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COVID-19 vaccination in patients with rheumatic diseases — status February 2022

ABSTRACT

Vaccination is the most effective strategy to prevent and reduce the effects of the COVID-19 pandemic. The purpose of this article is to summarize the current data and recommendations regarding vaccination against COVID-19 in children and adults with rheumatic diseases in Poland and worldwide. This paper also shows reports on vaccination in adults and children with rheumatic diseases, including efficacy, safety and adverse effects. Furthermore, ACR and PRES recommendations for COVID 19 vaccination in adults and children with rheumatic diseases were presented, including special situations that cause difficulties in daily clinical practice.

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KEY WORDS: COVID-19; vaccination; rheumatic diseases

INTRODUCTION

Vaccination is the most effective strategy to prevent and reduce the effects of the coronavirus disease 2019 (COVID-19) pandemic. Both in randomized studies and further observations proved of COVID-19 vaccines efficacy in reducing SARS-CoV-2 infection rates and severe disease. However, patients with an immune dysfunction related either to the rheumatic disease or the use of immune-modulating drugs, could have altered COVID-19 vaccination response. Some studies have shown a lower response in in this group of patients compared to healthy controls. It is unclear whether this is attributable to the underlying disease or its treatments [1].

Therefore, patients with rheumatic diseases need specific recommendations to improve the safety and effectiveness of vaccines.

The purpose of this article is to summarize the current data and recommendations regarding vaccination against COVID-19 in children and adults with rheumatic diseases.

COVID-19 IN CHILDREN AND ADULTS WITH RHEUMATIC DISEASES

The effect of the COVID-19 on patients with inflammatory rheumatic diseases remains unclear, also due to the different pathogenesis of diseases, additional disorders and different treatments.

Patients with a disorder of the immune system including inflammatory rheumatic diseases are characterized by immunocompromised and increased risk of infection, including by SARS-CoV-2. Additional risk factors associated with severe COVID-19 include older age and comorbidities like hypertension, diabetes, obesity, cardiovascular diseases, and chronic respiratory diseases. Some studies have shown a higher prevalence of COVID-19 in people with inflammatory rheumatic diseases compared with the general population [2].

Nevertheless, data from Spain, which is one of the countries heavily affected by the COVID-19 pandemic, demonstrated thatthe risk of SARS-CoV-2 infection in patients with

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rheumatic diseases, both adults and children, treated with disease-modifying antirheumatic drugs (DMARDs) is similar to that in the general population. Also, the course of the disease itself does not appear to have a more severe clinical picture. A study conducted in a reference rheumatology centre in Barcelona analysed data obtained from digital registries and via telephone from a group of 959 patients treated with synthetic, targeted or biologic DMARDs. In this group, 11 subjects (1.15%) with PCR-confirmed SARS-CoV-2 infection were identified. Six of them were patients requiring hospitalisation for COVID-19 respiratory symptoms. All confirmed cases involved adults. All 11 patients recovered; only one case required hospitalisation in an intensive care unit. The decision to discontinue disease-modifying therapy was made on a case-by-case basis. When comparing patients suspected with asymptomatic COVID-19 infection in the study population, it was found that patients treated with IL-6 blockers and abatacept were the least likely to have symptoms consistent with SARS-CoV-2 infection. IL-6 is associated with a cytokine storm, hence the study authors indicate the potential for COVID-19 patients to benefit from treatment that inhibits this cytokine. No confirmed case of COVID-19 has been reported in the paediatric population. When comparing the study group to the general population (living in the same administrative area), there were no significant differences in terms of the prevalence of the disease (0.48% vs. 0.58%) in persons with rheumatic diseases [3].

Differences in the incidence of COVID-19 have also been reported dependingto types of rheumatic disease, a higher incidence was found in patients with systemic connective tissue diseases compared to patients with chronic arthritis [2].

COVID-19 in children is it is most often a mild infection. Approximately 10% of all cases are pediatric. Among children requiring hospitalization about 25–60% of children have comorbidities [4].

