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REVIEW ARTICLE

Vaccination in children with immune-mediated disorders

Ana Karolina Barreto Berselli Marinho, PhD

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), Serviço de Imunologia Clínica e Alergia, São Paulo, SP, Brazil

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Abstract

Objective: To present an updated review of recommendations for the vaccination of children with immune-mediated diseases, with an emphasis on rheumatic and inflammatory diseases.
Source of data: Studies published in the PubMed and Scielo databases between 2002 and 2022, Guidelines of Brazilian Scientific Societies, Manuals and Technical Notes of the Ministry of Health of Brazil, on current immunization schedules for special populations.
Data synthesis: Immunosuppressive drugs and biological agents reduce the immunogenicity of vaccines and favor susceptibility to infections. The safety and efficacy of immunogens are important points for vaccination in children with immune-mediated diseases. The safety threshold of a vaccine applied to immunocompromised individuals can be reduced when compared to healthy individuals. Very often, the recommendations for the immunization of children with immune-mediated diseases follow the recommendations for immunocompromised patients. Vaccination against COVID-19, on the other hand, should ideally occur when the disease is stabilized and in the absence of a low degree of immunosuppression. The patients should be informed about the possibility that the immunization may fail during treatment with immunosuppressants. Specific vaccination schedules should be considered to ensure better protection.
Conclusions: Recent studies have allowed updating the recommendations on the safety and immunogenicity of vaccination in children with immune-mediated diseases, especially for live attenuated vaccines. There is a scarcity of data on the safety and efficacy of COVID-19 vaccines in patients, particularly pediatric patients, with rheumatic diseases. The completion of ongoing studies is expected to help guide recommendations on COVID-19 vaccines in this group of patients.

Introduction

Vaccination is the most effective method to prevent infection, which is especially important in immunocompromised children treated with immunosuppressive and/or immunomodulatory therapies. Children with immune-mediated diseases are usually treated with these medications; therefore, infections pose a great risk to their health. Despite the understanding of the disease prevention relevance, vaccination coverage is not

E-mail: ana.marinho@hc.fm.usp.br

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satisfactory in these children; the health professionals' approach to vaccination could be improved and parents could be adequately advised on the importance of vaccination for their children.

Inactivated vaccines are generally recommended regardless of the immunomodulatory therapy. Vaccination with live attenuated vaccines is not recommended in patients using high doses of corticosteroids or other immunomodulatory or immunosuppressive drugs, including immunobiological. However, in cases of high risk of infection, vaccination with live vaccines may be considered on a case-by-case basis, weighing the risk of natural infection *versus* the presumed risk of the vaccination. The level of evidence for this approach is still low. The authors need clearer evidence on the safety and immunogenicity of live attenuated vaccines in children undergoing treatment with immunosuppressive drugs.

Vaccination in children with immune-mediated diseases

Children with immune-mediated diseases, particularly rheumatic/inflammatory diseases, including those treated with biologics, are at increased risk of developing severe infections due to the triggering of underlying inflammatory processes. Immunomodulatory therapy contributes, in part, to this picture of immune dysfunction and immunosuppression.[1-3]

Many severe infections can be prevented with vaccination. Several studies have reported an increased incidence of infections, including severe ones, in pediatric rheumatic patients treated with biological therapy or synthetic drugs.[4,5]

However, the immunization coverage in children with immune-mediated diseases is far from ideal and is significantly lower when compared to the general population. A Slovenian study observed that approximately 35% of children with pediatric rheumatic diseases followed at the Children's Hospital of the University of Ljubljana have an incomplete vaccination schedule, being more susceptible to diseases preventable by immunization.[6]

Among the most neglected vaccines were hepatitis B (HBV) and the second dose of the vaccine against measles, mumps, and rubella (MMR).[6] Children with immune-mediated rheumatic diseases should receive additional doses of the pneumococcal vaccine, in addition to being immunized against influenza annually. However, the Slovenian study showed that vaccination coverage for influenza was only 10% and only 4% for pneumococcal infections in children whose parents answered the questionnaire.[6] It should be noted that both vaccines are "non-live" ones and are recommended for all children with immune-mediated rheumatic diseases.[7]

