REVIEW

COVID-19 Outcomes and Vaccination in Patients with Spondyloarthritis

Atul Deodhar · Suleman Bhana · Kevin Winthrop · Lianne S. Gensler

ABSTRACT

The rapid transmission of the highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), led to widespread infection throughout the world. Concerns and challenges regarding COVID-19 illness have emerged for patients with immune-mediated inflammatory diseases, such as spondyloarthritis (SpA), who receive treatment with biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs), because this population is vulnerable to infections and has a high prevalence of risk factors associated with severe COVID-19 illness. Available data on COVID-19 indicate that patients with SpA who are treated with DMARDs have SARS-CoV-2 infection rates comparable with those in the general population, with similar increased risk associated with older age and comorbidities. Novel vaccines against SARS-CoV-2 are approved or authorized for emergency use by the US Food and Drug Administration, and others are in development to prevent infection and serious illness. This review provides an overview of SpA, the mechanism of action for the SARS-CoV-2 infection, the clinical course of COVID-19, and the vaccines approved for, or in development against, SARS-CoV-2. Detailed information on the use of established vaccines in patients with SpA receiving DMARDs is provided, along with recommendations for COVID-19 vaccination. Available evidence has shown COVID-19 vaccination in patients with SpA, among other rheumatic diseases, to be safe and effective with most DMARD use; however, there is evidence of potential interference with some therapies used in SpA. Healthcare providers should educate patients to provide the knowledge and confidence to receive a COVID-19 vaccine, since the potential benefit outweighs the low risk of vaccine-related adverse events.

Keywords: Spondyloarthritis; COVID-19 vaccine; COVID-19; SARS-CoV-2; Disease-modifying antirheumatic drugs

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Key Summary Points

Why carry out this study?

Patients with immune-mediated diseases, such as spondyloarthritis (SpA), can have increased vulnerabilities to infections due to the disease-modifying antirheumatic drugs (DMARDs) they receive and often experience comorbidities which are associated with increased risk of coronavirus disease 2019 (COVID-19) disease.

This population experiences concerns and questions regarding COVID-19 illness and vaccination, as well as continuing treatment and disease management.

What did the study ask?

This narrative review assessed the available current research on COVID-19 illness and vaccination in patients with SpA who receive DMARDs.

What was learned from this study?

Available evidence does not demonstrate that patients with SpA who receive DMARDs are at increased risk of severe COVID-19 illness, hospitalization, or mortality, and COVID-19 vaccination in these patients is safe and effective with most DMARD use.

INTRODUCTION TO COVID-19 AND SPONDYLOARTHRITIS

Coronaviruses belong to the family *Coronaviridae* and are widely present in humans and other mammals [1]. Most infections with coronaviruses are mild, although severe respiratory infections that can be fatal occur in humans, as evident by the public health crises that emerged with two previous communicable coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. At the end of 2019, the emergence and rapid transmission of a novel coronavirus, SARS-CoV-2, appeared in Wuhan, China, and initiated an outbreak of severe febrile respiratory illness known as coronavirus disease 2019 (COVID-19) [3, 4]. SARS-CoV-2 is highly transmissible, which led to the rapid spread of infection throughout the world by March 2020, when the World Health Organization (WHO) declared a global pandemic [5]. The COVID-19 pandemic poses considerable concerns for healthcare providers (HCPs) who treat patients with comorbidities and/or immune-mediated disorders, such as spondyloarthritis (SpA).

SpA is a heterogeneous group of immune-mediated inflammatory conditions that primarily affect the peripheral joints and spine [6]. SpA comprises conditions with peripheral SpA [7], including psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease (IBD)-associated arthritis, and undifferentiated SpA; and axial SpA (axSpA), which includes radiographic axSpA (also known as ankylosing spondylitis [AS]) and nonradiographic axSpA [6]. The disease subtypes included in SpA share common clinical manifestations, family history, genetic traits, and imaging findings but are phenotypically different diseases [8]. SpA diseases share some common clinical features, including inflammatory back pain, peripheral arthritis, enthesitis, dactylitis, and extra-articular features such as anterior uveitis, psoriasis, and IBD [9, 10]; an increased prevalence of comorbidities, such as cardiovascular disease, metabolic syndrome, depression, osteoporosis and fractures, fibromyalgia, and infections, is also shared [8, 11]. Key proinflammatory cytokines, including interleukin (IL)-17, IL-23, and tumor necrosis factor (TNF), are associated with the pathogenesis of SpA, particularly in synovial and entheseal inflammation, and structural damage that consists of joint destruction as well as new bone formation [12–17].

Patients with SpA require treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying antirheumatic drugs (DMARDs), including biologic (bDMARDs), conventional synthetic (csDMARDs), or targeted synthetic (tsDMARDs) [18, 19]. These

immune-modulatory agents can alter normal immune regulation and function, may place patients with SpA at an increased risk for infections, and could potentially affect vaccine effectiveness. However, studies with historical non–COVID-19 vaccines (e.g., influenza or pneumococcal) have not raised significant concerns regarding safety in patients with SpA who received DMARDs, though methotrexate (MTX) has been reported to reduce influenza vaccine efficacy [20].

Vaccination in these patients is believed to be safe and is recommended when they are not experiencing an active disease flare [21]. Recent systemic literature reviews have initiated the assessment of the growing research that is available on COVID-19 illness and vaccination in rheumatic diseases [22, 23]. However, they proposed inconsistent conclusions about the rates of SARS-CoV-2 infection and odds of mortality related to COVID-19 for patients with rheumatic diseases compared with the general population, and these analyses do not focus specifically on SpA, which may impact findings that may be influenced by other rheumatic diseases. Although there are inadequate data specifically regarding COVID-19 vaccination in patients with SpA who are treated with DMARDs, lessons learned from extensive knowledge on the effect of DMARDs on the immune system and established vaccines can be applied to make educated recommendations for vaccination against SARS-CoV-2 in this patient population.