Children with rheumatic diseases in the observations of the Spanish national study accounted for 2.2% of hospitalized patients with COVID-19. The disease had moderately course, with 1 fatality. Juvenile idiopathic arthritis (JIA) was diagnosed in 62.5% of patients.Active disease and the use of corticosteroids was considered as risk factors of severe COVID-19 in the pediatric population similar to adults [4].

In contrast, in children without comorbid rheumatic diseases, COVID-19 infection may rarely manifest as a delayed inflammatory response to past infection in the form of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [5]. Other long-term complications of COVID-19 in children include fatigue, musculoskeletal pain, headache, insomnia, difficulty breathing, palpitations [6]. Based on data from the UK registry, 13% of children aged 2–11 years and 14% of those aged 12–16 years had symptoms of COVID-19 that persisted up to 5 weeks following infection. Data from other countries involving 1,475 cases indicate that 42% of children may have moderate/severe course of the disease [6, 7].

VACCINATION AGAINST COVID-19 IN POLAND AND WORLDWIDE

Vaccination against COVID-19 is the greatest opportunity to defeat the global SARS-CoV-2 pandemic and prevent further dramatic consequences. OnFebruary 21, 2022, the World Health Organisation (WHO) announced that 10.41 billion doses of COVID-19 vaccines were administered worldwide. A total of 4.87 billion people received at least 1 dose, and 4.29 billion are fully vaccinated, representing 55,4% of the global population [8]. In Poland, vaccination against COVID-19 for adults and adolescents over 16 years of agestarted on 27 December 2020, as in other European Union countries. According to the Republic of Poland website gov.pl [9], more than 53 million vaccines were administered until 27 February 2022. Currently, 22,187,035 people are fully vaccinated, representing 59.04% of total population. On June 7, 2021, the 1st COVID-19 vaccine for children aged 12–15 years was approved in Poland, on December 12, 2021 also from the age of 5.On January 22, 2022, a booster dose was approved for adolescents 12–15 years of age.

By February 27, 2022, approximately 3,2 million doses were administered in the 5–17 age group. According to Statistics Poland [10], the population aged 0–17 is 6.9 million, which means that many children and adolescents remain unvaccinated.

COVID-19 VACCINES FOR CHILDREN AND ADULTS

COVID-19 vaccination is now available in Poland and in many countries around the world for children and adolescents aged 5 years and

Table 1. COVID 19 vaccines in Poland and European Union countries [11–16]

Vaccine	Company	Vaccine type	Age of vaccine administration	Indications
Comirnaty* [12]	BioNTech Manufacturing GmbH	COVID-19 mRNA vaccine (with modified nucleosides)	≥ 5 years	Active immunisation for COVID-19 caused by SARS--CoV-2 virus
Spikevax* [13]	Moderna Biotech Spain, S.L	COVID-19 mRNA vaccine (with modified nucleosides)	≥ 12 years	
COVID-19 Vaccine Janssen* [14]	Janssen-Cilag International NV	COVID-19 vaccine (Ad26.COV2-S [recombinant vaccine])	≥ 18 years	
Vaxzevria*[15]	AstraZeneca AB	COVID-19 vaccine (ChAdOx1-S [recombinant vaccine])	≥ 18 years	
Nuvaxovid* [16]	Novavax CZ	COVID-19 vaccine (recombinant spike [S] protein, adjuvanted)	≥ 18 years	

i.m. — intramuscular
*The drug received a conditional marketing authorisation. It was granted in the interest of public health because the drug addresses an unmet medical need and the benefits of immediate availability outweigh the risk of less comprehensive data than usually required [11].

Table 2. Primary and booster vaccination against COVID-19 in Poland and EU countries [11–16]

