REVIEWS

Is vaccination against viral hepatitis B safe and immunogenic in patients with rheumatic diseases?

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Impressive successes have been achieved in the fight against viral hepatitis B (HBV), but victory over this infection has not yet been achieved. According to various estimates, there are 6–12.5 times more patients with resolved HBV who are carriers of the virus than carriers of the "Australian" surface antigen HBsAg. The basis for the prevention of HBV is passive and active immunization of the population, but the data on the safety and immunogenicity of this vaccine in patients with rheumatic diseases are contradictory.

This review examines the safety and immunogenicity of vaccination against hepatitis B virus (HBV) in patients with immune-inflammatory rheumatic diseases. Vaccination against HBV is indicated for patients at risk of infection and should be carried out before starting antirheumatic therapy, as immunogenicity and efficacy are significantly higher in this case. The necessity of a detailed, targeted medical history collection to clarify the risk of HBV infection before prescribing antirheumatic therapy and clarification of the immune status (presence of HBsAg, antibodies against HBc and HBs) before vaccination is emphasized.

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Hepatitis B virus (HBV) is a double-stranded DNA virus that can play a significant role as an inducer of both rheumatic pathology and a comorbid infection that worsens the prognosis in immunoinflammatory rheumatic diseases (IIRDs). The features of this infection include extremely rare cases of spontaneous recovery and a tendency to chronicity with a high risk of potentially fatal complications, such as liver cirrhosis and hepatocellular carcinoma. Studies conducted on large cohorts of patients have shown a possible association between chronic HBV infection and the development of extrahepatic malignancies (most often gastrointestinal). It has been shown that HBV infection significantly reduces the long-term survival of such patients [1]. In addition, HBV can stimulate the development of some IIRDs. In particular, the role of the virus in the development of polyarteritis nodosa (up to 20–30% of all cases) and cryoglobulinemic vasculitis (<5% of all cases) has been proven [2]. It is known that viral hepatitis B (HBV) can remain asymptomatic for several years. Latent ("occult") course of infection is complicated by periods of spontaneous reactivation (HBV-r), usually caused by immunosuppressive therapy for IIRD [3]. The infectious process goes through several stages, starting with the most active, when HBeAg is detected – a marker of active HBV replication (the so-called infectivity antigen), antibodies to which (anti-HBe) are gradually produced. Over time, the process moves to the stage of "inactive carriage" of HBV, in which HBeAg and anti-HBe levels become negative, but the surface "Australian" antigen (HBsAg) and antibodies to the core antigen (anti-HBc, or anti-HBcor) remain detectable. Subsequently, the stage of past-infection occurs, when HBsAg may not be detected, but a sufficient amount of antibodies to this antigen (anti-HBs) is produced. With inadequate screening, such patients drop out of sight of clinicians as carriers of the virus and a potential source of infection. As the anti-HBs titer increases and anti-HBe and anti-HBc titers decrease in the blood, the viral load (HBV DNA) ceases to be detected, which corresponds to a resolved infection and is the least dangerous condition in terms of the risk of both infection and HBV-r [4].

The problem of HBV-r is becoming increasingly relevant due to the widespread use of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) (i.e.janus-kinase inhibitors) in the treatment of IIRD.

We have previously shown that the frequency of HBV-r in patients with IIRDs was 10% [5]. In a meta-analysis performed by Lin TC et al., in patients with inflammatory arthropathies receiving synthetic disease-modifying antirheumatic drugs sDMARDs (methotrexale, leflunomide etc.) and bDMARDs, HBV-r was observed in 14.6% and 1.6% of cases of chronic HBV infection (HBsAg+) and past HBV infection (HBsAg-), respectively [6].

