SYSTEMIC LUPUS ERYTHEMATOSUS (G TSOKOS, SECTION EDITOR)

The Use of COVID-19 Vaccines in Patients with SLE

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Abstract

Purpose of Review Three COVID-19 vaccines obtained emergency authorization from the Food and Drug Administration (FDA) and are widely used in the USA. Unfortunately, there is a paucity of evidence on the safety and efficacy of these vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD), as these patients were excluded from all phases of vaccine development. Here we reviewed current data on COVID-19 vaccination in patients with AIIRD, with emphasis on systemic lupus erythematosus (SLE), and provided a comprehensive update on the benefits and risks of vaccination.
Recent Findings Patients with SLE have worse immune responses following SARS-CoV-2 vaccination than healthy controls. The efficacy of the COVID-19 vaccines seems to be further reduced by immunosuppressive medications, such as glucocorticoids (GC), methotrexate (MTX), mycophenolate/mycophenolic acid (MMF), and rituximab (RTX). However, these data do not substantiate that AIIRD patients are at greater risk of disease flares or have a higher incidence of side effects following vaccination. There is no significant safety concern for the use of COVID-19 vaccines in patients with AIIRD.
Summary The benefits of vaccination far outweigh the risks in patients with AIIRD, including SLE. More data are needed to determine the necessity of a booster vaccine dose and appropriate adjustment of immunosuppressants around the administration of vaccine.

Keywords COVID-19 vaccines · SARS-CoV-2 · Systemic lupus erythematosus · Rheumatic diseases · Immunosuppressive agents

Introduction

Since the start of the COVID-19 pandemic in March 2020, scientists and researchers have made enormous efforts to develop safe and effective vaccines against SARS-CoV-2 [1]. Three vaccines, two mRNA vaccines (Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273), and one adenovirus-based vaccine (Janssen Ad26.COV2.S) have completed phase III trials and received emergency use authorization (EUA) in the USA [2–4]. As of August 23, 2021, the Pfizer/

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BioNTech BNT162b2 obtained full approval for use in individuals ages 16 and older to prevent COVID-19 disease [5]. Another adenovirus-based vaccine (AstraZeneca ChAdOx1 nCoV-19) has been widely used in Europe while still awaiting EUA from the FDA to enter the USA [6]. Patients with SLE were reported to be at higher risk of SARS-CoV-2 infection and worse outcomes from COVID-19, possibly due to their intrinsic immune dysfunction, demographics, disease activity, medications, associated organ damage, and comorbidities [7]. Additionally, the immunomodulators and immunosuppressants commonly used to treat SLE have been associated with an increased risk of death from COVID-19 [8]. Therefore, patients with SLE are among the most vulnerable population in terms of SARS-CoV-2 infection and, as such, have been among the first to receive the vaccines [9]. However, a large proportion of patients with AIIRD express vaccine refusal or hesitancy due to concerns for adverse events and the lack of long-term research on their safety [10]. Phase III trials of all the above four vaccines excluded patients treated with immunosuppressants or

immune-modifying drugs within six months of enrollment, thus resulting in a visual absence of safety and efficacy data in patients with autoimmune inflammatory rheumatic diseases (AIIRD), including SLE [2–4, 6]. Furthermore, there is no evidence as to whether specific treatments should be delayed or paused around the administration of COVID-19 vaccines or whether patients with AIIRD can benefit from a booster dose of vaccination [11]. Hopefully, the ongoing ACV01 study, a randomized, multi-site, adaptive, open-label clinical trial investigating booster effects with autoimmune treatments in patients with poor response to initial COVID-19 vaccine, will provide further evidence on this topic [12].

This publication reviews the published data on SARS-CoV-2 vaccination in SLE patients to assist rheumatologists in organizing informed discussions with their lupus patients. A search of published and preprint databases in all languages was performed. The eligibility criteria were as follows: (1) described at least one relevant measurement of efficacy and/or safety profile regarding SARS-CoV-2 vaccine; (2) included patients with AIIRD that contained at least 1 patient with SLE; (3) was published after January 1, 2020; and (4) was original research. Three independent reviewers (WT, LK, and ADA) screened articles and extracted data. A meta-analysis of effect sizes using fixed- or random-effects model was performed on the topics of special interest when possible. All analyses were conducted using RevMan 5.4 software.