STATEMENT OF LITERATURE SEARCH

The development of this narrative review included the identification of publications based on a series of search strings on PubMed between April 2021 and March 2022. Search terms included "(COVID-19 OR SARS-CoV-2) AND (spondyloarthritis OR ankylosing spondylitis OR axial spondyloarthritis OR psoriatic arthritis OR reactive arthritis OR inflammatory bowel disease)"; "(COVID-19 OR SARS-CoV-2) AND (rheumatic and musculoskeletal disease)"; "(COVID-19 OR SARS-CoV-2) AND (biologic* OR disease modifying antirheumatic* OR csDMARD OR bDMARD OR tsDMARD)"; "(COVID-19 OR SARS-CoV-2) AND (nonsteroidal anti-inflammatory drug* OR NSAID)"; "(COVID-19 vaccin*) AND "(BNT162b2 OR mRNA-1272 ORAd26.COV2.S)"; "(COVID-19 vaccin*) AND (spondyloarthritis OR ankylosing spondylitis OR axial spondyloarthritis OR psoriatic arthritis OR reactive arthritis OR inflammatory bowel disease)"; "(COVID-19 vaccin*) AND (European Alliance of Associations for Rheumatology OR American College of Rheumatology OR National Psoriasis Foundation)"; "(COVID-19 vaccin*) AND (immune response OR efficacy OR T cell OR B cell OR immune memory)", and "(vaccin*) AND (influenza OR flu OR pneumococcal OR meningococcal)". These search strings were also used to identify abstracts and congress presentations from relevant professional societies, as well as through general Internet searches and the FDA site. Publications that detailed the COVID-19 disease, SARS-CoV-2 infections, non-COVID-19 vaccination, COVID-19 vaccination, and recommendations from professional societies for patients with SpA who were receiving DMARDs were included. References determined to be irrelevant based on authors' judgment were excluded from consideration. Relevant references cited within articles included in this review and publications previously known by authors were incorporated based on the criteria listed above. This narrative review is based on previously completed studies and does not contain any novel studies with human participants that were conducted by the authors.

COVID-19 AND PATIENTS WITH SPA

Accumulating evidence has elucidated the disease course and clinical manifestations of COVID-19, and clinical presentation encompasses systemic and respiratory manifestations [24]. Patients who develop severe cases of COVID-19 that can lead to hospitalization or death are generally older and/or have comorbidities, such as hypertension, diabetes, asthma, bronchitis, and cardiovascular disease [25–29].

A cytokine storm triggered by a dysregulated immune response to rapid replication of SARS-CoV-2 in the lungs can cause acute respiratory distress syndrome and respiratory failure [30], which has been established as the main cause of death in patients with COVID-19 [31–33].

Patients with COVID-19 can experience evidence of robust inflammatory responses and immune dysregulation. Elevated production of proinflammatory cytokines (e.g., IL-6, IL-10, TNF-α, IL-2R, and IL-8), some of which are associated with SpA, and the reduction and/or altered function of lymphocytes, particularly T cells, have been observed in patients with COVID-19 in most severe cases [34–38].

The pandemic presents considerable challenges and concerns for patients with immune-mediated inflammatory diseases, as their altered immune system and immunomodulatory treatments theoretically may increase the risk or severity of infection. Studies among patients with COVID-19 who have rheumatic diseases, including SpA, suggest that susceptibility to infection with SARS-CoV-2 and severity of COVID-19 are similar to the general population; further, the impact of older age and comorbidities on the risk of hospitalization and death is comparable between patients with rheumatic diseases, particularly SpA conditions, and the overall population [39–49].

Patients with SpA often receive NSAIDs as first-line treatment to help manage clinical manifestations of inflammation associated with their disease [19] and generally rely on continuous and/or long-term use of NSAIDs to maintain the benefits of these medications. At the early stage of the COVID-19 pandemic, widespread concerns were raised regarding the use of NSAIDs, particularly ibuprofen, which were thought to potentially lead to more severe COVID-19 [50]. These concerns have since been largely disproven by numerous studies. A prospective, multicenter, cohort study of 8410 evaluable patients hospitalized for COVID-19 in the United Kingdom reported no significant difference in the severity of COVID-19 among NSAID users compared with matched nonusers, and NSAID use was not associated with worse in-hospital mortality, critical care admission, or ventilation [51]. In a large meta-analysis of publications on COVID-19 and NSAIDs and/or ibuprofen, no increased risk of SARS-CoV-2 positivity with NSAIDs was found; among patients with COVID-19, NSAID use was not associated with increased hospital admission, death, or severe outcomes [52]. Additionally, a registry-based study of administrative claims from 248 Danish patients with NSAID prescription claims reported that NSAID treatment was not associated with 30-days mortality, risk of hospitalization, ICU admissions, or mechanical ventilation compared with matched non-NSAID users [53]. Furthermore, in a prospective, cohort, questionnaire-based study of patients with COVID-19 in Saudi Arabia, there was no significant risk of worse COVID-19 outcomes, including mortality, with acute or chronic NSAID use [54]. These findings are important for patients who receive NSAIDs for management of chronic inflammation and may develop increased SpA disease activity, a disease flare, or related complications with unnecessary cessation of NSAID use with COVID-19. Increased inflammation and worsened disease severity may also negatively impact the immune response to SARS-CoV-2 infection and/or COVID-19 vaccine [43, 55], so it is imperative that providers counsel patients who take NSAIDs on any changes to their disease management with these medications.