A systematic review noted that the combined prevalence of HBsAg and anti-HBc in patients with IIRD is 3% which is similar to that in the general population [7]. At the same time, according to a retrospective cross-sectional study by Chinese authors, which included 1461 patients with rheumatoid arthritis (RA), the frequency of chronic HBV infection detected during screening reached 10.1% [8]. In the study by N. Mahroum et al. chronic HBV infection in RA patients was significantly more common than in controls (1.19% and 0.64%, respectively; $p<0.001$) [9]. In multivariate logistic regression analysis, RA had a significant association with chronic HBV infection (odds ratio, OR 1.89; 95% confidence interval, CI 1.55–2.29; $p<0.001$). According to other authors, the number of HBsAg-negative and anti-HBc-positive patients is 6–12.5 times higher than that of patients with HBsAg [10–12].

The most important element of HBV prevention is passive and active immunization. The vaccine against HBV was developed

in 1987, and its widespread implementation began in the 1990s. This vaccine is a preparation based on the surface HBV antigen obtained by DNA recombination on a yeast culture transformed by inclusion in their genome of the gene encoding HBsAg. In 1992, WHO recommended that HBV immunization be included in national vaccination calendars. Currently, vaccination is carried out in 200 countries, including the Russian Federation [13, 14].

Vaccination is required for children from the first year of life and for adults. According to Russian recommendations on HBV vaccination, in case of contact with HBV, individuals from risk groups, as well as individuals who have not been previously vaccinated against HBV, or individuals whose vaccination is not complete, or if the level of HBs antibodies is below the protective level (<10 IU/l), after accidental infections as a result of contact with infected material, are administered specific immunoglobulin. Its use is indicated in the first 24–48 hours (up to 15 days, although the effectiveness of prophylaxis is sharply reduced) after contact with the infection, with simultaneous administration of the vaccine [13].

At the turn of the 20th and 21st centuries, there was a surge of interest in the safety of vaccination against HBV, reinforced by media reports about its adverse effects [15]. Separate studies on small samples demonstrated the safety of the recombinant DNA vaccine administered in a standard course (0–1–6 months) in relation to exacerbation of the disease in patients with RA as well as its immunogenicity (antibody production was noted in 68% of patients) [16]. Around the same time, cases of Sjogren's syndrome [17], polyarteritis nodosa [18], systemic lupus erythematosus (SLE) [19], adult Still's disease [20], lymphocytic vasculitis with diffuse skin edema [21] after vaccination against HBV were described. French rheumatologists reported 22 patients in whom deterioration of the condition was associated with vaccination. Inclusion criteria for this study were any rheumatic symptoms lasting ≥1 week, onset of symptoms within 2 months after vaccination against HBV, absence of previously diagnosed rheumatic disease (RD), and absence of other causes of symptoms. In 8 of 22 cases, symptoms appeared after the first dose of vaccine, in 5 – after the second, in 3 – after the third (1 month between 2 injections) and in 6 – after revaccination. Polyarthritis according to the ACR (American College of Rheumatology) RA criteria of 1987 developed in 6 cases, post-vaccination arthritis in 5, exacerbation of SLE in 2, polyarthralgia and myalgia in 4, fatigue in 3, vasculitis confirmed by biopsy in 1, and presumed vasculitis in 2 (biopsy was not performed to confirm it). A 43-year-old patient developed fever (38 °C), erythema nodosum, and oligoarthritis of the lower extremities after vaccination, which regressed within 1 month while taking nonsteroidal anti-inflammatory drugs. In the vast majority of the cases mentioned, continuing the vaccination course led to a deterioration in the patients' condition [22].

A number of papers have also been published on the development of autoimmune diseases after vaccination against HBV, but most of them rather confirmed the thesis: "After this does not mean because of this", such as, the case report about the development of erosive RA with rheumatoid nodules soon after vaccination [23].