Vaccine	Age	Route of administration	Primary vaccination	Booster dose	Additional dose
Comirnaty [12]	5 – 12	i.m.	2 doses of 10 μg (0.2 mL)/ /dose an interval of 3 weeks*	No data	No data
	≥ 12	i.m.	2 doses of 30 μg (0.3 mL)/ /dose an interval of 3 weeks*	≥ 12 years a single dose of 30 μg at least 6 months after the 2nd dose of the vaccine	≥ 12 years a single dose of 30 μg at least 28 days after the 2nd dose (severe immunodeficiency)
Spikevax [13]	≥ 12 years	i.m.	2 doses of 100 μg (0.5 mL)/dose an interval of 28 days*	≥ 18 years A single dose of 50 μg (0.25 mL) at least 6 months after the 2nd dose	≥ 12 years a single dose of 100 μg at least 28 days after the 2nd dose (severe immunodeficiency)
COVID-19 Vaccine Janssen [14]	≥ 18 years	i.m.	a single dose of 0.5 mL	A single dose of 0.5 mL at least 2 months after the 1st a dose of the homologous vaccine — may be administered after an mRNA vaccine (timing of administration as for the primary vaccine)	No data
Vaxzevria [15]	≥ 18 years	i.m.	2 doses of 0.5 mL/dose an interval of 28–84 days*	No data	No data
Nuvaxovid [16]	≥ 18 years	i.m.	2 doses of 0.5 mL each, an interval of 3 weeks*	No data	No data

i.m. — intramuscular
*To complete the primary vaccination cycle, the same vaccine is recommended.

older. The European Medicines Agency (EMA) granted conditional marketing authorisation for 4 COVID-19 vaccines in Europe until February 22, 2022 (Table 1 and 2) [11–16]. Another 5 vaccines are currently being evaluated.

In May 2021, the first COVID-19 vaccine (Pfizer-BioNTech), was approved by the EMA for children aged 12 years and older, followed by another vaccine, next (Moderna vaccine), in July 2021. On 20 September 2021, Pfizer-

-BioNTech announced positive results of clinical trials concerning the COVID-19 vaccine in children aged 5-11 years [17]. In the United States, as of 4 November 2021, the vaccine is recommended for all children aged 5 years and older to protect against COVID-19 [18]. In November 30, 2021 EMA approved (Pfizer--BioNTechvaccine for use in children 5 years of age and older in Europe.Clinical trials concerning mRNA COVID-19 vaccines in children aged 5-11 years and aged 6 months to 5 years are currently ongoing studies [11].

Vaccines using other technologies are also being tested worldwide. There are currently 184 COVID-19 vaccines being tested in preclinical studies and 105 in clinical trials; a total of 289 vaccines are currently being tested [19].

VACCINATION AGAINST COVID-19 IN CHILDREN WITH RHEUMATIC DISEASES

There are few reports on the safety and efficacy of vaccination against COVID-19 in children and adolescents with rheumatic diseases. Halsak et al. study indicates an acceptable safety profile of COVID-19 vaccines in children with inflammatory rheumatic diseases. 246 patients (receiving biological or other therapies and the control group) aged 12–20.1 years were monitored.The most common adverse events of COVID-19 mRNA vaccination were fatigue (27.6%), headache (17.9%), myalgia (15.4%), arthralgia (15.4%) and fever (14.2%). Only 3 subjects (2 patients with familial Mediterranean fever, and one healthy child) were considered to experienced serious adverse events with hospitalization. Local reactions were seen in 8.1%, and 12.1% had disease flares within 1 month after the vaccines. There was no significant relationship between adverse event frequency and age, gender, the diseases and treatment [20].

At the turn of 2020/2021, the results of phase 1 and 2 studies and an ongoing phase 3 study concerning the safety and efficacy of Pfizer-BioNTech (BNTb262) and Moderna (mRNA-1273) vaccines were published. In a multicentre placebo-controlled study, 2,260 participants aged 12–15 and randomised 1:1 received 2 injections at an interval of 21 days (30 μgBNT162b2 or placebo). The results revealed that the BNT162b2 vaccine in children aged 12–15 years has a good safety profile, producing a better immune response against COVID-19 than in young adults aged 16–25 years. The results confirmed 100% vaccine efficacy within 7 days after administration of the 2nd dose and a good safety profile. Side effects were mild: mainly local reactions, pain at the injection site. Systemic symptoms — weakness, headache, chills resolved within 24–48 hours [21]. Another randomised placebo-controlled phase 2–3 trial involving 3,732 participants aged 12–17 years demonstrated efficacy and a good safety profile of mRNA-1273 vaccine (100 μg), similar to young adults [22].