A study from the COVID-19 Global Rheumatology Alliance registry using physician-reported data from 2348 patients with inflammatory joint disease, including SpA, found that treatment with bDMARDs (drugs targeting TNF, IL-17, IL-23, and IL-12/23) and tsDMARDs was not associated with increased risk of death compared with MTX monotherapy [56]. Conversely, moderate or severe disease activity at the time of COVID-19 diagnosis (as measured by physician global assessment), treatment with glucocorticoids (GCs) > 10 mg/day or sulfasalazine were associated with increased risk of death compared with low disease activity or remission, no GC use, and MTX monotherapy. A study of 600 cases of COVID-19 in patients with rheumatic diseases across 40 countries, including 74 patients with PsA and 48 with axSpA or other SpA, found that treatment with b/tsDMARD

monotherapy prior to COVID-19 diagnosis was significantly associated with lower risk of hospitalization compared with no DMARD use, while csDMARD use, with or without concomitant b/tsDMARDs, did not impact the risk of hospitalization [57]. Furthermore, a retrospective analysis of medical records from 1668 patients in Spain reported 1.1% and 0.8% hospitalization rates for cases of severe COVID-19 in patients with SpA and PsA, respectively, and found no difference in mortality rates between patients admitted for COVID-19 with DMARD use vs. no DMARD use [58]. Patients who were treated with TNF inhibitors (TNFis) experienced significantly fewer hospitalizations compared with all patients in the study. In line with those findings, a large analysis of data pooled from three global registries for patients with rheumatic and musculoskeletal diseases (RMDs), including PsA and SpA, demonstrated that TNFi monotherapy was significantly associated with a decreased risk of COVID-19 hospitalization or death compared with MTX, Janus kinase inhibitors (JAKis), and azathioprine [59, 60]. Conversely, a large cohort analysis of administrative health data for cases of COVID-19 in British Columbia, including 1950 patients with PsA and 378 with AS, reported a significant increase in adjusted risk of hospitalization for COVID-19 in patients with psoriasis/PsA and AS and a significant increase in intensive care unit (ICU) admission for those with AS compared with corresponding matched control cohorts [61]. Additionally, a single-center study of 122 patients with rheumatic disease who had confirmed COVID-19 found that MTX use was an independent risk factor for hospitalization, and that GC use was associated with worse survival [39]. Another small observational study of 103 US patients (80 confirmed cases) with SpA or rheumatoid arthritis (RA) reported a significant increase in hospitalizations for patients receiving chronic oral GCs, but not in patients receiving b/tsDMARDs; patients with SpA were less likely to be hospitalized compared with patients with RA [62]. A meta-analysis of 65 observational studies, comprising 2766 patients with autoimmune diseases, found rheumatic diseases, which included PsA, AS, and other SpA, led to the highest hospitalization and mortality rates of all autoimmune diseases in the included studies [63]. However, an analysis of six case-controlled studies found no differences in hospitalization, death, ICU admission, or mechanical/noninvasive ventilation in patients with autoimmune diseases compared with controls. Further subgroup analyses determined that the event rate for each clinical outcome was two to three times higher in patients treated with GCs or csDMARD monotherapy, or combination treatment of b/tsDMARDs with csDMARDs, compared with patients treated with b/tsDMARD monotherapy.

Limited studies have focused on the clinical manifestations and disease course of COVID-19, as well as the impact of the pandemic on disease management in patients with rheumatic diseases. One observational, cohort study, which included data from 228 patients with rheumatic diseases across five centers in Spain, reported that radiographic pneumonia was present in significantly fewer patients with rheumatic diseases compared with matched controls [41]. There were no significant differences between patients with vs. without rheumatic diseases in any other clinical outcomes, which included hospitalization, ICU admission, death, respiratory symptoms, complications, laboratory tests, and COVID-19 therapies. An international web-based survey study of approximately 4700 subjects with SpA and 450 household contacts reported that SpA and typical medications for SpA (e.g., MTX, sulfasalazine, TNFis, NSAIDs, IL-17 inhibitors [IL-17is], and JAKis) did not impact the susceptibility to or severity of COVID-19 [44]. Similarly, a longitudinal survey study conducted a paired evaluation of US patients with SpA and household members that demonstrated SpA and SpA treatments (DMARDs) did not significantly impact the risk of developing COVID-19 or increase the severity of illness [64]. Additionally, an observational analysis of patient records in Wales found a significantly reduced incidence of COVID-19 positivity among patients with inflammatory arthritis (IA), including PsA and SpA, compared with those without IA; however, hospitalizations and mortality were significantly increased for those with IA who contracted COVID-19 compared with those without IA, which may

have been due to significantly older age and increased comorbidities among patients with IA [65]. A prospective observational study of 2166 patients with inflammatory disease, including PsA and SpA, from two university hospitals in Belgium reported low prevalence of COVID-19 symptoms and confirmed cases (5.0%), regardless of b/tsDMARD use, and found no difference in SARS-CoV-2 IgG seroconversion rates between patients with COVID-19 who received b/tsDMARDs vs. conventional treatment [45]. Furthermore, a multinational, web-based survey study (REUMAVID) evaluated data on how the first wave of the pandemic affected 1800 respondents with RMDs, including SpA [66]. A total of 58.4% of patients reported that their rheumatology appointments were canceled, and 45.6% reported that they did not receive any information regarding the potential impact that infection with SARS-CoV-2 may have on their RMDs. Conversely, an open-label extension study reported that disease activity and health-related quality of life remained stable during the pandemic among patients with AS who received IL-17i treatment [67]. Real-world data on the impact of COVID-19 symptoms and major lifestyle changes experienced during the pandemic in patients with RMDs should be taken into consideration to provide comprehensive patient care, increase patient education, and assess whether changes in treatment plans are warranted.

