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Vaccination and Multiple Sclerosis – Current Situation

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Active immunization of patients with autoimmune diseases is a current challenge. Vaccination of patients with multiple sclerosis (MS) has been shown not to be associated with increased risk of exacerbation. A personalized approach to immunization of this group of patients is required, taking account of ongoing therapy and the nature of the course of illness. MS is not an absolute contraindication for vaccination against the new coronavirus infection. Vaccination can be with any of the currently authorized immunoformulations.

Keywords: multiple sclerosis, autoimmune diseases, vaccination, COVID-19.

1. Vaccination and Autoimmune Diseases. Studies of vaccination in patients with chronic diseases are currently being pursued actively. Particular attention is paid to people suffering from a variety of autoimmune diseases (AAD), who not infrequently receive immunosuppressive therapy, making them particularly susceptible to infectious diseases. Despite the low proportion of AAD in the overall structure of morbidity, they have significant influences on population health indicators such as mortality, disability, longevity, disability-adjusted life years (DALY), and quality-adjusted life years (QALY) [1–3]. The total number of patients has increased in recent decades [4, 5]. Currently some 3–5% of people suffer from various AAD. The commonest are autoimmune thyroiditis and type 1 diabetes mellitus (DM) [5]. Furthermore, disease can occur in people of any age, though there are certain patterns for individual nosologies. For example, type 1 DM is characterized by onset at age 6–13 years, multiple sclerosis (MS) at age 20–40 years, and Graves' disease at age 50–60 years. Women have a higher risk of developing AAD. The exclusion is Crohn's disease, which in the structure of disease is more common in men in some countries [4, 5]. In addition, the incidences of different nosologies have geographical characteristics. For example, MS is found significantly more frequently in areas with a moderate climate (>200 cases per 100,000) than in tropical countries (<5 cases per 100,000). Type 1 DM is more common in the USA (10–20 cases per 100,000) but is diagnosed extremely rarely in China (<1 case per 100,000) [5].

The risk of developing AAD is directly linked with genetic predisposition [6]. Nonetheless, disease onset always requires trigger factors, the most common of which are infections. Various microbial agents are able to stimulate immunological cross-reactions with intrinsic human antigens [7]. These may be both antigen-specific and nonspecific interactions. In addition, both mechanisms can develop simultaneously. Some of the best studied variants are molecular mimicry, where antigenic determinants of various microorganisms may be similar to host body antigens. Molecular mimicry in the structure of lipopolysaccharides not infrequently leads to the development of various neuropathies. For example, about 1/3 of cases of Guillain–Barré syndrome show an association with infection with *Campylobacter jejuni* [8]. These bacteria contain a lipopolysaccharide with a

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structure similar to that of gangliosides in peripheral nerve fibers. In addition, there are more complex mechanisms of molecular mimicry involving T lymphocytes [8].

The nonspecific mechanisms of development of AAD include the ability of infectious agents to induce hyperstimulation of the immune response [7]. This can lead to both a sharp release of cells with autoimmune activity (particularly T lymphocytes), which in normal conditions are culled by natural selection, and hyperstimulation of the innate immune response with extreme activation of antigen-presenting cells. Mouse experiments have confirmed the development of DM as a result of infection with Coxsackie B4 virus [8].

On the background of rapid rates of development of mass vaccination, questions of the advisability of vaccination in patients with AAD are extremely relevant, as are those related to the safety of inoculations [9]. As active immunization is in essence a significant immunostimulator and the use of adjuvants promotes amplification of the immune response, there is always caution in relation to the potential risk of inducing AAD when new vaccines are under development. Because of the low incidences of the nosologies listed above, the probability of their development often cannot be evaluated adequately at the stage of clinical investigations. For this reason, postmarketing monitoring is of great importance [10].

2. Safety of Vaccination in AAD. The safety of mass vaccination is a priority issue throughout the world. Monitoring of diseases in the postvaccination period includes a vaccine safety tracking system in conditions of practical use of vaccines [11]. To evaluate possible adverse events arising as a result of immunization, in 1999 the World Health Organization (WHO) created a working group: the Global Advisory Committee on Vaccine Safety [12]. In addition, European countries operate the ADVANCE project, whose task is to study the epidemiology of nine AAD (acute disseminated encephalomyelitis, Bell's palsy, Guillain–Barré syndrome, thrombocytopenic purpura, Kawasaki disease, retrobulbar neuritis, narcolepsy, systemic lupus erythematosus, and transverse myelitis) and to monitor potential links between their development and vaccination [10]. In the Russian Federation, gathering of data on the occurrence of adverse events due to immunization is performed by the territorial body Rospotrebnadzor (Federal Consumer Rights and Human Wellbeing Surveillance Service) and the Central apparatus of Roszdravnadzor (Federal Health Surveillance Service). In addition, reports are submitted to the automated information system Farmakonadzor (Pharmacovigilance) subsystem of Roszdravnadzor (the Roszdravnadzor AIS) [11].

