMOSD, clinically isolated syndrome, autoimmune encephalitis).[172]

In contrast, the SARS-COV-2-specific T cell response was detectable in 100% of individuals with MS or NMOSD receiving the vaccination under rituximab.[171] A similar result with a reduced antibody response (23.8% vs 100% in healthy controls) and equivalent SARS-CoV-2-specific T cell response was shown in another study investigating anti-CD20 treated individuals ($n=16$ rituximab and $n=27$ ocrelizumab) compared to healthy controls.[173]

Ublituximab

The intravenous monoclonal antibody against CD20 ublituximab, approved for the treatment of MS in the USA in late 2022 and in Europe in 2023, also causes a complete depletion of CD20-positive B cells. Repopulation is reported after 70 weeks.[174] No studies have been reported as of yet on seroconversion following vaccination under ublituximab.

Consensus—anti-CD19/CD20

1. A significantly reduced humoral vaccination response is to be expected under anti-CD19/CD20 therapy. (93%)
2. Vaccinations recommended by the STIKO should be completed up to 4 weeks prior to the start of therapy. In the case of a highly active course, starting therapy before complete immunization should also be considered. (100%)
3. Basic immunization against VZV in the absence of antibody detection is recommended before therapy. (80%)
4. Live vaccination is contraindicated 4 weeks before, during therapy, and until B cell repopulation. (97%)

Cladribine

Treatment with cladribine induces apoptosis of T and B cells, in particular a long-lasting elimination of CD27+ memory B cells.[175] Repopulation of B cells takes around 30 weeks after the last dose of cladribine each treatment year, while CD4 T cells require around 43 weeks; CD8 T cells do not seem to drop below the lower normal limit.[176] Recent data collected during the SARS-CoV-2 pandemic showed antibody levels comparable to healthy controls and untreated pwMS when treated with cladribine ($n=48$).[177] Another study in 38 pwMS undergoing cladribine therapy described a seroconversion of 100% against SARS-CoV-2. An influence of the time between last cladribine dose and vaccination was rejected; however the variance was large and only nine people had been vaccinated within 4 months of cladribine administration. Titers were not compared to a control group in this study.[178] A seroconversion of 94% was described in 34 pwMS under cladribine after vaccination against SARS-CoV-2, again without correlation to the interval between cladribine administration and vaccination, but with only two subjects who had been vaccinated within 3 months of the last cladribine administration.[179] A seroconversion of 100% was also described in another study including 32 pwMS treated with cladribine in comparison to healthy controls ($n=30$). Similarly, there was no correlation between treatment interval and antibody levels, again with only two subjects vaccinated approximately 4 months after cladribine treatment.[180] SARS-CoV-2 titers equivalent to those in pwMS under glatiramer acetate or interferons were also described in 25 pwMS under cladribine, without specifying the interval between vaccination and the last cladribine dose.

Another small study showed that influenza ($n=12$) and VZV vaccinations (Shingrix, $n=14$) under cladribine therapy also induced a sufficient vaccination titer regardless of the time of vaccination or lymphocyte count.[181] Only two patients were vaccinated within 6 months of cladribine administration and still lymphopenic.[181]

A recent study investigated the vaccination response against influenza A and B in 90 patients under cladribine and showed a discretely reduced seroprotection rate (HI ≥ 40) against influenza B, but not against influenza A.[182] This study also showed no correlation with duration of treatment, interval between last administration of cladribine or with the lymphocyte count or number of B cells.[182] The rapid reconstitution of naïve B cells is suggested as an explanation.[183,184]

Consensus—Cladribine

1. Overall, there is relatively little data available for cladribine regarding vaccinations at short intervals after each cycle. To optimize seroconversion, a 3–4 month interval after

the cladribine therapy cycle or approximately 1–2 months after reaching the lymphocyte nadir appears to be sensible. (90%)
2. A completed basic immunization according to the STIKO recommendation should be sought before starting therapy with cladribine (4–6 weeks). (97%)
3. A basic immunization against VZV in case of seronegativity 4–6 weeks before starting cladribine therapy is indicated.[117] (83%)
4. Live vaccinations should only be given after a strict risk–benefit assessment and normalization of the leukocytes/lymphocytes. A subsequent treatment with cladribine should only be given at least 4–6 weeks after vaccination.[111] (93%)

Cyclophosphamide

Cyclophosphamide is a cytostatic drug that prevents the proliferation of lymphocytes; recovery is stated to take 1–2 months for CD8 T cells, 2–4 months for B cells, and more than 4 months for CD4 T cells.[185] There are hardly any studies on cyclophosphamide as a stand-alone therapy, but mainly in combination with other chemotherapeutic agents. None of these studies were conducted in people with neuroimmunological diseases. One study describes reduced antibody levels against SARS-CoV-2 after vaccination in a treatment group receiving cyclophosphamide or rituximab compared to those treated with sulfasalazine; it is not possible to determine with certainty how many of the nine patients with RA received rituximab or cyclophosphamide.[186] Seroconversion after vaccination against HPV 18 under cyclophosphamide in 10 children (9–20 years) with SLE was reduced by 50% compared to healthy controls, with preserved seroconversion against HPV16.[187] In three children with juvenile autoimmune rheumatic disease treated with cyclophosphamide, there was no effect on seroconversion or seroprotection after H1N1 vaccination (HI $\geqslant$40) compared to untreated children.[188]