AVAILABLE GUIDANCE FOR COVID-19 VACCINATION IN PATIENTS WITH SPA

Recommendations and guidelines created by professional organizations with input from leading experts provide HCPs with the most current evidence and knowledge related to the treatment and management of patients with SpA during the COVID-19 pandemic. The European Alliance of Associations for Rheumatology (EULAR) [68], American College of Rheumatology (ACR) [69], and National Psoriasis Foundation (NPF) [70] have developed guidance and recommendations for the management of rheumatic diseases, including SpA,

during the pandemic. EULAR recommends that patients with rheumatic diseases without suspected or confirmed COVID-19 diagnosis continue treatment without modifications, follow preventive and control measures, postpone in-person rheumatology visits if disease and treatment are stable, and update vaccination status according to the EULAR recommendations for routine vaccination [68]. The most recent clinical guidance released from ACR (updated August 4, 2021) recognizes that the risk of COVID-19 for patients with rheumatic diseases seems to be linked to the same risk factors as the general population and advises providers to counsel patients on preventative measures. ACR recommends continuation of treatment, including MTX, bDMARDs, and tsDMARDs, for patients with stable disease without SARS-CoV-2 infection or exposure; GC therapy should be used at the lowest tolerated dose to control disease. Further, if SARS-CoV-2 exposure and/or COVID-19 infection occurs, ACR recommends stopping or pausing immunosuppressant agents, including MTX and JAKis [71]. The NPF recommends avoiding the chronic systemic use of corticosteroids when possible for the management of PsA due to accumulating evidence showing that treatment with corticosteroids has been associated with worse COVID-19 outcomes [70].

HISTORICAL VACCINE USE IN PATIENTS WITH SPA

The risk associated with COVID-19 vaccines in patients with SpA treated with DMARDs cannot be definitively determined until more evidence of vaccination in this population has been collected and analyzed [72]. However, tentative predictions and guidance can be made using available clinical trial data for the vaccines in development coupled with the existing research on patients treated with DMARDs who receive established vaccines [20, 21, 73–80]. The evidence presented here for established non–COVID-19 vaccines demonstrates that patients with rheumatic diseases, particularly SpA, who were treated with various DMARDs have not experienced harmful outcomes, and no unusual

immune responses have been identified. Therefore, given what is known regarding the immunologic mechanisms of the authorized COVID-19 vaccines and those in late-stage development, the expected risk is low for patients with SpA receiving DMARDs. The effects of TNFis on vaccine response observed in previous studies show that treatment with TNFis does not generally pose a risk to patients or humoral responses to vaccination in most SpA diseases. However, treatment with TNFis with vaccine use needs further clinical investigation in patients with IBD-associated arthritis, as these agents may alter immune response to vaccines, as seen in patients with IBD [81].

Limited evidence suggests that the use of MTX and JAKis in patients with SpA may interfere with vaccine response, which is the reasoning for the recommended treatment modification advised by ACR. Alternatively, both MTX and the JAKis barcitinib and tofacitinib have been posed as promising potential treatments for COVID-19 [82–85]. Overall, no evidence indicates an increased risk of adverse events (AEs) with COVID-19 vaccination in patients with SpA who receive DMARDs, and the potential benefit of preventing COVID-19 illness in this population with high risk for severe illness and death (e.g., older age and increased comorbidities) is essential.

COVID-19 VACCINES AVAILABLE FOR USE AND IN DEVELOPMENT

As the global number of COVID-19 cases and hospitalizations remained high, prevention of infection became the focus as the most promising measure to decrease disease transmission and prevent overwhelming healthcare systems, which led to approval by the US Food and Drug Administration (FDA) of the first COVID-19 vaccine [86]. Additionally, the FDA issued an emergency use authorization (EUA) for Evusheld, a combination of long-acting monoclonal antibodies from AstraZeneca, as a prophylactic treatment for COVID-19 in adults and pediatric individuals (≥ 12 years of age and ≥ 40 kg in weight) with compromised immune systems or a history of severe adverse

reactions to a COVID-19 vaccine who are not infected and were not recently exposed with SARS-CoV-2. From November 2020 through February 2022, EUAs were issued by the FDA for the use of multiple oral anti-viral drugs (paxlovid [87] and molnupiravir [88]; FDA approval of remdesivir [89]) and monoclonal antibodies (casirivimab and imdevimab [90], bamlanivimab and etesevimab [91], sotrovimab [92], and bebtelovimab [93]) for the treatment of mild-to-moderate COVID-19 in adults who tested positive for SARS-CoV-2 and who are at high risk for progression to severe COVID-19; these treatments were also authorized for pediatric patients aged ≥ 12 years who met the same requirements, except molnupiravir. Present treatment for COVID-19 relies on supportive therapy and investigational use of drugs for other indications, some of which are approved for use in SpA diseases [84, 85, 94, 95].

COVID-19 vaccines that are currently available and in development use the following vaccine platform strategies, all of which are non-live vaccines: inactivated virus, nonreplicating viral vectors, messenger RNA (mRNA), self-amplifying RNA, DNA, and protein subunit [36] (Table 1). The vaccine strategies showing the most promise are mRNA and adenovirus based and have been studied in phase III randomized clinical trials (Table 2). As of September 29, 2021, the FDA granted EUA for the Moderna and Johnson & Johnson vaccines in the United States [96–98], and on August 23, 2021, the FDA approved the Pfizer-BioNTech COVID-19 vaccine for use in individuals ≥ 16 years of age [86]. Additionally, the FDA expanded the EUA of the Pfizer-BioNTech COVID-19 vaccine to include children aged 5–11 years on October 29, 2021 [99]. The FDA also issued a subsequent approval of the Moderna vaccine (Spikevax) for individuals aged ≥ 18 years on January 31, 2022 [100]. Widespread vaccination with each of these vaccines began at the end of 2020; as of March 16, 2022, the Centers for Disease Control and Prevention (CDC) COVID data tracker reported that 577,407,604 vaccine doses have been administered in the United States, with 216,738,180 people fully vaccinated, of whom 124,212,958 received the BNT162b2 vaccine,

