Vaccination in multiple sclerosis patients treated with highly effective disease-modifying drugs: an overview with consideration of cladribine tablets

Ralf Gold[iD], **Gerd Fätkenheuer, Hans-Peter Hartung**[iD]**, Christoph Kleinschnitz,
Reinhard Marks, Matthias Maschke, Antonios Bayas, Micha Löbermann,
Uwe K. Zettl and Heinz Wiendl**

Abstract: Infectious diseases are an important consideration in autoimmune conditions such as multiple sclerosis. Infective episodes may trigger relapses and significantly deteriorate the course of the disease. Some immunotherapies may cause increased rates of infection-related adverse events. Thus, infection and vaccine-related issues should be included in the individualized patient-specific treatment strategy and counseling before starting therapy and regularly on treatment. Clinical and epidemiological studies as well as pharmacovigilance data repeatedly demonstrated the safety of the great majority of vaccines in multiple sclerosis patients. Moreover, studies have shown that vaccinations with killed/inactivated vaccines do not increase the short-term risk of relapse or deterioration in multiple sclerosis, whereas infections have been shown to provoke relapses. The available evidence indicates reduced humoral vaccination efficacy on treatment with MS drugs acting on the S1P receptor, natalizumab, and B-cell depleting therapies. Recent data for cladribine tablets suggest the potential of effective immunization in the interval of the two treatment courses and after completion of therapy. Regardless of treatment, vaccine efficacy may be optimized with proper timing of application. Multiple sclerosis patients receiving highly effective therapies should be vaccinated according to general recommendations for healthy adults. Immunization against COVID-19 is highly recommended for all multiple sclerosis patients regardless of age and comorbidities. Preliminary data show the potential of adequate responses in patients treated with cladribine tablets.

Keywords: cladribine tablets, COVID-19, immunization, multiple sclerosis, vaccine

Correspondence to:
Ralf Gold
Department of Neurology,
St. Josef-Hospital,
Ruhr-University Bochum,
Gudrunstrasse 56,
Bochum, Germany
**Ralf.Gold@ruhr-uni-
bochum.de**

Gerd Fätkenheuer
Department of Clinical
Infectiology, University
Hospital of Cologne,
Cologne, Germany

Hans-Peter Hartung
Department of Neurology,
Medical Faculty, Heinrich
Heine University,
Düsseldorf, Germany
Brain and Mind Centre,
University of Sydney,
Australia

Department of Neurology,
Medical University of
Vienna, Austria

Christoph Kleinschnitz
Department of Neurology,
University Hospital Essen,
Essen, Germany

Reinhard Marks
Department of
Hematology, Oncology and
Stem Cell Transplantation,
Faculty of Medicine,
Medical Center-University
of Freiburg, Germany

Matthias Maschke
Department of Neurology,
Krankenhaus der
Barmherzigen Brueder,
Campus Trier, University
of Mainz, Germany

Antonios Bayas
Department of Neurology,
University Hospital
Augsburg, Augsburg,
Germany

Micha Löbermann
Department of Tropical
Medicine, Infectious
Diseases and Nephrology,
Rostock University Medical
Center, Rostock, Germany

Uwe K. Zettl
Department of Neurology,
Neuroimmunology Section,
University of Rostock,
Rostock, Germany

Introduction

In the last two decades, the treatment options for patients with multiple sclerosis (MS) have been considerably improved due to the approval of several drugs that allow for more effective immunotherapy.[1] These medications convey their effects in MS at least partially *via* alteration of the number and/or function of lymphocyte subpopulations – by depletion, sequestration, inhibition of migration, or functional modulation.

These interventions are expected to cause increased rates of infection-related adverse events, either by increasing the risk of *de novo* infections with certain pathogens or by exacerbating or reactivating (latent) chronic infections such as hepatitis B.[2,3]

Thus, infection-related issues should be included in individualized patient-specific treatment strategy and counseling.[4] Certain vaccine-preventable infectious diseases are particularly relevant, as the

Heinz Wiendl
Department of Neurology
with Institute of
Translational Neurology,
University Hospital
Münster, Münster,
Germany

risks of infection or an exacerbated course are elevated by MS itself or its therapy.[5] Of particular concern is reactivation of infections with hepatitis B virus and varicella zoster virus (VZV).[6]

Vaccinations in multiple sclerosis patients on treatment with disease-modifying drugs

While vaccination must be avoided in MS patients who are experiencing a relapse until clinical resolution or until the relapse is no longer active,[7] several studies have shown that vaccinations do not increase the short-term risk of relapses in MS.[8]