In the context of the safety of vaccination against HBV, the so-called ASIA syndrome (Autoimmune/inflammatory syndrome induced by adjuvants) was actively discussed – an autoimmune (autoinflammatory) syndrome induced by adjuvants [24]. In 2008, A.L. Nancy and Y. Shoenfeld [25] reported chronic fatigue syndrome in a 56-year-old woman, which was accompanied by fibromyalgia, a demyelinating process and the appearance of autoantibodies. The disease began after the second dose of the HBV vaccine and worsened after the third dose. In 2011, Y. Shoenfeld and N. Agmon-Levin [26] described a condition that included autoimmune phenomena that arose after exposure to adjuvants, i.e. substances that enhance both the innate and adaptive immune response. This phenomenon of hyperactivation of the immune system can lead to autoimmune reactions or chronic inflammation. The main criteria of post-vaccination ASIA syndrome are: exposure to external irritants (vaccine, adjuvant) before the onset of clinical symptoms, as well as typical clinical manifestations in the form of myalgia, myositis or muscle weakness, arthralgia and/or arthritis, chronic fatigue syndrome, poor sleep or sleep disorders, neurological disorders, cognitive impairments, memory loss, pyrexia, dry mouth. The minor criteria are: the appearance of autoantibodies or antibodies directed to the putative adjuvant (in post-vaccination ASIA syndrome, it is not precisely established), other clinical manifestations (for example, irritable bowel syndrome), a specific set of genes of the HLA system (HLA-DRB1, HLA-DQB1), the development of an autoimmune disease [26]. In some cases, fibromyalgia may also occur with ASIA syndrome.

Risk factors for ASIA syndrome manifestation include the occurrence of adverse events (AE) during the immunization course, the presence of an autoimmune predisposition and higher titers of autoantibodies [27].

According to the Global Vaccine Safety Plan issued by WHO in 2021, an Adverse Event Following Immunization (AEFI) is any health disorder that follows immunization but does not necessarily have a causal relationship with it. When assessing causality, it is important to consider all possible circumstances for the occurrence of AEFI and the likelihood of each before attributing the event to the vaccine product [28]. Accordingly, the incidence of new cases of autoimmune inflammatory diseases (as well as their exacerbations) that develop after any vaccination must be compared with that in the population of a particular region during the same period of time. This is confirmed by data from a retrospective review of medical records of almost 1 million people aged 15–59 years included in the HBV vaccination registry in Northern California: no significant association was found between the administration of this vaccine and the occurrence of RA [29].

According to the updated 2019 EULAR (European Alliance of Associations for Rheumatology) recommendations on vaccination of adult patients with autoimmune inflammatory diseases, vaccination against HBV is carried out only in patients with IIRDs from risk groups, which include HBV-seronegative patients traveling or living in endemic countries, as well as patients with an increased risk of HBV infection (e.g., healthcare personnel, household members, sexual partners of people with chronic HBV infection, intravenous drug users, men who have sex with men). This approach is effective and safe during any therapy, including glucocorticoids (GC), (sDMARDs) and bDMARDs [30]. Note that seronegativity should be understood as an anti-HBs <10 IU/L [31]. The true clinical efficacy of the vaccine under consideration is to reduce the incidence of HBV and mortality from HBV infection in patients with IIRDs, both in general and depending on the therapy with sDMARDs and bDMARDs. It can only be assessed in the course of a long-term prospective, probably multicenter, conducted (which is important!) according to a single protocol study, including thousands of patients. This condition can be fulfilled only with the involvement of large human and material resources. Therefore, to date, such a "surrogate marker" as the ability to initiate and

maintain protective levels of specific antibodies, i.e. immunogenicity, has been proposed as a measure of vaccine efficacy.

