Vaccination against infection in patients with multiple sclerosis

Micha Loebermann, Alexander Winkelmann, Hans-Peter Hartung, Hartmut Hengel, Emil C. Reisinger and Uwe K. Zettl

Abstract | Bacterial and viral infections have been shown to induce relapses and accelerate the progression of multiple sclerosis (MS). Vaccination to prevent communicable disease in such patients is, therefore, of key importance. Reports of potentially detrimental effects of immunization on the course of MS, however, have prompted patients and physicians to adopt a cautious attitude towards the use of vaccines. The risks associated with a number of vaccines have been investigated in patients with MS. Vaccines against some diseases, such as tetanus and hepatitis B, are not associated with an elevated risk of MS exacerbation, whereas vaccines against other diseases, such as yellow fever, are contraindicated in patients with MS. Many patients with MS receive immunosuppressive or immunomodulatory therapy, which could make them more susceptible to infectious diseases and might also affect their ability to respond to immunization. Here, we review the indications for and possible adverse effects of vaccines in patients with MS, and address issues of vaccination in the context of immunomodulatory therapy for MS.

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Introduction

Vaccination is a mainstay in the prevention of communicable infectious diseases. This intervention is particularly important in patients with chronic debilitating diseases, who are prone to infections that could aggravate their symptoms.[1,2]

Numerous studies in patients with multiple sclerosis (MS) have shown that the risk of relapse is increased by infections. For example, shortly after a bacterial urinary tract infection, a viral respiratory infection or gastroenteritis, patients with MS experienced significantly raised relapse rates and enhanced lesion activity as measured with MRI.[3] Another study found that infection increased the risk of relapse approximately twofold.[4] Moreover, relapses associated with an infection seem to be more prone to causing neurological dysfunction (as measured by the Expanded Disability Status Scale score) than are relapses not associated with infection.[4]

Vaccination elicits an immune response against modified antigens of the infective agent, which increases the speed and efficacy of the immune response to subsequent exposure to the pathogen, thereby providing protection. However, some evidence suggests that vaccines might inadvertently activate immune responses to autoantigens in patients with autoimmune disease which, in the case of MS, could trigger a relapse. Suggested mechanisms for this process include molecular mimicry (shared epitopes between microorganisms or vaccine antigens and CNS proteins in MS) and polyclonal bystander activation of T lymphocytes (Box 1).[5]

Concerns have been raised that in addition to eliciting relapses, vaccination might also trigger the onset of MS in susceptible individuals.[5] However, a recent extensive review from the US Institute of Medicine did not find sufficient evidence to accept or reject a causal relationship between the onset of MS and vaccination against measles, mumps and rubella (MMR), influenza, hepatitis A, hepatitis B, human papilloma virus (HPV), diphtheria, tetanus, acellular pertussis, or meningococcal disease.[6] Furthermore, pooled analyses found no evidence that vaccination against tuberculosis with the Bacillus Calmette–Guérin (BCG) preparation, or against hepatitis B, influenza, measles, typhoid fever, diphtheria or tetanus, was associated with an increased risk of developing MS.[7]

These conclusions are based on extensive studies applying principles laid down by the WHO.[8] These principles require a number of criteria to be fulfilled before a causal link can be considered between a distinct vaccine and subsequent emergence of adverse events—in this instance, exacerbation or worsening of MS (Box 2).

Another important issue related to the use of vaccines in patients with MS is that the expanding repertoire of

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Department of Tropical Medicine and Infectious Diseases (**M. Loebermann, E. C. Reisinger**), Department of Neurology (**A. Winkelmann, U. K. Zettl**), University of Rostock, Schillingallee 35, D-18057 Rostock, Germany. Department of Neurology (**H.-P. Hartung**), Institute for Virology (**H. Hengel**), Heinrich-Heine-University Düsseldorf, Moorenstraße 5, D-40225 Düsseldorf, Germany.