In Brazil, the National Immunization Program (PNI, *Programa Nacional de Imunizações*) has a history of success due to several immunization strategies that expand universal access to immunization for the entire population. Among these initiatives, the Reference Centers for Special Immunobiologicals were created, i.e., the CRIE (*Centros de Referência para Imunobiológicos Especiais*), which are centers that consist of specific infrastructure and logistics, aimed at the care of people with special clinical conditions, including immunosuppressed children with immune-mediated diseases. Therefore, some important vaccines offered free of charge at Reference Centers stand out, such as the 23-valent pneumococcal, hepatitis A, meningococcal C and diphtheria, tetanus, and acellular pertussis vaccines.[8]

Recommendations for the vaccination of children with immune-mediated rheumatic/inflammatory diseases

Recommendations regarding vaccination in children with immune-mediated diseases are well-established for pediatric patients with autoimmune/inflammatory rheumatic diseases (pedAIIRD). Recently, the European Alliance of Associations for Rheumatology (EULAR) published an update of recommendations for the vaccination of children with rheumatic diseases. This update took into account new studies on the safety of live attenuated vaccines and vaccine immunogenicity in patients treated with new anti-rheumatic drugs.[9] This update addresses three important aspects of vaccine safety: absence of serious adverse effects, non-aggravation of the underlying disease, and non-triggering of infections in the case of live attenuated vaccines.

In the recommendations, the term "immunosuppressed" is used for pediatric patients using the immunosuppressive drugs described in Table 1. In addition, pedAIIRD use DMARDs (disease-modifying antirheumatic drugs) biologic disease-modifying antirheumatic drugs (bDMARDs), or target-specific disease-modifying antirheumatic drugs (tsDMARDs). Finally, patients were also considered immunosuppressed when using a combination of the abovementioned drugs and, in the table, at any dose.[9]

Recommendations for inactivated ("non-live") vaccines

"Non-live" vaccines include inactivated, subunit, toxoid, purified polysaccharides, purified polysaccharides conjugated to proteins, or fragmented vaccines.

Table 1 Medications and doses used for the classification of pedAIIRD patients as immunosuppressed.

Class	Name	Dose
Corticoids	Prednisolone	$\geq$ 0.5mg/kg/day for $\geq$ 2 weeks
csDMARDs	Ciclosporin	$>$ 2.5mg/kg/day
	Azathioprine	$\geq$ 3mg/kg/day
	Oral cyclophosphamide	$>$ 2.0mg/kg/day
	Leflunomide	$\geq$ 0.5mg/kg/day
	Mycophenolate mofetil	$\geq$ 30mg/kg/day or $>$ 1000mg/day
	Methotrexate (MTX)	$\geq$ 15mg/m2/week or $\geq$ 25mg/week
	Tacrolimus	$>$ 1.5mg/day

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

Influenza vaccine

Immunization with the influenza vaccine is strongly recommended for all patients treated with immunosuppressive therapies.[10] This recommendation was based on studies carried out in adult patients, whose results were extrapolated to support influenza vaccination in pediatric patients using glucocorticoids or DMARDs.[7,11-13]

The influenza vaccine is well tolerated and induces a humoral response that protects against infections. The seroprotection rates observed in pedAIIRD patients did not differ from those observed in healthy individuals, except in those patients using high doses of glucocorticoids[13] and patients with juvenile-onset systemic lupus erythematosus (jSLE), mainly in the exacerbated active phase of the disease.[14] Differences in seroprotection were not observed in patients treated with bDMARDs (TNFi and anti-IL6) and healthy subjects, either. However, those using TNF1 showed a lower amount of specific antibodies and rapidly declining seroprotection.[14,15]

Therefore, influenza vaccination in pedAIIRD patients is safe and immunogenic. Since this group of patients has an increased risk of infections and complications, vaccination with the inactivated vaccine is strongly recommended in individuals who are being treated with immunosuppressants. On the other hand, the live attenuated influenza vaccine should be avoided in immunocompromised children.