Clinical and epidemiological studies as well as pharmacovigilance data repeatedly demonstrated the safety of the vast majority of vaccines in MS patients. Recently, a review concluded that there is no significant evidence for a causal relationship between a deterioration of MS and vaccination against a range of infectious diseases (including measles, mumps and rubella, influenza, hepatitis A, hepatitis B, human papilloma virus, diphtheria, tetanus, pertussis and meningococci).[9] Some studies even indicated reduced disease activity in preexisting MS in vaccinated individuals.[10]

Recent studies revealed that immunizations with inactivated or subunit vaccines are not associated with an increased risk of complications in MS patients.[5,8,11–13] However, this does not apply to live attenuated vaccines,[3,14] due to the replicative capacity of the pathogens in these preparations and the lack of comprehensive meaningful data. Serious complications have been reported after the application of live attenuated vaccines against, for example, yellow fever and measles in immunocompromised patients.[15,16]

While published data remain controversial,[17] these types of vaccines could deteriorate immune-mediated diseases as observed for the yellow fever vaccine in patients with relapsing MS.[18,19] Therefore, live attenuated vaccines (in particular against yellow fever) are relatively contraindicated in patients on immunosuppressive treatment,[4] particularly cell-depleting or sequestering agents, including alemtuzumab, fingolimod, ozanimod, siponimod, ocrelizumab or mitoxantrone. However, live-attenuated vaccines may be considered in patients having received a complete course of cladribine tablets after normalization of lymphocyte counts.[20]

In MS patients receiving highly effective immunotherapies, live-attenuated vaccines should only be used if the risk and potential consequences of the respective infection dominate the risk of vaccine-related complications. This may be the case in young female patients who may become pregnant without adequate vaccine-induced protection against rubella embryopathy.[7]

In contrast, there are no safety concerns for the use of killed or subunit vaccines in MS patients undergoing immunotherapy. As recommended by the Standing Committee for Vaccination of the German Public Health Institution (Robert Koch Institute)[21] and the U.S. Centers of Disease Control and Prevention[22] for adults, these include those (catch-up/refresh or *de novo*) vaccinations against tetanus, diphtheria, pertussis, poliomyelitis, influenza and pneumococcus (plus herpes zoster and hepatitis B in immunosuppressed individuals).

The antibody titer against VZV should be determined before starting therapy with sphingosine 1-phosphate receptor modulators, alemtuzumab, oral cladribine and ocrelizumab.[5] Patients with a negative or weakly positive titer and those without clear evidence of previous exposure should receive immunization with the live-attenuated varicella vaccine.

With these caveats in mind, MS patients should generally be vaccinated according to recommendations for adults. This recommendation must be adapted according to the individual patient profile or medical history and any ongoing immunotherapies (Table 1).

Whenever possible, necessary immunizations should be completed 4–6 weeks before starting cell-depleting drugs. Therefore, clinicians should discuss the advantage of vaccination with patients as soon as possible after MS diagnosis, regardless of initial therapeutic plans, to prevent future delays in initiation of immunotherapy.

On or after treatment with cell-depleting substances, vaccines should preferably be used 4–6 months after the last administration of the drug (and at least 4–6 weeks before the next cycle), when the immune system is at least partially reconstituted. Live attenuated vaccines may have to be delayed for 4–6 months after the last application of lymphocyte-altering substances or until lymphocyte numbers have returned to the normal range.[26]

Table 1. Overview of vaccine use in multiple sclerosis patients.

General recommendations for vaccine use in MS patients starting any new therapy including newly diagnosed patients:[23]

- **Complete all immunizations as recommended for the general population (according to applicable guidelines) in all patients (see below) until 4-6 weeks before start of therapy.**
- **In the case of MS therapies with a potential interference with vaccination effects, complete immunizations 4 -6 weeks before starting therapy, if possible.**
- **Special considerations for additional vaccines or modified immunization protocols:**
- **Immunization against hepatitis B virus is generally recommended (except for patients with documented protective anti-HBs antibody titers).**
- **Patients without a prior documented varicella episode should be vaccinated against varicella zoster virus (caveat: this is a live vaccine; do not use in patients on immunosuppressive therapies!).**
- **Immunization with the recombinant glycoprotein shingles vaccine should be considered in all MS patients.**
- **The annual seasonal influenza vaccine is recommended for all MS patients regardless of their age and the type of MS treatment**

