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Immune-mediated inflammatory disease patients in the era of COVID-19 — who, how and when to vaccinate against COVID-19

ABSTRACT

Patients with autoimmune diseases are a particularly vulnerable group, prone to developing infectious complications. At the same time, due to the immunosuppressive treatment of these patients, the use of vaccination may raise some concerns as to its effectiveness and, above all, its safety. This article presents the current recommendations of scientific societies indicating the efficacy, safety and, in particular, the necessity of immunization in all patients with inflammatory rheumatic diseases. Special emphasis in this study is placed on the efficacy and safety of vaccination against COVID-19

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KEY WORDS: inflammatory rheumatic diseases; immunization; COVID-19

INTRODUCTION

In December 2019, the outbreak of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first observed in Wuhan city, China. The virus spread rapidly around the world, leading the WHO to declare a pandemic of infectious disease caused by the virus on 11 March 2020 [1].

Coronaviruses (CoVs) are responsible for life-threatening syndromes: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 causing severe pneumonia, acute respiratory distress syndrome (ARDS), heart and kidney damage, especially in elderly patients and those with comorbidities [2].

Coronaviruses belong to the large Coronaviridae family, which is divided into 2 subfamilies: Orthocoronavirinae (within which alpha, beta, gamma and delta coronaviruses can be distinguished) and Torovirinae. SARS-CoV-2 belongs to beta-coronaviruses, contains a single strand of RNA (+ssRNA), and a very large genome (27–34 kb). Its natural host is probably bats [3].

The main structural proteins, encoded by the viral genome, which have a significant impact on the infectivity of the virus are:

— **S (spike) protein** — a highly glycosylated surface glycoprotein, consisting of 2 domains:
  • S1 domain: containing RBD (receptor-binding domain), binding to ACE2 (angiotensin-converting enzyme 2) on host cells (Fig. 1) and
  • S2 domain, which is responsible for the entry of the virus into the host cell [4].

S protein is responsible for the production of neutralising antibodies and is a major target in therapeutic approaches;

— **E (envelope) protein**;
— **M (mambrane) protein**;
— **N (nucleocapsid) protein** which antagonistically affects the synthesis of type 1 IFN, which plays an important role in the development of the host's non-specific immune response to viral infection [5] (Fig. 2).

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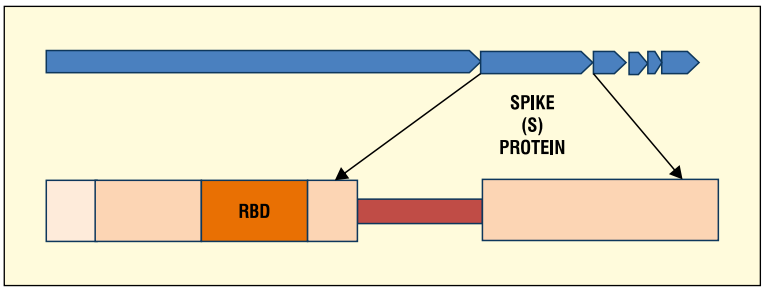

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome (based on: Suzuki Y.J., Gychka G.Y. 2021. SARS--CoV-2 spike protein elicits cell signaling in human host cells: implications for possible consequences of COVID-19 vaccines. Vaccines 9: 36. doi: 10.3390/vaccines9010036 [modified by the authors]). RBD (receptor binding domain) — site of binding of the virus to the ACE2 host cell receptor