Pneumococcal vaccine

Due to the relatively high incidence of infections in all age groups caused by *Streptococcus pneumoniae*, and also due to the high mortality, morbidity, and treatment costs, vaccination against this pathogen is a priority for the World Health Organization (WHO).[16]

According to the EULAR, vaccination against this pathogen using the 10-valent (PCV10) or 13-valent (PCV13) pneumococcal conjugate vaccine is recommended in all unvaccinated pedAIIRD patients.[9]

Previous studies, carried out with the 7-valent pneumococcal conjugate vaccine (PCV7), proved the efficacy of pneumococcal conjugate vaccines in immunocompromised patients, including AIIRD.[17,18] The conjugate vaccines showed good immunogenicity and safety in pedAIIRD, including those using MTX and glucocorticoids. Moreover, children on TNFi therapy showed seroprotection similar to the control group[19] but may have lower concentrations of specific antibodies.[20]

The 23-valent pneumococcal polysaccharide vaccine (PPSV-23) induces weak or absent responses in children younger than two years. Thus, the indication for PPSV-23 depends on the risk of developing severe pneumococcal infections in pedAIIRD, which are not covered by PCV10/13 vaccines, especially in children over two years of age.

There is a scarcity of studies on the effectiveness of the PPSV-23 vaccine in preventing invasive pneumococcal disease. Two studies with a small cohort confirmed the safety of this vaccine in juvenile idiopathic arthritis (JIA, n = 27)[21] and jSLE (n = 30).[22] In JIA patients, the vaccine showed moderate immunogenicity. The observed seroconversion was 53% in patients using MTX and 30% in those using a combination of MTX and TNFi.[21] In jSLE, the observed seroprotection was 77%, compared to 86% in healthy controls.[22]

Therefore, immunization with PCV10/13 is recommended for all children, including patients with pedAIIRD. Vaccination with PPSV-23 is recommended in the Brazilian vaccination calendar according to age and should be considered in immunosuppressed patients and with those with SLE.[8] According to the EULAR guidelines, the use of PPSV-23 in cryopyrin-associated periodic syndrome (CAPS) should be avoided for safety reasons.

Tetanus vaccine

The tetanus vaccination in pedAIIRD should be given according to recommendations for the general population.[9]

Some studies have observed low titers of antibodies against tetanus toxoid several years after the immunization.[23] Therefore, booster doses should be given to pedAIIRD patients when necessary. The tetanus vaccine is safe, and no adverse events (AEs) have been observed after the vaccination.[24]

Moreover, when tetanus immunization is necessary, passive immunization is recommended for patients receiving B-cell depletion therapy within the past six months.[9]

Vaccine against human papillomavirus (HPV)

Protection against HPV infection is especially important in patients with SLE since they are at greater risk of having persistent infections with this virus. These infections increase the risk of squamous intraepithelial lesions and cervical cancer.[9]

Several studies reported similar levels of antibody responses in most pedAIIRD patients vaccinated against HPV when compared to healthy individuals, being well tolerated by children and adolescents.[25-27]

Based on the increased risk of persistent high-risk HPV infections and premalignant lesions in patients with SLE, acceptable safety, and the good seroprotection rate, vaccination against HPV is highly recommended in unvaccinated jSLE patients.

Recommendations for live attenuated vaccines

Vaccines can also be produced from live attenuated microorganisms, presenting some risk of triggering the disease, especially in immunocompromised patients.

In Brazil, scientific societies do not recommend the immunization of people with rheumatological and autoimmune diseases with severe immunosuppression, for the following attenuated live vaccines: BCG, rotavirus, oral polio vaccine (OPV), yellow fever, MMR, varicella, MMR-V, attenuated herpes zoster and dengue. For moderately immunocompromised individuals, it is recommended to evaluate clinical parameters and the local epidemiological risk to decide whether or not to vaccinate with live attenuated vaccines.[8]

The EULAR recommendations discussed below are specific to systemic live attenuated vaccines administered intramuscularly or subcutaneously. Safety studies in pedAIIRD patients for mucosal vaccines (e.g., influenza and rotavirus) are not yet available.[9]

Measles, mumps, and rubella vaccine (MMR)

There are two recommendations regarding booster doses of MMR vaccine for pedAIIRD patients.