Correspondence to: H.-P. Hartung hans-peter.hartung@uni-duesseldorf.de

Key points

- Infections can trigger a relapse in patients with multiple sclerosis (MS), warranting appropriate vaccination
- Concerns of potential adverse reactions after immunization in MS have led to restriction of the use of some vaccines
- Some vaccines—in particular, inactivated vaccines—are safe and beneficial in MS
- Immunosuppressive and immunomodulatory treatment for MS could affect vaccine efficacy

Box 1 | Induction of autoimmune responses

Molecular mimicry and bystander activation are possible mechanisms by which infective agents and vaccination could trigger autoimmunity.

Molecular mimicry

- Antigenic similarity between microbial molecules and host antigens or epitopes causes immune-mediated destruction of host tissues

Bystander activation

- Antigen-nonspecific stimulation of innate immune responses, with emergence or heightened activity of autoreactive T cells and/or B cells
- Increased generation of proinflammatory cytokines
- Defective regulatory T-cell activity

powerful immunomodulatory and immunosuppressive MS drugs could limit the effectiveness of prophylactic vaccination. Furthermore, on rare occasions some of the new MS drugs are associated with viral infections as serious adverse events, suggesting the need to consider vaccination before initiation of the immunomodulatory or immunosuppressive therapy.

Here, we review studies on the use of vaccines in patients with MS, and identify and discuss risks and benefits of vaccines in patients undergoing treatment with disease-modifying drugs (DMDs).

Standard vaccines

The administration of a vaccine should be considered only when the vaccine-preventable disease has more serious consequences than the potential adverse effects associated with the vaccination.[3,9] Patients with MS should be offered immunizations against infections that they are at risk of contracting.[10] Existing patient care guidelines such as the UK National Health Service Clinical Guidelines for MS,[11] the MS Council for Clinical Practice Guidelines in the US[12] or the German Vaccine Commission guidelines[13] recommend applying the national standard vaccination strategies to patients with MS. Similar to the vaccination recommendations for healthy adults, those for patients with MS include immunizations against diphtheria, tetanus, influenza and pneumococcus (Table 1). The indications and contraindications in patients with MS are largely the same as for healthy individuals,[14] although data specific to MS are lacking for some vaccinations.

Tetanus

The highly immunogenic tetanus vaccine is primarily administered in combination with vaccines against other infectious diseases such as diphtheria, poliomyelitis or pertussis. A tetanus booster vaccination is recommended every 10 years in adults. In a case–control study involving 332 patients with MS and 722 healthy controls, the risk of developing MS or of relapse was not found to be enhanced by prior immunization (OR 0.6; 95% CI 0.4–0.8).[15] According to an investigation in 623 patients with MS who were registered in a European MS database, the risk of relapse was not increased after tetanus vaccination (relative risk [RR] 0.75; 95% CI 0.23–2.46).[16] Furthermore, in patients receiving combined vaccines, the risk of relapse was lower than in non-vaccinated patients (RR 0.26; 95% CI 0.06–1.12). Similarly, in a comparatively small trial in the Netherlands, no MS exacerbations occurred during the 6 weeks following tetanus vaccination.[17] A meta-analysis of case–control studies published between 1966 and 2005, which included 963 patients with MS and 3,126 controls, supports the findings outlined above, including a reduced risk of relapse in patients with MS who have received a tetanus vaccination, compared with those who have not (OR 0.67; 95% CI 0.55–0.81).[18] If available, combined vaccines (for example, tetanus, diphtheria, poliomyelitis and pertussis, discussed below) should be used in patients with MS when tetanus vaccination is indicated.