Consensus—Cyclophosphamide

1. A reduced seroconversion until normalization of lymphocyte levels can be expected under therapy with cyclophosphamide. (97%)
2. Vaccination with a live vaccine is contraindicated 4 weeks before, during and for at least 3 months after treatment with cyclophosphamide and until the differential blood count has normalized.[106] (93%)

Dimethyl fumarate/diroximel fumarate

Dimethyl fumarate and diroximel fumarate lead to a reduction in pro-inflammatory and cytotoxic T cells and an increase in regulatory T cells. In addition, the substances have an antioxidative effect within the CNS. Recovery of lymphopenia, if present, can take a median of 3.4 months after termination of treatment.[189] One study on the vaccination response under dimethyl fumarate therapy described maintained antibody-mediated and T cell-dependent vaccination responses against tetanus/diphtheria, pneumococcal (serotype 3 and 8), and meningococcal C vaccinations in comparison to persons treated with interferons ($n=38$).[190] Another study ($n=20$) showed an adequate antibody response against influenza after vaccination (seroprotection HI $\geqslant$40 and seroconversion) compared to healthy controls.[191] The vaccination response against SARS-CoV-2 under dimethyl fumarate was also described as equivalent to healthy controls (three independent studies with $n=114$, $n=74$, and $n=5$).[150,158,192] To date, there are no studies with a sufficient number of pwMS who have been vaccinated under diroximel fumarate. However, given the bioequivalence of both substances, a preserved vaccination response can also be assumed here.

Consensus—Dimethyl fumarate/diroximel fumarate

1. According to current data, a preserved vaccination response can be assumed under dimethyl fumarate/diroximel fumarate. (100%)
2. Vaccination with live vaccines should only be carried out after a strict risk–benefit assessment and is contraindicated in cases of severe lymphopenia (common terminology criteria for adverse events grade 2 or higher $<$800/µl).[193,194] (93%)

Complement inhibitors: Eculizumab/ravulizumab/zilucoplan

Eculizumab and ravulizumab are monoclonal antibodies that bind the complement C5 and thus inhibit its cleavage/activation preventing the

formation of the terminal membrane attack complex (MAC). Zilucoplan, on the other hand, is a macrocyclic peptide that binds both C5 and C5b, ultimately also preventing the formation of the MAC. During therapy, an increased risk of infections has been described, particularly from encapsulated bacteria (e.g., *Neisseria meningitides*, *Neisseria gonorrhoeae*, *S. pneumoniae*, and *H. influenzae* type B). Serious meningococcal infections can occur under complement inhibition and other infections such as Aspergillus have also been described. In this regard, vaccination against meningococci (serogroups A, C, Y, W135, B) is recommended at least 2 weeks prior to initial administration. Otherwise, prophylactic bridging with antibiotics (e.g., ceftriaxone, penicillin, azithromycin, rifampicin or other antibiotics effective against *N. meningitidis*) is recommended up to 2 weeks after vaccination if treatment is urgently indicated.[117,135,195]

A study in people with cold agglutinin disease (autoimmune hemolytic anemia, $n=9$) who received vaccinations against meningococcal ACWY (Menveo®; Glaxo Smith Kline GmBH & Co. KG) under eculizumab described seroprotection (defined by rabbit serum bactericidal assay ⩾1: 128; over 50% of bacterial growth is prevented) in 75% of patients against serogroup Y, 62.5% against serogroup W, 37.5% against serogroup C, and 25% against serogroup A, compared to the described seroprotection (here, however, human serum ⩾1: 8) of 88% (Y), 94% (W), 90% (C), and 87% (A) in healthy controls.[196] There was evidence that prior therapies play a relevant role for seroconversion after meningococcal vaccination before or during eculizumab therapy.[196,197]

In a study of 52 people with paroxysmal nocturnal hemoglobinuria under eculizumab or ravulizumab, a preserved formation of SARS-CoV-2 antibodies was described under therapy after vaccination with a vector vaccine or infection, but without comparison of the absolute values to a control group.[198] Corresponding data on zilucoplan is not yet available. It therefore remains unclear whether the additional binding of C5b has a comparable or different effect on vaccination success.