The evidence regarding immunogenicity, efficacy, and safety of the Pfizer-BioNTech COVID-19 vaccine among children aged 5–11 years are based on data from one randomized, double-blind, placebo-controlled phase II/III clinical trial that enrolled 2,268 participants aged 5–11 years, randomized 2:1 to receive vaccine or placebo. Vaccine efficacy was supported by two types of evidence: direct efficacy against symptomatic infection and data consisting of neutralizing antibody titers. Vaccine efficacy was 90.9% in preventing symptomatic, laboratory-confirmed COVID-19. The measure of immune response to COVID-19 vaccine in children aged 5–11 years without evidence of previous SARS-CoV-2 infection was at least as high as the response observed in persons aged 16–25 years. Among vaccine recipients aged 5–11 years, reactogenicity symptoms, defined as local or systemic reactions during the 7 days after vaccination, were frequent (86.2% local reaction, and 66.6% systemic reaction), the vast majority were mild to moderate. Reactogenicity symptoms were generally less frequent in children aged 5–11 years than in persons aged 16–25 years. Systemic adverse reactions were more commonly reported after the second dose than after the first dose, often 1–2 days after vaccination, and resolved after 1–2 days. Severe local and systemic adverse reactions (grade 3 or higher, defined as interfering with daily activity) occurred in 2.7% of vaccine recipients and 1.1% of placebo recipients and among vaccine recipients the most common symptoms were fatigue (0.9%), headache (0.3%), fever (0.8%) and injection site pain (0.6%) [23].

Data from clinical trials and from studies involving vaccinated young adults aged 16 and older in Israel revealed 95% vaccine efficacy [24].

COVID-19 VACCINATION IN ADULTS WITH RHEUMATIC DISEASES

Machado et al. evaluated the safety profile and tolerability of COVID-19 vaccine in adult patients with various rheumatic diseases treated with DMARDs based on the COVAX registry (EULAR registry of patients with rheumatic diseases vaccinated against COVID-19) comprising 1,519 adults. The authors concluded that the safety profile was similar to that in the general population (mild and short-term local or systemic symptoms). Only 0.1% of patients presented with serious side effects. Tolerability of the vaccine was good, with only a small percentage of exacerbations of rheumatic diseases (5%, including 1.2% severe cases). In the analysed group, 86% of vaccinated subjects achieved seroprotective levels of post-vaccination antibodies. Immunogenicity was impaired by taking anti-CD-20 drugs, with a seroprotection rate of approximately 39%. The use of glucocorticosteroids, mycophenolate mofetil and abatacept was also associated with reduced immunogenicity. Methotrexate therapy — either used in monotherapy or combined with other drugs — significantly reduced seropositivity, although to a lesser extent than anti-CD-20 drugs, mycophenolate mofetil or abatacept. More than 97% of patients treated with anti-cytokine drugs in monotherapy (anti-TNF, anti-IL-17, anti-IL-6) presented an adequate immunogenic response. However, in a combination with methotrexate, seropositivity significantly decreased to 93% ($p = 0.04$). Age over 65 years, diagnosis of rheumatoid arthritis, inflammatory myopathies, treatment with anti-CD-20 drugs and abatacept reduced the likelihood of seropositivity [25].

The study by Braun-Moscovici et al. assessed disease activity and humoral response in patients with variousinflammatory rheumatic diseases following 2 doses of Pfizer-BioNTechmRNA vaccine. In 264 patients (mean age 57 years) with stable disease who participated in the study (with no change in disease-modifying therapy before and after vaccination), protective levels of anti-SARS-CoV-2 IgG antibodies were achieved following the 2nd dose of vaccine in 227 subjects (86%) and no seroprotection was achieved in 37 subjects (14%) (they were patients who received treatment causing B-cell depletion, anti-CD-20 drugs). No serious side effects were observed and the rheumatic disease remained stable following vaccination [26].

RISK ASSESSMENT OF SERIOUS ADVERSE REACTIONS FOLLOWING COVID-19 VACCINATION

The safety of the COVID-19 mRNA vaccine in children has been demonstrated in clinical trials [21–23], and in further observations [27].