Diphtheria

The diphtheria vaccine is generally administered in combination with the tetanus vaccine. Large-scale studies on the association of diphtheria immunization with the risk of MS exacerbation have not been conducted, but an analysis of patients registered in the European MS database did not show an increased risk of relapse: in patients immunized with a combined tetanus–diphtheria vaccine, the relative risk of relapse was 0.22 (95% CI 0.05–0.99) compared with patients receiving tetanus vaccine alone.[16]

Influenza

Infection with influenza does not seem to lead to worsening of symptoms in primary progressive MS, according to a study involving 53 patients with this form of the disease.[19] By contrast, in 180 patients with relapsing–remitting MS (RRMS), 12 of the 36 patients (33%) who became infected with influenza developed an acute relapse within 6 weeks. Moreover, only four of the 80 patients (5%) who received vaccination against influenza had a relapse.[19] In another study, vaccination with standard inactivated influenza vaccines induced comparable T cell responses and influenza A-specific antibody titers to those in healthy controls.[20]

Vaccination against influenza does not seem to exacerbate MS, although in a small study involving six patients with MS, contrast-enhanced cerebral MRI showed increased lesion activity 15 and 45 days after vaccination in one patient.[21] Another study in 11 patients with RRMS, however, did not report clinical exacerbation after vaccination. Cerebral MRI revealed a mean of three new gadolinium-enhancing lesions in the 3-week prevaccination period, compared with only one new inflammatory lesion in the 3-week postvaccination period.[22] In an older study, published in 1976, only one of 93 patients with MS showed emerging neurological symptoms after influenza vaccination.[23] In addition, a placebo-controlled,

double-blind study involving 104 patients with MS did not demonstrate significant differences in the rate of MS exacerbations (3.7% versus 6.1%).[24]

In June 2009, the WHO announced a pandemic caused by the new H1N1 influenza virus (nH1N1, also known as swine flu), and vaccines against this novel type of influenza A were developed. In a recently published case series of 60 patients with MS, the monovalent nH1N1 vaccine did not increase relapse rates 30, 60, or 90 days following vaccination, compared with equivalent time periods before vaccination.[25] In another recent study involving 49 patients with MS who had been vaccinated with the pandemic H1N1 vaccine, the seasonal influenza vaccine or both, none of the patients reported a deterioration of neurological status after vaccination.[26] Furthermore, population-based studies have not found an association between vaccination and the triggering of MS relapses.[27–29] However, in a small case series of 18 patients with MS, relapses occurred within 3 weeks in six of seven patients receiving H1N1 vaccine alone, in four of eight patients receiving simultaneous H1N1 and seasonal vaccine, and in two of three patients receiving seasonal vaccine alone.[30]

In summary, although further monitoring for adverse effects is warranted when using influenza vaccines, the data obtained so far encourage the use of such vaccines in patients with MS.

Supplementary vaccines

Supplementary vaccines are recommended for adults exposed to situations with an elevated risk of a severe course of infection or worsening of an underlying disease. These situations include chronic disease, professional exposure, travel to endemic areas, and asplenia (Table 2). Of note, trials have not been conducted to investigate the tolerability of vaccines against hepatitis A—the most widely used travel vaccine—or Japanese B encephalitis in MS. Other vaccines of importance in MS are discussed in this section.

Viral diseases

Tick-borne encephalitis

During the past 30 years, rising numbers of tick-borne encephalitis (TBE) cases have been registered across Europe and Russia,[31] as the disease spreads from Europe through parts of China to eastern Japan.[32] Immunization against this viral disease seems to be warranted in endemic regions, particularly in people who are frequently involved in outdoor activities.

In a small Austrian case–control study, 15 patients with MS from TBE-endemic areas were vaccinated with standard TBE vaccine doses and compared with 15 matched, non-immunized control patients with MS.[33] MS progression did not differ between the two groups over 36 months of follow-up. In addition, no differences were observed in the MRI lesion activity and load 45 days after immunization.