Consensus—Complement inhibitors

1. With very little evidence on the efficacy of vaccination under complement inhibitors, reduced seroconversion after vaccination is likely, possible effects of pre-/co-therapies should be taken into account. (90%)
2. Due to the immunosuppression induced by complement inhibition, an update of the vaccination status including vaccination against pneumococci and Haemophilus influenza B is indicated and obligatory against meningococci. (83%)
   (a) If there is an increased risk of relapse in NMOSD, treatment with steroids may be necessary until the start of therapy, especially in the context of highly active NMOSD, or bridging antibiotic treatment may be necessary until vaccination is completed.[47] (97%)
   (b) Seroconversion after vaccination may be reduced under long-term oral steroid therapy and therapy with other immunosuppressants. Monitoring the success of vaccination by means of antibody determination appears to be useful with regard to these vaccinations. (87%)
3. With regard to the application of live vaccines, there is no reliable evidence; we recommend an interval of 4 weeks before the start of therapy and up to 3 months after therapy and in any case a strict benefit-risk assessment. (97%)

FcRn inhibitors: Efgartigimod alfa, rozanolixizumab

Efgartigimod alfa is a fragment of the human IgG1 antibody with increased affinity for the neonatal Fc receptor (FcRn), while rozanolixizumab is a monoclonal antibody that binds to the FcRn directly. Both substances prevent the recycling of IgG antibodies including pathogenic myasthenia gravis-causing autoantibodies. This reduces serum IgG levels to approximately 40%; IgA and IgM are not affected.[195] FcRn inhibitors are currently only approved for neurological indications in seropositive myasthenia gravis.

One investigation of the humoral vaccination response after vaccination as part of the open-label study Extension ADAPT+ in 17 people with myasthenia treated with efgartigimod is available.[199] An increase in titers after mRNA vaccination against SARS-CoV-2 compared to before mRNA vaccination, as well as

seroconversion, was described in three people with myasthenia gravis treated with efgartigimod alone.[199] Reduced antibody levels after influenza vaccination (H1N1, H3N2, Victoria, and Yamagata) were detected in nine people with myasthenia gravis treated with efgartigimod compared to placebo-treated patients, with preserved seroprotection (HI ⩾40).[199] In this context, an increase in titers after discontinuation of the medication to the same extent as the increase in total IgG levels was described.[199]

Only one person with myasthenia gravis under efgartigimod after vaccination with PCV13 and one after PPSV23 were described, in each case without comparison to a control. Both showed antibody levels borderline to below the defined protective level of 350 ng/ml.[199]

No comparable data are available for rozanolixizumab. However, similar effects are likely with a similarly pronounced reduction in serum IgG levels during therapy.

Consensus—FcRn inhibitors

1. With very little data available, a moderately reduced seroconversion is to be expected when vaccinated under FcRn inhibitors according to the mechanism of action and initial data. A temporary reduction in titer is to be expected to the same extent as the reduction in total IgG. (100%)
2. Live vaccinations are contraindicated up to 4 weeks before and 2 weeks after therapy.[200] (93%)

Glatirameroids

Glatiramer acetate has an immunomodulatory effect without quantitatively influencing adaptive immunity. Overall, in two studies ($n = 23$ and $n = 26$), no reduced influenza antibody levels were detectable after vaccination of pwMS under glatiramer acetate compared to healthy controls.[201,202] However, another study reported a halved antibody titer (21.6% vs 43.5%) in the hemagglutination inhibition test after H1N1 vaccination ($n = 37$).[203] An additional study showed no change in the T cell response to a tetanus toxoid in vitro.[204] Vaccination titers against SARS-CoV-2 were also found to be comparable to healthy controls.[150,192]

Live vaccination is not listed as a contraindication in the product information of glatiramer acetate. There are also no reports of infection as a result of live vaccination under glatiramer acetate therapy.[106,205] A special note on yellow fever vaccination according to the expert consensus of the RKI recommends against the administration of this vaccine.[106]

Consensus—Glatirameroids

1. The vaccination response under glatiramer acetate therapy is maintained. (100%)

Glucocorticoids

Glucocorticoids act by inhibiting pro-inflammatory protein synthesis, inhibiting the pro-inflammatory signaling cascade NF-κB, and activating lipocortins. A study in a cohort of patients with chronic inflammatory diseases (including inflammatory bowel disease, RA, spondyloarthritis, SLE, MS ($n = 9$), NMOSD ($n = 1$), and vasculitis ($n = 5$)) showed a reduced immune response after vaccination against SARS-CoV-2 under continuous glucocorticoid therapy ($n = 17$), although the study does not clearly describe how many MS, NMOSD, and vasculitis patients were treated with glucocorticoids.[206] A study in people with SLE, MS, autoimmune CNS disease, vasculitis, myositis, sarcoidosis, and other immunologically mediated diseases ($n = 11$) showed a reduced (odds ratio 8.38) T cell-mediated and humoral vaccination response against SARS-CoV-2 (mRNA and vector vaccines) under glucocorticoids alone (⩾10 mg/day prednisone) compared to healthy controls.[207] Another study in individuals with RA, SLE, vasculitis, other rheumatic diseases, other inflammatory bowel diseases, MS, inflammatory neuro- and myopathies, or myasthenia gravis ($n = 51$) under oral glucocorticoid therapy (median 7.5 mg/day) showed equally high SARS-CoV-2 antibody levels compared to healthy controls.[208]

A seroconversion of 93% after hepatitis A vaccination was described in people with ulcerative colitis or Crohn's disease under glucocorticoids (⩾20 mg prednisolone equivalent over ⩾2 weeks, $n = 30$)—comparable to healthy controls.[209]