Table 1 COVID-19 vaccines in development

Vaccine strategy	Organization	Clinical stage	Clinical trial identifier
Inactivated virus			
Absorbed inactivated COVID-19 vaccine (PiCoVacc) [140]	Sinovac	Phase III	NCT04456595, NCT04582344
Inactivated COVID-19 vaccine (Vero cells) [141]	Wuhan Institute of Biological Products/ Sinopharm	Phase I/II	NCT04352608, ChiCTR2000034780
BBIBP-CorV [142]	Beijing Institute of Biological Products/ Sinopharm	Phase III	NCT04560881, ChiCTR2000034780
Inactivated SARS-CoV-2 [143]	Chinese Academy of Medical Sciences	Phase I/II	NCT04470609
QazCovid-in [144]	Research Institute for Biological Safety Problems, Republic of Kazakhstan	Phase I/II	NCT04530357
BBV152A/B [145, 146]	Bharat Biotech (whole virion inactivated)	Phase I/II	NCT04471519
Nonreplicating viral vector			
AZD1222 [147]	University of Oxford/AstraZeneca	Phase III	NCT04516746
Ad5-nCoV [148]	CanSino Biologics Inc/Beijing Institute of Biotechnology	Phase III	NCT04526990, NCT04540419
Gam-COVID-Vac [149]	Gamaleya Research Institute	Phase III	NCT04530396, NCT04564716
Ad26.COV2.S [98]	Janssen Pharmaceutical Companies (Johnson & Johnson)	Phase III	NCT04505722
mRNA			
mRNA-1273 [96]	Moderna/NIAID	Phase III	NCT04470427
BNT162b2 [97, 150]	BioNTech/Fosun Pharma/Pfizer	Phase III	NCT04368728, NCT04816643
CVnCoV [151]	CureVac AG	Phase I/II	NCT04515147
saRNA			
ARCT-021 [152]	Arcturus/Duke-NUS	Phase II	NCT04480957
DNA			
INO-4800 [153]	Inovio Pharmaceuticals/International Vaccine Institute	Phase I/II	NCT04447781
AG0301-COVID19 [154], AG0302-COVID19 [155]	Osaka University/AnGes/Takara Bio	Phase I/II	NCT04463472, NCT04527081

Table 1 continued

Vaccine strategy	Organization	Clinical stage	Clinical trial identifier
nCoV Vaccine	Cadila Healthcare Limited	Phase I/II	CTRI/2020/07/026352
GX-19 [156]	Genexine Consortium	Phase I/II	NCT04445389
Protein subunit			
SARS-CoV-2 rS/Matrix-M1 Adjuvant (NVX-CoV2373) [157]	Novavax	Phase III	2020-004123-16, NCT04533399
Recombinant new coronavirus vaccine (CHO cell) [158]	Anhui Zhifei Longcom Biopharmaceutical/ Chinese Academy of Sciences	Phase II	NCT04466085
KBP-COVID-19/KBP-201 [159]	Kentucky Bioprocessing, Inc	Phase I/II	NCT04473690
SARS-CoV-2 vaccine formulation 1/2 [160]	Sanofi Pasteur/GSK	Phase I/II	NCT04537208
EpiVacCorona [161]	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Phase I/II	NCT04527575

COVID-19 coronavirus disease 2019, *GSK* GlaxoSmithKline, *mRNA* messenger RNA, *NIAID* National Institute of Allergy and Infectious Diseases, *saRNA* self-amplifying RNA, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

75,595,568 the mRNA-1273 vaccine, and 16,812,730 the Ad26.COV2.S vaccine; 146,699 did not have available data for the second dose [101].

These vaccines have been reported to be effective at preventing severe COVID-19 illness and death with favorable safety profiles. Exclusion from clinical trials is not uncommon for those with a diagnosis of an immunocompromising condition and/or who receive immunosuppressive treatment; however, real-world data on COVID-19 vaccines in these populations are emerging. Overall, the safety profile of COVID-19 vaccines approved or granted EUA in patients with RMDs has been reported to be satisfactory, reported AEs are consistent with those in the general population, and disease flares are generally experienced at a low rate with spontaneous recovery across real-world studies [60, 102–106]. A study of the EULAR COVID-19 Vaccination (COVAX) Registry included 5121 patients (91% with inflammatory

RMDs, including axSpA [11%] and PsA [10%]) who received ≥ 1 dose of a COVID-19 vaccine (74% received two doses) [106]. Disease flares (e.g., arthritis, polyarthralgia, and increased fatigue) were reported by 4.4% of patients with inflammatory RMDs, and patients receiving TNFis (5.5%), other biologics (5.3%), other csDMARDs (4.7%), and tsDMARDs (4.6%) reported marginally higher flare rates compared with other medication groups. AEs (i.e., pain at the injection site, fatigue, and headache) and severe adverse events, respectively, were reported in 37% and 0.4% of participants with inflammatory RMDs. Additionally, an observational study of self-reported systemic side effects and Disease Activity Index for Psoriatic Arthritis-assessed disease flares following COVID-19 vaccination in 180 patients with rheumatic diseases, including PsA and SpA, reported mild or moderate disease flares at low rates with the first (0.6%) and second (3.4%) dose of mRNA vaccines. Three patients who experienced flares

Table 2 Key findings from phase III randomized clinical trials for COVID-19 vaccines

