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Review / Derleme

Vaccination in Individuals with Multiple Sclerosis – Part I

Multipl Skleroz Tanılı Bireylerde Aşılama – Bölüm I

Bilge Piri Çınar[1], Aslı Tuncer[2], Nuray Bilge[3], Sena Destan Bünül[4], Rabia Gökçen Gözübatık-Çelik[5], Eda Derle Çiftçi[6], Gencer Genç[7], Bedriye Karaman[8], Ahmet Kasım Kılıç[9], Alp Sarıteke[10], Meral Seferoğlu[11], Bedile İrem Tiftikçioğlu[12], Abdulkadir Tunç[13], Gülgün Uncu[14], İrfan Yavaş[15], Mehmet Fatih Yetkin[16], Hüsnü Efendi[4], Aksel Siva[17]

[1]Samsun University Faculty of Medicine, Department of Neurology, Samsun, Türkiye
[2]Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Türkiye
[3]Ataturk University Faculty of Medicine, Department of Neurology, Erzurum, Türkiye
[4]Kocaeli University Faculty of Medicine, Department of Neurology, Kocaeli, Türkiye
[5]University of Health Sciences Türkiye, Istanbul Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Neurology, Istanbul, Türkiye
[6]Baskent University Faculty of Medicine, Department of Neurology, Ankara, Türkiye
[7]University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Clinic of Neurology, Istanbul, Türkiye
[8]Ege University Faculty of Medicine, Department of Neurology, Izmir, Türkiye
[9]Kartal Dr. Lutfi Kirdar Training and Research Hospital, Clinic of Neurology, Istanbul, Türkiye
[10]University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital, Clinic of Neurology, Izmir, Türkiye
[11]Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Neurology, Bursa, Türkiye
[12]Bakircay University Training and Research Hospital, Clinic of Neurology, Izmir, Türkiye
[13]Sakarya University Training and Research Hospital, Clinic of Neurology, Sakarya, Türkiye
[14]Eskisehir City Hospital, Clinic of Neurology, Eskisehir, Türkiye
[15]Karabuk University Faculty of Medicine, Department of Neurology, Karabuk, Türkiye
[16]Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Türkiye
[17]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Neurology, Istanbul, Türkiye

Abstract

Multiple sclerosis (MS) is an autoimmune and demyelinating disease of the central nervous system. It is a chronic disease, and in the evaluation of all other health and vital processes, decisions should be made by considering the disease process and the drugs used by the patient. Since vaccination can be performed at every stage of life, from childhood to adulthood, immune system activity, except where it is characteristic of the vaccine, should be reviewed in patients with MS. In this review, the applications of different vaccines in individuals with MS are discussed in two separate sections.

Keywords: Multiple sclerosis, vaccination, safety

Address for Correspondence/Yazışma Adresi: Prof. Aslı Tuncer MD, Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Türkiye
Phone: +90 312 305 10 80 E-mail: maslituncer@gmail.com ORCID: orcid.org/0000-0001-9449-4483
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Öz

Multipl skleroz (MS) merkezi sinir sisteminin otoimmün ve demiyelinizan hastalığıdır. Kronik bir hastalık olup bireye ait tüm diğer sağlık ve yaşamsal süreçlerin değerlendirilmesinde hastalık süreci, hastanın kullandığı ilaçları göz önüne alarak karar vermek gereklidir. Aşılama, çocukluktan yetişkinliğe yaşamın her döneminde uygulanabildiği için MS tanılı bireylerde de her bir aşının özelliği dışında hastanın immün sistem etkinliği mutlaka gözden geçirilmelidir. Bu derlemede MS tanılı bireylerde farklı aşıların uygulamaları tartışılacak olup, farklı iki bölüm halinde yayınlanacaktır.

Anahtar Kelimeler: Multipl skleroz, aşılama, güvenlik

Introduction

Vaccination is crucial in preventing infectious diseases and limiting the problems that may arise from them. With the initiation of vaccination, the prevalence of infectious diseases, which are among the most important causes of mortality, has decreased rapidly, and some infectious diseases have been brought to the point of eradication. The efficacy and safety of vaccines depend on many factors, such as the age of the person vaccinated, their occupation, the status of their immune system, and the drugs they use. In individuals with autoimmune diseases, the status of the immune system and the drugs used to modulate or suppress the immune system are decisive in this regard. In this review, the principles of vaccination in individuals diagnosed as having multiple sclerosis (MS), an autoimmune demyelinating disease of the central nervous system, are discussed in the light of current scientific knowledge.

1. Measles–Mumps–Rubella Vaccination

The MMR vaccine, which is an attenuated live vaccine, is included in the routine vaccination program for children. Combined and monovalent forms are available. In children, the first dose is administered at 12–15 days, and it is recommended that the second dose be administered at 4–6 months. At least one dose of vaccine can be administered to children over 6 years of age and to young individuals and adults who have not been previously vaccinated with MMR or have not had the disease. For individuals with recent contact or exposure to measles, rubella, or mumps infection, two doses of vaccine, 28 days apart, are recommended. The MMR vaccine should not be administered to pregnant women, and pregnancy should not be planned for 1 month following vaccination. The MMR vaccine is safe and effective. Common side effects include fever, rash, and pain at the injection site, but serious side effects are rare (https://vk.ovg.ox.ac.uk/mmr-vaccine).