Another study described reduced seroconversion after vaccination against pneumococci (PPSV23)

in a cohort of 16 people with immune-mediated inflammatory disease under high-dose glucocorticoid therapy (⩾20 mg/day) with a rate of 22% seropositivity.[210]

In addition, another study described an association between lower seroconversion rates and antibody levels compared to healthy controls in children with juvenile autoimmune rheumatic disease under add-on (to azathioprine, MMF, MTX, cyclosporine, leflunomide, cyclophosphamide) or singular glucocorticoid therapy after influenza vaccination (H1N1), correlating with the dose of glucocorticoid therapy (mean 17.4 mg/day).[188]

Consensus—Glucocorticoids

1. In case of short-term high-dose therapy, vaccination under high-dose glucocorticoids is not advisable, if clinically justifiable, as the efficiency of the immune response may be reduced. (100%)
2. In patients undergoing short-term steroid therapy, a regular vaccination response can be expected after about 4 weeks. (97%)
3. In case of long-term steroid administration (⩾10 mg/day prednisolone equivalent over ⩾2 weeks), reduced seroconversion can be assumed until up to 3 months after the end of therapy. (97%)
4. During long-term high-dose steroid therapy (⩾10 mg/day prednisolone equivalent for ⩾2 weeks), vaccination with a live vaccine is contraindicated and an interval of 2–4 weeks before and at least 2 months after therapy should be observed.[106] (97%)

Interferon-beta preparations

Interferons influence a variety of transcription and translation programs of cells and thus have a broad immunomodulatory effect. Previous studies on SARS-CoV-2 and influenza have shown no limited seroconversion under therapy with interferons.[150,192,201,211]

Consensus—interferon-beta preparations

1. Preserved seroconversion is to be expected under interferons. (100%)

Intravenous immunoglobulins

IVIG are concentrates of homologous (human) IgG antibodies. A study in children with Kawasaki disease showed reduced seroconversion after live vaccination against measles, mumps, rubella, and varicella within 6 months, with an increase in seroconversion after booster vaccination 12 months after administration of IVIG.[212] A single study described slightly increased vaccination titers against SARS-CoV-2 in people with idiopathic inflammatory myopathies under IVIG therapy depending on the dosage. As such, vaccination titers could also be increased from healthy convalescents in the donor pool.[213] Product information describes a possibly reduced vaccination response for up to 3 months after IVIG. After application of live vaccinations against mumps, rubella, and measles, the vaccination response could be decreased even up to 1 year; the RKI even recommends an interval of the MMR vaccination of 3 weeks before and up to 8 months after IVIG, as the replication of the vaccine virus could be influenced by the antibodies of the blood product.[145,214] The mechanistic reason given here is that in contrast to activated vaccines, antigens contained in inactivated vaccines could continue to be presented and therefore IVIG administration would evoke no influence on the immune response after vaccination.[145]

Since it is difficult to assess whether the antibodies originate from the donor pool or the recipient, it only makes sense to check the antibody status after the therapy has been completed.[214]

Consensus—IVIG

1. Seroconversion after vaccination may be reduced during treatment with IVIG. (93.33%)
2. Live vaccines should only be administered during therapy after a strict risk–benefit assessment. (93%)

Methotrexate

MTX is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase and thereby RNA/DNA synthesis and thus the proliferation of lymphocytes. Recovery of lymphopenia is stated to be <12 weeks.[215] Evidence on seroconversion rates after vaccination under MTX is mainly

limited to people with rheumatic disease. Here, compared to healthy controls and untreated individuals with RA, antibody levels against SARS-CoV-2 were found to be reduced after vaccination under MTX ($n=23$) with a direct correlation between dose and antibody response.[216] No significantly reduced vaccination response was described at low doses below 10 mg/week.[217–221] In contrast, a study of 50 people with RA taking 7.5–25 mg MTX/week described moderately reduced absolute antibody levels after pneumococcal (PPSV23) vaccination compared to healthy controls.[222] Another study described the possibly improved vaccination success (fourfold increase in antibodies compared to before vaccination) after a short break in MTX therapy for 2 weeks before and up to 2 weeks after vaccination.[223]

Consensus—MTX

1. Maintained to moderately reduced absolute antibody levels are to be expected after vaccination under MTX, which can be increased by taking a short break from therapy. However, the latter should only be done after a strict benefit–risk analysis. (93%)
2. Application of live vaccines should be avoided and are contraindicated, especially under high-dose therapy (>20 mg/week). Under low-dose MTX therapy (⩽20 mg/week), immunizations with vaccines against mumps, measles, rubella, or varicella can be considered after an individual benefit–risk assessment.[106,217,220] (83%)

Mitoxantrone

Mitoxantrone leads to an inhibition of topoisomerase II and DNA intercalation. This prevents T cell activation and proliferation of B and T cells. In a study of 11 pwMS treated with mitoxantrone, no protective seroconversion (HI ⩾40) against influenza was achieved.[203] Furthermore, to our knowledge, no studies on seroconversion after vaccination under mitoxantrone have been published. Due to increased cardiotoxic side effects and the development of secondary lymphomas, mitoxantrone has disappeared from neurological therapy.