Efficacy of COVID-19 Vaccines in Patients with Systemic Lupus

Erythematosus

SLE is characterized by profound dysregulation of the immune system. Both qualitative and quantitative lymphocyte defects are prevalent in SLE as a result of both the underlying disease activity and treatment with immunosuppressants [9]. SLE patients have been reported to have poor immune responses to vaccines against several pathogens [13].

A total of 11 studies evaluated COVID-19 vaccine efficacy in AIIRD patients that included SLE. Two types of responses were considered, anti-spike IgG and/or IgM seroconversion rates and neutralizing antibody activity against SARS-CoV-2. These data are summarized in Table 1. Izmirly et al. showed that fully vaccinated SLE patients (*n*=90) produced significantly lower IgG antibodies against SARS-CoV-2 spike receptor binding domain (RBD) than healthy controls (HCs) (*n*=20) [14]. Boekel et al. reported that among participants without previous SARS-CoV-2 infection, seroconversion rates after first COVID-19 vaccination in patients with AIIRDs (*n*=432) were lower than HCs (*n*=210), an effect that was mainly driven by those treated with MTX or B cell-depletion therapies; however, differences in seroconversion rates were similar

across autoimmune disease types examined [15]. Similarly, Ammitzbøll et al. observed a higher seroconversion rate following BNT162b2 vaccine in SLE (*n*=73) than RA (*n*=64) patients, but the difference was not statistically significant after adjusting for RTX treatment [16]. Decreases in vaccine efficacy have also been observed in B cell lymphoma patients following B cell depletion therapy [17]. Taken together, these studies suggest that immunosuppressive treatments, rather than the underlying autoimmune diseases, might be the main factor limiting the immune responses against SARS-CoV-2 vaccines. Unexpectedly, Simon et al. reported lower antibody responses to SARS-CoV-2 vaccine in untreated AIIRD patients (*n*=24) than HCs (*n*=182), and further comparison between conventional synthetic disease-modifying antirheumatic drugs (DMARDs)- and biological/target-synthetic DMARDs-treated patients revealed no differences in antibody responses [18]. Furer et al. found that the seroconversion rates and neutralizing antibody levels following COVID-19 vaccination were significantly lower in patients with AIIRD as compared to HCs and significantly different across different disease diagnoses with the lowest seroconversion observed in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and idiopathic inflammatory myositis (IIM). Notably, seroconversion rates in SLE patients were also significantly lower as compared to HCs in this study, and treatment with immunomodulatory and immunosuppressive agents was found to be the major risk factor for reduced immunogenicity [19].

In order to better define the immunogenicity of COVID-19 vaccines in patients with SLE, we review studies containing both SLE and HC groups with granular information on immunogenicity data available for extraction and analysis. Studies without a HC group and/or studies without detailed immunogenicity data in SLE patients were excluded from further analysis.

A meta-analysis (Fig 1a) that included three studies of SLE patients and HC (pooled *n*=382) demonstrated that SLE patients had a lower seroconversion rate following SARS-CoV-2 vaccination than HCs (pooled OR=0.14 [95% CI 0.03, 0.74]). We performed another meta-analysis (Fig 1b) that included four studies of SLE and RA patients (pooled *n*=571) and found that compared to RA patients, SLE patients had a lower seroconversion rate following vaccination.

Effects of Immunosuppressive Agents on COVID-19 Vaccine Immunogenicity

Emerging data have demonstrated that immunosuppression delays or impairs immune responses to SARS-CoV-2 vaccines in patients with AIIRD, as suggested by previous experience with influenza and pneumococcal vaccines [20]. As shown in Table 1, multiple studies compared vaccine

Table 1 Summary of studies on COVID-19 vaccine efficacy in patients with autoimmune inflammatory rheumatic disorders