In Türkiye, according to the current vaccination calendar established by the Ministry of Health in 2020, the first MMR vaccine dose is administered to all children at the end of their 12th month and the second dose at the end of their 48th month. For adults, there is no need to be vaccinated when a person has a history of two doses of measles-containing vaccine, when an MMR vaccine has been administered or there is a record of having had measles, or when laboratory tests verify that the person is immune. In other cases, two doses of MMR vaccine should be administered 4 weeks apart to all adults, except during pregnancy. The rubella vaccine was only added to Türkiye's childhood national vaccination calendar in 2006. Therefore, since the measles vaccine administered by the Ministry of Health before 2006 was not combined with the rubella vaccine, those vaccinated with this vaccine were not protected against the rubella virus (https://vk.ovg.ox.ac.uk/mmr-vaccine).

1.1. Vaccination in Multiple Sclerosis

Routine vaccines, including MMR, can be administered to patients with MS who are not receiving immunosuppressive drugs and who have not had a recent attack. However, individuals with MS who receive immunosuppressive drugs or have recently had an attack should delay vaccination until they are in remission (often 4–6 weeks from the onset of the attack) (1,2). In patients with MS, the MMR vaccine is thought to have a similar safety profile to that of the healthy population.

Studies have concluded that vaccination against hepatitis B, influenza, tetanus, measles, or rubella does not increase a person's risk of developing MS or optic neuritis (3,4,5,6,7). The VACCIMUS study (5), which was published in the New England Journal of Medicine in 2001, revealed no increased risk of developing MS or attacks for vaccinated individuals compared with those who were unvaccinated. However, since live vaccines can cause active infection, vaccination can trigger attacks or cause pseudo attacks. Although there are rare reports of MS attacks occurring after live vaccines, a causal link between the MMR vaccine and MS or MS attacks has not been identified, and there is insufficient evidence that it increases the frequency of attacks or disability (8).

Concerns have arisen that vaccination may also trigger the onset of MS in susceptible individuals (9). However, a recent comprehensive review from the US Institute of Medicine did not find sufficient evidence to accept or reject a causal relationship between MS onset and vaccination against MMR (10). In addition, pooled analyses have demonstrated no evidence that vaccination against measles was associated with an increased risk of developing MS (11).

1.2. Multiple Sclerosis Treatment and Vaccination

The centers for disease control and prevention recommend that patients with MS or other autoimmune diseases have their routine vaccinations, including the MMR, unless there is a medical reason not to. The use of immunosuppressive or immunomodulatory therapies in MS raises two general concerns about vaccines. The first is immunogenicity, which may result in a limited decrease in efficacy when individuals are immunized during these treatments. The second is the possible safety issues related to vaccine administration. Live vaccines are contraindicated during a course of immunosuppressive therapy. Whenever possible, all vaccinations should be given prior to the initiation of immunosuppressive or immunomodulatory therapy. There is a risk that immunomodulatory and immunosuppressive drugs used in the treatment of MS may reduce the effectiveness of the MMR vaccine; thus, the effectiveness of the vaccine may need to be evaluated through a valid test such as antibody measurement (8).

Corticosteroids are widely used in MS and can reduce the immune response to vaccines, potentially reducing the efficacy of

the MMR vaccine. Delaying the MMR vaccine until corticosteroid therapy is completed may be an appropriate approach. In the case of treatment with high-dose steroids, the MMR vaccine should be administered 3 months after the last steroid dose (evidence level B2b) (12). There are no studies examining the direct effect of the MMR vaccine on the immune response in patients with MS receiving interferon beta (IFNβ) and glatiramer acetate, and there is no conclusive evidence that the MMR vaccine exacerbates MS activity in patients with MS receiving interferon therapy. Moreover, no study has examined the effect of the MMR vaccine on immune response under dimethyl fumarate, teriflunomide, or fingolimod treatments. However, MMR vaccination is not recommended because the efficacy may not be sufficient during these treatments.

The MMR vaccine is not recommended during natalizumab and ocrelizumab treatments (13). Patients who will receive treatment targeting B-cells should wait at least 4 weeks for the treatment after receiving the MMR vaccination. After the discontinuation of the treatment, the replacement of B-cells should be delayed before the MMR vaccination. The MMR vaccination is not recommended during alemtuzumab treatment, and the vaccine should be administered at least 6 weeks before starting alemtuzumab therapy. The MMR vaccine is not recommended during cladribine treatment, although recent data on cladribine demonstrate the potential for effective immunization between two treatment cycles and after the completion of treatment (1). Thus, the timing of the administration of this vaccine during all MS treatments is extremely important in terms of efficacy and side effects.

2. Tetanus Vaccine, Tetanus–Diphtheria Vaccine (Td), and Tetanus–Diphtheria–Acellular Pertussis (Tdap) Vaccine

The tetanus vaccine is toxoid. With age, antitoxin levels in the body decrease considerably, even becoming negative in some patients. This vaccine is included in the routine vaccination program during infancy and childhood in Türkiye. However, if the individual has never been vaccinated before, primary vaccination in adulthood consists of three doses. The first two doses are recommended 4 weeks apart, and the third dose is recommended 6 months after the second dose. A booster should be administered every 10 years after primary vaccination, and at least one of these boosters should be the Tdap vaccine (14). The vaccine is administered intramuscularly (IM) into the deltoid muscle, and the most common side effects after vaccination are pain, redness, and swelling at the injection site (14).