The problem of the HBV-vaccine immunogenicity in different diagnosis and therapy remains open. It was shown in small cohorts with only one vaccination cycle, that vaccination of patients with IIRD against HBV leads to the production of antibodies in 66–68% of them [32, 33]. S. Intongkam et al. [33] studied the vaccine response in 46 RA patients, 33 of whom received sDMARDs, and 13 received both sDMARDs and bDMARDs. Achieving a protective level of antibodies (seroprotection) in RA patients was observed less often than in patients in the control group (64% and 100%, respectively; p=0.045). Patients using bDMARDs and sDMARDs also achieved seroprotection less often than the control group (50% and 100%, respectively; p = 0.02; 69.7 and 100%; p = 0.09). Patients with RA who responded to vaccine were younger compared to those who did not respond to vaccine and less often received rituximab (RTM). The frequency of RA exacerbations did not increase after hepatitis B vaccination. It is possible that the results of the study may be distorted by the small size of the control group (n = 9). A study that included 13 patients showed that vaccination against HBV did not lead to changes in disease activity in patients with RA and Behcet's disease, and immunogenicity was comparable in the main and control groups [34]. A. Haykir Solay and F. Eser [35] found that in 106 patients with IIRD who were prescribed TNFα inhibitors (TNFαi), the response rate to the vaccine was 53.2%, and in the infliximab (INF) group the response was minimal – 16.7%, and in the etanercept (ETC) group it was significantly higher – 88.9%. Moreover, the use of a double dose of the vaccine did not increase the level of the immune response. Perhaps, the obtained results are due to the fact that the anti-HBs titer was measured only once – 1 month after the last dose of the vaccine. P. Richi et al. [36] studied the immunogenicity of the HBV vaccine in 187 patients with RA receiving bDMARD: TNFαi, RTM, tocilizumab (TCZ), abatacept or anakinra. It is noteworthy that more than 60% of patients included in this study had not previously been vaccinated against HBV. Over 80% of patients responded to the vaccine, but additional revaccinations and a second series of vaccines were required. Patients who achieved seroconversion (anti-HBs >10 mIU/ml) were younger than those who did not seroconvert (47.10±12.99 and 53.18±10.54 years, respectively; p=0.012). Seroconversion was detected in 93.75% of patients taking sDMARDs and in 97.96% of healthy individuals in the control group. The seroconversion rate in the bDMARDs group was significantly lower than in the sDMARD group (p=0.043) and tended to be lower than that in healthy individuals (p=0.056), while treatment with sDMARDs and/or GCs did not affect the vaccine response. The highest response rate to the vaccine was observed in patients receiving ETC (91.38%) and golimumab (100%). Patients who were prescribed ETC were more likely to respond to the vaccine than those who used other bDMARDs (OR 3.074; 95% CI 1.124–8.405; p=0.023). At the same time, the majority of patients who received RTM did not respond to the vaccine (OR 0.064; 95% CI 0.019–0.222; p<0.001). In this group, patients were older than those who did not use RTM (mean 56.0 ± 9.6 and 47.6 ± 12.8 years, respectively; p = 0.017), but the association between RTM and a worse response persisted after adjusting for age (OR 0.077; 95% CI 0.019–0.222; p < 0.001). In this study, INF did not reduce the immune response. This result differs from the data obtained previously by P.K. Jr. Pratt et al. [37], who studied the immunological response to HBV vaccine in patients with inflammatory bowel diseases. These authors found that with IFN treatment, the probability of