Disease/pathogen	Recommended indication and vaccination procedure (according to STIKO)[24,25]
COVID-19	Prioritized immunization due to preexisting condition (autoimmune disease) with elevated risk
Tetanus	Standard: refresh/catch up as required
Diphtheria	Standard: refresh/catch up as required
Pertussis	Standard: refresh/catch up as required
Poliomyelitis	Standard: catch up as required
Meningococci	Immunodeficiency or immunosuppression, hypogammaglobulinemia
Rubella	Women of childbearing age if vaccination status is uncertain: two doses MMR; if one prior vaccination: one dose MMR (*caveat*: this is a live vaccine; do not use in patients on immune therapies!)
Pneumococci	Standard (≥60 years)[a]: polysaccharide vaccine (PPSV23), repeat after 6 years Immunosuppression/immunodeficiency (any age): PCV13 conjugate vaccine, followed by PPSV23 after 6–12 months[b]
Measles	Standard: single dose MMR in all adults born after 1970[c] if vaccination status is uncertain, or only one dose received during childhood (*caveat*: this is a live vaccine; do not use in patients on immune therapies!)
Hepatitis B	Risk of severe disease in patients with preexisting/expected immunodeficiency/immunosuppression; increased risk of exposure
Influenza	Standard: yearly immunizations in autumn using seasonal vaccine
Shingles (i.e. VZV reactivation)	>60 years[d], or with underlying chronic diseases: recombinant adjuvanted VZV glycoprotein vaccine
Varicella	Seronegative patients, prior to immunosuppressive therapy: live VZV vaccine (contraindicated on immunosuppressive therapy!)

Divergent recommendations of the U.S. Centers of Disease Control and Prevention:
[a]≥65 years.
[b]after >1 year.
[c]after 1959.
[d]≥50 years.
MMR, measles, mumps and rubella; MS, multiple sclerosis; STIKO, Standing Committee for Vaccination; VZV, varicella zoster virus.

Studies on the effectiveness of vaccines in MS patients receiving immunotherapies

A number of studies have been conducted on the effectiveness of various vaccines in MS patients receiving disease-modifying therapy. Several studies in MS patients receiving treatment with interferon beta preparations indicated adequate immune responses to vaccines, mostly against influenza, pneumococci and tetanus/diphteria.[27]

An open study in 72 patients with relapsing–remitting MS (RRMS) investigated the efficacy of vaccines administered in individuals on therapy with dimethyl fumarate or interferon beta.[28] Vaccination with recall antigens (tetanus, diphtheria), T-cell independent vaccination (pneumococci) and vaccination with a neo-antigen (meningococcus) achieved sufficient protection in patients on either therapy.

Studies comparing the effect of inactivated vaccines suggested reduced responses in MS patients on treatment with glatiramer acetate *versus* interferon beta and *versus* healthy volunteers.[29–31]

The results of the TERIVA study demonstrated that patients on teriflunomide mount an effective immune response after vaccination against influenza. In addition, the generation of primary immune responses against neoantigens (rabies) is not significantly impaired.[32]

Vaccinations in 24 MS patients on therapy with alemtuzumab achieved sufficient immune protection with recall antigens (tetanus, diphtheria, polio).[33] For the pneumococcal polysaccharide vaccine, the response showed high inter-patient and strain-specific variability. However, the study population was very heterogenous and vaccinations were given at highly variable time intervals after the last administration of alemtuzumab.

Effectiveness of immunization with a seasonal influenza vaccine[31] and tetanus toxoid in MS patients receiving fingolimod is reduced compared with placebo-treated patients[34] and may be limited for up to 2 months after discontinuation.[26] A prospective randomized study revealed reduced efficacy of influenza vaccination in patients receiving siponimod *versus* placebo.[35]

While natalizumab treatment does not appear to affect responses to primary or secondary immunization in a clinically relevant extent,[36] responses to a H1N1 pandemic influenza vaccine were reduced by a similar margin to that with glatiramer acetate.[29] A lowered response to immunization with a seasonal influenza vaccine was also observed in two subsequent studies involving few patients on treatment with natalizumab.[30,31] Recently, the case of a young female RRMS patient who developed a vaccine-associated measles infection underscored the need to avoid live-attenuated vaccines in patients receiving treatments that profoundly affect lymphocyte functions.[15]

For ocrelizumab, the randomized VELOCE study[37] revealed a reduced humoral immune response to vaccination with tetanus toxoid and seasonal influenza vaccines given 12–20 weeks after the anti-CD20 antibody as compared with treatment with placebo or interferon beta. Similarly, the response to the 23-valent pneumococcal polysaccharide vaccine was impaired substantially, with fewer patients mounting positive responses against at least 12 strains. Accordingly, the success of vaccination in patients receiving cell-depleting therapies may be gauged by measuring antibody titers if feasible and redosing might be considered in patients with insufficient response.

Immunization of patients receiving treatment with cladribine tablets

As with any disease-modifying MS treatments, clinicians should review a patient's vaccination status before initiation of therapy with cladribine tablets and consult their local vaccination guidelines. No formal studies are currently available on the safety and efficacy of vaccines in MS patients receiving treatment with cladribine tablets.