To further characterize safety of the COVID-19 vaccine in children aged 5–11 years, Centers for Disease Control and Prevention (CDC) reviewed adverse events. Approximately 8.7 million doses COVID-19 vaccine were administered to children in this age in the period November–December 2021 and received 4,249 reports of adverse events, 97.6% of which were not serious. Approximately 42,504 children aged 5–11 years were enrolled in "v-safe" program after vaccination with COVID-19 vaccine. After dose 2, a total of 17,180 (57.5%) local and 12,223 systemic (40.9%) reactions (including injection-site pain, fatigue, or headache) were reported [27].

Also, safety monitoring systems operated by the US Food and Drug Administration's (FDA) indicate that COVID-19 vaccines are safe [28]. More than 432 million doses of COVID-19 vaccine were administered in the United States in the period from December 2020 to November 2021. The most common side effects of COVID-19 vaccines include swelling, tenderness, redness at the injection site, fever, headache, fatigue, muscle pain, chills, nausea. To date, FDA safety systems have detected 2 serious but rare health problems following vaccination:anaphylaxis and thrombosis with thrombocytopenia syndrome (TTS) following vaccination using Janssen COVID-19 vaccine — 7 cases per 1 million vaccinated women aged 18–49 [28].

The prevalence of confirmed anaphylaxis following mRNA vaccines was determined to be 4.8–5.1 per 1 million doses. In an evaluation of nearly 12 million doses of COVID-19 mRNA vaccines (57% BioNTech, 43% Moderna) that were administered to 6.2 million people aged 12 or older, the rate ratios (RRs) were highest for thrombotic thrombocytopenic purpura (2.6), cerebral venous sinus thrombosis (1.55) and transverse myelitis (1.45). The RR for the prevalence of venous thromboembolism in the risk interval compared to the comparison interval was 1.16. The risk of ischaemic stroke, appendicitis , myocardial infarction or other events in relation to mRNA vaccine administration has not been confirmed [29, 30].

Table 3. COVID-19 vaccination in children with rheumatic diseases — PRES recommendations [33]

General recommendations	The new COVID-19 vaccines approved by health authorities for patients aged 5 years and older are also recommended for paediatric patients with rheumatic diseases
	Paediatric patients should be vaccinated against COVID-19 using vaccines approved by relevant national health authorities for children in this age group
Rheumatologist consultation	Before deciding to COVID-19 vaccinate, it is recommended to consult a pediatric rheumatologist to assess the activity of the disease and the medications taken
Booster vaccine	A booster vaccine should be administered in accordance with local recommendations (in Poland from the age of 12)
Treatment	If prednisone > 20 mg/day or > 0.5 mg/kg/day is used, the decision to vaccinate should be discussed with a rheumatologist
Patient after COVID-19	COVID-19 vaccination should be administered in children after SARS-CoV-2 infection no earlier than 3 months aftter the day of full recovery.This is valid for the first vaccine dose as well as the second dose
	In situations where a child becomes ill with COVID-19 after receiving the first dose, a second dose may be given at least 3 months after the day of full recovery
Patient after PIMS-TS	COVID-19 vaccination in patients with a history of PIMS-TS should be in accordance with the recommendation of local health authorities
	COVID-19 vaccinate is recomended after 6 months, following full clinical recovery from PIMS-TS and normal cardiac function. If IVIG was not given as therapy, consider vaccination after 3 months
	For children who had PIMS-TS following Covid-19 vaccine, it is recommended to withhold further COVID-19 vaccination
Masks and physical distancing	Vaccinated patients should still wear masks and practice physical distancing, according to the local health guidelines because it is possible that vaccinated people can carry the virus and be contagious to others
Fluvaccine	Annual flu vaccine is recommended for children with rheumatic diseases. The flu vaccine should not be recommended together with the COVID-19 vaccine (preferably with an interval of 2 weeks)

COVID-19 — coronavirus disease 2019; PRES — Peadiatric Rheumatology European Society; EMA — European Medicines Agency

There have also been several recent reports concerning a potential complication Following COVID-19 vaccination in the form of myocarditis. Although mRNA vaccines were not associated with an overall increased risk of myocarditis/pericarditis, they were associated with an excess risk of myocarditis/pericarditis among those aged 12–39 years, with an estimated risk of 6.3 per million doses on days 0 to 7 after vaccination [30].