Author	Design	Vaccine	Cohort	Diseases	Therapy	Sample Collection	Outcome measure	Results
Izmirly et al.	Cohort	Pfizer, Moderna, J&J	90 SLE 20 HC	SLE 90 (100%)	GC 26 (29%), MTX 8 (14.9%), MMF 21 (23%), RTX 3 (3%), BLyS 10 (11%)	Within 4 months of 1st dose, 2 weeks post 2nd dose of Pfizer/ Moderna or 1st dose of J&J	Anti-S IgG, functional neutralization titers, Ag-specific IFN-γ production	Lower* Ab and neutralization titers in SLE vs HC. Ab levels of 26 (29%) SLE patients below the lowest level of HCs; Independent predictors of low responses: any immunosuppressant, normal anti-dsDNA, lower platelets, and normal C3
Furer et al.	Cohort	Pfizer	686 AIIRD 121 HC	SLE 101 (14.7%); RA 263 (38.3%); SpA 165 (33.9%)	SLE patients: GC 22 (22%), MTX 8 (8%), BCDT 7 (7%), MMF 17 (17%) All patients: GC 55 (21%), MTX 116 (44%), TNFi (18%), BCDT 87 (13%), MMF 38 (4%)	2–6 weeks post 2nd dose	Anti-S IgG	All AIIRD vs HC: lower* anti-S IgG seroconversion (86% vs 100%); lower* seroconversion rate in patients on GC (66%), MMF (64%), MTX (84%), and RTX (36%). Lower* seroconversion rate in SLE than HCs (92% vs 100%)
Deepak et al.	Cohort	Pfizer, Moderna	133 IMID 53 HC	SLE 15 (11.3%); RA 38 (28.6%); SpA 20 (15%); IBD 42 (31.6%)	GC 17 (12.8%), MTX 29 (21.8%), HCQ 30 (22.6%), MMF 9 (6.8%), BCDT 10 (7.5%).	Within 2 weeks prior to 1st dose, 20 days post 2nd dose	Anti-S IgG, functional neutralization titers, circulating S-specific plasmablasts	Reduction in anti-S Ab and neutralization titers vs HCs: IMID 3X; GC 10X; Antimetabolites 2–3X, BCDT 36X; TNFi, antimalarial = minimal
Ammitzbøll et al.	Cohort	Pfizer	134 AIIRD	SLE 61 (45.5%); RA 73 (54.5%)	SLE patients: GC 29 (47.5%), MMF 16 (26.2%), MTX 6 (9.8%), RTX 2 (3.3%)	Prior to the first dose, 7 days after the second dose	Anti-S IgM and IgG	Seroconversion rate: AIIRD 103/134 (77%), SLE 54/61 (88%), RA 49/73 (67%); RTX 4/17 (23%), time since RTX did not influence the Ab levels
Ruddy et al.	Cohort	Pfizer, Moderna	404 AIIRD	SLE 87 (22%); IA 180 (45%); overlap CTDs 84 (21%); Myositis 24 (6%); SS 19 (5%)	GC 117 (29%), MTX 94 (23%), MMF 41 (10%), RTX 19 (5%)	Median of 29 (IQR 28, 32) days after the second dose	Anti-RBD Abs	Seroconversion rate: all patients 378/404 (94%), SLE 78/87 (90%). Lower* seroconversion rate in patients on MMF (73%), RTX (79%), and GC (82%)
Geisen et al.	Cohort	Pfizer, Moderna	26 IMID 42 HC	SLE 2 (7.7%); RA 8 (30.8%); SpA 5 (19.2%); PsO 4 (15.4%); IBD 3 (11.5%)	GC 7 (26.9%), TNFi 13 (50%), csDMARDs 8 (30.8%)	Prior to 1st dose, days 0 and 7 post 2nd dose	Anti-SARS-CoV-2 IgG, neutralizing antibody; anti-SARS-CoV-2 IgA	Lower anti- SARS-CoV-2 IgA and IgG levels, neutralizing activities in IMID patients than HC. TNFi vs cDMARDs vs anti-IL–17 showed no significant difference between these therapies
Simon et al.	Cohort	Pfizer	84 IMID 182 HC	SpA 27 (32.1%); RA 25 (29.8%); PsO 8 (9.5%); IBD 8 (9.5%); systemic disorders 16 (19.1%)	Biologics (42.9%); csD-MARDs (23.9%); no treatment (28.6%)	>10 days post 2nd dose	Anti-S IgG	Compared to HCs, AIIRD patients had delayed and reduced immune responses to COVID-19 vaccines as reflected by a higher incidence of failure to develop neutralizing antibody activity (9.5% vs 0.5%) and longer time period to reach positive for anti-SARS-CoV-2 antibodies

Table 1 (continued)