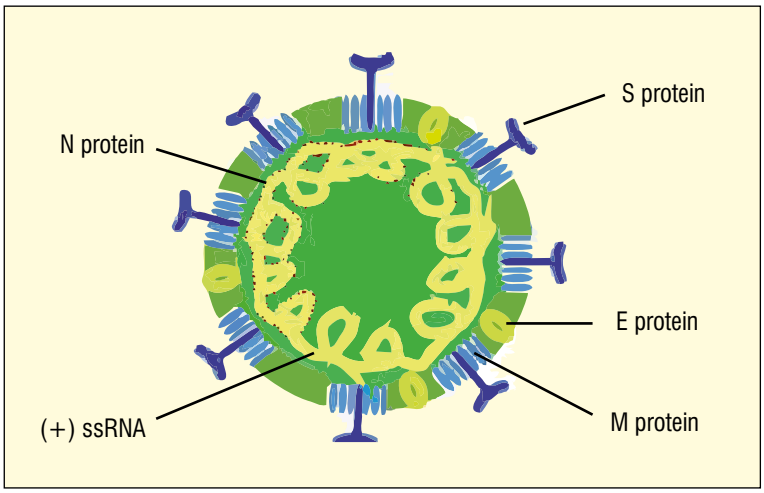

Figure 2. Coronavirus (based on: Tufan A., Güler A.A., Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk. J. Med. Sci. 2020; 50 (SI-1): 620-632 [modified by the authors])

An effective antiviral response requires activation of both the host's non-specific response and targeted specific response and is associated with the production of multiple pro--inflammatory cytokines, activation of CD4+ and CD8+ T-cells, which limits the spread of the virus and enables virus elimination [6]. In some cases, however, tissue damage caused by the virus may result in increased production of pro-inflammatory cytokines, recruitment of macrophages and granulocytes to the sites of damage and consequently lead to the so-called „cytokine storm" (CS), which leads to further tissue destruction [7].

Serum levels of IL-6, considered a marker for the development of MAS (macrophage activation syndrome), are increased in both mild and severe COVID-19 compared with healthy subjects, and levels of this cytokine are significantly increased in severe disease. A high level of lung involvement (> and equal to 50 %) is closely associated with increased serum IL-6 levels. Data from recent studies indicate that SARS-CoV-2 infection causes the dysregulation of, and damage to, the immune system, which is manifested by lymphopenia, including a decrease in T-cell count. A lower count of T-cells (helper CD3+, CD4+ T-cells) and cytotoxic CD8+ T-cells, as well as regulatory T-cells, have been observed in COVID-19 patients, particularly in severe disease [8]. In severe cases, the number of T-memory cells is also reduced and the number of naive T-cells is increased. Maintaining a balance between these cell types is important for the proper functioning of the immune system [9].

The risk of severe course and development of serious complications of COVID-19 concerns patients with concomitant respiratory, cardiovascular, and diabetic diseases. Autoimmune-mediated rheumatic diseases (ARDs) are a group of diseases that require immunomodulatory and immunosuppressive treatment. For patients with ARDs, COVID-19 incidence data are inconclusive. On the basis of meta-analyses and registry data to date, it appears that the incidence is comparable or only slightly higher in patients with

ARDs and that there is a potential association between increased COVID-19 incidence and prednisone intake >10 mg/day. No difference has been shown between patients treated with biologic drugs (b-DMARDs) and those using ts-DMARDs (targeted synthetic disease-modifying anti-rheumatic drugs), such as Janus kinase inhibitors, which include tofacitinib [10].

Due to the widespread transmission of the virus and its high infectivity, in addition to the principles of social distancing, frequent handwashing and the wearing of protective masks, it is necessary to carry out preventive vaccinations to reduce and, in the long term, eliminate diseases caused by this virus from the human population.

The two main issues of concern in relation to COVID-19 vaccination in patients with ARDs are:

— the effect of immunosuppressive and immunomodulatory drugs used in these patients on the effectiveness of producing a normal response to vaccination;
— the effect of vaccination on the exacerbation of inflammatory rheumatic disease [11].

MRNA VACCINES

SARS- CoV-2 is the first pathogen against which novel mRNA-based vaccine technology has been used on a large scale. These vaccines have many advantages over vaccines based on viral vectors or on plasmid DNA. The mRNA vaccines do not generate infectious particles, nor are they integrated into the genome of host cells. They can induce antigen expression without crossing the barrier of the nuclear membrane to synthesise antigenic protein. The vaccinated person is thus given only the genetic information to produce viral proteins. Following vaccination, the mRNA vaccine mimics viral infection, resulting in the induction of both humoral and cytotoxic T-cell responses.