achieving seroconversion was significantly lower. It was also noted that patients receiving bDMARDs required revaccination (34.22 and 12.5%, respectively; p=0.003) and a repeat series of vaccinations (23.53 and 8.33%, respectively; p=0.02) significantly more often than patients using sDMARDs. Thus, patients on bDMARDs therapy can achieve high rates of immune response to the HBV vaccine if they follow the full vaccination schedule. However, to achieve such a high level of seroconversion, revaccination and a second series of vaccinations are more often required. In this regard, the authors supported the proposal to vaccinate patients with IIRD against HBV immediately after diagnosis, rather than when the possibility of using bDMARDs is being considered [36]. In a prospective study by V.C. Romao et al. [38] 62 patients with IIRDs of varying activity (from remission to very high), receiving bDMARDs, not previously vaccinated and not in contact with HBV, were vaccinated against HBV. The level of anti-HBs was re-evaluated 1 month or more after the last dose. Follow-up included examination and blood testing every 3 months, up to a maximum of 3 months after the third dose. Response was defined as achieving an anti-HBs level ≥10 IU/L. The control group consisted of healthy volunteers who had also undergone a course of vaccination. A positive response to vaccination was recorded in 32.3% of patients and 94.7% of age-matched controls (p<0.001). The mean anti-HBs titer after vaccination was significantly lower in patients who responded to vaccination than in controls (569±772 and 1370±827 U/L, respectively; p<0.001). The response rate to vaccination was 25.8% in RA and 38.7% in spondyloarthritis. Post-vaccination response was observed in 37.3% of patients receiving TNFαi and in 9.1% of patients using other inhibitors (p=0.07). None of the 4 patients using RTM responded to vaccination. It is noteworthy that only 16.7% of patients prescribed TCZ responded to vaccination, while in a previously published study the proportion of such patients reached 78% [36]. Against the background of TNFαi treatment, the frequency of post-vaccination response varied from 18% (for INF) to 57% (for ETC). The authors suggest that this may be due to the different pharmacokinetics of these drugs and the timing of vaccination in relation to the date of INF infusion. The response was independent of the dose of GC used. Four patients missed at least one bDMARDs administration for reasons unrelated to vaccination, but none of them responded to vaccination. Disease exacerbations were observed in 16 patients (25%): in 9 they were mild and did not require a change in therapy, 5 patients required minimal treatment/dose correction, and 2 developed secondary treatment failure that led to a change in therapy. In terms of vaccination safety, no clinically significant adverse events were identified. The authors also support the recommendation to vaccinate against HBV before starting bDMARDs, possibly immediately after diagnosis. In patients already receiving bDMARDs, alternative strategies for HBV vaccination should be explored, such as increasing the vaccine dose, using different adjuvants, or even temporarily stopping antirheumatic therapy [38]. It is also important, that the status of a patient who has not responded to vaccination must be officially registered due to the possibility of using post-HBV intervention measures in case of contact with HBV [39]. Unfortunately, vaccination coverage of patients with IIRDs remains suboptimal. The main reason for this is considered to be low patient awareness [40]. M. Feuchtenberger et al. [41] conducted a survey and analyzed titers of post-vaccination antibodies to various infections (HBV, rubella, mumps, measles,