The diphtheria vaccine is also toxoid, whereas the pertussis vaccine is inactivated. Preparations with the adult Td form or Tdap combination are recommended when administered in adulthood. At least one of the booster doses for adults should be administered in a form containing Tdap (14). In individuals who have never been vaccinated, primary immunization in adulthood is the same as for vaccination against tetanus.

2.1. Vaccination in Multiple Sclerosis

Studies have found no evidence that tetanus, diphtheria, and pertussis vaccines cause the development of MS. In some studies, data also reveal that the tetanus and diphtheria vaccines reduce the risk of developing MS (7). Due to the effects of the treatments used in patients with MS on the immune system, the ideal period for vaccination is before starting the treatment (15).

2.2. Multiple Sclerosis Treatment and Vaccination

Vaccination for tetanus, diphtheria, and pertussis is the same in patients with MS as in the general population (15). However, the need for continuity of treatment may require vaccination under treatment. Therefore, the appropriate time for vaccination should be determined according to the type of treatment used (16). The drugs used may have different levels of negative effects on vaccine responses, depending on their mechanism of action. Although the immune response development after the toxoid tetanus vaccination when using fingolimod and ocrelizumab is lower than when using placebo, studies have revealed it to be sufficient (17,18). Similar rates of vaccine response are provided during dimethyl fumarate and IFNβ treatments (19). The effect of natalizumab treatment on vaccine response is similar to that of the control group (20).

3. Rabies Vaccine

Rabies is a vaccine-preventable, zoonotic, rapidly progressive neurodegenerative infection caused by *Rabies lyssavirus*. Every year, 59,000 people die from rabies globally, of which 40% are children under the age of 15 (21). Türkiye is an endemic region for rabies, with one or two rabies cases every year (22). Of the carriers of the virus to humans, 99% are dogs. Vaccine prophylaxis is crucial before exposure because it is 100% fatal when clinical symptoms occur after an incubation period, which can vary from weeks to months. The vaccination of dogs and oral dog vaccines developed for this purpose are also a key strategy for disease elimination (21).

Current rabies vaccines (RV) have been used for 40 years and are inactivated vaccines (23,24), purified from cell cultures or embryonated eggs. They do not carry the risk of infection, are safe, and rarely have serious side effects; those that occur are mostly allergic reactions. They can be categorized according to the material from which they originate, such as cell-culture vaccines, chicken embryo vaccines, and cell-purified vaccines, which include human diploid cell vaccines and duck embryo-purified vaccines. These vaccines can be intradermally (ID) or IM administered, with ID application being recommended; application to the gluteal region is not recommended. They are safe for pregnant and breastfeeding women (25).

In the normal population, RV is administered in two ways: as pre-exposure prophylaxis (PEP) and post-exposure prophylaxis (POP). For at-risk groups, PEP is recommended. This group includes laboratory staff working with the live rabies virus, staff professionally working with bats, veterinarians, those involved in nature-related activities who are at risk of encountering wild animals, forest rangers, animal keepers, and those traveling to endemic areas. PEP is ID administered with a total of four doses at two different sites on days 0 and 7 or as a single dose on the same days if IM administered. In those with immunodeficiency, a third vaccination can be administered between days 21 and 28. Individuals who are unable to receive a booster should be ID vaccinated with two doses on day 0 at two different sites or IM vaccinated through a single dose, completing the vaccination schedule as soon as possible. In terms of POP, there are three categories:

Category 1: Skin integrity is preserved, the animal has been touched, or the skin has been licked while the animal is feeding.

Category 2: A small bite or scrape on the exposed skin but no bleeding.

Category 3: Single or multiple transdermal bites, disruption of skin integrity, saliva or mucus contact in this area, bleeding or direct bat contact.

POP is also recommended in cases of unusual contact: breathing the air in caves where bats are numerous; being bitten by rabies-infected humans; butchering infected animal meat; healthcare workers coming into contact with the urine, saliva, mucus, and nerve tissue of an infected patient; or the transplantation of an infected organ. The vaccine is not required in category 1 contacts. In category 2, wound cleaning and vaccination is required, and POP is administered on days 0, 3, and 7, either performed ID as a double dose at two sites or IM as a single dose at one site. In IM administration, a fourth booster vaccine is required between days 14 and 28. Alternatively, the IM vaccine can be administered three times at two sites on day 0 and at a single site on days 7 and 21. In category 3, the vaccination days and numbers are the same as for category 2, but immunoglobulin (Ig) must be administered in addition to the vaccine. If the contact person has been vaccinated before, the ID vaccine is administered as a single dose instead of a double dose and only on days 0 and 3. In IM administration, a single dose of vaccine is administered on days 0 and 3 instead of four boosters. Post-RV antibody testing is not recommended. In immunocompromised patients, all doses should be administered and Ig added. After 2–4 weeks, the antibody level should be checked and the immune response evaluated (25). Türkiye's Rabies Prophylaxis Guide, published in 2019, recommends this scheme in general.