3. Vaccination of MS Patients. There are currently no official guidelines on the vaccination of patients with MS. Decisions to immunize patients depend largely on factors such as the epidemiological situation and treatment using immunomodulatory or immunosuppressive therapy [13]. In general, vaccination is not contraindicated in immunocompromised people or patients on immunosuppressive therapy. There is a number of key recommendations which are universal and do not depend on the main disease. In particular, inactivated vaccines can be used with virtually no restrictions. However, a degree of caution is needed in relation to live vaccines [14]. Active immunization must be organized prior to treatment initiation in patients in whom immunosuppressive therapy is planned. Live vaccines must be given no less than four weeks before treatment initiation and inactivated vaccines no less than two weeks before. Annual influenza immunization is advised in patients aged over 6 months except those in whom there is a very low probability of an immune response. Vaccination against chickenpox and shingles is not undertaken in patients with severe immunodeficiency [15]. In addition, there are separate indications for active immunization depending on nosology and concomitant immunocompromised states. Experience of vaccination of patients with MS is significantly limited. Overall, there are no data confirming a link between inoculation and exacerbations of MS. However, any unvaccinated patient is in the risk group for developing the corresponding infectious disease, especially on the background of immunosuppressive therapy [16].

Given the mean age at onset of MS, most patients have probably been vaccinated in compliance with the national calendar. Catch-up vaccination and adult vaccine-based immunoprophylaxis of adults are subjects of special attention [17]. Catch-up vaccination is the process of vaccinating people who have not received their scheduled vaccinations [18]. In addition, there is a new WHO strategy based on the concept of "vaccination throughout life" [19]. This aims to achieve successes as a result of effective prophylactic technologies regardless of age [20].

As yet, no link has been established between the development of MS and vaccination [21]. One previous study on the safety of vaccination against hepatitis B noted an increase in the frequency of cases of MS. This campaign was run in France from 1995 to 1997 using a recombinant vaccine [22]. Many subsequent clinical trials throughout the world have refuted this association [21]. Safety has been studied in relation to the development of MS in the cases of vaccines such as tetanus, influenza, and papillomavirus, though no link has been established [23].

Despite the lack of special guidelines and the practice of mass vaccination of MS patients, the question of immunization of these patients is not infrequently solved on an individual basis. Each specific case requires the risks of the possible development of disease to be weighed against the benefit of vaccination. For example, patients receiving fingolimod are advised to consider the question of vaccination against chickenpox when specific antibodies are absent. In this case, the risk of developing severe disease is significantly greater than the potential adverse consequences of active immunization [14, 15, 24]. Study results indicate that the use of live chickenpox vaccine is safe in MS patients. Immunization produces an adequate immune response. The

level of protective antibodies resulting from vaccination is independent of patients' ages, the stage of the main disease, and the level of disability [25].

It is now known that there is a high probability of a lower response to vaccination against influenza in MS patients than in a control group [26]. Nonetheless, patients receiving interferon β did not show nay reduction in protective antibody levels as compared with controls [27]. Furthermore, the agent itself has antiviral activity, providing an additional protective effect [27]. Decreases in the immune response to administration of influenza vaccine can occur on the background of glatiramer acetate, fingolimod, teriflunomide, natalizumab, and mitoxantrone therapy. However, these studies have not led to unambiguous conclusions. Decreases in the protective effects of antibodies are seen at different time periods (three months, six months, etc.) after use of different drugs. Furthermore, the compositions of the vaccines used in different studies are significantly different. The result is that there are no clear conclusions as to which vaccine should be preferred in specific therapeutic schemes [26, 28].

Patients receiving ocrelizumab showed decreases in protective antibody levels 12 weeks after active immunization against influenza, tetanus, and pneumococcal infection as compared with a group of patients receiving interferon β. Decreases in immune responses can occur at three weeks on administration of booster doses of tetanus vaccine on the background of fingolimod treatment [29]. Nonetheless, the possibility of achieving adequate antibody levels is not excluded [16].