Yellow fever

For several countries, yellow fever is the only disease against which international travelers must be vaccinated before they can gain entry to the country. Owing to the risk of severe adverse effects, the yellow fever vaccine is largely contraindicated in immunosuppressed patients, including patients with MS who are undergoing immunomodulatory treatment. Recent studies, however, have shown that immunization is feasible in asymptomatic patients with HIV who have $CD4^+$ helper T-cell counts above 200 per 1 μl.[34] A small study in MS showed a significant increase in exacerbation rates within 3 months following yellow fever vaccination compared with pre-vaccination exacerbation rates.[35] In light of this evidence, yellow fever vaccines are not recommended in patients with MS.

Box 2 | Vaccine-related adverse events

The WHO criteria for vaccine-related adverse events are as follows:

- A consistent and strong association between a vaccine and an adverse event
- Specificity—a distinctive, unique relationship of an adverse event with the vaccine concerned
- Temporal relationship—the adverse event follows vaccination usually within a few weeks
- Biologically plausible relationship—the adverse event cannot reasonably be attributed to concurrent disease or other drugs

Hepatitis B

Following the implementation of a hepatitis B vaccination program in France, CNS demyelination was linked with the vaccine,[36] initially leading to governmental compensation of patients with MS.[37] However, none of the subsequent studies identified hepatitis B vaccination as a risk factor for developing MS.[38,39]

Anecdotal observations describing a deterioration of existing CNS demyelinating disease following hepatitis B vaccination[40,41] prompted caution in prescribing this vaccine for patients with RRMS, owing to the concern of eliciting an MS relapse. However, in a case-crossover study involving 643 patients with MS who experienced a relapse, hepatitis B vaccination was not found to be a risk factor for developing a relapse during the 2-month risk period following vaccination (RR 0.67; 95% CI 0.20–2.17).[16] A study of a French cohort of children aged 0.5–16 years who had experienced a first episode of CNS inflammatory demyelination found that hepatitis B vaccine exposure was not associated with a significant increase in the risk of relapse during a mean follow-up of 5.8 years. The adjusted hazard ratio of developing a second episode of CNS inflammation within 3 years after vaccination was 0.78 (95% CI 0.32–1.89).[42] Overall, the hepatitis B vaccination can be considered safe, with no increased risk of developing MS after vaccination[36] and no increased risk of relapse in patients with MS.[7,16]

Human papilloma viruses

Two vaccines—one against two HPV subtypes (HPV-16 and HPV-18) and the other against four HPV subtypes (HPV-6, HPV-11, HPV-16 and HPV-18) that are most commonly associated with cervical cancer and genital

Table 1 | Recommendations for use of standard vaccines in the general population and in MS

Disease or pathogen	UK[78]	USA[79]	France[80]	Germany[13]	Use in patients with MS*
Diphtheria	Five doses in lifetime (including childhood vaccines)	All individuals	All individuals	All individuals	Inactivated vaccine; vaccine possibly associated with decreased risk of MS[7]
Influenza	Individuals >65 years old, those with chronic diseases, and pregnant women	All individuals	Not reported	Individuals >65 years old, those with chronic diseases, and pregnant women; recommended in patients with MS	Inactivated vaccine; no restrictions; recommended in patients with risk of influenza exposure[16,19,24,25,81,82]
Human papilloma virus	Females 12–13 years old	Females 11–12 years old	Females 14 years old	Females 12–17 years old	Inactivated vaccine; inadequately investigated in MS
Measles, mumps and rubella	Unprotected individuals	Individuals <50 years old with lack of immunity, and at-risk individuals >50 years old	Not reported	Unprotected individuals and following contact with an infected person	Live attenuated vaccine; MS relapse risk not increased by vaccination;[15,46,83,84] not recommended in immunosuppressed patients
Meningococcal meningitis	Individuals unprotected against meningococcus C, at-risk individuals and those with an underlying medical condition	At-risk individuals	At-risk individuals	Individuals with immunodeficiency or asplenia; before immunosuppression; in endemic areas or where risk of exposure exists	Inactivated vaccine; inadequately investigated in MS; consider vaccination before immunomodulatory therapy
Pertussis	Three doses in childhood	All adults: one dose combined with tetanus and diphtheria	Individuals 26–28 years old	All adults: one dose; no booster recommended	Inactivated vaccine; insufficient data in MS; combination vaccines only
Pneumococcus	At-risk individuals; no longer recommended for individuals >65 years old[85]	At-risk individuals and those >65 years old	Not reported	Individuals >60 years old, and those who are immunocompromised or have a chronic disease	Inactivated vaccine; insufficient data in MS; consider vaccination before immunomodulatory therapy
Tetanus	Five doses in lifetime (including childhood vaccines)	All individuals	All individuals	All individuals	Inactivated vaccine; no restrictions;[15,16,18] vaccine possibly associated with decreased risk of MS[7]
Varicella	Non-immune individuals in close contact with those at risk	Individuals lacking evidence of immunity	Not reported	Seronegative patients before immunosuppressive therapy	Live attenuated vaccine; risk of MS relapse not increased by vaccination; possible positive effect on MS;[52] not recommended in immunosuppressive therapy
Zoster reactivation	Not reported	Individuals >60 years old	Not reported	Not recommended	Live attenuated vaccine; not studied in MS