In keeping with the paradigm of "de-risking immunotherapy",[38] any required immunizations should generally be applied before starting therapy with oral cladribine. While data from B-cell depleting antibody therapies cannot be fully extrapolated to oral cladribine, completion of vaccination regimens 4–6 weeks before starting therapy appears reasonable. In particular, due to a potential risk of vaccine-associated infection, immunization with live-attenuated vaccines should be completed at least 4–6 weeks before starting treatment with cladribine tablets[20] in accordance with the manufacturer's recommendations. During and after treatment with cladribine, vaccination with live-

attenuated vaccines must be avoided while the lymphocyte count remains below the normal range.

In patients scheduled for treatment with cladribine, special caution is required in those without known history of exposure to VZV or previous varicella vaccination. In antibody-negative patients, immunization with the live attenuated varicella vaccine is recommended before initiating oral cladribine therapy. The start of cladribine treatment should be postponed by 4–6 weeks to allow the vaccination to take full effect and to avoid any potential complications.

Since 2018, a recombinant glycoprotein vaccine has been approved for the prevention of herpes zoster episodes. However, it is mandatory that patients previously had VZV infection or vaccination since the herpes zoster vaccine only provides a booster immunization and does not protect against primary infection with VZV.[39]

During the 2-year prospective phase IV study MAGNIFY conducted in patients with highly active relapsing MS, 15 individuals treated with cladribine tablets received a seasonal influenza vaccine ($n = 12$) or a recombinant adjuvanted glycoprotein herpes zoster vaccine ($n = 31$) as standard of care less than 1 month before treatment initiation or at different time points during year 1 or 2 of therapy.[40] Seroprotective anti-VZV titers were maintained in three patients over 6 months post treatment initiation with cladribine tablets.

Since herpes zoster can be a more common problem during immunotherapies including B-cell depleting drugs and cladribine, vaccination against herpes zoster should be considered in MS patients who start one of these treatments. The vaccine is currently licensed for use in people aged 50 years and older and in adults of all ages with an elevated risk of having herpes zoster episodes.[41,42]

Seroprotection or increases in seasonal influenza titers were observed in cladribine tablet treated patients ($n = 12$) who were vaccinated early or late after the previous treatment period during the MAGNIFY study. Seroprotection was maintained or increased irrespective of lymphocyte count.[43]

Immunizations with live attenuated vaccines should be completed 4–6 weeks before starting treatment with cladribine tablets. Oral cladribine is applied as a pulse therapy characterized by short application cycles followed by extended treatment-free time periods (1 year after the first cycle, and at least 3 years after the second cycle).

Regarding immunizations needed after the first treatment cycle, the pivotal role of B-cell functions[43] in lasting immunity – for example, in terms of the immunoglobulin class switch from IgM to IgG and mucosal IgA – and the recovery kinetics of B-cell counts after completing a cycle of cladribine tablets should be considered.

According to the temporal pattern of B-cell depletion and reconstitution observed in clinical trials, a time window from 6 months after the treatment cycle in year 1 to 4–6 weeks before the treatment cycle in year 2 appears adequate for vaccination. B-cell counts may be measured to estimate the degree of recovery before vaccination.

It should be considered that the second treatment cycle can be delayed by 6 months to allow more time for lymphocyte recovery, thus substantially expanding the time window for vaccination. After the second cycle, the tentative window begins 6 months after intake of the last dose. Since no further treatment is scheduled in years 3 and 4 after starting treatment with oral cladribine, this window remains open at least until the end of year 4, or until 4–6 weeks before the initiation of any further disease-modifying treatment, whichever comes first.

The relevance, if any, of the interpatient variability of B-cell recovery in the peripheral compartment (i.e. in blood) for the effectiveness of vaccinations in the individual patient remains to be determined. It is well conceivable that B-cell kinetics in central compartments are more homogeneous than in the periphery. Any consequences of the variable recovery for vaccine efficacy may further be mitigated by the facts that (i) CD8 cells are less affected by cladribine, (ii) B-cells are less relevant for the immediate immune response, and (iii) memory B-cells come into play late in the immune response process.

Deep immune phenotyping performed in the MAGNIFY-MS study[44] is expected to provide more information on the kinetics of B-cell subpopulations, possibly providing a broader rationale for recommendations on the timing and choice of vaccines. Ongoing *ex vivo* studies on immune cells in patients receiving therapy with oral cladribine are expected to provide more detailed

information on the effect of the drug on B-cell function in MS patients, possibly allowing for more evidence-based immunization protocols.

