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REVIEWS

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Practical tips on vaccination in multiple sclerosis patients

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Summary Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system of unclear aetiology which involves genetic and environmental factors, including infections. Infections in MS patients increase the risk of exacerbation of the disease. It has been shown that preventing infections reduces the risk of MS relapse and quality of life outcome. Over the past 20 years, the number of drugs available for disease modifying therapy (DMT) in MS patients has grown significantly. Some of the DMT may entail an increased risk of infections, including life-threatening ones such as measles... etc. These infections include measles, infections caused by human papilloma virus (HPV), varicella zoster virus (VZV), hepatitis B virus (HBV), pneumococci and, recently, serious acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Therefore, at the time of MS diagnosis, the patient should be interviewed and screened for prior vaccination and/or serological status prior to starting DMT so that any missing vaccinations can be performed. Most infections can be effectively and safely prevented. Vaccinations should be integral part of the treatment process. They not only prevent life-threatening diseases but also increase the safety of drugs used to change the course of the underlying disease. Some specific recommenadation regarding the use of vaccinations in MS patients treated with DMT are included in summary of product characteristic for particular drugs. Additionally, scientific boards publish guidelines on recommended vaccinations due to changing epidemiological situations with special emphasis on immunocompromised patients.
Key words: vaccination, multiple sclerosis, drugs, influenza, COVID-19.

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Background

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system of unclear aetiology which involves genetic and environmental factors, including infections. The disease is believed to be autoimmune in nature, with subsequent secondary neurodegeneration. The first symptoms of MS occur mainly in young adults. It is about 3 times more common in women than in men, and the peak incidence is observed in patients aged 20–40 years. However, MS might also occur in children (childhood form) and in the elderly. The dominant form of the disease is of a relapsing-remitting character and occurs in about 85% of patients (periodic exacerbations followed by periods of remission). The disease may also present as primary progressive MS or secondary progressive MS with overlapping relapses [1].

Infections in MS patients increase the risk of exacerbation of the disease, which then has a more severe course and causes a permanent neurological deficit more often than other types of exacerbation (not related to infection) [2, 3]. It has been shown that preventing infections reduces the risk of MS relapse and simultaneously improves patients' quality of life [4].

Over the past 20 years, the number of drugs available for disease modifying therapy (DMT) in MS patients has grown significantly. Considering the mechanisms of their action, some drugs may entail an increased risk of infections, including life-threatening infections. These infections include measles, infections caused by human papilloma virus (HPV), varicella zoster virus (VZV), hepatitis B virus (HBV), pneumococci and, recently, serious acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Therefore, at the time of MS diagnosis, the patient should be interviewed and screened for prior vaccination and/or serological status prior to starting DMT so that any missing vaccinations can be performed. Most infections can be effectively and safely prevented. It should be clearly stated that vaccinations in most MS cases are not only safe and effective but are also an indispensable part of the treatment process and increase the safety of the drugs that are used to change the course of the underlying disease. Thus, vaccinations are an integral part of the treatment process aimed at preventing infectious and drug related complications [5–7].

Vaccinations and drugs used in the MS treatment programme

MS patients in Poland can be treated under the B.29 treatment programme: treatment of patients with multiple sclerosis.

The drugs are administered [8]:

- subcutaneously or intramuscularly (interferon-beta and glatiramer acetate preparations), and recently subcutanously given ofatumumab,
- intravenously (natalizumab, alemtuzumab, ocrelizumab),
- orally (teriflunomide, dimethyl fumarate, fingolimod, siponimod, ozanimod, ponesimod, cladribine).

The principles of vaccination in patients taking preparations administered subcutaneously or intramuscularly (interferon-beta and glatiramer acetate preparations) do not differ from those applicable in the general population: both inactivated and live attenuated vaccines are effective and safe [9, 10].

However, administration of live attenuated vaccines is contraindicated in MS patients taking oral immunosuppressive

drugs, and inactivated vaccines may be less effective in this group of patients [9, 10].

All drugs used in MS therapy that are available in drug programmes and mitoxantrone, which is sometimes, though rarely, used in the treatment of secondary progressive MS, are presented in Table 1.