3.1. Vaccination in Multiple Sclerosis

In MS, RV is found to be "probably safe," and its use is recommended for POP (26). Since RV is an inactivated vaccine, it can also be administered to patients with immunodeficiency (27). Since cell-based RV is not associated with relapse or with increased disease activity on imaging in patients with MS, PEP can be considered, especially for those in the at-risk group, because there is no treatment for rabies and it is 100% fatal after clinical signs appear (28).

Data are insufficient because rabies is a rare disease. Neurological complications after RV are mostly in the form of case reports. For example; a patient who developed encephalomyelitis after RV was reported in 2004 by Kulkarni et al. (29). Britton et al. (30) reported a case of primary progressive MS diagnosed in year 4 after RV in 1978; an old-style brain tissue-containing vaccine had been administered to this patient when he was 24 years old. In 2015, two patients with post-RV acute disseminated encephalomyelitis were reported, one from India and the other, an 8-year-old child, from France (31,32).

Few studies have investigated the risk of developing MS after RV. In these studies, no correlation was found between RV and the development of MS (11). In a retrospective study by Huttner et al. (28), published in 2021, on the triggering of MS attacks after RV, no increase in the risk of relapse after RV was identified. More frequent relapses were observed in the pre-vaccine period, and a sharp decrease was observed in the relapse rate in the post-vaccine period (28).

3.2. Multiple Sclerosis Treatment and Vaccination

In the only study investigating the effects of drugs used in the treatment of MS on the RV response, antibody levels in the group using teriflunomide were found to be at a protective level even though they were lower than those of the untreated group (33). As a result, POP is recommended because the benefit of RV outweighs the risk and PEP is recommended for those at high risk (34).

4. Pneumococcal Vaccine

Streptococcus pneumoniae is the leading bacterial cause of pneumonia (35). Other diseases caused by *S. pneumoniae* include meningitis, bacteremia, septic arthritis, osteomyelitis, acute purulent sinusitis, mastoiditis, and otitis media. These pneumococcal infections are important causes of morbidity and mortality (36). The pneumococcal vaccine is indicated for adults with risk factors for pneumococcal disease or who will have serious adverse outcomes when disease occurs. Pneumococcal vaccination is a routine part of infant and childhood immunization programs worldwide. The purpose of vaccination in adults is to prevent invasive pneumococcal disease (e.g., bacteremic pneumonia, meningitis) and non-bacteremic pneumonia. The microorganism's polysaccharide capsule determines the serotype and the virulence factor and is the target of the vaccine. Two types of pneumococcal vaccines are available for clinical use in Türkiye, pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV). The active ingredients of both vaccines are capsular polysaccharides from the pneumococcal serotypes that commonly cause invasive disease.

Table 1. Differences between polysaccharide vaccine and conjugated vaccine

	Pneumococcal polysaccharide vaccine PPSV23 (Pneumo 23/Pneumovax 23)	**Pneumococcal conjugated vaccine PCV13 (Prevnar 13)**
Content	Polysaccharide	Polysaccharide + diphtheria protein
Immune response	T-lymphocyte-independent, immune memory is not formed	T-lymphocyte-dependent immune memory is formed
Antibody level	Low functional antibody level	High functional antibody level
Short- or long-term immune response	Short term	Long term
Nasopharyngeal carriage (long-term reduction)	No	Yes
Effect of repeated doses	Decreased activity against some serotypes	Single dose in adults ≥18 years, protective efficacy

Pneumococcal polysaccharide vaccine: Consists of partially purified pneumococcal capsular polysaccharides. The only available formulation contains 23 pneumococcal polysaccharides (PPSV23; Pneumovax or Pnu-Imune) from the 23 serotypes that were the most common cause of pneumococcal disease in adults in the 1980s. The 23 different serotypes in PPSV23 constitute more than 90% of the serotypes responsible for invasive pneumococcal infections, and PPSV23 only stimulates B-lymphocytes. The antibodies formed strengthen and accelerate neutrophil functions without forming immune memory (Table 1). The effectiveness of the vaccine is between 50% and 85%. Antibody response is low for patients under 2 years of age when administered alone. For improved antibody response, it should be administered following a conjugate vaccine (14).

Pneumococcal conjugated vaccine: Consists of pneumococcal capsular polysaccharides covalently bound (conjugated) to a protein. Different carrier proteins have been used for conjugation, the most common being CRM197, which is a non-toxic variant of the diphtheria toxin. Among the available PCV formulations are 10-valent PCV (PCV10; Synflorix), 13-valent PCV (PCV13; Prevnar 13), 15-valent PCV (PCV15; Vaxneuvance), and 20-valent PCV (PCV20; Prevnar 20), which are named according to the numbers of pneumococcal capsule types in the vaccine. Another formulation, 7-valent PCV (PCV7; Prevnar 7), is an older formulation that is no longer manufactured. The form used in Türkiye is PCV13, which contains 13 serotypes. It is associated with a better antibody response by stimulating T and B-lymphocytes, and it induces the response of memory cells (Table 1). Immunologically, the quality and affinity of the antibodies formed after PCV is much higher than those of the polysaccharide vaccine. This vaccine provides an IgG-type antibody response and immune memory, and it is immunogenic for those under 2 years of age.