On 11 December 2020, the US Food and Drug Administration (FDA) approved the Pfizer/BioNtech COVID-19 vaccine for emergency use (emergency use approval, EUA). This vaccine encodes a full-length SARS--CoV-2 spike protein with two amino acids mutated to proline in the S2 subunit.

In contrast, Moderna's mRNA-1237 vaccine contains an mRNA transcript of the full--length SARS-2/CoV spike protein [11]. This vaccine encodes a SARS-CoV-2 glycoprotein with a transmembrane portion and an intact S1-S2 cleavage site.

However, due to mRNA instability, these vaccines require specific transport conditions.

After entering the cell, ssRNA activates TLR (mainly TLR3 and TLR7) receptors and inflammasomes in the cytosol, resulting in the activation of the synthesis of type 1 interferons which exhibit antiviral activity [12].

However, due to the „interferon signature" underlying several autoimmune diseases (e.g. in SLE), there was some doubt whether the vaccine would exacerbate the inflammatory chronic disease. However, vaccine manufacturers have introduced some modifications to reduce the activation of interferon-dependent pathways.

RNA VACCINES BASED ON VIRAL VECTORS

The AZD1222 vaccine (University of Oxford, AstraZeneca, UK) is based on a chimpanzee adenoviral vector ChAdOx1 encoding the S protein together with tissue plasminogen activator (tPA), which boosts immunogenicity.

The Russian Gam-COVID-Vac Sputnic V vaccine (Gamaleya Research Institute, Russian Federation) uses a combination of adenoviruses encoding the coronavirus S protein. In August 2020, the Ministry of Health of the Russian Federation approved the registration of Gam-Sputnik V.2 [13].

Adenovirus vector-based vaccines are considered safe and have previously been used in immunocompromised individuals who are considered to be at higher risk of developing severe COVID-19.

However, vaccines based on the adenoviral vector may carry a low risk of thrombosis associated with thrombocytopenia, which is probably related to the production of antibodies against platelet factor 4. Thrombosis occurs approximately 1–2 weeks after vaccination, mostly in women, and affects the area of venous sinuses in the brain [14]. These vaccines do not need to be frozen for transport, which makes them easier to distribute.

A number of specialist societies including ACR and EULAR have issued recommendations for COVID-19 vaccination in IMID patients. None of these bodies suggests contraindications to vaccination in these patients. The main concern appears to be the efficacy of the post-vaccination response in these patients, as patients receiving biologic therapy, especially those receiving RTX, may have a reduced post-vaccination response. Attention is also drawn to the fact that the peak of antibody

levels is reached more slowly (after approx. 2 weeks after vaccination).

EFFECTS OF DMARDS, B-DMARDS AND TS-DMARDS ON VACCINE RESPONSE

Observational studies conducted to date evaluating the effect of DMARDs on antibody response following vaccination (influenza virus, pneumococcus) have not provided conclusive answers.

Several evaluated the effect of MTX on the response after pneumococcal vaccination; taking MTX was associated with a lower vaccine response [15].

Several studies have assessed the effect of TNF-alpha inhibitors on the post-vaccination response for the pH1N1 influenza virus vaccine, and TNF-alpha inhibitors were not associated with a reduced post-vaccination response [16].

Several data on abatacept (ABA) indicated a significantly worse humoral response to influenza vaccination in patients using ABA compared with an age-matched group of patients receiving MTX [17].

A normal humoral response to pH1N1 vaccination was observed in patients using tocilizumab (TCZ), but combination therapy of TCZ with MTX led to a reduced vaccine response. Tocilizumab monotherapy did not reduce antibody production in response to pneumococcal vaccination (PPV23) [18].