Consensus—Mitoxantrone

1. It can be assumed that vaccination success is reduced under therapy with mitoxantrone and only increases again after discontinuation of therapy and repopulation of lymphocytes. (97%)
2. Application of a live vaccine is contraindicated during therapy, 4 weeks before the start of therapy and up to 3 months after therapy.[106] (97%)

Mycophenolate mofetil

MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, thus interfering with the synthesis of guanosine and reducing cell growth. The vaccination response under therapy with MMF was primarily investigated in rheumatic diseases. Studies have shown that there is a dose dependency with regard to antibody levels after HPV ($n=9$) and SARS-CoV-2 ($n=100$) vaccination.[224,225] In patients with renal disease ($n=130$), MMF therapy (dose 500–1000 mg) was described as a negative predictor of lower antibody levels after SARS-CoV-2 vaccination (vector and mRNA).[226] Another small study on three patients with NMOSD under MMF reported that all patients developed antibodies after vaccination or infection with SARS-CoV-2; the dose of therapy is not stated in this article.[154]

Furthermore, a study on people with NMOSD ($n=5$) receiving MMF (2 g/d) described seroconversion in only 40% of people after vaccination against influenza A (H1N1).[153] The higher dose compared to the studies described above should be noted here in particular.

Consensus—MMF

1. A dose-dependent reduced vaccination response is to be expected under therapy with MMF. (100%)
2. Application of a live vaccine should be avoided during therapy with MMF. Under low-dose MMF therapy (⩽1.2 g/m^2 body surface area), immunization with the vaccines against mumps, measles, rubella, or varicella can be considered after individual benefit–risk assessment.[106,217,220] (90%)

Natalizumab

Natalizumab prevents immune cells from crossing the blood–brain barrier by binding the adhesion molecule α-4 integrin. Data on seroconversion after vaccination with natalizumab therapy is controversial. Three studies describe reduced seroprotection (HI ⩾40; $n=12$, 11%–30% vs 58%–69% in healthy controls against H3N2 and 72.7%–75% vs 94%–94.5% against H1N1; $n=17$, 23.5% vs 43.5% in healthy controls against H1N1; $n=14$, 14.3% vs 73% in interferon-treated against H1N1, H3N2, and B combined).[201–203] In contrast to these stands one study ($n=17$) describing equivalent antibody levels compared to healthy controls after vaccination against influenza.[227] Immune responses against tetanus toxoid and KLH were comparable to untreated controls in another study ($n=30$).[228] The latter is a large protein complex (obtained from the hemolymph of the large Californian keyhole snail of the slit snail family) that induces a strong humoral and cellular immune response. This can therefore be used as an immunostimulator to assess immunocompetence. The antibody response against SARS-CoV-2 was also similar to those of healthy controls ($n=100$ and $n=41$).[150,192] A recent study showed a 93% seroprotection against hepatitis A, hepatitis B, and SARS-CoV-2 vaccinations under natalizumab therapy in a cohort of 60 pwMS.[229]

With regard to live vaccination under natalizumab, two case reports describe a live vaccination against VZV under natalizumab therapy without side effects, in particular without evidence of triggered relapse activity or infection.[230,231] In contrast, there is a case report of vaccine-associated measles infection following MMR vaccination under natalizumab.[105] There is also a described case of VZV meningoencephalitis under natalizumab therapy.[232] The balance between the risk of infection and benefit of vaccination is difficult to assess; with currently only case reports available, this can only be decided on a case-by-case basis.

Consensus—Natalizumab

1. Overall, a slightly reduced but sufficiently efficient vaccination response after immunization under natalizumab is likely. (97%)
2. Vaccination with a live vaccine is contraindicated and should only be carried out after a strict risk-benefit analysis and, if necessary, in consultation with infectious disease specialists. (90%)

Plasmapheresis and immunoadsorption

Plasmapheresis is the exchange of plasma, while immunoadsorption extracts antibodies from the blood.

A single study ($n=8$) even showed an increased titer of pneumococcal antibodies (against 12 antigens) in patients with myasthenia gravis 28 days after plasmapheresis under co-therapy with prednisolone compared to myasthenia patients without therapy, but not to healthy controls.[233] This effect was eliminated by therapy with azathioprine and is explained in the study by a rebound effect after antibody removal by plasmapheresis.[233] A study on 10 people with myasthenia gravis described no achievement of normal IgG levels in up to 5 weeks, but rising levels after completion of plasmapheresis. Normal immunoglobulin A and M levels were sustained.[234] Antibody levels against VZV and Epstein–Barr virus, diphtheria, and tetanus toxoid were also still detectable at reduced levels within 4 weeks after plasmapheresis compared to previous values with an upward trend.[234]