diphtheria, tetanus) in 301 patients with RA. It was shown that patients who received bDMARDs were better informed about the increased risk of infections.

An obvious discrepancy was found between vaccination awareness and actual vaccination rates for all cohorts of patients, according to medical records. In a cross-sectional prospective study, U. Kiltz et al. [42] studied the vaccination status and screening status for infections before starting sDMARDs/bDMARDs in 975 patients with IIRD. Almost all patients receiving bDMARDs (n=499) were tested for HBV (94%). The combined HBsAg-positivity and anti-HBc-positivity in patients with IIRD was the same as in the general population, 3% and 15%, respectively. Sixteen patients with chronic HBV used lamivudine (3.4%), less than 30% were vaccinated against HBV. None of the patients complied with the German national vaccination recommendations, which require complete documentation of vaccination records. The authors emphasize that although patients with IIRD and general practitioners regularly receive information on the need for vaccination against the most common infections, the level of immunization varied from low to moderate. To improve the results, it is necessary to plan interdisciplinary quality projects.

Conclusion. Thus, vaccination against HBV is indicated for patients with IIRD from risk groups for HBV infection, which requires a detailed, targeted survey before prescribing treatment. According to most authors, HBV vaccination should be carried out before prescribing antirheumatic therapy, in which case its immunogenicity significantly increases. It is necessary to clarify the immunological status with respect to HBV (HBsAg, anti-HBc, anti-HBs) before vaccination. Existing vaccines against HBV have a good safety profile, at least in patients with RA. Further clinical studies are required to clarify issues related to the immunogenicity and safety of these vaccines in other IIRDs.