Table 1. Drugs administered to multiple sclerosis patients

Drug	Trade name of the preparations available in Poland and registered as innovative medicinal products (reference medicine)	Mechanism of action	Effects	Dosing regimen and route of administration
Interferon-beta (IFN-*β*)	IFN-*β*-1a: Rebif®, Avonex® IFN-*β*-1b: Betaferon® PegIFN-*β*: Plegridy®	Human beta interferon analogues	Inhibits the inflammatory reaction min. T-cell division, matrix metalloproteases, migration across the blood-brain barrier and production of pro-inflammatory cytokines. Induces Tregs, B lymphocytes B CD19 + CD24 + CD38 +	Rebif® 44 µg; 3 x a week **subcutaneous** Avonex® 30 µg a week **intramuscular** Betaferon® 250 µg every other day **subcutaneous** Plegridy® 125 µg every 2 weeks **subcutaneous**
Glatiramer acetate	Copaxon®	Mixture of acetate salts of synthetic polypeptides composed of glutamic acid, alanine, tyrosine and lysine	Binds to MHC histocompatibility antigens (possibly antigenic mimicry between MBP and glatiramer), increases levels of anti-inflammatory cytokines Il-10, Il-4, TGF*β* and increases the number of CD8 regulatory lymphocytes	20 mg 1 x a day or 40 mg 3 x a week **subcutaneous**
Natalizumab	Tysabri®	Monoclonal antibody against *α*4 integrin	Blocks the migration of lymphocytes through the blood-brain barrier	300 mg every 4 weeks **intravenous infusion** or 300 mg every 4 weeks **subcutaneous**
Fingolimod	Gilenya®	Modulator of sphingosine-1-phosphate receptors located on T and B lymphocytes (S1PR1, S1PR3, S1PR5)	Inhibits the release of lymphocytes from the lymph nodes; inhibits the migration of dendritic cells to lymphoid organs	0.5 mg 1 x a day **oral**
Siponimod	Mayzent®	Modulator of sphingosine-1-phosphate receptors located on T and B lymphocytes (S1PR1, S1PR5)	As above	Increase the dose gradually from 0.25 mg/day by 0.25 mg in 4 consecutive days to 1.75 mg on day 5, then 2 mg a day **oral** Attention! Perform CYP2C9 genotyping prior to the initiation of treatment; dose dependent on CYP2C9 genotype
Ozanimod	Zeposia®	Modulator of sphingosine-1-phosphate receptors located on T and B lymphocytes (S1PR1, S1PR5)	As above	Increase the dose gradually from 0.23 mg/day (days 1–4) to 0.46 mg/day (days 5–7) to target dose 0.92 mg/day **oral**
Ponesimod	Ponevory®	Modulator of sphingosine-1-phosphate receptors located on T and B lymphocytes (S1PR1)	As above	Increase the dose gradually from 2 mg/day (days 1–2), to 3 mg/day (days 3–4), to 4 mg/day (days 5–6), then increase the dose by 1 mg/day to 10 mg/day (days 12, 13 and 14) to the target dose of 20 mg/day from day 15 **oral**