Patients who started tofacitinib (TOF) therapy 2–3 weeks after receiving LZV (Live-Zoster-Vaccine) had an adequate humoral response and the vaccine was found to be safe for them [19]. Data on altered vaccine response in patients using immunosuppressive drugs are summarised in Table 1. However, it should be noted that live vaccines are not recommended for patients on immunosuppressive therapy. Based on previous knowledge of the biology of SARS-CoV-2, it has been postulated that B-cell depletion does not necessarily result in a more severe course of COVID-19, but may be important in an incomplete response to vaccination, although neither non-specific response mechanisms nor CD8 T-cell responses are affected [20].

ADE — ANTIBODY DEPENDENT ENHANCEMENT

In relation to vaccines that activate the humoral response, there is a potential danger of inducing the enhancement of viral infection via an antibody-dependent enhancement mechanism, whereby weak-neutralising antibodies produced during infection or vaccination cause amplification of the subsequent infection.

The ADE (antibody dependent enhancement) reaction was the reason for the withdrawal of the widely used dengue fever virus vaccine in Asia. The possibility of an ADE reaction for coronaviruses, including SARS-CoV and MERS, is described in several publications that appeared in 2019 and 2020 [21].

The manufacturers of currently used vaccines have introduced some modifications that have eliminated this effect.

MONITORING THE EFFECTS OF VACCINATION IN RMD PATIENTS

Patients with rheumatic and musculoskeletal diseases (RMD) should be monitored for vaccine effectiveness.

As T-cell stimulation is longer than the humoral response, it may be a more reliable effect of vaccination — many authors suggest assessing virus-specific T-cells rather than antibody levels alone in assessing vaccination efficacy. To evaluate the response from T-cells, tests assessing IFN-gamma release are used.

Studies suggest that therapies that affect B-cells (RTX) but also other therapies that affect lymphocytes (MMF and MTX therapies) may impair the appropriate response to mRNA vaccines. The optimal timing of vaccination in these patients has not been determined. An observational study involving 123 patients with

Table 1. Effect of immunosuppressive and immunomodulatory drugs on post-vaccination response (compiled based on: Subesinghe S., Bechman K., Rutherford A.I. et al. A systematic review and metaanalysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. J. Rheumatol. 2018; 45: 733–744; Friedman M.A., Winthrop K. Vaccinations for rheumatoid arthritis. Curr Opin Rheumatol 2016; 28: 330)

	Methotrexate	Anti-TNF-α	Anti-CD20	CTLA-4 inhibitors	JAK inhibitors	Anti-IL-6
Pneumococcal vaccination	Reduces	Negligible impact	Significantly reduces	Reduces	Reduces	Negligible impact
Influenza vaccination	Reduces ?	Negligible impact	Significantly reduces	Reduces	Unknown	Negligible impact
Vaccination against hepatitis B	No data	Reduces	No data	No data	No data	No data

RMD, mostly treated with immunosuppressive drugs, showed that patients treated with RTX and MMF were less likely to develop a complete response to vaccination with the first dose of mRNA vaccine compared to patients treated with other immunosuppressive drugs.

Administration of a second dose of mRNA vaccine improved seroconversion in patients treated with MMF but had no effect in patients treated with RTX [22].

In another study involving 82 patients from the USA and Germany treated with immunosuppressive therapy for IMID who received two doses of mRNA vaccine, humoral response was judged to be inadequate more often in patients treated with MTX than in those not treated with this drug and in healthy volunteers (62 *vs.* 92 and 98%). Among them were patients treated with biologic TNF-alpha inhibitors, only one patient received RTX (without MTX), none of the patients used MMF. Induction of cytotoxic CD8+ T-cells, was also impaired in patients receiving MTX, but not in patients treated with other drugs [23].

The American College of Rheumatology (ACR) has issued recommendations for the management of RMD patients regarding the timing of vaccination and the use of supplemental doses.