The WHO recommends general immunization against diphtheria, hepatitis B, measles, pertussis, poliomyelitis and tetanus. Vaccination against *Haemophilus influenzae* type B or tuberculosis (with the Bacillus Calmette–Guérin preparation) is recommended in countries with a high incidence of these diseases. *In patients receiving immunosuppressive therapy, additional vaccination recommendations—particularly for live vaccines—must be taken into account. Abbreviation: MS, multiple sclerosis.

warts—are licensed in the USA, Europe and many other countries. Recommendations generally include HPV vaccination for female adolescents aged 11 years and older. Five cases of MS relapses in association with quadrivalent HPV vaccination have been reported,[43] and a small case series documented three young females who developed neuromyelitis optica following HPV immunization.[44] However, the relapses or development of neuromyelitis optica may well have occurred by chance in this target population. Current data on the effects of the HPV vaccine on established MS are insufficient to determine whether a link exists between vaccination and the triggering of MS relapses.

Measles, mumps and rubella

Immunization against MMR with a live attenuated vaccine is generally recommended in childhood or in unprotected adults after contact with infected individuals. Immunosuppressed patients, however, may develop overt vaccination-induced disease.[45] Vaccination against measles should, therefore, be avoided in patients with MS who are receiving immunosuppressive therapy. The effect of MMR vaccination on the course of MS has not been studied. Until further evidence is available, alternative strategies such as passive immunization with hyperimmunoglobulin should be used in the rare cases of unprotected adults with MS who have been exposed to the diseases.

Poliomyelitis

Immunization with the inactivated polio vaccine is recommended for all children, and booster vaccinations are advisable when travelling to an area in which the disease is endemic. To eliminate the risk of vaccine-associated paralytic poliomyelitis, use of the live oral polio vaccine is no longer recommended for routine immunization in many countries. A prospective investigation of the formerly used live polio vaccine in 20 patients with MS did not find evidence of worsening of MS symptoms.[46] A recent meta-analysis of clinical trials concluded that the

Table 2 | Recommendations for use of supplementary vaccines in the general population and in MS