Vaccine	Key findings
Pfizer-BioNTech BNT162b2[a] [97]	Primary end point (*n* = 36,523): BNT162b2 resulted in 95% (95% CI 90.3–97.6%) efficacy against confirmed SARS-CoV-2 infection ≥ 7 days after the second vaccine dose in patients without evidence of prior infection
	Secondary end point (*n* = 40,137): efficacy was 94.6% (95% CI 89.9–97.3%) for BNT162b2 against confirmed COVID-19 cases from ≥ 7 days after the second vaccine dose in participants with and without evidence of prior infection with SARS-CoV-2
	Safety analysis: safety data from all study participants with a median follow-up of 2 months after the second dose indicate a favorable safety profile. Most common AEs reported in more than one-third of patients were ISRs (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), and chills (31.9%); AEs occurred more frequently among participants who received BNT162b2 compared with PBO. The incidence of SAEs was low (< 0.5%) and was comparable between study groups
Moderna mRNA-1273[b] [96]	Primary end point (*n* = 28,207): vaccine efficacy for mRNA-1273 was 94.1% (95% CI 89.3–96.8%) compared with PBO for prevention of symptomatic COVID-19 illness ≥ 14 days after the second dose in participants without prior SARS-CoV-2 infection
	Secondary end point: mRNA-1273 vaccine efficacy 14 days after dose one was 95.2% (95% CI 91.2–97.4%), and efficacy at preventing severe COVID-19 was 100%
	Safety analysis: AEs were reported among all participants; 4.5% of patients in the PBO arm and 8.2% in the mRNA-1273 arm experienced treatment-related AEs; the most common among both groups were fatigue and headache
Johnson & Johnson Ad26.COV2.S[c] [98]	Coprimary end points (*n* = 39,321): reported efficacy was 66.9% (95% CI 59.0–73.4%) and 66.1% (55.0–74.8%) for the coprimary end points of vaccine efficacy against moderate-to-severe COVID-19 illness with onset ≥ 14 and ≥ 28 days' post vaccine, respectively
	Safety analysis (*n* = 6736): safety subpopulation analysis included data for participants during the 7-day period after administration of vaccine or PBO and indicated a favorable safety profile. The most common AEs reported with the Ad26.COV2.S vaccine were injection-site pain (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%)

AE adverse event, *COVID-19* coronavirus disease 2019, *EUA* emergency use authorization, *FDA* US Food and Drug Administration, *ISR* injection site reaction, *PBO* placebo, *SAE* serious adverse event, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

[a]The FDA expanded the EUA for the BNT162b2 vaccine to include adolescents aged ≥ 16 years on December 11, 2020 [100], and further extended use of this vaccine on May 10, 2021, to include adolescents aged 12–15 years [101]. Similar safety profiles were seen among both age groups in the ongoing placebo-controlled clinical trials of BNT162b2 vaccine in adolescents; the most commonly reported AEs were similar in adolescents as reported in adults [99]. In adolescents without evidence of prior infections with SARS-CoV-2, the BNT162b2 vaccine was 95% and 100% effective in preventing COVID-19 in participants aged ≥ 16 years and in those aged 12–15 years, respectively [100, 101]. On August 23, 2021, the FDA approved the Pfizer-BioNTech COVID-19 vaccine for use in individuals aged ≥ 16 years [86]. The FDA further expanded the EUA for this vaccine to include children aged 5–11 years on October 29, 2021 [99]. No serious side effects were detected in the ongoing study in children, immune responses were comparable to those seen in individuals aged 16–25 years, and the vaccine was found to be 90.7% effective in preventing COVID-19 among children aged 5–11 years

[b]The Moderna vaccine (Spikevax) was granted FDA approval for individuals aged ≥ 18 years on January 31, 2022 [100]

[c]Administration of the Ad26.COV2.S vaccine was temporarily halted in April 2021 due to the investigation of 6 reported cases of cerebral venous sinus thrombosis among the 6.8 million administered doses; however, after further inquiry, the hold was removed, and administration of the vaccine resumed with a warning of the rare risk for blood clots among women aged < 50 years [162]

after the second dose, all of whom received the BNT126b2 vaccine, had PsA; however, all systemic side effects reported were mild and resolved spontaneously [107]. Similarly, an observational longitudinal study of 866 patients with RMDs, including SpA, enrolled in the German COVID-19 vaccination registry who received one dose of an available vaccine found that AEs were similar to those reported in the general population, and 13% of patients had a self-reported disease flare (median score, 5; scale 1–10). Of these patients, 6% required a change in immunomodulation therapy, and an increased GC dose was sufficient to manage the disease flare in 41% [102]. Furthermore, in an observational study of 70 adult US patients with immune-mediated diseases, including SpA (axSpA and PsA), nearly all patients (dose 1, 96%; dose 2, 100%) reported an AE following vaccination, the most common of which were consistent with clinical trials; AEs following dose 1 were generally mild, and those following dose 2 had increased proportions of moderate (47.8%) and severe (30.5%) AEs [103]. Additionally, significant improvements in sleep disturbance, anxiety, and fatigue were reported after completion of the SARS-CoV-2 vaccine series by individuals with anxiety and sleep disturbances due to concerns related to social confinement, health, and finances; the beneficial impact of receiving the vaccine on the mental health and wellbeing was demonstrated by these significant improvements in a prospective study of patients with chronic inflammatory diseases (CID), including SpA [108]. These studies emphasize the importance of a comprehensive understanding of vaccine-related AEs to inform patients of possible expected side effects following vaccination and to educate patients on the overall long-term safety of vaccination.