REFERENCES

1. Min Y, Wei X, Xia X, et al. Hepatitis B virus infection: An insight into the clinical connection and molecular interaction between hepatitis B virus and host extrahepatic cancer risk. *Front Immunol.* 2023 Mar 1;14:1141956. doi: 10.3389/fimmu.2023.1141956. eCollection 2023.
2. Белов БС, Абдурахманов ДТ. Вирус гепатита В и ревматические болезни. Научно-практическая ревматология. 2020; 58(2):207-213.
[Belov BS, Abdurakhmanov DT. Hepatitis B virus and rheumatic diseases. *Nauchno-prakticheskaya revmatologiya*. 2020;58(2):207-213. (In Russ.)].
3. Балабанова РМ. Ревматические заболевания и вирусная инфекция: есть ли связь? Современная ревматология. 2020;14(4): 98-102.
[Balabanova RM. Rheumatic diseases and viral infection: is there an association? *Sovremennaya Revmatologiya = Modern Rheumatology Journal.* 2020;14(4):98-102. (In Russ.)]. doi: 10.14412/1996-7012-2020-4-98–102
4. Chen YM, Yang SS, Chen DY. Risk-stratified management strategies for HBV reactivation in RA patients receiving biological and targeted therapy: A narrative review. *J Microbiol Immunol Infect.* 2019 Feb;52(1):1-8. doi: 10.1016/j.jmii.2017.10.002. Epub 2017 Nov 5.
5. Гриднева ГИ, Аронова ЕС, Белов БС. Хронический гепатит В у пациентов ревматологического стационара: проблемы скрининга и реактивации инфекции. Современная ревматология. 2023;17(5):67-72.
[Gridneva GI, Aronova ES, Belov BS. Chronic hepatitis B in hospitalized rheumatologic patients: problems of screening and reactivation of infection. *Sovremennaya Revmatologiya = Modern Rheumatology Journal.* 2023;17(5): 67-72. (In Russ.)]. doi: 10.14412/1996-7012-2023-5-67-72.
6. Lin TC, Yoshida K, Tedeschi SK, et al. Risk of Hepatitis B Virus Reactivation in Patients With Inflammatory Arthritis Receiving Disease-Modifying Antirheumatic Drugs: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)*. 2018 May;70(5):724-731. doi: 10.1002/acr.23346. Epub 2018 Apr 12.
7. Furer V, Rondaan C, Heijstek M, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. *RMD Open*. 2019 Sep 19;5(2):e001041. doi: 10.1136/rmdopen-2019-001041. eCollection 2019.
8. Zheng HW, Ouyang ZM, Pan J, et al. Hepatitis B virus infection status and clinical characteristics in patients with rheumatoid arthritis. *Zhonghua Yi Xue Za Zhi*. 2024 Jan 16;104(3):205-211. doi: 10.3760/cma.j.cn 112137-20230802-00132
9. Mahroum N, Watad A, Tiosano S, et al. Chronic hepatitis B viral infection among RA patients-a cross-sectional control study. *Clin Rheumatol.* 2019 May;38(5):1237-1241. doi: 10.1007/s10067-019-04448-x. Epub 2019 Feb 8.
10. Capkin E, Yaz c A, Karkucak M, et al. Evaluation of hepatitis serology and frequency of viral reactivation in patients with inflammatory arthritis receiving biologic agents: a multicenter observational study. *Rheumatol Int*. 2023 Mar;43(3):523-531. doi: 10.1007/s00296-022-05169-2. Epub 2022 Sep 5.
11. Aguirre A, Yazdany J. Hepatitis B Screening Before Biologic or Targeted Synthetic Disease-modifying Antirheumatic Drug Therapy: Many Roads to Improvement. *J Rheumatol.* 2022 Jan;49(1):1-4. doi: 10.3899/jrheum. 211000. Epub 2021 Nov 1.
12. Canzoni M, Marignani M, Sorgi ML, et al. Prevalence of Hepatitis B Virus Markers in Patients with Autoimmune Inflammatory Rheumatic Diseases in Italy. *Microorganisms.* 2020 Nov 16;8(11):1792. doi: 10.3390/microorganisms8111792.
13. Министерство здравоохранения Российской Федерации. Клинические рекомендации. Острый гепатит В (ОГВ) у детей.
[The Ministry of Health of the Russian Federation. Clinical recommendations. Acute hepatitis B (AHB) in children].
https://cr.minzdrav.gov.ru/schema/488_2
14. Приказ от 6 декабря 2021 г. n 1122н об утверждении национального календаря профилактических прививок, календаря профилактических прививок по эпидемическим показаниям и порядка проведения профилактических прививок.
[Order № 1122n dated December 6, 2021 on approval of the national calendar of preventive vaccinations, the calendar of preventive vaccinations for epidemic indications and the procedure for preventive vaccinations].
https://normativ.kontur.ru/document?moduleId=1&documentId=410331.
15. Grotto I, Mandel Y, Ephros M, et al. Major adverse reactions to yeast-derived hepatitis B vaccines – a review. *Vaccine*. 1998 Feb; 16(4):329-34. doi: 10.1016/s0264-410x(97) 00214-4.
16. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2002 Jul;61(7):623-5. doi: 10.1136/ard. 61.7.623.
17. Toussirot E, Lohse A, Wendling D, Mougin C. Sjögren's syndrome occurring after hepatitis B vaccination. *Arthritis Rheum*. 2000 Sep;43(9):2139-40. doi: 10.1002/1529-0131 (200009)43:9<2139::AID-ANR27>3.0. CO;2-3.
18. Saadoun D, Cacoub P, Mahoux D, et al. Vascularites postvaccinales: a propos de trois observations. *Rev Med Interne*. 2001 Feb; 22(2):172-6. doi: 10.1016/s0248-8663(00) 00307-6.
19. Fineschi S. Can recombinant anti-hepati-