Unlike PPSV, PCV stimulates mucosal immunity and thus prevents nasal colonization by *S. pneumoniae*. At the population level, mucosal immunity has two effects: indirect (herd) immunity and the emergence of new strains. The widespread use of PCV in infants and children reduces pneumococcal transmission, thus providing protection to unvaccinated individuals (including adults). Therefore, the serotypes found in PCV7 have almost disappeared in pediatric and adult populations. However, as these serotypes disappear, new pneumococcal serotypes, called "spare strains," emerge (14).

Both types of vaccines are IM administered at a dose of 0.5 ml. It is recommended that both the conjugate vaccine and polysaccharide vaccine be administered in adults. The polysaccharide vaccine can be repeated up to three times at 5-year intervals, and the third booster should be administered at ≥65 years. The conjugate vaccine is administered as a single dose (except for patients undergoing bone marrow transplant) in the adult population. In severe immunosuppressive conditions, cerebrospinal fluid (CSF) leakage, cochlear implant, and in cases where rapid titration of antibodies is desired, such as asplenia, there should be a period of 8 weeks between the conjugate vaccine and the polysaccharide vaccine. For adults who are not at risk, there should be at least 1 year between the two pneumococcal vaccines (preferably PCV13 first, then PPV23) (14).

Conditions for which pneumococcal vaccine is indicated are as follows:

At-risk disease groups

1. Chronic lung disease
2. Chronic cardiovascular disease
3. Diabetes mellitus
4. Chronic liver disease
5. People living in nursing homes

High-risk disease groups

1. Functional or anatomical asplenia
2. Immunosuppressive diseases
3. Cochlear implants
4. CSF leaks
5. HIV infection

Individuals aged ≥65 years should be vaccinated against pneumococcus. In these individuals, the conjugate vaccine (PCV13) should be administered first, followed by the polysaccharide vaccine (PPSV23) 1 year later. Those aged 19–64 years who are in the at-risk group and those aged ≥65 years with immunodeficiency, asplenia, CSF leak, or cochlear implant should undergo PPSV23 eight weeks later if PCV13 is performed first, and if PPSV23 is performed first, PCV13 should be performed at least 1 year later. In hematopoietic stem-cell recipients, regardless of age and vaccination status, three doses of PCV13 are administered at 2-month intervals, starting 6 months after transplantation (14).

After vaccination, pain, swelling, and redness may develop at the injection site. Fever usually occurs immediately after vaccination and disappears within 24 hours. Headache, fatigue, chills, decreased appetite, myalgia and joint pain, skin rash, urticaria, and Arthus-type (local, allergic) reactions at the injection site are very rare (14).

4.1. Vaccination in Multiple Sclerosis

The pneumococcal vaccine is recommended for individuals with MS at high risk of pulmonary infection, including patients who use wheelchairs or are bedridden. There is no causal relationship between pneumococcal vaccine and MS or MS attacks.

4.2. Multiple Sclerosis Treatment and Vaccination

IFNβ-1a and IFNβ-1b are cytokines with immunomodulatory effects. Various studies have compared patients with MS vaccinated with inactivated seasonal influenza and H1N1 vaccines with a healthy group and patients with MS not using drugs, reporting that vaccine responses were not adversely affected by IFNβ treatment (37,38,39,40,41). In a study examining pneumococcal vaccine responses, patients with relapsing remitting MS (RRMS) receiving dimethyl fumarate and IFNβ were compared (42). The Td toxoid vaccine, PPSV23, and meningococcal conjugate vaccine (MCV4) were used to examine different types of immune responses. The study revealed that post- and pre-vaccination immune responses to other vaccines and pneumococcal vaccines were similar in the dimethyl fumarate and IFNβ groups. Consequently, interferons do not appear to attenuate humoral or cellular responses to vaccines (37,38,39,40,41,42).

Glatiramer acetate consists of peptides that resemble the myelin basic protein and have immunomodulatory effects. Studies have shown that patients receiving glatiramer acetate have decreased antibody responses to an inactivated influenza vaccine compared with patients treated with IFNβ and healthy controls. Evidence to date indicates that live and inactivated vaccines are

safe for patients receiving glatiramer acetate therapy, but their immune responses may be inadequate (41,42,43,44).

Teriflunomide inhibits pyrimidine synthesis as well as the proliferation of rapidly dividing cells such as activated T cells. There has been no study of pneumococcal vaccine in patients with MS using teriflunomide, but in reported studies, the effect of teriflunomide on responses to multiple vaccine types has been determined to be sufficient; however, the effect is slightly lower than in placebo, and teriflunomide does not seem to have a clinically significant effect on vaccine responses (45,46).

Dimethyl fumarate is a prodrug metabolized to monomethyl fumarate, which has immunomodulatory effects via the Nrf2 pathway. The vaccine response to the pneumococcal, Td, and meningococcal vaccines in patients with MS treated with dimethyl fumarate is similar to that of patients with MS treated with IFNβ and has been demonstrated to achieve adequate seroprotection. Response rates have been observed to vary between the two groups, with 53% for meningococcal serotype and 95% for pneumococcal serotype (42). Overall, immune responses to vaccination appear to be preserved in patients treated with dimethyl fumarate (47). Fingolimod is a non-selective sphingosine 1 phosphate (S1P) receptor modulator that prevents lymphocyte egress from lymphoid tissues. Studies have revealed that the fingolimod group has significantly lower response rates to various vaccines (seasonal influenza, tetanus toxoid booster) and decreased protection at all time points after vaccination (17,43,48). The effect of another S1P blocker, siponimod, on inactivated seasonal influenza vaccine and PPSV23 vaccine responses was investigated, and similar responses were observed for influenza A strains among groups, as well as a lower seroprotective response rate for multiple influenza strains in the siponimod groups; however, higher response rates to PPSV23 were reported in all groups (49). In conclusion, evidence shows that fingolimod reduces the humoral immune responses induced by vaccination (17,43,48).