IMMUNOGENICITY AND EFFECTIVENESS OF COVID-19 VACCINES

Each vaccine aims to provide protection through B-cell– and T-cell–dependent mechanisms, including antibody production and induction of immune memory [109, 110]. When immunization is complete, the vaccinated individual should be able to mount a protective immune response in a fast and robust manner when encountering the SARS-CoV-2 virus. While substantial evidence exists for the efficacy of the COVID-19 vaccines in the prevention of severe illness, hospitalization, and death, limited data are available regarding the vaccine-induced immune response elicited by COVID-19 vaccines available for EUA; however, preliminary studies suggest that the mRNA vaccines may induce the development of persistent robust humoral immunity. An observational study of samples (e.g., peripheral blood and aspirates from draining lymph nodes) from 41 adults who received the BNT162b2 vaccine reported that circulating plasmablasts that targeted the S protein peaked a week after the second dose of the vaccine and then declined and were undetectable 3 weeks later [111]. Subsequently, this study found that germinal center B cells were able to bind S protein in all study participants following primary immunization, and high numbers of germinal center B cells specific to S protein and plasmablasts were maintained in the draining lymph nodes for up to 12 weeks after the second immunization. Further studies need to be conducted to assess the induction of immune memory from germinal center B cells elicited by the COVID-19 vaccines, since this component of the immune response is essential for sustained protection, response to successive infections, and potentially the ability to fight emerging variants. As the pandemic has continued, sequencing of samples from individuals with COVID-19 has revealed the emergence of variants (alpha [B.1.1.7] [112], beta [B.1.351] [113], and gamma [P.1] [114]), including the B.1.617 (delta) lineage of the SARS-CoV-2 virus, which has been detected across 43 countries as of May 19, 2021 [115]. Preliminary estimates predict that the available mRNA vaccines will be effective against symptomatic disease with the delta variant after full vaccination [115]; however, studies need to be conducted to evaluate the real-world effectiveness of the COVID-19 vaccines against these emerging strains. Additionally, on November 26, 2021, the WHO

designated the omicron variant (B.1.1.529), which has numerous mutations with potential to increase transmissibility, to be a variant of concern [116, 117].

Increasing data are available regarding studies evaluating the immunogenicity and efficacy of COVID-19 vaccines in patients with RMDs; however, it is prudent to be aware that guidance from the FDA and ACR recommend against routine measures of immunogenicity with commercially available serologic assays for SARS-CoV-2 antibodies against the spike antigens. Based on studies of the immunogenicity of the COVID-19 vaccines, particularly in immunocompromised individuals [118–121], on August 12, 2021, and September 22, 2021, respectively, the FDA authorized an additional dose of either Pfizer-BioNTech BNT126b2 (ages $\geq$ 12 years) or Moderna mRNA-1272 (ages $\geq$ 18 years) for immunocompromised individuals who may not have produced a sufficient immune response from the primary series [122] and a vaccine booster dose of the Pfizer-BioNTech BNT126b2 vaccine for certain populations at risk of severe COVID who have the potential for a waning immune response from the primary series [123, 124]. Subsequently, the FDA further expanded the EUA on November 19, 2021 to include the administration of a single booster dose $\geq$ 6 months after completion of the primary vaccination series for all individuals aged $\geq$ 18 years for both the Moderna and Pfizer-BioNTech COVID-19 vaccines [125]; and on December 9, 2021 and January 3, 2022, the EUA was updated to include a single booster dose for individuals aged $\geq$ 16 years [126] and 12–15 years (and certain immunocompromised children aged 5–11 years) [127], respectively, for the Pfizer-BioNTech vaccine.

A multicenter study in Israel of 686 patients with autoimmune and inflammatory rheumatic diseases (AIIRDs), including PsA and axSpA, reported that rates of seropositivity (86 vs. 100%) and the level of S1/S2 antibodies were significantly reduced for all patients with AIIRDs compared with control participants 2–6 weeks after the second dose of the BNT162b2 mRNA vaccine [128, 129]. However, the seropositive rate for patients in a subgroup

(PsA, axSpA, systemic lupus erythematosus, and large-vessel vasculitis) was $\geq$ 90%, which excluded those with RA, antineutrophil cytoplasmic antibody–associated vasculitis, and idiopathic inflammatory myositis. Nearly all patients (95.2%) were receiving immunomodulatory medications at the time of the study; of the therapeutics recommended for patients with SpA, GCs, MTX, and abatacept were associated with significantly lower rates of seropositivity. The majority of patients (97%) who received TNFis and IL-17is as monotherapy achieved an appropriate immunogenic response; however, compared with TNFis with concomitant MTX use, seropositivity was significantly reduced to 93%. In-line with those findings, several observational studies of US patient cohorts, which included patients with PsA, AS, or axSpA, reported that most patients (range, 71.0–91.8%) developed anti-SARS-CoV-2 IgG antibodies to the receptor-binding domain of the S1 antigen following COVID-19 vaccination, and that patients receiving TNFis (range, 82.0–90.9%), IL-17is (80%), IL-12/23is (100%), IL-23is (100%), or JAKis (91%) achieved consistent detectable levels of humoral response across studies [121, 130, 131]. However, patients who received abatacept (45.0–52.0%) or MTX monotherapy (50.0–80.0%) were less likely to develop an antibody response [131]. Similar findings were reported in a prospective study, showing that patients with CID, including SpA, had a threefold reduction in anti-S IgG titers and SARS-CoV-2 neutralization to the D614G variant compared with immunocompetent control participants; this effect was strongest with B-cell depletion and GC treatment, with significant reductions also seen with JAKis and MTX [132]. Additionally, the impaCt of bioLogic therApy on saRs-cov-2 Infection and immunitY (CLARITY) study in the United Kingdom found that patients with IBD who were receiving infliximab at the time of vaccination with either the BNT162b2 or ChAdOx1 nCoV-19 vaccine had attenuated immunogenicity to a single dose of either vaccine compared with a cohort treated with vedolizumab [133]. Following a single dose of either vaccine, patients who experienced a prior SARS-CoV-2 infection and those who received two doses of

the BNT162b2 vaccine achieved higher seroconversion rates. Overall, vaccination with BNT162b2 demonstrated an adequate immunogenic response in the majority of patients with RMDs, and continuing treatments that may impair immunogenicity achieved with this vaccine should be considered on an individual basis. HCPs can use the knowledge gained from preliminary studies and the use of other non–COVID-19 vaccines in patients with rheumatic diseases who are receiving DMARDs to help educate their patients to be knowledgeable and confident to receive vaccination against COVID-19 and to make shared decisions for treatment continuation on an individual basis.