Vaccination against SARS-CoV-2

People with MS patients should generally be vaccinated against COVID-19 as recommended for the healthy population. Moreover, infectious episodes may significantly deteriorate the course of autoimmune diseases or trigger relapses. Therefore, MS patients should be considered as one of the populations prioritized for vaccination.[45]

A large study performed in Israel[46] on the vaccination against COVID-19 with an mRNA vaccine (BNT162b2), in 555 MS patients, found substantial differences regarding the IgG levels elicited in patients on three different high-efficacy immune therapies. In cladribine recipients first vaccinated at a median time of 9.2 months (range: 4.5–22.7) after the previous treatment course, the mean titers of newly elicited IgG antibodies were similar to those observed in the control groups of healthy subjects and untreated MS patients. In contrast, patients on treatment with fingolimod or ocrelizumab achieved lower IgG antibody responses with mean values below the target titer. No peculiarities of the vaccine side-effect profile were observed.

Another recent publication reported on the humoral responses of RRMS patients (age 29 and 61 years) who became infected with SARS CoV-2 while being treated with oral cladribine. One patient developed no signs of illness, the other fully recovered after an episode of mild symptoms. Despite grade 3 and grade 1 lymphopenia measured before the onset of COVID-19 (390 and 860 cells/µl, respectively), both patients produced antiviral IgG antibodies as measured by immunoassays.[47] An adequate antibody response to SARS-CoV-2 was described in another case report of mild COVID-19 in a patient who developed symptoms after having received the first half of the second treatment course of oral cladribine.[48] These findings indicate that protective antiviral antibody titers can be elicited by immunization with SARS-CoV-2 vaccines in MS patients being treated with oral cladribine.

Monitoring vaccination efficacy

As the reaction to vaccines has been shown to be compromised in MS patients receiving immunotherapies,[37] it may be worthwhile to monitor the response by measuring antibody titers in individual patients.

Protection against infection cannot be reliably ascertained for the individual patient *via* antibody titers for all pathogens, particularly in patients receiving cell-depleting or immunosuppressive therapies.[49] In addition, immune defense against viral infection also relies on cellular immunity, thus further impeding the use of serological markers to gauge vaccine effects in MS patients receiving immune therapies.

However, for several infectious agents, anti-pathogen antibodies may at least provide rough surrogate measures of immune protection. For hepatitis B virus, titers of antibodies directed against the surface protein (HBs) above a threshold of 10 mIU/ml indicate adequate protection.[50] This is the only test of antibodies directed against a pathogen which is currently established in routine practice as an estimate of immune protection.

In the case of VZV, antibodies directed against the viral glycoprotein E membrane antigen could be measured by immunoassays and used to estimate a potential protective immunity against infection.[51] For poliovirus, a positive neutralization test indicates protection.[52] Regarding measles virus, data of limited evidence level suggest that protective efficacy correlates with antibody levels measured in the neutralization test, with values above the threshold of 120 mIU/ml indicating protection against disease but not against infection and thus transmission, which requires substantially higher antibody levels.[53] As seasonal influenza vaccines regularly contain newly emerging viral subtypes, protective titer thresholds are variable per virus strain, and immunity against infection cannot be reliably prognosticated.

For pneumococci, the large number of pathogenic strains impairs the ability to gauge the protection against infection by specific antibody titers.[53] Conversely, protection against diphtheria and tetanus is based on antitoxin antibodies and may be determined with antibody titers.[54,55] For *Bordetella pertussis*, no clear immunological correlates of protection have been identified.[53]

Conclusions

In summary, the available evidence indicates reduced vaccination efficacy on treatment with

---

Vaccine-preventable infections in patients treated with cladribine tablets

In the clinical trial program of cladribine tablets, the incidence rate of total infections [cladribine 24.9 *versus* placebo 27.1 events per 100 patient-years (PY)] and serious infections (0.8 *versus* 0.9/100 PY) were similar in patients receiving cladribine tablets and placebo.[56]

Among the vaccine-preventable diseases, herpes zoster occurred more frequently on cladribine tablets compared with placebo (0.83 *versus* 0.2 episodes per 100 PY).[57]

The incidence rate was higher in cladribine-treated patients with grade 3–4 lymphopenia (4.5/100 PY) *versus* grade 0–2 lymphopenia (0.73/100 PY). Most herpes zoster episodes occurred 1–3 years after the start of therapy. Severe or disseminated herpes zoster episodes have not been reported to date.

Other observed vaccine-preventable diseases were limited to influenza, with similar incidence rates in the oral cladribine and placebo groups (2.75 *versus* 2.69 cases per 100 PY with lymphopenia grade 0–2; and 3.35 *versus* 2.69/100 PY with lymphopenia grade 3–4).

MS drugs acting on the S1P receptor, natalizumab and B-cell depleting therapies. Recent data for cladribine tablets suggest the potential of effective immunization in the interval of the two treatment courses and after completion of therapy. Regardless of treatment, vaccine efficacy may be enhanced with optimized timing of application. Study results indicate that protective antiviral antibody titers can be elicited by immunization with SARS-CoV-2 vaccines in MS patients being treated with oral cladribine.