However, not all variants of MS therapy lead to reductions in immune responses to vaccination. For example, a pilot study showed that alemtuzumab produced adequate antibody levels after immunization against diphtheria, tetanus, poliomyelitis, *Haemophilus*, *Meningococcus* (a conjugated vaccine), and *Pneumococcus* (a polysaccharide vaccine). Thus, patients receiving this drug were found to have a preserved immune response. Thus, vaccination may be an additional tool for preventing infectious diseases in this category of patients [30].

In addition, postmarketing monitoring of drugs such as fingolimod and alemtuzumab has demonstrated increases in morbidity with papillomaviruses, along with increases in the frequency of dysplasia of the cervix uteri [31,32]. The incidence of human papillomavirus in the cervical canal in a group of patients receiving alemtuzumab therapy was 2%. In this case, there was a risk of developing malignant neoplasms of the cervix uteri [33]. For this reason, women receiving treatment are advised to undergo annual screening [33]. In addition, patients may be additionally advised to receive vaccination against papillomavirus infections [31].

4. Vaccination against the New Coronavirus Infection in MS. The question of vaccination against the new coronavirus infection is relevant in the present world. A total of 69 vaccines are currently in the clinical phase of trials around the world. A further 181 formulations are in the preclinical phase of trials [34]. Some vaccines are already in use in MS patients. In particular, these are vaccines based on mRNA from Moderna and Pfizer-BioNTech, as well as vector-based vaccines from Oxford-AstraZeneca and Janssen. American guidelines from the National Multiple Sclerosis Society indicate that the Moderna, Pfizer-BioNTech, and Janssen vaccines are safe and are advised for use in patients. In general, they can be used regardless of ongoing pathogenetic therapy, though some dugs may decrease vaccination efficacy [35].

In the UK, MS patients are also a priority group and are advised to receive vaccination before others. Active immunization can be delivered without interrupting the main course of therapy, though there are certain exceptions. Use of vaccines from Pfizer-BioNTech and Oxford-AstraZeneca is recommended. It is important to note that the use of particular immune drugs currently depends primarily on their availability in countries [36].

Three immune formulations are authorized and available in in the Russian Federation. Gam-COVID-Vac is a vector-based two-component vaccine. The first dose consists of recombinant adenovirus serotype 26 particles while the second contains serotype 5. Both components contain the gene for the SARS-CoV-2 virus S protein.[a] The second available vaccine is EpiVacCorona, which consists of chemically synthesized peptide antigens corresponding to three fragments of the SARS-CoV-2 S protein, conjugated with a carrier protein. This vaccine contains an adjuvant (aluminum hydroxide) to enhance the immune response.[b] The third vaccine is CoviVac, from the Chumakov Center, which is an inactivated whole-virus immunoformulation [34]. An important question is that of the safety of vaccination for patients with MS and receiving targeted therapy. Vaccine selection depends directly on efficacy levels [37]. All vaccines currently authorized in the Russian Federation are potential candidates for vaccine prevention in MS patients. This disease is not an absolute contraindication for vaccination. Nonetheless, all current vaccines against the new coronavirus infection should be used with caution in patients with central nervous system diseases.[a,b]

Conclusions. Thus, no link has been established between the occurrence and/or exacerbation of MS and vaccination. MS Patients generally have good tolerance of immunization regardless of the vaccine used. MS patients may have decreased responses to vaccination but nonetheless often achieve sufficient levels of protective antibodies. Patients receiving fingolimod can be advised to undergo vaccination against chickenpox because of the high risk of severe disease. Patients with exacerbations of MS are

[a] Instructions for use. Gam-COVID-Vac Combined Vector Vaccine for the Prevention of Coronavirus Infection due to SARS-CoV-2 Virus.

[b] Instructions for use. EpiVakCorona Vaccine based on Peptide Antigens for Prevention of COVID-19. 2021.

advised to postpone vaccination until recovery of exacerbations and stabilization of neurological status for at least 30 days. Administration of inactivated vaccines to patients receiving immunosuppressive therapy should not interrupt that treatment. The immunogenicity of live attenuated herpes zoster vaccine in naïve patients can be optimized by immunizing at least 2–4 weeks before initiating immunosuppressive therapy. Determination of the time to initiate immunosuppressive therapy in naïve patients undergoing vaccination with live attenuated vaccines requires the duration of viremia after immunization to be considered.