Another study examined the antibody levels in 14 people with myasthenia gravis, Waldenström's disease, or other autoimmune diseases who received plasmapheresis at regular intervals (every 3.5 weeks on average) and were also vaccinated against SARS-CoV-2 with mRNA ($n=13$) or vector ($n=1$) vaccine.[235] A drop in SARS-CoV-2 titers by 60.7% was observed after plasmapheresis in comparison to before the intervention. Right before the next intervention a proportion of 32.7% of the original titer was detected.[235] It should be noted that 64.3% of the subjects were co-treated with other immunotherapies (primarily glucocorticoid, followed by azathioprine and MMF). According to the study, this had no significant influence on the antibody levels.[235] Similar results with a transient drop in SARS-CoV-2 titers after immunoadsorption and a subsequent rise within 12 weeks were found in a study of six people with an autoimmune disease (four with myasthenia gravis) who had been vaccinated during therapy.[236]

Overall, studies indicate a transient reduction in antibodies after plasmapheresis or immunoadsorption; vaccination within the first 4 weeks after

intervention may possibly result in a reduced vaccination success. However, other studies support the hypothesis that cellular immune responses and antibody levels are normalized again within days and therefore no restriction in the vaccination response is to be expected.[107,234–236] With time, previously existing titers also rise again, so a sufficient immune response after previous vaccination is likely.

Consensus—Plasmapheresis and immunoadsorption

1. During and up to 1 month after plasmapheresis/immunoadsorption, seroconversion after vaccination may be reduced. (100%)
2. Live vaccinations should only be considered after a strict risk–benefit analysis and only after the acute phase of a relapse. (90%)

S1P receptor modulators

S1P receptor modulators functionally antagonize S1P receptors selectively, for example, ponesimod (receptor 1) or siponimod and ozanimod (receptors 1 and 5) or nonselectively, that is, fingolimod (receptors 1, 3, 4, and 5), thereby preventing lymphocyte egress from lymph nodes. Although lymphocyte levels are reported to normalize around 3 months after fingolimod cessation, recovery to pretreatment levels might take more than 12 months.[237] The cellular and antibody-mediated vaccination response against influenza A and B in individuals treated with the S1P modulator fingolimod compared to healthy controls was the same in one study ($n = 14$).[238] The binding strength of anti-influenza antibodies as a sign of qualitative function in pwMS treated with fingolimod ($n = 10$) was described as lower compared to healthy controls and pwMS treated with interferon-beta.[239] Other studies ($n = 95$ and $n = 15$) showed reduced seroconversion (54% vs 85% in placebo-treated individuals with MS) and seroprotection (HI $\geq$40; 40% vs 90.6% in healthy controls) after influenza vaccination.[201,240] Similarly, another study in 24 healthy individuals treated with fingolimod showed a vaccination response with mild to moderately reduced antibody levels after KLH exposure and pneumococcal vaccination (PPSV23) with equivalent cellular response against recall antigens (KLH, tetanus toxoid, and candida albicans).[241] In this study, as well as in another previously described study in pwMS taking fingolimod versus placebo ($n = 93$), there was a slightly reduced antibody formation against tetanus toxoid (40% vs 61%).[240,241] Recent studies described a reduced T cell and antibody-mediated vaccination response against SARS-CoV-2 after vaccination under fingolimod ($n = 25$, 26-fold lower antibody levels compared to untreated pwMS; $n = 42$, 9.5% seroconversion vs 100% in untreated pwMS, 0% vs 56.7% SARS-CoV-2 specific memory T-cells; $n = 28$, seroconversion 86% vs 100% in untreated pwMS with significantly reduced antibody levels).[150,177,192]

Recent evidence suggests a better vaccination response with higher absolute antibody levels and seroconversion with selective S1P modulators, such as ozanimod, ponesimod, and siponimod, compared to the nonselective S1P modulator fingolimod, after SARS-CoV-2 vaccination (fingolimod: $n = 20$, selective S1P: $n = 13$; fingolimod: $n = 143$, siponimod: $n = 31$, ozanimod: $n = 41$).[192,242] After vaccination against influenza, there was an equivalent proportion of seroprotection (HI $\geq$40) with reduced antibody titers and after vaccination against pneumococci (PPSV23) equally high antibody levels under siponimod compared to placebo-treated healthy individuals ($n = 90$).[243]

Consensus—S1P receptor modulators

1. A preserved, but quantitatively and/or qualitatively reduced vaccination response can be assumed under S1P receptor modulators, in particular under fingolimod, possibly less pronounced under siponimod/ozanimod/ponesimod. (93%)
2. Vaccination against VZV is mandatory for seronegative pwMS before starting treatment with fingolimod, ponesimod, or siponimod, and recommended before ozanimod. (90%)
3. Vaccinations with live vaccines are contraindicated during therapy and up to 4 weeks before and 4 weeks after siponimod, 4 weeks before and 3 months after ozanimod, 1 week before and 4 weeks after ponesimod, as well as 8 weeks after therapy with fingolimod and until the differential blood count normalizes.[106] (97%)