Conflict of interest statement
Ralf Gold received research support, and speaker's honoraria from Bayer Schering, Biogen-Idec, Chugai, Eisai, Janssen, Merck Serono, Nikkiso Pharma, Novartis, Roche, Sanofi Genzyme, Sandoz and Teva. He received consulting honoraria from ZLB Behring, Baxter, Roche and Talecris. RG holds personal stock options in Bayer, Merck and Roche.

Gerd Fätkenheuer received honoraria for acting as a member of advisory boards for Gilead, GSK, Janssen, Merck-Serono, MSD, Pfizer, Roche, Sanofi, AstraZeneca; speaker honoraria from Biogen, Gilead, Janssen, Merck-Serono, Akademie für Infektionsmedizin (Academia of Infection Medicine), Med Update; and financial support for congress attendance from Gilead and Janssen. He received research funding from Gilead, Janssen, ViiV, MSD, Roche, Deutsches Zentrum für Infektionsforschung (German Center for Infection Research), Bundesministerium für Bildung und Forschung (Federal Ministry for Education and Research), and Deutsche Forschungsgemeinschaft (German Research Council).

Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, Geneuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi, Genzyme and Teva.

Christoph Kleinschnitz received remuneration for lectures and advisory boards from Almirall, Merck Serono, Desitin, Sanofi-Genzyme, Biogen, Teva, Bayer, Novartis, Boehringer Ingelheim, Pfizer, Bristol Myers-Squibb, Daiichi Sankyo, Siemens, Eisai, Biotronik, Roche, Stago, Ever Pharma, CSL Behring, Mylan, MedDay Pharmaceuticals, Amgen, Celgene, GE Healthcare, Alexion and Amicus.

Reinhard Marks received honoraria for acting as a member of advisory boards for Merck.

Matthias Maschke received personal honoraria for advisory boards and talks from Merck Serono, Biogen, Novartis, Teva, Roche, and Sanofi/Genzyme.

Antonios Bayas received personal compensation from Merck Serono, Biogen, Novartis, Teva, Roche, Sanofi/Genzyme, Janssen and Celgene; he received grants for congress travel and participation from Biogen, Teva, Novartis, Sanofi/Genzyme, Merck Serono and Celgene.

Micha Löbermann received research grants from Sanofi Pasteur, and personal fees from Merck Healthcare, AbbVie, Bristol Myers Squibb, Pfizer, Bayer and Sanofi Pasteur.

Uwe K. Zettl received speaker honoraria, travel support and/or financial support for research activities from Alexion, Almirall, Bayer, Biogen, Janssen, Merck Serono, Novartis, Octapharm, Roche, Sanofi Genzyme, and Teva as well as from the European Union, Bundesministerium für Bildung und Forschung (Federal Ministry for Education

ORCID iDs
Ralf Gold https://orcid.org/0000-0002-7223-3052

Hans-Peter Hartung https://orcid.org/0000-0002-0614-6989

References

1. Brown JWL, Coles A, Horakova D, *et al.* Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 2019; 321: 175–187.

2. Pourcher V. What are the infectious risks with disease-modifying drugs for multiple sclerosis and how to reduce them? A review of literature. *Rev Neurol* 2020; 176: 235–243.

3. Winkelmann A, Löbermann M and Zettl UK. Varicella-zoster- und Herpes-zoster-Impfindikation bei Multipler Sklerose: aktuelle situation [Indications for varicella zoster and herpes zoster vaccination in multiple sclerosis: current situation]. *Nervenarzt* 2019; 90: 1254–1260. (German).

4. Winkelmann A, Loebermann M, Reisinger EC, *et al.* Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol* 2016; 12: 217–233.

5. Zrzavy T, Kollaritsch H, Rommer PS, *et al.* Vaccination in multiple sclerosis: friend or foe? *Front Immunol* 2019; 10: 1883.

6. Moiola L, Rommer PS and Zettl UK. Prevention and management of adverse effects of disease modifying treatments in multiple sclerosis. *Curr Opin Neurol* 2020; 33: 286–294.

7. Farez MF, Correale J, Armstrong MJ, *et al.* Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2019; 93: 584–594.

8. Confavreux C, Suissa S, Saddier, *et al.* Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in multiple sclerosis study group. *N Engl J Med* 2001; 344: 319–326.

9. Mailand MT and Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. *J Neurol* 2017; 264: 1035–1050.

10. Hernán MA, Alonso A and Hernández-Díaz S. Tetanus vaccination and risk of multiple sclerosis: a systematic review. *Neurology* 2006; 67: 212–215.