Vaccine	Recommended in	Vaccine type	Use in patients with MS*
Cholera	Country-specific entry regulations may apply	Inactivated vaccine	Insufficiently investigated in MS
Tick-borne encephalitis	Endemic areas and tick exposure	Inactivated vaccine	No influence of vaccine on disease activity[33]
Yellow fever	Endemic areas; country-specific entry regulations may apply	Live attenuated vaccine	May cause worsening of MS[35]
Haemophilus influenzae	Underlying medical condition or at-risk individuals with asplenia; may only be available in combination with tetanus/diphtheria	Inactivated vaccine	Insufficiently investigated in MS
Hepatitis A	At-risk individuals including those with chronic hepatic disease or other underlying medical condition	Inactivated vaccine	Insufficiently investigated in MS
Hepatitis B	Endemic areas; at-risk individuals including those with chronic hepatic disease or other underlying medical condition	Inactivated vaccine	Extensive studies without evidence of increased risk of MS induction or relapse[16,39,42,81,86–88]
Japanese B encephalitis	Endemic areas	Inactivated vaccine	Insufficiently investigated in MS
Rabies	Endemic areas and for post-exposure prophylaxis in combination with hyperimmunoglobulin	Inactivated vaccine	No studies in MS
Poliomyelitis	Booster before travel to endemic areas	Inactivated vaccine	Insufficient data in MS for risk evaluation[46]
Tuberculosis	Children at risk	Live vaccine	Protective effect questionable;[54] not recommended; meta-analysis showed no increased risk of MS induction or relapse[7]
Typhoid fever	Endemic areas	Inactivated vaccine (intramuscular) or live vaccine (oral)	Insufficiently investigated in MS; avoid live vaccine and use inactivated vaccine[89,90]

*In patients receiving immunosuppressive therapy, additional vaccination recommendations—particularly for live inactivated vaccines—must be taken into account. Abbreviation: MS, multiple sclerosis.

risk of developing MS was not increased after vaccination against polio (OR 0.87; 95% CI 0.61–1.25).[7] This meta-analysis included seven nonrandomized trials, conducted between 1989 and 2004, in 570 patients with MS and 725 controls from Europe, Israel and India. Further clinical studies evaluating the risk of triggering MS relapse after vaccination against polio have not been conducted.

Rotavirus

Rotavirus causes gastroenteritis, often in epidemic outbreaks, and is mostly transmitted via the fecal–oral route. Two live attenuated vaccines are available for vaccination of infants. Immunosuppressed patients who have household contact with recently vaccinated infants should follow strict personal hygiene because the vaccine virus is shed after vaccination.[47] No studies have yet been conducted on the effect of the vaccine on the course of MS.

Rabies

The current rabies vaccine, which is grown on human diploid cells or chicken fibroblasts, is considerably more tolerable than the formerly used rabies vaccine grown on neural tissues.[48] No studies concerning rabies vaccine tolerability in MS have been conducted. Given the invariably fatal course of rabies, immediate active immunization in combination with immunoglobulins is imperative for post-exposure prophylaxis (for example, after being bitten by a rabies-suspected animal) in non-immune individuals.

Varicella zoster virus

Varicella zoster virus (VZV) is a neurotropic virus that causes chickenpox and—on reactivation from latent infection—shingles. VZV infection in adults can be a severe and sometimes life-threatening disease. Vaccination of non-immune adults with live attenuated VZV is recommended before the start of an immunosuppressive or powerful immunomodulatory therapy, and is explicitly required in the case of some DMDs, such as fingolimod,[49,50] the sphingosine 1-phosphate receptor modulator that was recently approved for the treatment of MS.[51] Immunocompromised individuals who have not been vaccinated and are exposed to VZV should receive hyperimmunoglobulin for post-exposure prophylaxis.

In a 1-year study investigating the neurological status of 47 patients with MS who received VZV vaccination, improvement was observed in 14 individuals (29.8%), deterioration was observed in four patients (8.5%), and no change was seen in 29 patients (61.7%).[52] Of note, four patients developed mild vaccine-associated chickenpox. Thus, vaccination may lead to adverse effects in MS and should be avoided, especially in the presence of DMDs.