Simone et al. described 15 cases of confirmed myocarditis in patients aged 12–18 years (14 male subjects)hospitalised within 30 days of vaccination (8 subjects received BNT-162b2vaccine PfizerNBionTech and 7 received mRNA-1273 vaccine Moderna). None of subjects had a history of cardiovascular diseases. Within 1–6 days following vaccination, 14/15 patients had chest pain, 10/15 fever, 8/15 musculoskeletal pain and 6/15 headache. Additional tests revealed elevated troponin levels and a reduction in cardiac ejection fraction. Symptoms resolved within a few days using standard treatment [31].

As in adolescents, Diaz et al. highlight the risk of myocarditis in adults (20 cases/2,000,287 vaccinated persons) and pericarditis (37 cases/2,000,287 vaccinated persons) after the first or second dose of Pfizer-BioN-Tech mRNA or mRNAModerna vaccines [32].

The Summary of Product Characteristic (SmPC) of Pfizer-BioNTech) mRNAvaccine states that „Vaccinated persons should be instructed to seek immediate medical attention if symptoms indicative of myocarditis or pericarditis occur, such as (acute and persistent) chest pain, dyspnoea or palpitations following vaccination" [12].

PRES RECOMMENDATIONS FOR VACCINATION IN CHILDREN WITH RHEUMATIC DISEASES

The Paediatric Rheumatology European Society (PRES), an European scientific society for healthcare professionals in paediatric rheumatology, has issued recommendations on vaccination for children with rheumatic diseases (last update: December 2021) (Table 3) [33].

Current observations indicate that COVID-19 vaccines are as safe and effective for children with rheumatic diseases as they are among the healthy paediatric population. Based on the data available so far, there is no evidence of risk exacerbation of rheumatic di-

Table 4. Guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases [34]

General considerations related to patients with rheumatic diseases
The rheumatology healthcare provider is responsible for engaging the patient in a discussion to assess COVID-19 vaccination status and engage in a shared decision-making process to discuss receiving the vaccine
Acknowledging heterogeneity due to disease- and treatment-related factors, and after considering the influence of age and sex, patients are at higher risk for hospitalized COVID-19 and worse outcomes compared to the general population
patients should be prioritized for vaccination before the nonprioritized general population of similar age and sex
Beyond known allergies to vaccine components, there are no known additional contraindications to COVID-19 vaccination for patients
The expected response to COVID-19 vaccination for many patients on systemic immunomodulatory therapies is blunted in its magnitude and duration compared to the general population
A theoretical risk exists for flare or or worsening of rheumatic disease following COVID-19 vaccination. However, the benefit of COVID-19 vaccination for patients outweighs the potential risk for new onset autoimmunity
Recommendations for primary and supplemental dosing of the COVID-19 vaccine in patients COVID-19 vaccine with rheumatic diseases
Patients should receive COVID-19 vaccination, consistent with the age restriction of the EMA and Polish Ministry of Health approval
Patients who are on immunomodulatory therapy should be vaccinated in a similar fashion regardless of diagnosis
For patients not yet vaccinated, either of the mRNA vaccines is recommended over the Janssen vaccine. There is no recommendation for one mRNA vaccine over another
For a multi-dose vaccine (e.g. the mRNA Pfizer or Moderna), patients should receive the second dose of the same vaccine, even if there are non-serious adverse events associated with receipt of the first dose
In patients receiving any immunosuppressive medication, if they have completed the two-dose mRNA vaccine series or received the single-dose Janssen vaccine, a supplemental (booster) dose of COVID-19 vaccine is recommended at least 28 days after completion of the vaccination series
For patients who previously completed the mRNA COVID-19 vaccine series or 1-dose Janssen vaccine, and who are receiving a supplemental dose, an mRNA vaccine dose of either type (Pfizer or Moderna) is preferred
Primary vaccination, supplemental dosing, and booster doses should be given regardless of whether patients have experienced natural COVID-19 infection.
Healthcare providers should not routinely order any lab testing (e.g., antibody tests for IgM and/or IgG to spike or nucleocapsid proteins) to assess immunity to COVID-19 post-vaccination, nor to assess the need for vaccination in a yet--unvaccinated person
For high-risk patients, pre-exposure prophylaxis monoclonal antibody treatment is recommended when available, if licensed or approved under EMA and national health authorities
Patients at high risk for poor outcomes related to COVID-19 should receive monoclonal antibody therapy, either as prevention (i.e., post-exposure prophylaxis for asymptomatic, recently exposed patients) or as treatment for newly symptomatic patients, if licensed or approved under EMA and national health authorities
Following COVID-19 vaccination, patients should continue to follow all public health guidelines regarding physical distancing and other preventive measures
Household members and other frequent, close contacts of patients should undergo COVID-19 vaccination when available to them to facilitate a ‚cocooning effect' that may help protect the patient. No priority for early vaccination is recommended for household members
While vaccination would ideally occur in the setting of well-controlled disease, except for those patients with life-threatening illness (e.g., in the ICU for any reason), COVID-19 vaccination should occur as soon aspossible, irrespective of disease activity and severity