Cladribine is a synthetic analog of deoxyadenosine that participates in the DNA structure, leading to apoptosis and the depletion of B and T-cells (50,51,52). No studies other than those on the SARS-CoV-2 vaccination have been conducted to examine vaccination responses during oral cladribine therapy, but patients treated with cladribine can elicit an intact cellular response to SARSCoV-2 mRNA vaccines (50,51,52). Inactivated vaccines appear to be safe during cladribine therapy, although evidence is scarce. Natalizumab is a humanized monoclonal antibody that binds to α4β1 integrin on lymphocytes and blocks their interaction with the cell adhesion molecules necessary for lymphocytes to cross the blood–brain barrier. The effects on responses to vaccines in patients receiving natalizumab have been investigated in various studies, but there are no studies on pneumococcal vaccine in patients with MS.

Alemtuzumab is an anti-CD52 monoclonal antibody that depletes CD52+ T and B-cells. In a current prospective case-control study, patients who received alemtuzumab had a lower response rate to vaccination with multiple vaccine types, including PPSV23, within 6 months of vaccination, although vaccine responses were maintained. Although a weak immune response was observed when the vaccine was administered 2 months after the start of alemtuzumab treatment, an adequate immune response developed 6 months after treatment. This suggests that vaccination may not be effective in the very early period after alemtuzumab administration (53). In conclusion, although vaccine responses appear to persist after treatment with alemtuzumab, a 6-month interval between the previous course of therapy and vaccination is recommended to ensure an adequate immune response. Ocrelizumab is an anti-CD20 humanized monoclonal antibody that depletes CD20+ B-cells. Immune responses to vaccination were investigated 12 weeks after the start of treatment in patients with MS receiving ocrelizumab, with mean IgG levels and the proportion of patients with positive responses reported to be lower 4 and 8 weeks after vaccination with tetanus toxoid, PPSV23, and booster PCV13 compared with control participants. The PCV13 booster did not significantly increase the response to the 12 serotypes common to the PPSV23 vaccine (18). In addition, immune response when using ocrelizumab has been reported as effective until week 12, but the effectiveness of the vaccine begins to decrease in the following weeks. Similarly, the immune response of these patients has been observed to be lower than that of patients using IFNβ or not receiving treatment (12,15,54).

Although specific studies have not been conducted to determine the appropriate timing of vaccination in patients receiving ocrelizumab, inactivated vaccines should be administered >4–6 weeks before ocrelizumab, and 1 month before the next administration if the individual is under treatment, to provide sufficient time for the immune response to develop (16,55).

5. Hepatitis B Vaccine

Hepatitis B, which is caused by a small, circular, enveloped, double-stranded DNA virus belonging to the Hepadnaviridae family, can cause both acute and chronic liver disease at a high rate and is transmitted through blood and other body fluids venereally or from mother to child during birth. It is a viral infection and is recognized as the leading cause of hepatocellular carcinoma worldwide. In Türkiye, viral hepatitis causes more than half (50–70%) the cases of chronic liver disease, cirrhosis, and hepatocellular carcinoma (56). The vaccine against hepatitis B virus is effective in preventing infection and its secondary complications.

Hepatitis B vaccine is produced using a method called recombinant DNA technology, which eliminates the risk of viral DNA contamination in a protein synthesized *in vitro* by inserting the hepatitis B virus surface protein (HBsAg; HBs-antigen) gene into yeast cells. In addition to the surface antigen of the virus, hepatitis B vaccine contains low amounts of aluminum (enhancing and prolonging the immune response), yeast protein, formaldehyde, and acidity-regulating compounds as adjuvants; it does not contain live viruses or viral DNA. Hepatitis B vaccine is commercially produced either alone (monovalent), together with hepatitis A vaccine (bivalent), or in combination with six vaccines (hexavalent). The protective response of the vaccine depends on the presence of IgG antibodies against the HBs-antigen in the serum after completion of the vaccine scheme. This protective antibody response may decrease in conditions such as advanced age, obesity, smoking, and the presence of chronic disease (57).

The vaccination (primary immunization) program before exposure to the virus with a monovalent vaccine is applied in three doses (months 0, 1, and 6). In patients with a continuing risk of exposure or decreasing levels of hepatitis B antibodies, booster doses can be administered after years 1 and 5. When a rapid effect is desired in adults over the age of 18, four doses of hepatitis B vaccine can be administered at days 0, 7, and 21 and year 1 (58). If

the vaccination schedule is interrupted, it is not restarted from the beginning. If the second dose is delayed, it should be administered as soon as possible, and the third dose should be administered, at the earliest, 1 month after the second dose. If the third dose is delayed, it should be administered as soon as possible (59). Hepatitis B vaccine is effective against hepatitis B infection in the early period following contact with the virus. Vaccination is effective in preventing infection when it is performed in the first few weeks of exposure to the virus (60), preferably within the first 24 hours. Subsequently, booster doses are administered at months 1 and 2.