11. Farez MF and Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. *J Neurol* 2011; 258: 1197–1206.

12. Winkelmann A, Metze C, Frimmel S, *et al.* Tick-borne encephalitis vaccination in multiple sclerosis: a prospective, multicenter study. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e664.

13. Frederiksen JL and Topsøe Mailand M. Vaccines and multiple sclerosis. *Acta Neurol Scand* 2017; 136(Suppl. 201): 49–51.

14. Berger JR. Varicella vaccination after fingolimod: a case report. *Mult Scler Relat Disord* 2013; 2: 391–394.

15. Miauton A, Tan R, Pantazou V, *et al.* Vaccine-associated measles in a patient treated with natalizumab: a case report. *BMC Infect Dis* 2020; 20: 753.

16. Löbermann M, Boršo D, Hilgendorf I, *et al.* Immunization in the adult immunocompromised host. *Autoimmun Rev* 2012; 11: 212–218.

17. Pool V, Gordon DM and Decker M. Methodological issues with the risk of relapse study in patients with multiple sclerosis after yellow fever vaccination. *Arch Neurol* 2012; 69: 144.

18. Farez MF and Correale J. Yellow fever vaccination and increased relapse rate in travelers with multiple sclerosis. *Arch Neurol* 2011; 68: 1267–1271.

19. Rolfes L, Pawlitzki M, Pfeuffer S, *et al.* Fulminant MS reactivation following combined fingolimod cessation and yellow fever vaccination. *Int J Mol Sci* 2019; 20: 5985.

20. Mavenclad® (cladribine tablets). Summary of product characteristics, Amsterdam: European Medicines Agency, 2020.

21. Robert Koch Institut. Empfehlungen der Ständigen Impfkommission beim Robert Koch-Institut – 2020/2021. [Recommendations of the Standing Committee on vaccinations at the Robert Koch Institute 2020/2021]. *Epidemiologisches Bulletin* 2020; 34: 4–60.

22. U.S. Centers of Disease Control and Prevention. *Recommended adult immunization schedule for ages 19 years or older, United States*, 2020, https://www.cdc.Gov/vaccines/schedules/hcp/imz/adult.html (accessed 6 February 2021).

23. Merkblatt des Kompetenznetzes Multiple Sklerose (KKNMS) [German Competence Network Multiple Sclerosis KKNMS.] Pocket card for patients: vaccination and MS, https://www.kompetenznetz-multiplesklerose.de (accessed 12 April 2021).

24. Mitteilung der Ständigen Impfkommission am Robert Koch-Institut: Beschluss der STIKO zur 2. Aktualisierung der COVID-19-Impfempfehlung und die dazugehörige wissenschaftliche Begründung [Communication of the Standing Committee on vaccination at the Robert Koch Institute: resolution of the STIKO on the 2nd update of the COVID-19 vaccination recommendation and the associated scientific rationale.] *Epidemiologisches Bulletin* 2021; 5: 3–79.

25. Aktuelle Daten und Informationen zu Infektionskrankheiten und Public Health. Empfehlungen der Ständigen Impfkommission beim Robert-Koch-Institut 2020/2021. [Current data and information on infectious diseases and public health. Recommendations of the Standing Commission on vaccination at the Robert Koch Institute.] *Epidemiologisches Bulletin* 2020; 34: 2–63.

26. Kompetenznetz Multiple Sklerose (KKNMS) Qualitätshandbuch MS/NMOSD. [Competence network multiple sclerosis quality handbook], https://www.kompetenznetz-multiplesklerose.de (2020, accessed 6 February 2021).

27. Ciotti JR, Valtcheva MV and Cross AH. Effects of MS disease-modifying therapies on responses to vaccinations: a review. *Mult Scler Relat Disord* 2020; 45: 102439.

28. von Hehn C, Howard J, Liu S, *et al.* Immune response to vaccines is maintained in patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm* 2017; 5: e409.

29. Olberg HK, Cox RJ, Nostbakken, *et al.* Immunotherapies influence the influenza vaccination response in multiple sclerosis patients: an explorative study. *Mult Scler* 2014; 20: 1074–1080.

30. Olberg HK, Eide GE, Cox RJ, *et al.* Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy. *Eur J Neurol* 2018; 25: 527–534.

31. Metze C, Winkelmann A, Loebermann M, *et al.* Immunogenicity and predictors of response to a single dose trivalent seasonal influenza vaccine in multiple sclerosis patients receiving disease-modifying therapies. *CNS Neurosci Ther* 2019; 25: 245–254.

32. Bar-Or A, Wiendl H, Miller B, *et al.* Randomized study of teriflunomide effects on immune responses to neoantigen and recall antigens. *Neurol Neuroimmunol Neuroinflamm* 2015; 2: e70.