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REFERENCES

1. S. Pazmino, A. Boonen, V. Stouten, et al., "Two-year cost-effectiveness of different COBRA-like intensive remission induction schemes in early rheumatoid arthritis: a piggyback study on the pragmatic randomised controlled CareRA trial," *Ann. Rheum. Dis.*, **79**, No. 5, 556–665 (2020), https://doi.org/10.1136/annrheumdis-2019-216874.
2. S. Ghabri, A. Binard, Y.-M. Pers, et al., "Economic evaluation of sequences of biological treatments for patients with moderate-to-severe rheumatoid arthritis and inadequate response or intolerance to methotrexate in France," *Value Health*, **23**, No. 4, 461–470 (2020), https://doi.org/10.1016/j.jval.2019.12.003.
3. P. Katz, G. J. Wan, and P. Daly, et al., "Patient-reported flare frequency is associated with diminished quality of life and family role functioning in systemic lupus erythematosus," *Qual. Life Res.*, **29**, No. 12, 3251–3261 (2020), https://doi.org/10.1007/s11136-020-02572-9.
4. Ø. Hovde, "Epidemiology and clinical course of Crohn's disease: Results from observational studies," *World J. Gastroenterol.*, **18**, No. 15, 1723 (2012), https://doi.org/10.3748/wjg.v18.i15.1723.
5. L. Wang, F.-S. Wang, and M. E. Gershwin, "Human autoimmune diseases: a comprehensive update," *J. Intern. Med.*, **278**, No. 4, 369–395 (2015), https://doi.wiley.com/https://doi.org/10.1111/joim.12395.
6. X. Li, H. Thomsen, K. Sundquist, et al., "Familial risks between pernicious anemia and other autoimmune diseases in the population of Sweden," *Autoimmune Dis.* (Internet), **2021**, 8815297 (2021), https://doi.org/10.1155/2021/8815297.
7. J. Anaya, Y. Shoenfeld, A. Rojas-Villarraga, et al., *Autoimmunity from Bench to Bedside*, El Rosario University Press, Bogota, Colombia (2013).
8. D. C. Wraith, M. Goldman, and P.-H. Lambert, "Vaccination and autoimmune disease: What is the evidence?" *Lancet*, **362**, No. 9396, 1659–1666 (2003), https://doi.org/10.1016/S0140-6736(03)14802-7.
9. S. Goriely and M. Goldman "From tolerance to autoimmunity: Is there a risk in early life vaccination?" *J. Comp. Pathol.*, **137**, 57–61 (2007), https://doi.org/10.1016/j.jcpa.2007.04.013.
10. C. Willame, C. Dodd, L. van der Aa, et al., "Incidence rates of autoimmune diseases in European healthcare databases: A Contribution of the ADVANCE project," *Drug Saf.*, **4**, 35–39 (2021), https://doi.org/10.1007/s40264-020-01031-1.
11. Russian Federation Ministry of Health, *Methodological Guidelines for the Detection, Investigation, and Prevention of Side Effects after Vaccination*, Moscow (2019).
12. World Health Organization, Global Advisory Committee on Vaccine Safety (GACVS) (2021), cited Feb. 8, 2021, https://www.who.int/vaccine_safety/committee/ru.
13. A. Winkelmann, M. Loebermann, E. C. Reisinger, et al., "Disease-modifying therapies and infectious risks in multiple sclerosis," *Nat. Rev. Neurol.*, **12**, No. 4, 217–233 (2016), https://doi.org/10.1038/nrneurol.2016.21.
14. T. Zrzavy, H. Kollaritsch, P. S. Rommer, et al., "Vaccination in multiple sclerosis: Friend or foe?" *Front. Immunol.*, **10**, 1883 (2019), https://doi.org/10.3389/fimmu.2019.01883.
15. L. G. Rubin, M. J. Levin, P. Ljungman, et al., "2013 IDSA clinical practice guideline for vaccination of the immunocompromised host," *Clin. Infect. Dis.*, **58**, No. 3, 44–100 (2014), https://doi.org/10.1093/cid/cit684.
16. M. F. Farez, J. Correale, M. J. Armstrong, et al., "Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis," *Neurology*, **93**, No. 13, 584–594 (2019), https://doi.org/10.1212/WNL.0000000000008157.
17. The World Health Organisation, *Table 1: WHO Recommendations for Routine Immunization*, September 2020, https://www.who.int/publications/m/item/table-1-who-recommendations-for-routine-immunization.
18. *Guidelines for Catch-Up Immunization*, Letter from the Federal Medical Biological Agency, August 20, 2020, No. 32-024/634.