Satralizumab/tocilizumab

Satralizumab and tocilizumab block membrane-bound and soluble IL-6 receptors, thereby preventing the interleukin's pro-inflammatory effect. One study on 13 people with NMOSD or MOGAD regarding the vaccination response against SARS-COV-2 under IL-6 receptor antibodies showed a 100% seroconversion, albeit moderately reduced absolute antibody levels in comparison to healthy controls.[244] In seven subjects with RA, vasculitis, or adult-onset Still's syndrome, tocilizumab resulted in 83.3% seroconversion after SARS-CoV-2 vaccination.[245] In 10 individuals with RA, vasculitis, idiopathic inflammatory myositis, SLE, systemic sclerosis, or variable immunodeficiency syndrome, seroconversion was preserved with slightly reduced absolute antibody levels and preserved T cell response to SARS-CoV-2 after vaccination compared to healthy controls.[246] However, 60% of these were co-treated with low-dose steroids, 30% with MTX, 10% with leflunomide, 10% with cyclosporine, and 10% with MMF.[246]

A study on 50 people with RA treated with tocilizumab showed the same increase in titers against pneumococcal serotypes 6B and 23F after vaccination with PPV23 as in untreated people with RA.[247] In another cohort of 38 people with RA or Castleman's disease treated with tocilizumab, seroprotection against influenza (H1N1, H3N2; defined here as a 40-fold increase in titer) and pneumococci (PPSV23; doubling of titer in 9 of the 12 serotypes) was described in 88%–100% of patients, but without a control group.[248] In a further study of 13 people with NMOSD/MOGAD under IL-6 receptor therapy (4 under satralizumab, 9 under tocilizumab), preserved seroconversion was described with lower antibody levels compared to controls, equivalent compared to oral immunotherapies ($n = 9$; azathioprine, MMF) and higher than anti-CD20-treated patients ($n = 17$) after mRNA or vector vaccination against SARS-COV-2.[244]

Consensus—Satralizumab/tocilizumab

1. Under therapy with satralizumab or tocilizumab, a reduced humoral vaccination response with most likely preserved T cell-mediated vaccination response is to be expected. (93%)
2. The application of live vaccines is contraindicated during, 4 weeks before, and up to 2 months after therapy.[106] (97%)

Tacrolimus

By forming a complex with FKBP-12, calcium, calmodulin, and calcineurin, tacrolimus acts as an inhibitor of the serine/threonine phosphatase activity of calcineurin. This blocks the dephosphorylation and translocation of NF-κB and prevents T cell activation.

A lot of evidence relates to nonneurological patients, particularly those who have undergone whole organ transplantation, usually in combination therapy with glucocorticoids and MMF.

A study on 23 people with glomerulonephritis treated with tacrolimus showed a seroconversion of 26% after the first and 67.7% after the second vaccination against SARS-COV-2 with a significantly reduced SARS-CoV-2-specific T cell response compared to other immunotherapies.[249]

Another study on 43 people with SLE showed seroconversion after two mRNA vaccinations against SARS-CoV-2 in 65%—however, it should be noted that people with nephritis received co-therapy with MMF, although it is not clear how many this affected in the study.[250] Another study showed a correlation between T cell immunity after SARS-CoV-2 vaccination and the concentration of tacrolimus in the blood, but again in combination with MMF and prednisolone in 40 people after kidney transplantation.[251]

Reduced antibody levels were also reported after vaccination against pneumococci (PPSV23) in 18 people under tacrolimus after kidney transplantation (most of whom had been additionally treated with glucocorticoids ($n = 11$), 6 patients were additionally treated with azathioprine and 2 with MMF) compared to those who had been treated with cyclosporine without further control.[252] In 29 people with RA under tacrolimus, pneumococcal vaccination (PPSV23) resulted in equivalent antibody concentration and functionality, as assessed by a multiplex opsonophagocytic killing assay, compared to healthy controls.[253]

Another study on 32 people with rheumatic and musculoskeletal diseases (RA, SLE, Sjögren's,

spondyloarthritis, etc.) after SARS-CoV-2 mRNA vaccination showed significantly but moderately reduced antibody levels compared to healthy controls (antibody titers median 374.4 U/ml (interquartile range 43.7–823.2) compared to median 741.6 U/ml (interquartile range 509.2–1103.0)). Of those, 21 were without and 11 with co-therapy with MTX, through which no significant influence on the antibody level was observed.[254] The cumulative dose of tacrolimus received was higher in women with SLE ($n = 50$) who had negative antibody detection 5 years after initial seroconversion following HPV vaccination (seroreversion, $n = 7$).[255]

Consensus—Tacrolimus

1. With little data available and, to our knowledge, no studies in people with myasthenia, moderately reduced antibody levels can be assumed under therapy with tacrolimus, as well as a moderately reduced vaccine-specific T cell response. (97%)
2. A live vaccination should only be considered after a strict risk–benefit assessment. (90%)

Teriflunomide

Teriflunomide blocks the mitochondrial enzyme dihydroorotate dehydrogenase, resulting in reduced pyrimidine synthesis. This leads to reduced proliferation of activated immune cells. A previous study described a preserved seroprotection (titer >0.5 IU/ml) with discretely reduced antibody levels against rabies in 23 pwMS compared to placebo-treated individuals.[256] The delayed hypersensitivity reaction as a mediator of the cellular response against recall antigens (candidin, trichophytin, and tuberculin) was also investigated in this context and no difference was found compared to the placebo group.[256] After influenza vaccination in pwMS treated with teriflunomide, preserved seroprotection (HI ⩾40) was described in 97% against H1N1 and B strains and in 77% against H3N2.[257] Recent studies also showed equally high antibody levels after SARS-CoV-2 vaccination under teriflunomide compared to healthy controls and untreated pwMS ($n = 48$ and $n = 15$).[150,192]