33. McCarthy CL, Tuohy O, Compston DA, *et al.* Immune competence after alemtuzumab treatment of multiple sclerosis. *Neurology* 2013; 81: 872–876.

34. Kappos L, Mehling M, Arroyo R, *et al.* Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. *Neurology* 2015; 84: 872–879.

35. Ufer M, Shakeri-Nejad K, Gardin A, *et al.* Impact of siponimod on vaccination response in

a randomized, placebo-controlled study. *Neurol Neuroimmunol Neuroinflamm* 2017; 4: e398.

36. Kaufman M, Pardo G, Rossman H, *et al.* Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. *J Neurol Sci* 2014; 341: 22–27.

37. Bar-Or A, Calkwood JC, Chognot C, *et al.* Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology* 2020; 95: e1999–e2008.

38. Klotz L, Havla J, Schwab N, *et al.* Risks and risk management in modern multiple sclerosis immunotherapeutic treatment. *Ther Adv Neurol Disord* 2019; 12: 1756286419836571.

39. European Medicines Agency. Summary of product characteristic; Shingrix. Amsterdam: European Medicines Agency, 2020.

40. Roy S and Boscher U. *Analysis of influenza and varicella zoster virus vaccine antibody titers in patients with relapsing multiple sclerosis treated with cladribine tablets. Presented at the ACTRIMS/ECTRIMS*, 13–15 October 2021, Virtual Congress.

41. Racine É, Gilca V, Amini R, *et al.* A systematic literature review of the recombinant subunit herpes zoster vaccine use in immunocompromised 18–49 year old patients. *Vaccine* 2020; 38: 6205–6214.

42. Shingrix (recombinant, adjuvanted herpes zoster vaccine). Summary of product characteristics, Amsterdam: EMA, 2020.

43. Kratzer B, Trapin D, Ettel P, *et al.* Immunological imprint of COVID-19 on human peripheral blood leukocyte populations. *Allergy* 2020; 76: 751–765.

44. De Stefano N, Achiron A, Barkhof F, *et al. A 2-year study to evaluate the onset of action of cladribine tablets in subjects with highly active relapsing multiple sclerosis: results from magnify-MS baseline analysis; deep immune phenotyping.* Presented at Annual Congress of the German Neurological Society, 4–7 November 2020, Virtual. IP012.

45. Stellungnahme des Kompetenznetzes Multiple Sklerose KKNMS zu Impfungen einschließlich gegen SARS-CoV-2 bei MS-Betroffenen [Statement of the German competence network multiple sclerosis KKNMS on vaccinations including those against SARS-CoV-2 in people with MS], https://www.kompetenznetz-multiplesklerose.de/wp-content/uploads/2020/12/Stellungnahme-COVID-19-Impfung-MS_Pressetext_KKNMS_DMSG-2.pdf (2020, accessed 6 February 2021).

46. Achiron A, Mandel M, Dreyer-Alster S, *et al.* Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Dis* 2021; 14: 1–8.

47. De Angelis M, Petracca M, Lanzillo R, *et al.* Mild or no COVID-19 symptoms in cladribine-treated multiple sclerosis: two cases and implications for clinical practice. *Mult Scler Relat Disord* 2020; 45: 102452.

48. Celius EG. Normal antibody response after COVID-19 during treatment with cladribine. *Mult Scler Relat Disord* 2020; 46: 102476.

49. Plotkin SA. Immunologic correlates of protection induced by vaccination. *Pediatr Infect Dis J* 2001; 20: 63–75.

50. Centers for Disease Control and Prevention. Pink-Book. Epidemiology and Prevention of Vaccine-Preventable Diseases. *Chapter 10: Hepatitis B*, https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html (2015, accessed 6 February 2021).

51. Gershon AA. Varicella vaccines. In: Plotkin SA (ed.) *Plotkin's vaccines*. 7th ed. Philadelphia: Elsevier, 2018.

52. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* 2010; 17: 1055–1065.

53. Edwards KM. Pertussis vaccines. In: Plotkin SA (ed.) *Plotkin's vaccines*. 7th ed. Philadelphia: Elsevier, 2018.

54. Borrow R, Balmer P and Miller E. Meningococcal surrogates of protection--serum bactericidal antibody activity. *Vaccine* 2005; 23: 2222–2227.

55. World Health Organization. WHO immunological basis for immunization series module 3: tetanus update 2018, https://www.who.int/immunization/documents/ISBN9789241513616/en/ (accessed 6 February 2021).

56. Sorensen PS and Sellebjerg F. Pulsed immune reconstitution therapy in multiple sclerosis. *Ther Adv Neurol Disord* 2019; 12: 1756286419836913.

57. Cook S, Leist T, Comi G, *et al.* Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. *Mult Scler Relat Disord* 2019; 29: 157–167.