19. N. I. Briko and I. V. Fel'dblyum, "Current concept in the development of vaccine prevention in Russia," *Epidemiol. Vaktsionoprof.*, **18**, No. 5, 4–13 (2019), https://www.epidemvac.ru/jour/article/view/825, https://doi.org/10.31631/2073-3046-2019-18-5-4-13.
20. L. S. Namazova-Baranova, M. V. Fedoseenko, and A. A. Baranov, "New horizons of the national preventive immunization calendar," *Vopr. Sovrem. Pediatr.* (Internet), **18**, No. 1, 13–30 (2019), https://vsp.spr-journal.ru/jour/article/view/2022, https://doi.org/10.15690/vsp.v18i1.1988.
21. D. Jakimovski, B. Weinstock-Guttman, M. Ramanathan, et al., "Infections, vaccines and autoimmunity: A multiple sclerosis perspective," *Vaccines*, **8**, No. 1, 50 (2020), https://doi.org/10.3390/vaccines8010050.
22. E. Marshall, "Immunology: A shadow falls on hepatitis B vaccination effort," *Science*, **281**, No. 5377, 630–631 (1998), https://doi.org/10.1126/science.281.5377.630.
23. C. Confavreux, S. Suissa, P. Saddier, et al., "Vaccinations and the risk of relapse in multiple sclerosis," *N. Engl. J. Med.*, **344**, No. 5, 319–326 (2001), https://doi.org/10.1056/nejm200102013440501.
24. U. Wiedermann, H. H. Sitte, H. Burgmann, et al., "Impfungen bei Immundefekten/Immunsuppression – Expertenstatement und Empfehlungen," *Wien. Klin. Wochenschr.*, **128**, No. S4, 337–376 (2016), https://doi.org/10.1007/s00508-016-1033-6.
25. R. Ross, M. Dawood, M. Cheang, and L. E. Nicolle, "Antibody response in seropositive multiple sclerosis patients vaccinated with attenuated live varicella zoster virus," *Can. J. Infect. Dis.*, **7**, No. 5, 303–306 (1996), https://doi.org/10.1155/1996/417061.
26. N. F. Moriabadi, S. Niewiesk, N. Kruse, et al., "Influenza vaccination in MS: Absence of T-cell response against white matter proteins," *Neurology*, **56**, No. 7, 938–943 (2001), https://doi.org/10.1212/WNL.56.7.938.
27. H. K. Olberg, R. J. Cox, J. K. Nostbakken, et al., "Immunotherapies influence the influenza vaccination response in multiple sclerosis patients: an explorative study," *Mult. Scler. J.*, **20**, No. 8, 1074–1080 (2014), https://doi.org/10.1177/1352458513513970.
28. H. K. Olberg, G. E. Eide, R. J. Cox, et al., "Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy," *Eur. J. Neurol.*, **25**, No. 3, 527–534 (2018), https://doi.org/10.1111/ene.13537.
29. C. Sirbu, A. Florea, M. Ghinescu, et al., "Vaccination in multiple sclerosis – Challenging practices (Review)," *Exp. Ther. Med.*, **20**, No. 6, 1–1 (2020), https://doi.org/10.3892/etm.2020.9347.
30. C. L. McCarthy, O. Tuohy, D. A. S. Compston, et al., "Immune competence after alemtuzumab treatment of multiple sclerosis," *Neurology*, **81**, No. 10, 872–876 (2013), https://doi.org/10.1212/WNL.0b013e3182a35215.
31. J. Triplett, A. G. Kermode, A. Corbett, et al., "Fingolimod and unusual HPV-associated lesions," *Mult. Scler. J.*, **25**, No. 11, 1547–1550 (2019), https://doi.org/10.1177/1352458518807088.

32. L. Klotz, J. Havla, N. Schwab, et al., "Risks and risk management in modern multiple sclerosis immunotherapeutic treatment," *Ther. Adv. Neurol. Disord.*, **12**, 175628641983657 (2019), https://doi.org/10.1177/1756286419836571.
33. A. Michailidou, H.-J. Trenz, and P. de Wilde, "Summary of product of characteristics. Lemtrada," *EMA*, **145**, No. 5, 67–172 (2019).
34. World Health Organization, *COVID-19 Vaccine Tracker and Landscape* (2021),https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
35. National Multiple Sclerosis Society, *COVID-19 Vaccine Guidance for People Living with MS* (2021), https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance.
36. MS Society Medical Advisers Consensus Statement on MS Treatments and COVID-19 Vaccines (2021), https://www.mssociety.org.uk/what-we-do/news/ms-society-medical-advisers-release-consensus-statement-covid-19-vaccines.
37. C. Zheng, I. Kar, C. K. Chen, et al., "Multiple sclerosis disease-modifying therapy and the COVID-19 pandemic: Implications on the risk of infection and future vaccination," *CNS Drugs*([Internet), **34**, No. 9, 879–896 (2020), https://doi.org/10.1007/s40263-020-00756-y.