The first concerns administering MMR booster doses in patients using MTX. In patients with JIA, the booster dose with the attenuated virus-induced protection, without causing the disease. There was a significant increase in antibody concentrations, indicating seroprotection.[28]

The second informs that booster doses of the MMR vaccine can be considered in patients treated with low doses of glucocorticoids or therapies with TNFi, anti-IL1, and anti-IL6. Several studies have shown the safety of booster doses of MMR in pedAIIRD patients using bDMARDs, including a multicenter study (n = 234 patients). There was no triggering of infection associated with this vaccine. Thirteen mild AEs (local skin reaction, fever, and pain) were reported. There was no occurrence of any moderate or severe AE.[9,29]

Varicella vaccine

Immunocompromised individuals are at greater risk of complications after infection with the Varicella-zoster virus (VZV), including secondary bacterial infection of skin lesions, pneumonia, encephalitis, hepatitis, or hemorrhagic complications, increasing the risk of hospitalizations.[9,30] The pedAIIRD children who have not yet had contact with the virus are very susceptible to infections.

Vaccination with the VZV vaccine showed good immunogenicity and safety in pedAIIRD patients. A humoral response was induced in most patients and VZV-specific T-cell responses were comparable between pedAIIRD patients and healthy controls.[31,32]

The safety of this live attenuated vaccine is extremely important in patients who have not yet had contact with the virus. Studies have shown that vaccination in this group of patients, including those on low-dose glucocorticoids, MTX, and bDMARDs (TNFi, anti-IL6, and anti-IL1), did not show complicated or disseminated varicella infections. Three patients had a mild rash similar to VZV, and one underwent intravenous treatment with acyclovir for safety reasons.[31,32]

Therefore, vaccination against VZV is strongly recommended in patients who are not yet vaccinated or infected with the virus and who are taking MTX. Likewise, vaccination may be considered in these patients when they are treated with low-dose glucocorticoids, TNFi, anti-IL1, and anti-IL6 therapy.[9]

Yellow fever vaccine

There are no data in the literature on the safety of primary immunization of immunosuppressed pedAIIRD patients with the yellow fever vaccine.[9] In general, the yellow fever vaccine (YFV) is contraindicated in immunocompromised individuals.

In Brazil, given the epidemiological situation of high risk of exposure to the yellow fever virus, the vaccination can be considered after medical evaluation in a certain group of immunocompromised rheumatic patients. When indicated, it is recommended not to apply the yellow fever vaccine concomitantly with other attenuated live virus vaccines, considering a minimum interval of 28 days between this vaccine and, for instance, the triple viral vaccine (MMR). Additionally, there is no contraindication to the vaccine for people living with immunocompromised patients.[10,33]

The use of biologics and immunosuppressants contraindicates the yellow fever vaccine; however, given the epidemiological risk context, the vaccine can be administered, depending on the immunological condition of the underlying disease, three months after drug withdrawal (DMRADs), and at least six to twelve months after therapy with anti-B-cell antibodies (e.g., rituximab).[10] The drug withdrawal for this purpose should be carefully evaluated by a specialist to consider the benefits of vaccination in this population and the potential risk of disease decompensation due to drug withdrawal (Table 2).[33]

Regarding disease activity, the vaccine should not be administered if the individual has a decompensated underlying disease or if the disease is highly active. Children with stable, controlled, and low-activity diseases may receive the vaccine if recommended.[33]

Vaccination in patients with rheumatic and autoimmune diseases in Brazil

The immunization of people with chronic diseases is a very complex matter, with different recommendations depending on each disease, clinical condition, and availability of immunobiological in public and private services. The Brazilian Society of Immunizations (SBIm, *Sociedade Brasileira de Imunizações*) recently published an update of the vaccination schedule for special patients (Calendar 2021-2022), which lists the main recommendations for the immunization

Table 2 Recommended minimum interval between discontinuation of immunosuppressive therapy and administration of YFV in patients with chronic immune-mediated inflammatory diseases (Adapted from Pillegi et al., 2019).[33]

Treatment drug	Minimum Interval
Prednisone > 20 mg/day	1 month
Methylprednisolone pulse	1 month
Hydroxychloroquine, sulfasalazine, acitretin, methotrexate ≤ 20 mg/week	Consider vaccination without interval
Leflunomide = 20mg/day*	Consider vaccination without interval
Methotrexate > 20 mg/week	1 month
Azathioprine, mycophenolate mofetil, sodium mycophenolate, cyclosporine, tacrolimus or cyclophosphamide	3 months
Tofacitinib	2 weeks
Anti-cytokines and co-stimulation inhibitor	4 to 5 half-lives**
B lymphocyte depleting drugs	6 to 12 months

* It is at the physician's discretion to perform the drug withdrawal protocol before recommending the vaccination.