Table 1. Drugs administered to multiple sclerosis patients

Drug	Trade name of the preparations available in Poland and registered as innovative medicinal products (reference medicine)	Mechanism of action	Effects	Dosing regimen and route of administration
Dimethyl fumarate	Tecfidera®	Transcriptional pathway activator of the nuclear factor erythroid 2-related factor 2	Increases the expression of nrf2-dependent antioxidant protection genes; inhibits the activation of immune system cells and the release of pro-inflammatory cytokines (including IL-2, IFN*γ* i IL-17)	240 mg 2 x a day **oral**
Teriflunomide	Aubagio®	Inhibitor of dihydroorotate dehydrogenase required for pyrimidine synthesis	Inhibits cell proliferation, including T lymphocytes	14 mg 1 x a day **oral**
Alemtuzumab	Lemtrada®	Monoclonal antibody against CD52 – a glycoprotein present on lymphoid cells primarily on mature T and B lymphocytes	Reduces the total number of T and B lymphocytes through antibody-mediated cytotoxicity and complement activation	12 mg/day over 5 consecutive days, after 12 months, increase the dose to 12 mg/day over 3 consecutive days **intravenous infusion**
Cladribine	Mavenclad®	Purine antagonist, a synthetic derivative of deoxyadenosine	Induces apoptosis of lymphocytes; it is cytotoxic in high doses; causes a permanent reduction in the number of T lymphocytes CD4+ and CD8+ and a temporary reduction in B lymphocytes	2-year treatment, 1 cycle per year, each cycle is 2 weeks of 4 or 5 days, the dose of the drug depends on body weight; there is no need for treatment in year 3 and 4 **oral**
Okrelizumab	Ocrevus®	Monoclonal antibody against CD20, a glycoprotein present on B lymphocytes, at various stages of maturation	Reduces the total number of B lymphocytes	starting dose: 300 mg every 2 weeks, then 600 mg every 6 months **intravenous infusion**
Ofatumumab	Kesimpta®	Monoclonal antibody against CD20, a glycoprotein present on B lymphocytes, at various stages of maturation	Reduces the total number of B lymphocytes	starting dose: 20 mg in week 0, 1 and 2, then 20 mg/month from week 4 **subcutaneous**
OTHER RARELY USED DRUGS (NOT IN THE DRUG PROGRAM)				
Mitoxantrone	Mitoxantron®	Anthracenedione derivative, binds to DNA, disrupting DNA transcription and repair	Inhibits the proliferation of T and B lymphocytes and macrophages; impairs the presentation of antigens, the secretion of IFN-*γ*, TNF-*α* and IL-2	12 mg/m^2 of the body every 3 months, the maximum total dose of 140 mg/m^2 of the body **intravenous infusion**

Recommended vaccinations:

- **influenza vaccination**; it has been shown that influenza increases the risk of MS relapse; MS patients with influenza and its complications more often require hospitalisation, which justifies the need for vaccination in this group of patients [11, 12]. Vaccination with an inactivated vaccine (split virion or subunit) is safe and can be performed regardless of the type of treatment [9, 10]. The inactivated influenza vaccine is safe, but the immune response after vaccination may be reduced (this applies to patients who take natalizumab, fingolimod, teriflunomide, ocrelizumab, cladribine, and mitoxantrone) [11–15]. Alemtuzumab has not been studied, but it is recommended to administer the vaccine at least 6 weeks before starting treatment due to the risk of an insufficient immune response [10]. It is additionally advisable to implement a cocoon vaccination strategy (i.e. influenza vaccination of persons from the immediate environment of patients in order to reduce the risk of virus transmission in the patient's environment);
- **vaccination against hepatitis B**; it has been shown that MS patients are at an increased risk of hepatitis B complications and hepatitis B treatment failure, which indicates the need for vaccination [10, 16]. The hepatitis B vaccine is safe and effective. It does not increase the risk of MS or other demyelinating diseases, and it does not increase the risk of an MS relapse [16–18];
- **vaccination against tetanus, diphtheria and pertussis**; adults should receive a booster dose every 10 years, and the vaccine is safe and effective in patients with MS [19, 20]. The tetanus vaccine has not been found to increase the risk of developing MS or exacerbating the course disease, but several studies suggest that it may reduce the risk of having another relapse [19–21]. It has been shown that the immune response after a tet-

anus vaccination was good (sufficient to create the immune protection) in patients treated with natalizumab, fingolimod and alemtuzumab [21–24].