Hepatitis B vaccination in adults is recommended for individuals at risk. These include "healthcare workers, individuals at high risk of occupational exposure, those with chronic liver disease other than hepatitis B, those with chronic kidney failure, diabetes mellitus, hemodialysis patients, HIV-positive or other immunocompromised patients, solid organ and bone marrow transplant candidates and recipients of blood products, drug addicts, people with multiple sexual partners, gay/bisexual men, convicts in prisons and correctional facilities, people in nursing homes, orphanages, and immigrants" (56,61).

The recombinant hepatitis B vaccine is generally recognized as one of the safest vaccines. The hepatitis B vaccine is safe for all age groups, immunocompromised patients, and pregnant women, except for individuals with a history of severe allergic reaction to one of the ingredients in the vaccine. Mild side effects have been reported, including pain at the injection site, which resolves within the first 24 hours, myalgia, and transient fever. The risk of serious side effects (anaphylaxis) has been reported at a rate of 1/1.1 million (27).

5.1. Vaccination in Multiple Sclerosis

The Global Advisory Committee on Vaccine Safety reported no significant causal relationship between the hepatitis B vaccine and neurological diseases (e.g., Guillain–Barré syndrome, MS), diabetes mellitus, chronic fatigue syndrome, autoimmune diseases, demyelinating diseases, asthma, or sudden infant death (62). Studies have established no significant relationship between hepatitis B vaccine and the development of MS or the triggering of an MS attack (3,4,5,63). Consequently, the American Academy of Neurology declared in its 2019 practice guide that there was insufficient data to support or refute the relationship between the development of MS and a history of hepatitis B vaccination (6).

5.2. Multiple Sclerosis Treatment and Vaccination

The US Federal Drug Administration (FDA) and European Medicines Agency stipulate that hepatitis B screening should be performed before starting cladribine, ofatumumab, ocrelizumab, or cyclophosphamide treatments in MS. In addition, hepatitis B screening should be performed before starting all immunosuppressive or immunomodulatory treatments, except for treatments with glucocorticoids, glatiramer acetate, and IFNβ, and the hepatitis B vaccine should be administered before starting fingolimod, ocrelizumab, ofatumumab, ozanimod, ponesimod, or rituximab treatments (16).

Disease-modifying treatments (especially those targeting B-cells) with high-dose glucocorticoids can cause hepatitis B infection or reactivation of the virus (64,65). Prophylaxis is recommended for patients that are HBsAg positive and those that are HBsAg negative and anti-Hbc positive, even if hepatitis B DNA is negative (66). Although the risk of reactivation is lower in patients that are anti-HBs positive, it remains present (65). When hepatitis B infection or reactivation develops in patients, immunosuppressive treatment should be interrupted, and the necessary treatment and follow-up program should be arranged by consulting an infectious diseases or related specialist clinic. Therefore, before starting disease-modifying treatments in patients with MS, their vaccination status should be questioned and serological screening tests for hepatitis B (HBs-Ag, anti-HBc IgM, anti-HBc IgG, anti-HBs IgG) should be checked, and disease-modifying treatments should not be initiated during this period. If hepatitis B vaccine is to be administered, it should be planned at least 2 weeks (ideally 4–6 weeks) before starting the treatment because it is not a live virus vaccine (6).

Studies have reported that IFNβ, azathioprine, and rituximab treatments do not reduce the existing anti-HBs antibody titer in serum (16). However, the antibody response to vaccines administered during or just before treatments that decrease the number and functions of B-lymphocyte may be low. In patients without an adequate antibody response, the three-dose vaccination scheme can be repeated or a double dose can be applied in immunocompromised patients (67,68).

6. Hepatitis A Vaccine (HAV)

HAV is a non-enveloped RNA virus that causes infection in humans. It is the most common cause of acute viral hepatitis in the world (69). Hepatitis A infection has a self-limiting acute course and is generally transmitted through a fecal–oral route, person-to-person contact, or contaminated food and drink. Since HAV has an acid-resistant structure, it reaches the liver by passing through the stomach and replicates in hepatocytes, creating viremia. The virus concentration in serum is lower than in feces. The virus is excreted in feces, which is the primary source of infection (70,71). Since rapid IgG-type immunity develops against the virus, it is not considered to become chronic and results in permanent immunity for life. Hepatitis A is asymptomatic in 90% of children and 25–50% of adults. Cholestatic hepatitis, hepatitis with relapses, autoimmune hepatitis, and fulminant hepatic failure are considered the most serious complications during the disease process. One of the main causes of more than 100,000 deaths worldwide is fulminant hepatitis A infection, which can be prevented by vaccines (69). Those with concomitant liver disease and individuals over the age of 50 are at risk. In middle endemic regions such as Türkiye, HAV exposure occurs at older ages. Immunization becomes even more important in young adults, as this may cause a relative increase in the risk of HAV-related complications.