COVID-19 — coronavirus disease 2019; EMA — European Medicines Agency; ICU — intensive care unit

sease in children following vaccination. The risk of myocarditis is low. Vaccines should be considered for each child based on national recommendations. The PReSVaccination Study Group is conducting an ongoing registry that aims to evaluate the safety and immunogenicity of the COVID-19 vaccines among patients with childhood rheumatic diseases. So far there are no safety concerns following available data on about 100 patients. Registries regarding the efficacy, immunogenicity and safety of COVID-19 vaccines for patients with pediatric rheumatic diseases allow to conduct an evaluation on a large group of patients [33].

Table 5. Guidance related to the use and timing of vaccine dosing and immunomodulatory therapy in relation to COVID-19 vaccination in RMD patients [34]

Medication	Recommended time between vaccine and treatment
Hydroxychloroquine, IVIG	No modifications to either immunomodulatory therapy or vaccination timing
Cyclophosphamide IV	Suspend administration for 1 week after each dose of vaccine, if possible
Abatacept SQ	Suspension of the drug for 1–2 weeks (depending on disease activity) after each dose of the vaccine
Abatacept IV	Vaccination 1 week before the next dose of the drug
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors	No consensus has been reached on on temporary drug discontinuation after each dose of vaccine, including both primary and booster doses
Belimumab SQ	Suspend administration for 1–2 weeks (depending on disease activity) after each dose of vaccine
Acetaminophen, NSAIDs	Assuming that the disease is stable, hold for 24 hours prior to vaccination. No restrictions on use post-vaccination once symptoms develop
Rituximab or other anti-CD20 B-cell depleting agents	For the decision of the rheumatologist
All other conventional and targeted immunomodulatory or immunosuppressive medications except those listed above	Suspension of drug administration for 1-2 weeks (depending on disease activity) after each dose of vaccine

NSAIDs — non-steroid anti-inflammatory drugs; IL-6R — sarilumab; tocilizumab; IL-1R — anakinra, canakinumab; IL-17 — ixekizumab, secukinumab; IL-12/23 — ustekinumab; IL-23 — guselkumab, rizankizumab; JAK inhibitors — baricitinib, tofacitinib, upadacitinib; CDC — Centers for Disease Control and Prevention; IVIG — intravenous immune globulin

ACR GUIDANCE FOR VACCINATION IN ADULTS WITH RHEUMATIC DISEASES

The American College of Rheumatology (ACR), an American scientific society, presented guidance for the use of COVID-19 vaccines in patients with rheumatic and musculoskeletal diseases. The guidance is continuously updated (current version 5 of February 2, 2022) (Tables 4 and 5). The guidelines are based on weak and/or indirect evidence and expert opinions. Therefore, all guidelines should be considered conditional or temporary [34].