tis B vaccine be a cause of systemic lupus erythematosus? *Lupus*. 2001;10(11):830. doi: 10.1177/096120330101001114.
20. Grasland A, Le Maotre F, Pouchot J, et al. Maladie de Still de l'adulte aprиs vaccination contre l'hйpatite A et B? *Rev Med Interne*. 1998 Feb;19(2):134-6. doi: 10.1016/s0248-8663(97)83425-x.
21. Drucker Y, Prayson RA, Bagg A, Calabrese LH. Lymphocytic vasculitis presenting as diffuse subcutaneous edema after hepatitis B virus vaccine. *J Clin Rheumatol.* 1997 Jun;3(3):158-61. doi: 10.1097/00124743-199706000-00010.
22. Maillefert JF, Sibilia J, Toussirot E, et al. Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)*. 1999 Oct;38(10):978-83. doi: 10.1093/rheumatology/38.10.978.
23. Treves R, Lacoste L, Bontoux D, et al. Polyarthrite rhumatoide nodulaire erosive declenchee par une vaccination contre l'hepatite B. *Presse Med.* 1997 Apr 26;26(14):670.
24. Заяева А., Юнси СИ, Заусалина АИ и др. Аутоиммунный/воспалительный синдром, индуцированный адъювантами. Архивъ внутренней медицины. 2023;13(6):405-412.
[Zayaeva AA, Younsi SI, Zausalina AI, et al. Autoimmune/Inflammatory Syndrome Induced by Adjuvants. *Arkhiv vnutrennei meditsiny.* 2023;13(6):405-412. (In Russ.)].
25. Nancy AL, Shoenfeld Y. Chronic fatigue syndrome with autoantibodies – the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant. *Autoimmun Rev*. 2008 Oct;8(1):52-5. doi: 10.1016/j.autrev.2008.07.026. Epub 2008 Aug 24.
26. Shoenfeld Y, Agmon-Levin N. 'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun*. 2011 Feb;36(1):4-8. doi: 10.1016/j.jaut.2010.07.003. Epub 2010 Aug 13.
27. Agmon-Levin N, Zafrir Y, Kivity S, et al. chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA). *Immunol Res.* 2014 Dec;60(2-3):376-83. doi: 10.1007/s12026-014-8604-2.
28. WHO. Global vaccine safety blueprint 2.0 (GVSB2.0) 2021-2023/. https://iris.who.int/bitstream/handle/10665/348966/9789240036963-eng.pdf?sequence=1
29. Ray P, Black S, Shinefield H, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age. *Vaccine*. 2011 Sep 2;29(38):6592-7. doi: 10.1016/j.vaccine.2011.06.112. Epub 2011 Jul 16.
30. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis.* 2020 Jan;79(1):39-52. doi: 10.1136/annrheumdis-2019-215882. Epub 2019 Aug 14.
31. Rondaan C, Furer V, Heijstek MW, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open*. 2019 Sep 9;5(2):e001035. doi: 10.1136/rmdopen-2019-001035. eCollection 2019.
32. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2002 Jul;61(7):623-5. doi: 10.1136/ard.61.7.623.
33. Intongkam S, Samakarnthai P, Pakchotanon R, et al. Efficacy and safety of hepatitis B vaccination in rheumatoid arthritis patients receiving disease-modifying antirheumatic drugs and/or biologics therapy. *J Clin Rheumatol.* 2019 Dec;25(8):329-334. doi: 10.1097/RHU.0000000000000877.
34. Erkek E, Ayaslioglu E, Erkek AB, et al. Response to vaccination against hepatitis B in patients with Behcet's disease. *J Gastroenterol Hepatol.* 2005 Oct;20(10):1508-11. doi: 10.1111/j.1440-1746.2005.03903.x.
35. Haykir Solay A, Eser F. High dose hepatitis B vaccine is not effective in patients using immunomodulatory drugs: a pilot study. *Hum Vaccin Immunother.* 2019;15(5):1177-1182. doi: 10.1080/21645515.2019.1574151. Epub 2019 Mar 19.
36. Richi P, Alonso O, Martin MD, et al. Evaluation of the immune response to hepatitis B vaccine in patients on biological therapy: results of the RIER cohort study. *Clin Rheumatol.* 2020 Sep;39(9):2751-2756. doi: 10.1007/s10067-020-05042-2. Epub 2020 Apr 4.
37. Pratt PK Jr, David N, Weber HC, et al. Antibody Response to Hepatitis B Virus Vaccine is Impaired in Patients with Inflammatory Bowel Disease on Infliximab Therapy. *Inflamm Bowel Dis.* 2018 Jan 18;24(2):380-386. doi: 10.1093/ibd/izx001.
38. Romao VC, Avila-Ribeiro P, Goncalves MJ, et al. Hepatitis B vaccination associated with low response in patients with rheumatic diseases treated with biologics. *RMD Open*. 2023 Dec 6;9(4):e003597. doi: 10.1136/rmdopen-2023-003597.
39. Schillie S, Harris A, Link-Gelles R, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018 Apr 20;67(15):455-458. doi: 10.15585/mmwr.mm6715a5.
40. Белов БС, Муравьева НВ. Современные представления о вакцинации больных ревматическими заболеваниями: взгляд экспертов ACR. Антибиотики и химиотерапия. 2023; (5–6):77-84.
[Belov BS, Muravyeva NV. Modern Ideas about Vaccination of Patients with Rheumatic Diseases: the View of ACR Experts. *Antibiotiki i khimioterapiya*. 2023; (5–6):77-84. (In Russ.)].
41. Feuchtenberger M, Kleinert S, Schwab S, et al. Vaccination survey in patients with rheumatoid arthritis: a cross-sectional study. *Rheumatol Int.* 2012 Jun;32(6):1533-9. doi: 10.1007/s00296-011-1808-z. Epub 2011 Feb 15.
42. Kiltz U, Celik A, Tsiami S, et al. Are patients with rheumatic diseases on immunosuppressive therapies protected against preventable infections? A cross-sectional cohort study. *RMD Open*. 2021 Apr;7(1):e001499. doi: 10.1136/rmdopen-2020-001499.

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