In Türkiye, the first hepatitis A vaccination scheme started in 2012 as two doses at months 18 and 24 (14). There are three different types of vaccines: inactivated, attenuated, and combined. A live attenuated HAV vaccine is only available in some countries (e.g., The Philippines, Bangladesh, Nepal, Uzbekistan, and Chile). The live attenuated vaccine is well tolerated and has high immunity (70); however, these vaccines are not preferred because of the high efficacy of inactivated vaccines. All children and young people between the ages of 2 and 18 who have not been vaccinated before should be vaccinated against hepatitis A. Vaccination is recommended in individuals with chronic liver

disease (hepatitis B and hepatitis C), those who use coagulation factor concentrate because of a coagulation factor disorder, HIV-infected individuals, homosexual and bisexual men, drug addicts, staff working with HAV in research laboratories, and those traveling from low endemic areas to medium or high endemic areas (14). In immunocompromised individuals over 40 years of age, two doses of vaccine are recommended, and if time is limited, Ig administration together with the first dose of vaccine is recommended (72).

The vaccine is administered in two doses, at 0 and 6 months. In patients who miss the second dose, vaccination can be administered up to month 18. Combined vaccine administrations should be completed as three doses at months 0, 1, and 6. Although a single dose provides adequate protection, since the vaccine provides high efficacy in 10–12 days, a second dose is recommended to provide long-term immunization (14). Post-vaccine serological testing is not considered necessary due to the high response to the vaccine in adults and children. With the completion of the vaccination program, lifelong protection is accepted without requiring a booster. In case of a second dose delay during immunization, restarting the vaccination scheme is considered unnecessary; the scheme should continue with the same vaccine used at the start. The pregnancy risk category of the HAV vaccine is C. Its transition to breast milk is unknown (70), but inactivated vaccines are not considered to affect the breastfeeding safety of mother or infant. Injection site reactions, such as local pain, tenderness, and redness at the injection site, are the most common post-vaccine adverse effects. Fever, headache, rash, weakness, and gastrointestinal symptoms are less commonly encountered, and Guillain–Barré syndrome, elevated liver enzymes, and immune thrombocytopenia are very rarely encountered. The combined hepatitis A and B vaccine was approved by the FDA in 2001, and studies have reported no difference in antibody response in the combined vaccine compared with the single vaccine. The combined vaccine has both child and adult forms, and it is IM administered at months 0–1 and 6 as three doses in total (14).

6.1. Vaccination in Multiple Sclerosis

There is insufficient evidence to indicate that hepatitis A vaccine has any role in the risk of MS development or MS attacks. There are no guidelines recommending routine screening and vaccination for individuals with MS. It is generally accepted that two doses of inactivated hepatitis A vaccine should be administered to individuals who are seronegative as a result of screening, especially in patients over 40 years of age receiving immunosuppressive therapy (73,74).

7. Bacille Calmette–Guérin Vaccine (BCG)

In the 1920s, Calmette and Guérin produced a vaccine from bovine-type live tuberculosis bacilli (TB) with reduced virulence, and the vaccine was named BCG due to the initials of the bacillus and its discoverers (75). Although vaccination techniques and dosage application vary, intradermal application is the most commonly used and effective technique (76). Undiluted, it maintains its effectiveness for 1 month at room temperature and 1–2 years at +2°C to +8°C in the refrigerator. It is highly resistant to light and heat and should be used within 6 hours of reconstitution (77). The BCG vaccine should not be administered to patients who are immunocompromised or receiving immunosuppressive therapy, patients with malignancies, or patients receiving antineoplastic therapy. It can be safely administered with other routine childhood vaccines (76).

The BCG vaccine is recommended by the World Health Organization in countries or settings with a high TB incidence or high leprosy burden. Existing live attenuated vaccines are safe and effective in preventing leprosy as well as particularly severe forms of TB such as childhood TB meningitis and miliary TB (76). The BCG vaccine is administered by the Turkish Ministry of Health to all infants who are 2 months old for ease of administration and for stronger immunization. It is not administered to children who have been vaccinated with BCG, whether they have a scar or not. In children aged 3 months and older who have not had the BCG, a tuberculin skin test (TST) is performed up to 6 years of age. If the result is 0–5 mm, the vaccine is administered; if the TST result is 6–9 mm, the vaccine is not administered (77).

7.1. Vaccination in Multiple Sclerosis

In general, studies have not identified a significant relationship between the BCG vaccine and the risk of developing MS (11). In the experimental autoimmune encephalomyelitis model, BCG administration has had positive effects on experimental encephalomyelitis by suppressing encephalitogenic Th17 cells in the central nervous system (78). In a pilot study conducted in 1999, the BCG vaccine reduced magnetic resonance imaging (MRI) activity in patients with relapse and patients with RRMS (79). In a double-blind placebo-controlled study, monthly MRI scans were performed for 6 months in individuals with clinically isolated syndrome who received the BCG vaccine or placebo. In addition, the risk of conversion to clinically definite MS was found to be lower in the BCG group at the end of a 60-month follow-up (80). In a study investigating the relationship between TST and the risk of developing MS, increased TST reactivity was associated with a lower risk of developing MS (81).

In conclusion, further studies are needed to confirm the positive effects of the BCG vaccine on MS pathophysiology. However, in the light of current information, the BCG vaccine does not increase the risk of developing MS, does not trigger attacks in patients with MS, and its use in patients with MS seems generally safe.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.P.Ç., A.T., Al.S., H.E., Design: B.P.Ç., A.T., Data Collection or Processing: All authors, Analysis or Interpretation: B.P.Ç., A.T., Ak.S., H.E., Literature Search: All authors, Writing: B.P.Ç., A.T.

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