COVID-19 VACCINE BOOSTER DOSE — ACR RECOMMENDATIONS

A single supplementary dose of Pfizer-BioNTech COVID-19 vaccine (age ≥ 12 years) or Moderna COVID-19 vaccine (age ≥ 18 years) is recommended ≥ 28 days after completion of the two-dose mRNA vaccine series in patients with rheumatic disease receiving any immunosuppressive or immunomodulatory therapy. These include the therapies listed in Table 5, including long-term corticosteroids, with the exception of hydroxychloroquine. Attempts should be made to match the supplemental mRNA dose to the type administered in the original mRNA series; however, if this is not possible, an alternative booster dose should be administered [34].

EXCEPTIONAL SITUATIONS RELATING TO VACCINATION AGAINST COVID-19

The Centers for Disease Control and Prevention (CDC), an agency within the US Department of Health and Human Services, regularly updates recommendations for exceptional health situations related to COVID-19 vaccination. The guidelines are based on indirect evidence and expert opinion and drawn up in respect of vaccines used in the United States (Pfizer-BioNTech, Moderna, Janssen). Nevertheless, they are valuable recommendations for doctors in other countries. In view of the expected new scientific reports, all recommendations should be considered conditional or provisional [35] (Table 6).

CONCLUSIONS

1. Patients with systemic rheumatic diseases are more likely to be hospitalised for COVID-19 and have poorer outcomes, compared to the general population.
2. To the best of current knowledge, the benefits of the vaccine in preventing severe illness and hospitalisation for SARS-CoV-2 infection outweigh the risk of adverse effects, including myocarditis.

Table 6. Exceptional situations (CDC recommendation) [35]

Interchangeability of vaccines	Primary series doses and additional primary dose (for moderately and severely immunocompromised people) should be with the same mRNA vaccine product. In exceptional situations, such as a contraindication to a second dose of mRNA vaccine or when the previous product cannot be determined or is not available, another approved vaccine may be used
Coadministration with other vaccines	COVID-19 vaccines may be administered without regard to timing of other vaccines on the same day, including simultaneous administration. When deciding whether to administer COVID-19 and other vaccines, providers should consider whether the patient has delayed or is at risk of delaying recommended vaccines, the risk of vaccine-preventable diseases (e.g. during an epidemic) and the reactogenicity profile of vaccines
Persons with prior or current COVID-19	COVID-19 vaccines can be given safely to people with prior SARS-CoV-2 infection. Vaccination of people diagnosed with COVID-19 should be postponed until recovery from acute infection and completion of isolation
Persons with a known SARS--CoV-2 exposure	People in community or outpatient setting should defer vaccination until quarantine period has ended
Persons who received monoclonal antibodies or convalescent plasma for COVID-19 treatment	People who previously received antibody products (anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma) as part of COVID-19 treatment, post-exposure prophylaxis, or pre-exposure prophylaxis can be vaccinated at any time People who previously received a COVID-19 vaccine, administration of tixagevimab/cilgavimabfor pre-exposure prophylaxis should be deferred for at least two weeks after vaccination
Pregnancy Breastfeeding Fertility	Pregnant and breastfeeding women and those trying to get pregnant are recommended to receive a COVID-19 vaccine primary series, additional primary dose (if indicated) and booster dose, they should be informed of risk of TTS after receipt of Janssen COVID-19 Vaccine and the availability of other options
Moderate and/or severe immunodeficiency	Patient may receive any approved COVID-19 vaccine — After the two-dose primary mRNA series, persons ≥ 12 years of age should receive an additional dose (same mRNA vaccine) at least 28 days after the second dose, followed at least 6 months later by a single booster (any approved vaccine) — Following the first primary dose of Janssen vaccine, immunocompromised persons ≥ 18 years of age should receive a single booster dose (any FDA-authorised or approved vaccine) at least 2 months (8 weeks) after the first dose of Janssen. There is currently no recommendation that people who have received the Janssen primary series should receive an additional dose in the primary series

TTS — thrombosis with thrombocytopenia syndrome

3. Physicians and other health care professionals should advocate and promote COVID-19 vaccination in patients with rheumatic diseases.
4. mRNA COVID-19 vaccines are recommended for all children and adolescents aged 5 years and older.

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