Possible vaccinations:

- vaccinations recommended in tourist traffic, e.g. vaccination against hepatitis A (hepatitis A), poliomyelitis (an inactivated vaccine for intramuscular administration), typhoid (an inactivated vaccine). Vaccinations in tourist traffic should be planned at least 6–8 weeks before departure [9, 10];
- **vaccination against HPV infections**; three vaccines are currently registered: bivalent, tetravalent and nine-valent. The vaccine is safe and effective in patients with MS. It is recommended to have the vaccination before sexual initiation (both in girls and boys), although those vaccinated at a later age may also benefit from vaccination [25, 26]. Since 2021, the bivalent vaccine has been subject to a 50% refund, which may be important when choosing a vaccine if the financial aspect is of decisive importance to the patient;
- **vaccination against pneumococcal and meningococcal infections** [9, 10]; pneumococcal vaccinations are recommended for all adults over 50 years of age and for younger patients from high-risk groups (including immunocompromised patients and those with neurological diseases predisposing to aspiration). The vaccines are safe and should be administered to patients with respiratory disorders, e.g. advanced MS, who use a wheelchair or do not leave the bed. Since 2022 the 13-valent pneumococcal conjugate vaccine is subject to a 50% refund in patients aged > 65 years with impaired immunity;
- **rabies vaccination**; due to the fact that in the case of rabies the mortality rate reaches 100%, MS is not a contraindication to post-exposure rabies vaccination, regardless of the treatment used. It is possible to administer the vaccine as part of the pre-exposure procedure, and it has been shown that patients treated with teriflunomide have lower levels of post-vaccination antibodies compared to the general population [9, 27].

Possible vaccinations (patients treated with interferon-beta or glatiramer acetate preparations):

- vaccination against measles, mumps, rubella; to be administered in persons who have not been vaccinated before or who have not been ill [10]. Recovery from one of the above-mentioned diseases is not a contraindication to the administration of the three-component vaccine;
- varicella vaccination; to be performed in non-immune persons (previously unvaccinated or those who have no evidence of recovering from varicella). It is recommended to perform the vaccination before starting immunosuppressive treatment, especially treatment with fingolimod and alemtuzumab [7, 9, 10], cladribine in tablets, ocrelizumab and mitoxantrone [5, 6];
- vaccination against tuberculosis; after vaccination, no increased risk of MS relapse was found; however, a reduction in MRI lesion activity was observed in patients with relapsing-remitting MS after the BCG vaccination. in another study, it was found that this vaccination statistically significantly reduced MRI lesions in the period of 6 months before the start of the disease modifying therapy [28, 29].

Contraindicated vaccinations:

- yellow fever vaccination; in a study on seven patients, an increase in the risk of another MS relapse and intensification of lesions in magnetic resonance imaging was observed after the vaccination [30].

Contraindicated vaccinations (patients taking oral medications) [2, 3]:

- vaccination against measles, mumps, rubella;
- varicella vaccination;
- influenza vaccination (live attenuated vaccine for intranasal administration that is registered in Poland for use in persons under 18 years of age). A patient receiving immunosuppressive treatment should be separated from a person vaccinated with an attenuated vaccine [5].

Extensive updated recommendations for vaccinations in MS patients can be found on the website of the American Academy of Neurology (AAN) [7]. The recommendations were developed in cooperation with the panel of experts of the Multiple Sclerosis Council for Clinical Practice and are also published on the website of the National Multiple Sclerosis Society [31].

Vaccination against SARS-CoV-2 in MS patients

Recommendations for vaccination against SARS-CoV-2 in Poland are constantly updated. They are developed by a team of experts of the Polish Neurological Society and include recommendations on the use of the third booster of mRNA vaccines [32, 33]. According to these recommendations, patients with multiple sclerosis should adhere to the general rules of prevention of SARS-CoV-2 infection and the rules of vaccination against this virus in Poland, including those described in the summary of the vaccine characteristics. Recovery from COVID-19 is not a contraindication to vaccination. The decision regarding vaccination should be made in cooperation with the patient, taking into account the risk of exposure to SARS-CoV-2 infection, the type of therapy, the condition of the immune system, the patient's general health and comorbidities [32, 33].

Patients taking some immunosuppressive drugs should be informed of the risk of a decreased immune response to the vaccination. This includes:

- Sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, ponesimod, siponimod);
- Alemtuzumab;
- Anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab);
- In cases of some drugs such as ocrelizumab and alemtuzumab, the time point of administering the third booster dose of the vaccine is crucial. Specific information is given in the summary of each product characteristic.