Author	Design	Vaccine	Cohort	Diseases	Therapy	Sample Collection	Outcome measure	Results
Boekel et al.	Cohort	Pfizer, Moderna, AZ, J&J	632 IMID 289 HC	SLE 33 (5%); RA 260 (41%); SpA (142); MS 58 (9%); SS 33 (5%); vasculitis 11 (2%)	GC 109 (17%), MTX 223 (35%), TNFi 141(22%), BCDT 27 (4%),	IMID: 34 days (IQR 31, 38) post 1st dose, and 38 days (IQR 30–61) post 2nd dose; HC: 36 days (IQR 34–41) days (IQR 35–85) post 2nd dose	Anti-RBD IgG	Post 1st dose - Anti-SARS-CoV-2 IgG IMID (210/432, 49%) vs HCs (154/210, 73%); MTX and BCDT lower* seroconversion than HC. Post 2nd dose: seroconversion rates similar in all treatment groups, except for patients on BCDTs. S/p COVID-19: post 1st dose, seroconversion rates and IgG titers were similar to HC post 1st dose and patients without previous COVID-19 post 2nd dose
Boyarsky et al.	Cohort	Pfizer, Moderna	123 AIIRD	SLE 24 (20%); IA 34 (28%); CTD 35 (29%); SS 16 (13%); myositis 7 (6%)	MTX 13 (11%), MMF 11 (9%), TNFi 17 (14%), RTX 6 (5%), BLyS 10 (8%)	Median (IQR) of 22 (18–26) days after 1st dose	Anti-RBD Abs	1st dose only; Patients on MMF or RTX less likely* to develop a detectable Ab response
Spiera et al.	chart review	Pfizer, Moderna	89 AIIRD	SLE 9 (10%); RA 23 (26%); SS 10 (11%); GPA 12 (13%)	GC 17 (19%), MTX 13 (15%), MMF 7 (8%), TNFi 9 (10%), BLyS 2 (2%), RTX 30 (34%)	N/A	Anti-S Abs	SLE patients: 7/9 (78%) seropositive All patients: 68/89 (69%) patients seropositive; of 21 seronegative patients, 20 received RTX, one received BLyS
Al-Janabi et al.	Cohort	Pfizer, AZ	120 IMID	SLE 1 (0.8%); RA 10 (8.3%); PsA (20.8%); PsO (89.2%)	Not applicable	Median 34 days (IQR 23-46) after 1st dose	Anti-S IgG	1st dose only: 15% no detectable Ab; 41% no detectable anti-S1 IgG. MTX reduced response relative to biologics (adjusted OR = 0.31)

*Statistically significant; X, fold reduction

Pfizer, Pfizer/BioNTech BNT162b2; Moderna, Moderna mRNA-1273; J&J, Janssen Ad26.COV2.S; AZ, AstraZeneca ChAdOx1 nCoV-19

AIIRD autoimmune inflammatory rheumatic diseases, *IMID* immune-mediated inflammatory disease, *HC* healthy control, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *PsO* psoriasis, *PsA* psoriatic arthritis, *IBD* inflammatory bowel disease, *SS* Sjogren syndrome, *GPA* granulomatosis with polyangiitis, *MS* multiple sclerosis, *IA* inflammatory arthritis, *CTD* overlap connective tissue disorders, *DMARD* disease-modifying antirheumatic drug, *csDMARDs* conventional synthetic DMARDs, *HCQ* hydroxychloroquine, *GC* glucocorticoid, *MTX* methotrexate, *AZA* azathioprine, *LEF* leflunomide, *MMF* mycophenolate mofetil, *RTX* rituximab, *BCDT* B-cell depletion therapy, *BLyS* belimumab, *ABA* abatacept, *TNFi* tumor necrosis factor inhibitor, *IL-6i* interleukin-6 inhibitor, *IL-23i* interleukin-23 inhibitor, *IL-17i* interleukin-17 inhibitor, *JAKi* Janus kinase inhibitor, *IQR* interquartile range, *OR* odds ratio, *RBD* receptor binding domain, *anti-dsDNA* anti-double-stranded DNA antibody, *S* SARS-CoV-2 spike protein

responses among AIIRD patients on different immunosuppressive regimens to define the immunosuppressants responsible for the reduction in these humoral responses. Deepak et al. conducted a cohort study to compare immunogenicity of SARS-CoV-2 mRNA vaccines in AIIRD patients (n=133) and immunocompetent controls (n=53). They identified that the strongest effect on humoral responses was due to B-cell depleting therapies (BCDT) and GC (36- and 10-fold reduction of anti-spike IgG titers), followed by JAKi and antimetabolites including MTX [21]. Another large observational study by Furer et al. identified treatment with GC, RTX, MMF, and abatacept (ABA) as risk factors for the reduced immunogenicity of mRNA BNTb262 among AIIRD patients (n=686) [19]. Similarly, in the SLE cohort study by Izmirly et al., treatment with any non-antimalarial immunosuppressants was independently associated with decreased responses to COVID-19 vaccines in SLE patients (n=90) [14].