Bacterial diseases

A notable lack of studies exists on the effects of vaccination against bacterial infections on disease course in MS. Immunization against tuberculosis with the attenuated live BCG vaccine is no longer recommended in some low-prevalence regions because of limited efficacy and

a comparatively high rate of complications.[53] In one case series, 14 patients with RRMS experienced a 57% reduction of active brain lesions on MRI within 6 months of vaccination,[54] and a meta-analysis did not reveal any adverse effects on MS relapse rates.[7]

Other vaccines against bacterial diseases are widely used, including those to prevent meningococcal, pneumococcal or *Haemophilus influenzae* type b infections, but none of these has been specifically evaluated in patients with MS. Similarly, travel vaccines such as those against typhoid fever or cholera have not been assessed in relation to MS. This gap in our knowledge emphasizes the need to conduct appropriate studies designed to evaluate the safety of vaccines to prevent major bacterial infections in patients with MS.

Effect of MS drugs on vaccine efficacy

MS is treated with DMDs[55] that can modulate or suppress the generation of adaptive immune responses and/or the maintenance of immunological memory. These treatments might diminish the effectiveness of vaccines. Conversely, live attenuated vaccines, such as the yellow fever vaccine, may be contraindicated because of the risk of harmful infection or chronic carriage of the attenuated—but actively replicating—pathogen.[35]

Case studies have shown good efficacy of vaccination in patients receiving DMD treatment,[56] but large studies are scarce, especially in MS. Moreover, systematic prospective studies are virtually absent,[12] representing a knowledge gap that demands further clinical studies. No studies have so far been conducted into the effects of immunization in patients receiving the synthetic copolymer glatiramer acetate, intravenous immunoglobulin (IVIg), or the monoclonal antibody natalizumab, which are all used in the treatment of MS. According to FDA prescribing information, the application of IVIg may impair the immunogenicity of live viral vaccines such as MMR or VZV for 6–12 months.[57]

The available information on interactions between DMDs and vaccination is discussed in this section. The degree of immunosuppression and the response to immunization can vary considerably between the different groups of DMDs that are used in the treatment of MS.

Corticosteroids

Corticosteroids are widely used in MS and have a broad dose-dependent suppressive effect on immune reactions. This effect could lead, on one hand, to an impaired antibody response following immunization with inactivated vaccines and, on the other, to vaccine-induced infection following immunization with live attenuated vaccines. However, the immune response to influenza or pneumococcal vaccines did not seem to be impaired in recipients of organ transplants, some of whom were receiving corticosteroids.[58] This response has not been evaluated in MS.

Interferons

Interferons do not seem to impair immune responses in patients with MS, and these drugs have an antiviral effect.[59] In a prospective study of 88 patients with MS who were treated with IFN-β1a, and 77 untreated patients with MS, similar proportions (93.0% and 90.9%, respectively) of each group developed protective immune responses after receiving seasonal influenza vaccine.[60] Seasonal influenza vaccines can, therefore, be considered safe and effective in patients with MS receiving IFN-β.

Fingolimod

Fingolimod causes redistribution of lymphocytes[51] and may interfere with the immune response. Following influenza vaccination, patients with MS who are being treated with fingolimod have been shown to develop antibody responses comparable to those of healthy controls.[61,62] As discussed above, VZV vaccines are live vaccines that are contraindicated during treatment with DMDs or during MS progression. VZV antibody status should, therefore, be determined early in the disease course, before initiation of disease-modifying therapy, to allow vaccination against VZV if necessary.[49]

Rituximab

Rituximab, a chimeric anti-CD20 monoclonal antibody that induces sustained depletion of B cells, is used to treat lymphomas and various autoimmune diseases. Rituximab and the follow-up humanized anti-CD20 monoclonal antibody ocrelizumab improved outcomes in patients with RRMS in phase II trials.[63,64] A number of studies have evaluated antibody responses in patients receiving rituximab, although none has examined patients with MS. Patients with lymphoma who were receiving rituximab did not develop protective antibody titers after vaccination against influenza.[65,66] In patients with rheumatoid arthritis, rituximab reduced the humoral response to influenza vaccine[67–69] but did not affect the cell-mediated response.[70] By contrast, rituximab treatment in patients with rheumatoid arthritis was associated with an impaired cell-mediated response after administration of a pneumococcal polysaccharide vaccine.[71] These results suggest that inactivated vaccines can be administered during rituximab therapy if vaccination before initiation of rituximab is not feasible, as is the case for seasonal influenza vaccines.