RECOMMENDATIONS ON COVID-19 VACCINATION IN PATIENTS WITH SPA

The development of vaccines for COVID-19 is a promising step toward the end of the global pandemic; however, it also poses questions for patients with inflammatory rheumatic diseases, including SpA, who receive treatments that may alter their immune system. Providers should counsel and educate patients on the available data, benefits of vaccination, and expert recommendations regarding COVID-19 vaccination to dispel misinformation and prevent vaccine hesitancy. Numerous studies have found varying levels of COVID-19 vaccine hesitancy in patients with RMDs in the United States and Canada, with potential side effects and/or trust in the evidence/review process for the development of the vaccines among the top concerns of patients surveyed [134–138]. Physician recommendation was determined to be a key factor in vaccine acceptance [135]. EULAR and ACR have developed guidance based on the limited available data on COVID-19 in this patient population and on experience with prior vaccination in patients with rheumatic diseases to offer HCPs the best available evidence and knowledge for COVID-19 vaccination (Table 3).

EULAR and ACR acknowledge the limited data on safety and efficacy of the COVID-19 vaccines in this patient population; however, both recommend that all patients with rheumatic diseases, including SpA, receive any available COVID-19 vaccine as soon as possible since the potential benefit outweighs the low likelihood of potential harm [69, 72]. EULAR advises vaccination ideally when patients are in a controlled disease state and prior to a planned immunosuppression when possible; similarly, ACR suggests that vaccination would be optimal when disease is well controlled, but as soon as available, regardless of disease activity and severity. EULAR guidance does acknowledge that vaccination would be most effective with low immune suppression but recognizes that this may not be attainable in patients with rheumatic diseases who are receiving biologics that suppress the immune system. Therefore, reduction of medication is not advised by EULAR in these patients to prevent the risk of a disease flare [72]. Both EULAR and ACR recommend patients continue to follow all public health guidelines for preventive measures following COVID-19 vaccination.

Further, ACR provides more detailed guidance regarding patient care and recommends medication-specific modifications to routine care for patients with rheumatic diseases alone or with an AIIRD, such as systemic lupus erythematosus or giant cell arteritis [69]. For patients with a rheumatic disease and an AIIRD who receive a multidose vaccine and experience nonserious AEs related to the first dose, ACR recommends that patients receive the corresponding second dose of the same vaccine without delay. HCPs are advised against ordering routine laboratory tests to assess immunity to COVID-19 post vaccination or to evaluate the need for vaccination in patients who have not been vaccinated, as there is variability among commercial assays in their ability to detect vaccine-induced antibody responses to spike protein. There are no recommended modifications to therapy or vaccination timing for most DMARDs typically used for treatment of rheumatic diseases, particularly SpA. However, ACR does recommend cessation of treatment with MTX and JAKis for 1 week following each vaccine dose in patients with well-controlled disease, with no modifications to vaccination

timing; MTX is also advised to be paused for 2 weeks after single-dose COVID vaccination. Treatment with subcutaneous abatacept should be held for 1 week before and after the first COVID-19 vaccine dose only, with no modifications when receiving the second dose; vaccine administration is recommended to be timed for the first dose to occur 4 weeks after intravenous abatacept treatment, with 1-week delay for subsequent abatacept infusion after the first dose (total 5-week gap). Additionally, due to concerns that acetaminophen and NSAIDs may somewhat impair vaccine response, they are advised to be held for 14 h prior to vaccination for patients with stable disease [139].

COVID-19 vaccine recommendations for patients with rheumatic diseases have been developed by experts with extensive knowledge of rheumatic diseases; however, guidance is based on limited and indirect evidence due to the nature of a novel disease and recently developed vaccines without adequate follow-up data. EULAR and ACR recommendations should be considered alongside the judgment of the treating rheumatologist who can make optimal treatment and vaccination decisions for patients based on their individual circumstances.

CONCLUSIONS

The novel coronavirus SARS-CoV-2, which causes COVID-19 illness, is highly communicable, and the rapid spread of infection throughout the world led to the COVID-19 pandemic of 2020. The pandemic presents challenges and concerns for patients with immune-mediated inflammatory diseases, such as SpA. Patients with SpA are often treated with DMARDs and can be vulnerable to increased severity of infections due to the dysregulated immune system and immunosuppressive action of treatments for these diseases.

Accumulating data on SARS-CoV-2 infection and COVID-19 illness have led to a better

Table 3 Guidelines and resources for SpA and COVID-19

COVID-19 vaccine information (FDA)	The FDA provides up-to-date information on COVID-19 vaccines
	Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines
COVID-19 guidance (ACR)	The ACR has produced clinical guidance documents for patients during the COVID-19 pandemic
	Available online: https://www.rheumatology.org/Practice-Quality/Clinical-Support/COVID-19-Guidance
Viewpoints on vaccination (EULAR)	EULAR has created guidance for vaccination in patients with rheumatic diseases and compiled FAQs
	Available online: https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm
COVID-19 (CDC)	The CDC has developed information and guidance on COVID-19 illness and vaccination
	Available online: https://www.cdc.gov/coronavirus/2019-ncov/index.html
COVID-19 and SpA (SAA)	The SAA has created a central hub for information and news regarding COVID-19 and SpA
	Available online: https://spondylitis.org/coronavirus/

ACR American College of Rheumatology, *CDC* Centers for Disease Control and Prevention, *COVID-19* coronavirus disease 2019, *EULAR* European Alliance of Associations for Rheumatology, *FDA* US Food and Drug Administration, *SAA* Spondylitis Association of America, *SpA* spondyloarthritis

understanding of the disease course, clinical characteristics, and the mechanisms of action of the virus. Many promising vaccines are in development for the prevention of infection and serious illness. The available data on disease course of COVID-19 in patients and knowledge from established vaccines against other infectious diseases indicate that patients with SpA are not at an increased risk for infection with SARS-CoV-2 or severe illness and death compared with the general population, and there do not appear to be any factors that would negatively affect vaccination against COVID-19 in these patients.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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