1. For patients treated with HCQ, SSZ, LEF, AZA and CYC orally, with TNF inhibitors, IL-6 inhibitors, IL-1 inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, belimumab, IVIG, GCs and apremilast — there is no need to modify treatment.
2. For patients treated with MTX, it is suggested that MTX should be withheld one week before each dose of mRNA vaccine and should not be administered for a further 2 weeks after each dose.
3. MMF and oral calcineurin inhibitors — it is suggested that these drugs should be withheld for one week after each dose of vaccine.
4. JAK inhibitors — it is suggested to withhold these drugs for one week after each dose of vaccine.
5. Subcutaneous abatacept — it is suggested that the drug should be stopped one week before and one week after the first dose of the vaccine, but it should not be stopped during the administration of the second dose of the vaccine.
6. Intravenous abatacept — it is suggested that the first dose of vaccine be administered 4 weeks after the abatacept infusion and the next infusion be withheld for one week (a total interval of 5 weeks between abatacept administrations). There are no recommendations to withhold the drug during the second dose of the vaccine.
7. Intravenous cyclophosphamide — it is suggested that an infusion of the drug be given approximately one week after each dose (if the patient's health permits).
8. Rituximab — it is suggested that the vaccination cycle be started approximately 4 weeks before the next anticipated RTX administration cycle and that RTX administration be delayed 2 to 4 weeks after the second vaccination dose.

It is recommended that patients with AIIRD (autoimmune inflammatory rheumatic disease) be vaccinated with mRNA vaccines rather than the Johnson&Johnson single-dose vaccine.

For mRNA vaccines (Pfizer or Moderna), patients with AIIRD should receive a second dose of the same vaccine [24].

BOOSTER DOSE

Patients with chronic autoimmune inflammatory diseases treated with immunosuppressive and immunomodulatory drugs should receive a third dose of mRNA vaccine: BNT 162b2 Pfizer-BioNTech COVID-19) or mRNA-1273 (Moderna COVID-19) at least 28 days after completing the 2-dose vaccination cycle. This includes patients treated with SSZ, LEF, MTX, AZA, MMF, CYC, TNF inhibitors, IL-6 inhibitors, IL-1, IL-17, IL 12/23, IL-23 inhibitors, belimumab, oral calcineurin inhibitors, IVIG, GCs, RTX and ABA and apremilast.

The use of NSAIDs and HCQ is not considered as immunosuppressive treatment and therefore there is no recommendation in respect of a third dose.

It is acceptable for the third dose to be an alternative mRNA vaccine if identical preparations cannot be administered.

For patients receiving most immunosuppressive and immunomodulatory drugs, with the exception of GCs and anti-cytokine therapies (TNF, IL-1, IL-6, IL-17, IL-12/23, IL-23 inhibitors), it is recommended to withhold the drug dose 1–2 weeks after the supplemental vaccine dose, if the activity of the underlying disease permits. Some experts, but there is no consensus, also suggest withholding GCs and anti-cytokine drugs. In patients treated with RTX, the 3rd dose of vaccine should be given 2–4 weeks before the next administration of RTX.

There are no guidelines for a supplemental dose following vaccination with Johnson&Johnson's single-dose Ad26.COV.S vaccine (Janssen COVID-19); however, a supplemental dose appears to be recommended at least 2 months after the administration of the first series.

For patients who would receive a booster dose of this vaccine, the recommendations for the use of immunosuppressive drugs are identical to those for mRNA vaccines.

The American College of Rheumatology does not recommend laboratory testing (determination of IgM and IgG antibody levels against protein S or viral nucleocapsid proteins) to assess seroconversion after vaccination or to assess the need for vaccination in yet unvaccinated individuals. This is due to, among other things, a lack of knowledge of what level of antibodies should be considered to provide adequate protection and a lack of clinical relevance in the interpretation of such results [24].

Many questions about the response to vaccination still need to be answered. Among other things, it is being considered whether patients who have had a SARS-CoV-2 infection complicated by MIS (multisystem inflammatory syndrome) are at risk of abnormal vaccine response.