Cytostatic treatment

Studies are lacking on the immune response to vaccination and vaccine safety in patients with MS who are receiving cytostatic treatment.[72] Patients with systemic lupus erythematosus (SLE) who were being treated with azathioprine showed a trend towards a diminished antibody response after vaccination against influenza.[73] By contrast, antibody responses to pneumococcal vaccine were not impaired in patients with SLE who were receiving azathioprine, cyclophosphamide or prednisolone.[74] The effectiveness of hepatitis B vaccination in recipients of organ transplants was reduced by immunosuppression with azathioprine or glucocorticosteroids.[75] In addition, in patients with inflammatory bowel disease, TBE vaccination was associated with lower IgG titers and reduced immune protection during azathioprine treatment than

during a period without cytostatic treatment.[76] No studies have been conducted on the effects of mitoxantrone on the response to immunization.

Implications for clinical practice

Given the possible negative effect of MS drugs on vaccine efficacy, patients should be checked for missing vaccinations before initiation of treatment with immunosuppressive agents or a new immunomodulator, such as fingolimod. Provided that the course of MS allows a delay in starting treatment with such agents, vaccination should be performed in advance.[77]

The timing of vaccination in relation to MS-specific treatments should be planned according to the DMD manufacturers' recommendations. For example, immunization should be delayed for at least 2 weeks following high-dose glucocorticosteroids. Immunization during mitoxantrone or cyclophosphamide treatment should be performed between drug cycles.

To evaluate the success of vaccination in patients treated with immunosuppressants, antibody testing should be performed 4 weeks after administration of the vaccine. If titers fail to increase, revaccination should be considered. With new DMDs such as fingolimod, antibody status against specific communicable diseases, such as VZV, needs to be monitored and appropriate measures taken to ensure adequate protection against the communicable disease.

Conclusions and future directions

Avoidance of infection in patients with MS generally reduces the risk of relapse and deterioration of health status, which improves quality of life and minimizes additional socioeconomic burden. Patients with MS should receive vaccination against tetanus and diphtheria; adequate protection by previous vaccination against or infection with influenza, pneumococci, pertussis and hepatitis B should be ensured. Whereas inactivated vaccines are generally considered safe for use in patients with MS, live attenuated vaccines may provoke MS relapses, as particularly shown for yellow fever, and can cause vaccine-associated infection in patients undergoing immunosuppressive therapy.

For a number of vaccines, adequate evidence is available to exclude these vaccines as a cause for the induction of MS. Some vaccines might, however, trigger relapses in MS, warranting further investigation. In contrast to vaccines against viral infections, the safety and efficacy of vaccines against bacterial diseases in patients with MS have been evaluated to a very limited extent. In future studies, special attention needs to be directed to vaccinations given during treatment with DMDs, to determine their safety and efficacy in this context.

Review criteria

The US National Library of Medicine's PubMed and the ScienceDirect databases were searched for articles published before or during September 2011. Search terms included "multiple sclerosis", "CNS inflammation", "vaccination", "immunization", "disease progression" and specific vaccines (for example "tetanus vaccine"). Abstracts of retrieved citations were reviewed and prioritized by relevant content. Full articles were obtained and references were checked for additional material when appropriate. Online material was searched to retrieve relevant guidelines and FDA or European Medicines Agency drug information.

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Author contributions

M. Loebermann, A. Winkelmann, H.-P. Hartung and U. K. Zettl researched data for the article. All authors contributed to discussion of the article content. M. Loebermann and A. Winkelmann made equal contributions to writing the article. All authors contributed to review and/or editing of the manuscript before submission.