** based on the drug half-life (except for B-lymphocyte depleting drugs).

of patients with rheumatological and autoimmune diseases (Table 3).[8]

COVID-19 vaccines in children with immune-mediated rheumatic diseases

During the pandemic, despite the fact that children and adolescents more frequently developed the asymptomatic and oligosymptomatic forms of COVID-19, which would lead to a lower rate of identification and, consequently, testing, it was observed that children and adolescents had a lower number and severity of symptoms of SARS-CoV-2 infection compared to adults, and they are also less likely to develop severe COVID-19 than adults.[34]

Although the clinical presentation of COVID-19 is milder in children compared to adults and the elderly, underlying medical conditions may contribute to the risk of severe illness, when compared to children without underlying diseases.[34]

The SARS-CoV-2 virus can trigger a late manifestation of the disease known as a multisystem inflammatory syndrome in children. This picture is characterized by high and persistent fever, with gastrointestinal, dermatocutaneous, and circulatory manifestations, among others.[35]

In addition to severe illness, children and adolescents may experience prolonged clinical symptoms (known as "long COVID-19," post-COVID-19 illness, or post-acute sequelae of SARS-CoV-2 infection), with the frequency and the characteristics of these diseases still being under investigation. A study in the United Kingdom showed that 7-8% of children who had COVID-19 persisted with some symptoms for more than 12 weeks of illness, including fatigue, insomnia, muscle pain, cough, and difficulty concentrating. Such changes directly impact the quality of life, including social and school life.[36]

With the aim of guiding health professionals about the safety and effectiveness of COVID-19 vaccines in children with rheumatological diseases, the Brazilian Society of Rheumatology carried out a task force to reach a consensus on vaccination in this group of patients. The document emphasizes that the recommendations are not intended to replace clinical judgment, and the decision to vaccinate must be individualized and shared between patients and rheumatologists.[37]

Among the recommendations, it is highlighted that, due to the risk of contracting COVID-19, patients should be encouraged to be immunized, based on a shared decision. The best time to get vaccinated should be individualized, considering the patient's age, type of rheumatic disease they have, and treatment, thus optimizing the vaccine response. It should also be noted that the vaccine against COVID-19 can be administered simultaneously with other vaccines in this group of patients.[37]

Ideally, the vaccination against COVID-19 should occur when the disease is stabilized and in the absence of or with a low degree of immunosuppression. Patients should be informed about the possibility of immunization failure in case of immunosuppressive treatment.[37]

Additionally, the immunomodulatory treatment should not be discontinued before or after the vaccination, except for agents that lead to B-cell depletion. In this case, ideally, immunization should occur at least six months after the last

Table 3 Vaccines recommended for patients with rheumatological and autoimmune diseases (adapted from SBIm, 2021).[8]

Vaccine	Recommendation
Influenza	- 4V or 3V. Preferably 4V. - From 6 months of age (follow the calendar for the age group).
PCV10 or PCV13*	- Preferably PCV13. - Children: from 2 months of age (the number of doses varies according to the age at which vaccination begins) - Children who received only PCV10 between 12 and 71 months: 2 doses of PCV13 (with a two-month interval) - Children from 6 years of age, adolescents, adults and elderly people not vaccinated with PCV13: one dose of PCV13.
PPSV-23*	> 2 years of age: 2 doses (5-year interval). 2nd dose applied < 60 years: 3rd dose recommended after this age, with a minimum interval of five years from the last dose.
MenC or MenACWY	- Preferably ACWY - Children and adolescents: according to the vaccination calendar for each age group. - For adults who were never vaccinated: one dose. - Children > one year, adolescents and unvaccinated adults, if immunosuppressed: two doses (two-month interval. Undergoing immunosuppressive treatment: a booster dose every five years for the duration of immunosuppression
MenB	- Children and adolescents: according to the vaccination calendar for each age group - Adults up to 50 years: two doses (1-2 month interval)
Hepatitis A	- Immunization according to the recommendations for the age group
Hepatitis B	- Immunocompetent individuals: three doses: 0 - 1 - 6 months –

Table 3 (*Continued*)