It is also uncertain whether vaccination against COVID-19 will not provoke an exacerbation of symptoms of multisystem inflammatory disease (in response to non-specific adjuvants, for example). A case of symptom exacerbation after vaccination in an RA patient has been described [25], but the causal relationship with vaccination is uncertain. If there is even a theoretical risk of exacerbation of RMD symptoms after vaccination for COVID-19, the benefits of vaccination outweigh the potential risk of exacerbation of the underlying disease.

The EULAR (European League Against Rheumatism) recommendations for the management of RMD patients in the context of SARS-CoV-2 infection formulated in July 2021 are divided into overarching principles and recommendations.

The overarching principles state, among other things, that:

— patients with RMD are not at increased risk of SARS-CoV-2 infection compared to those without RMD and do not have a worse prognosis for COVID-19;
— rheumatologists should be involved in the decision whether to continue or withhold immunosuppressive treatment;
— immunomodulatory drugs should not be used for COVID-19 treatment (off-label use) outside of established protocols and clinical trials.

The recommendations state, among others, that:

— RMD patients should be effectively encouraged to follow the general recommendations of social distancing, wearing a protective mask and frequent handwashing both before and after vaccination;
— patients who have been vaccinated against COVID-19 should continue RMD treatment unchanged; those who have not been vaccinated should also continue treatment, with the awareness that certain therapies are associated with an increased risk of worse course of COVID-19;
— if a patient is using chronic GCs and COVID-19 is suspected or confirmed, this treatment should be continued;
— if a patient with RMD is receiving RTX and is found to have COVID-19, deferral of the next cycle of RTX should be considered;
— if a patient with RMD is treated with RTX or other drugs that cause B-cell depletion, vaccination should be scheduled to achieve optimal post-vaccination immunogenicity;
— if a patient with RMD has not received immunosuppressive treatment to date and such treatment is planned, vaccination should be carried out before commencing immunosuppression;
— RMD patients should be encouraged to receive influenza and pneumococcal vaccination.

AIIRD patients at high risk of severe COVID-19 should receive REGEN-COV therapy (casirivimab and imdevimab administered together) either as post-exposure prevention in asymptomatic patients or as treatment in symptomatic patients (as early as possible).

The FDA has issued an emergency use approval (EUA) for REGEN-COV therapy as post-exposure prevention in adult and paediatric patients aged 12 years of age and weighing at least 40 kg who are at high risk of developing severe COVID-19 (hospitalisation or death). These recommendations are in line with recommendations for vaccination of patients with rheumatic diseases. According to these recommendations, all patients should be vaccinated as needed with inactivated vaccines (hepatitis, influenza, pneumococcus). The currently applicable recommendations are shown in Table 2.

Table 2. Immunizations recommended in patients with autoimmune diseases (compiled based on: Grohskopf L.A., Sokolow L.Z., Broder K.R. et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2018–2019 influenza season. MMWR Recomm. Rep. 2018; 67: 1; Singh J.A., Saag K.G., Bridges S.L. Jr. et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016; 68:1; van Assen S., Agmon-Levin N., Elkayam O. et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann. Rheum. Dis. 2011; 70: 414)

Type of vaccine	Against	Indications
Inactivated	Pneumococci (PCV13 and PCV23)	In all patients
	Influenza virus	Seasonally all patients
	Hepatitis A	In patients at risk
	Hepatitis B	In patients at risk
	Meningococci	In patients at risk
	Haemophilus influenzae	In patients at risk
	Papilomavirus	In patients at risk
	Tetanus, diphtheria, pertussis	According to the immunisation schedule
	Recombinant varicella vaccine	In patients before starting treatment or receiving low doses of immunosuppressive drugs
Live attenuated	Live varicella vaccine	**Not recommended** in patients receiving medium/high doses of immunosuppressive drugs
	Measles, rubella, mumps	**Contraindicated in patients receiving immunosuppressive drugs**
	Yellow fever	**Contraindicated in patients receiving immunosuppressive drugs**

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