Consensus—Teriflunomide

1. Based on current evidence, no relevant restriction of seroconversion after vaccination with teriflunomide can be assumed. (97%)
2. Vaccination with a live vaccine is contraindicated 4 weeks before, during and up to 6 months after therapy with teriflunomide.[106,258] (97%)

TNF-alpha blockers (infliximab, etanercept, adalimumab)

TNF-alpha blockers inhibit the effect of the pro-inflammatory cytokine TNF-alpha.

Infliximab

Reduced seroprotection (HI ⩾40; 45% against H3N2 and 66% against H1N1) against influenza was described in two separate cohorts of people with inflammatory bowel disease ($n = 23$ and $n = 137$) treated with infliximab.[259,260] In 96 people with inflammatory bowel disease, there was also reduced seroconversion after vaccination against pneumococcal pneumonia (PPSV23; 57.6%) compared to those treated with mesalazine (88.6%).[261] In 46 individuals with inflammatory bowel disease, antibody levels after vaccination against SARS-CoV-2 were described to be lower than in healthy controls with an equivalent specific T cell response.[262] After hepatitis B vaccination, significantly reduced seroprotection (14% and 35.5%; antibodies ⩾10 IU/ml) was described in 14 and 62 individuals, respectively, with inflammatory bowel disease treated with infliximab compared to untreated individuals (67.1%).[263,264] One study interpreted reduced antibody levels against SARS-CoV-2 after vaccination under anti-TNF-alpha therapy in people with inflammatory bowel disease ($n = 19$) compared to healthy controls by the impaired plasticity of memory B cells and thus reduced long-term antibody response.[265]

One study described no influence of the interval since the last infliximab infusion on seroprotection against influenza (day 21–28 vs day 0–4).[260]

Adalimumab

Interestingly, the antibody levels after vaccination against influenza or pneumococcus (PPSV23) under adalimumab (soluble TNF receptor; $n=111$) are described as equivalent compared to placebo-treated individuals with RA.[266] After vaccination against hepatitis B, seroprotection rate (antibodies $\geqslant$10 IU/ml) was also equivalent to that of untreated subjects with inflammatory bowel disease.[264]

Etanercept

A study on 94 people with psoriatic arthritis and 17 children with juvenile idiopathic arthritis receiving etanercept (soluble TNF receptor) described comparable seroconversion after pneumococcal (PPSV23 or PCV13) vaccination compared to placebo in combination therapy with MTX.[267,268] Another study on seven people with RA taking etanercept also described equivalent antibody levels to a control group with osteoarthritis after pneumococcal vaccination (PCV13).[269] Antibody levels against influenza A and even more so against influenza B were reduced in 30 children with juvenile idiopathic arthritis under etanercept compared to healthy controls with preserved seroconversion and seroprotection (HI $\geqslant$40).[270]

Consensus—TNF-alpha blockers

1. In the absence of evidence, particularly with regard to neurosarcoidosis, a reduced vaccination response is possible under therapy with TNF-alpha antibodies. (97%)
2. Live vaccinations during therapy are contraindicated and should be given at the earliest 2 months after discontinuation of therapy with TNF-alpha blockage. (97%)

Discussion

Here, we summarize and evaluate currently available evidence on vaccinations among a variety of medications used to treat neurological autoimmune diseases. The scope of this work did not include a formal but an expert-based evaluation of the available data, which could be named as a limitation. The compilation of this data has not been without challenges as studies on vaccinations under several immunotherapies are rare, outcome measures vary greatly, real-world data is often lacking and studies are typically of a small number of cases or only focus on a specific type of vaccines. The "real protection" induced through vaccination is hardly assessable. In the future, further large-scale studies would be needed to accurately evaluate the clinical protection from infection through vaccination under immunotherapies. Furthermore, people with neuroimmunological illnesses and those involved in their care might remain hesitant toward vaccination until large controlled studies investigating disease activity after vaccination are presented.

Conclusion

This summary and consensus of the main recommendations on vaccination in people with neurological autoimmune diseases is intended to help ensure that these people receive the most adequate vaccination possible without putting them at unnecessary risk. This is important, as existing uncertainties regarding the handling of immunotherapies leads to hesitation surrounding necessary vaccinations in both doctors and patients. Establishing a close interdisciplinary construct including general practitioners and neurologists will further support a safe patient-centered vaccination and treatment regimen.

Declarations

Ethics approval and consent to participate

Since this study used available literature to develop a German evidence-based expert consensus on vaccination under immunotherapies in neurological autoimmune diseases.

Consent for publication

Not applicable.

Author contributions

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Availability of data and materials

All data are provided in the manuscript or Supplemental Material.

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Supplemental material

Supplemental material for this article is available online.

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