Vaccine	Recommendation
	Immunosuppressed individuals: four doses: 0 - 1 - 2 - 6 months (administer twice the recommended volume for the age group) - Perform Anti HBs serology 1-2 months after completing the vaccination schedule. Seroconversion: ≥10 mIU/mL. If serology is negative, repeat the above recommended vaccination schedule only once.
HPV	- three doses: 0 - 1 to 2 - 6 months (three doses are mandatory for immunosuppressed individuals, even between nine and 14 years old)
***Haemophilus influenzae* b**	- < 1 year: according to the vaccination calendar - People vaccinated in childhood, but who did not receive a booster dose after 12 months of age: one dose. If immunosuppressed, two doses (two-month interval) - > 1 year and previously unvaccinated adolescents: two doses (two-month interval)

[*] Start immunization schedule with PCV13, followed by PPSV23, respecting the minimum interval of two months between them. For individuals already immunized with PPSV23 (and not PCV13), a 12-month interval is recommended for the application of PCV13 and of five years for the application of the second dose of PPSV23, with a minimum interval of two months between PCV13 and PPSV23.

dose of rituximab and four weeks before the next dose, considering the full vaccination schedule. This recommendation must be followed at least for the first dose of the vaccine.[37]

An additional dose of the COVID-19 vaccine should be considered in immunocompromised patients and it is recommended that this dose be given on the same platform as the primary schedule. In addition, a booster dose is recommended, preferably with the mRNA platform (Pfizer-BioNTech) for all persons over 12 years of age.[38] The temporary interruption of immunomodulatory therapies (including rituximab) is not recommended during the performance of the vaccination schedule, under the risk of the individual going into a crisis or decompensating their underlying disease.[37]

The immunization schedule for COVID-19 vaccines currently recommended by the National Immunization Program (PNI, Programa Nacional de Imunizações) for children and adolescents is as follows:

(i) Children aged six months to less than three years of age **with comorbidities**, including immunocompromised ones: three doses of mRNA vaccine (pediatric Pfizer-BioNTech) with four-week intervals between the first two doses and eight weeks between the second and third doses;[39]
(ii) Immunocompromised children aged three to four years: two doses of the CoronaVac vaccine with a 4-week interval between the doses;[40]
(iii) Immunocompromised children aged five to 11 years should receive: two doses of the mRNA vaccine (pediatric Pfizer-BioNTech) with an eight-week interval between the first and second doses;[41]
(iv) Immunocompromised adolescents aged 12 to 17 years should receive three doses for primary vaccination and a fourth booster dose, four months after completing the primary vaccination schedule, always using the Pfizer vaccine.[42]

In addition to the above recommendations, the EULAR has published two recommendations regarding vaccination against COVID-19 in patients with rheumatic and musculoskeletal diseases.[43]

The first highlights that in those patients who are not yet undergoing treatment with an immunomodulator or immunosuppressant, vaccination against SARS-CoV-2 should precede the start of the treatment, if clinically feasible. The second corroborates the recommendations of the Brazilian Society of Rheumatology and stresses that for patients using rituximab or other B-cell depletion therapy, immunization against SARS-CoV-2 should be programmed aiming to optimize the vaccine immunogenicity.[43]

Vaccination of cohabitants

Vaccination of people who live with children and adolescents with immune-mediated diseases receiving immunosuppressants and/or immunobiological is strongly recommended and must follow the vaccination schedules for each age group. The CRIE makes the influenza, varicella, and MMR vaccines available to susceptible people living with immunocompromised patients.

The oral polio vaccine (OPV) is contraindicated for people living with immunosuppressed people and, when recommended, it is advised that the vaccine used to be the inactivated polio vaccine (IPV).[8]

Considerations

Studies carried out over the past decade have provided new data regarding the safety and immunogenicity of vaccines in children with immune-mediated rheumatic diseases. This fact allowed the updating of recommendations on the safety of immunization in this group of patients, mainly with live attenuated vaccines, and also the evaluation of safety and immunogenicity in patients treated with immunosuppressants and immunomodulatory therapies.

There is still a scarcity of data on the safety and efficacy of COVID-19 vaccines in patients, particularly pediatric patients, with rheumatic diseases. The completion of ongoing studies is expected to help guide recommendations on COVID-19 vaccines in pedAIIRD patients.

Conflicts of interest

The author declares no conflicts of interest.

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