Practical recommendations. Do not perform vaccinations in the active phase of the disease. During this time, additional immune stimulation should be avoided, and vaccinations should not be given within 4–6 weeks of the last MS attack and stabilisation of the patient's condition. If immunosuppressive treatment is applied, vaccinations should be scheduled for 2–6 weeks before the planned treatment or 2–3 months after the end of treatment; the time interval depends on the type of vaccine (live/inactivated) [7, 9, 10] and type of the drug used. Detailed recommendations for most drugs are included in particular summaries of product characteristics. A summary of comments on the use of individual vaccines is presented in Table 2. Due to the potential decrease in the immunological effectiveness of inactivated vaccines in patients on immunosuppressive treatment, it is recommended to carry out vaccinations in persons from the closest environment of patients (family, caregivers, medical staff) in order to reduce the risk of infection transmission. If persons from the immediate environment of immunosuppressed patients are given live attenuated vaccines, particular care should be taken to isolate the vaccinated persons from the patient or to introduce a sanitary regime in the patient's immediate environment. The rotavirus vaccines available in Poland contain live attenuated viruses that multiply in a child's gastrointestinal tract after the administration of the vaccine. Excretion of the vaccine virus has been observed in the

stool: in the case of the RotaTeq® vaccine, this applies to 9% of children after the first dose but is rare after subsequent doses; however, transmission of the infection to persons from the immediate environment of the patients has not been confirmed. Considering Rotarix®, the vaccine virus is excreted in the stool by approximately 25% of vaccinated patients, with the peak excretion around the seventh day after the first dose (after the second dose, this is less frequent). In isolated cases, transmission of the vaccine virus to persons from the immediate environment was observed, but these persons did not develop symptoms of rotavirus gastroenteritis. Due to the potential risk of virus transmission to persons from the immediate environment of a vaccinated child, it is recommended to follow the rules of personal hygiene (washing hands after changing diapers) [34]. The varicella vaccine also contains a live attenuated virus, but there is no risk of the transmission of the vaccine virus to persons with immunodeficiency. Abortive varicella (exanthema) occurs rarely after the vaccination, but if it does, the vaccinated person should be isolated from immunosuppressed patients until the lesions have dried [35].

Table 2. Comments and recommendations on vaccinations in multiple sclerosis patients [2, 3]

Vaccination	Comments and recommendations
Hepatitis B	inactivated vaccine safe, does not cause MS, does not cause MS relapse may be less effective in patients on immunosuppressive therapy
Hepatitis A	inactivated vaccine recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Diphtheria, tetanus, pertussis	inactivated vaccine safe, does not cause MS, does not cause MS relapse may be less effective in patients on immunosuppressive therapy
Measles, mumps, rubella	live attenuated vaccine contraindicated in patients on immunosuppressive therapy
Viracella	live attenuated vaccine contraindicated in patients on immunosuppressive therapy
Tuberculosis	live attenuated vaccine contraindicated in patients on immunosuppressive therapy
HPV	inactivated vaccine safe, does not cause MS, does not cause MS relapse may be less effective in patients on immunosuppressive therapy
Rabies	inactivated vaccine used for post-exposure procedures: necessary for use recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Typhoid	inactivated vaccine recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Japanese encephalitis	inactivated vaccine recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Yellow fever	mandatory or recommended in tourist traffic contraindicated in patients on immunosuppressive therapy the benefit-risk balance should be carefully assessed in patients for whom this vaccine is indicated
Cholera	inactivated vaccine recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Poliomyelitis	inactivated vaccine recommended in tourist traffic probably safe may be less effective in patients on immunosuppressive therapy
Pneumococcal infections	inactivated vaccine recommended for patients from the risk group probably safe may be less effective in patients on immunosuppressive therapy
Meningococcal infections	inactivated vaccine recommended for patients from the risk group probably safe may be less effective in patients on immunosuppressive therapy
Influenza	inactivated vaccine for intramuscular administration: recommended every season safe, does not cause MS, does not cause MS relapse may be less effective in patients on immunosuppressive therapy attenuated vaccine for intranasal administration contraindicated in patients with MS

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