Below we reviewed updated evidence on the impacts of several immunosuppressive agents on the serological responses to SARS-CoV-2 vaccines in patients with AIIRD. These immunosuppressants are of particular interest as they are frequently used in the treatment of SLE.

Glucocorticoids

Prednisone dose of ≥10 mg/day was reported to hamper serological responses to pneumococcal vaccination in patients with various immune-mediated inflammatory disorders (IMID) [22]. In SLE patients, high-dose (>20mg/day) prednisone resulted in lower seroconversion after vaccination against influenza A/H1NA [23]. Multiple studies on vaccination against SARS-CoV-2 in AIIRD patients confirmed an association between GC use and dampened antibody responses [14, 19, 21, 24]. Of note, Deepak et al. observed very low anti-SARS-CoV-2 antibody titers and neutralizing activity in some patients taking prednisone < 5mg/day and pointed out that GC had a dose-independent effect on reduction in antibody titers following SARS-CoV-2 vaccination [21].

In our meta-analysis (Fig 2) including 6 observational studies (pooled n=1435), GC use was associated with a lower seroconversion rate following SARS-CoV-2 vaccination (pooled OR=0.29 [95% CI 0.15, 0.57]) in patients with AIIRD; we believe this should hold true in SLE. Of concern this meta-analysis included a highly heterogeneous population, with multiple AIIRDs, and incomplete data on non-GC users.

Methotrexate

MTX is a decades-old antimetabolite widely used in rheumatic diseases. A 2013 meta-analysis including a total of 1303 RA patients from 12 studies concluded that MTX decreased the immune responses to pneumococcal and influenza vaccination [25]. Two randomized clinical trials (RCT) by Park et al. further revealed that a temporary discontinuation of MTX following seasonal influenza vaccination, specifically for a duration of 2 weeks, improved its immunogenicity in RA patients [26, 27].

A more recent cohort study by Haberman et al. compared humoral and cellular immune responses to two doses of BNT162b2 mRNA COVID-19 vaccine among individuals with IMID on MTX (n=45), with IMID not on MTX (n=37), and HCs (n=208). Individuals with IMID on MTX demonstrated up to 62% reduced rate of adequate antibody response, while those on non-MTX medications demonstrated levels of immunogenicity comparable to HCs [28]. Notably, this study identified decreased induction in the frequencies of activated and granzyme B-producing CD8+ T cells in participants with IMID on MTX. Robust expansion of functional CD8+ T cells early after COVID-19 vaccination has been suggested to play important roles in protection against SARS-CoV-2 infection [29]. Studies in non-human primates suggest that CD8+ T cells contribute to protection against rechallenge with SARS-CoV-2, especially in the setting of waning antibody titers [30]. Taken together, these suggest that MTX may impair the immunogenicity of COVID-19 vaccine by blunting both cellular and humoral responses.

Four other cohort studies on immune responses against SARS-CoV-2 vaccination among patients with AIIRD further confirmed a lower seroconversion rate in those being treated with MTX [14, 19, 21, 31]. However, a larger cohort study by Boekel et al. demonstrated a significantly lower rate of seroconversion in AIIRD patients without previous SARS-CoV-2 infection as compared to healthy controls following the first dose of SARS-CoV-2 vaccination, while the seroconversion rate reached similar after the second dose. This discrepancy may be explained the relatively long median time between vaccination and sampling in the patient cohort (38 days), which suggests that MTX might delay rather than impair the development of humoral immunity [15].

Our meta-analysis (Fig 3) including 6 observational studies (pooled n=1508) did not show an association between MTX use and a lower seroconversion rate following SARS-CoV-2 vaccination in patients with AIIRDs (pooled OR=1.02 [95% CI 0.56, 1.85]). It is not unexpected as the patients were highly heterogeneous with different autoimmune disorders and on various immunosuppressive regimens other than MTX monotherapy. For example, patients identified as "No MTX" might be on RTX or MMF, which would have significantly reduced their immune responses against vaccination, thus confounding the result. Additionally, it is possible that some patients held their MTX around
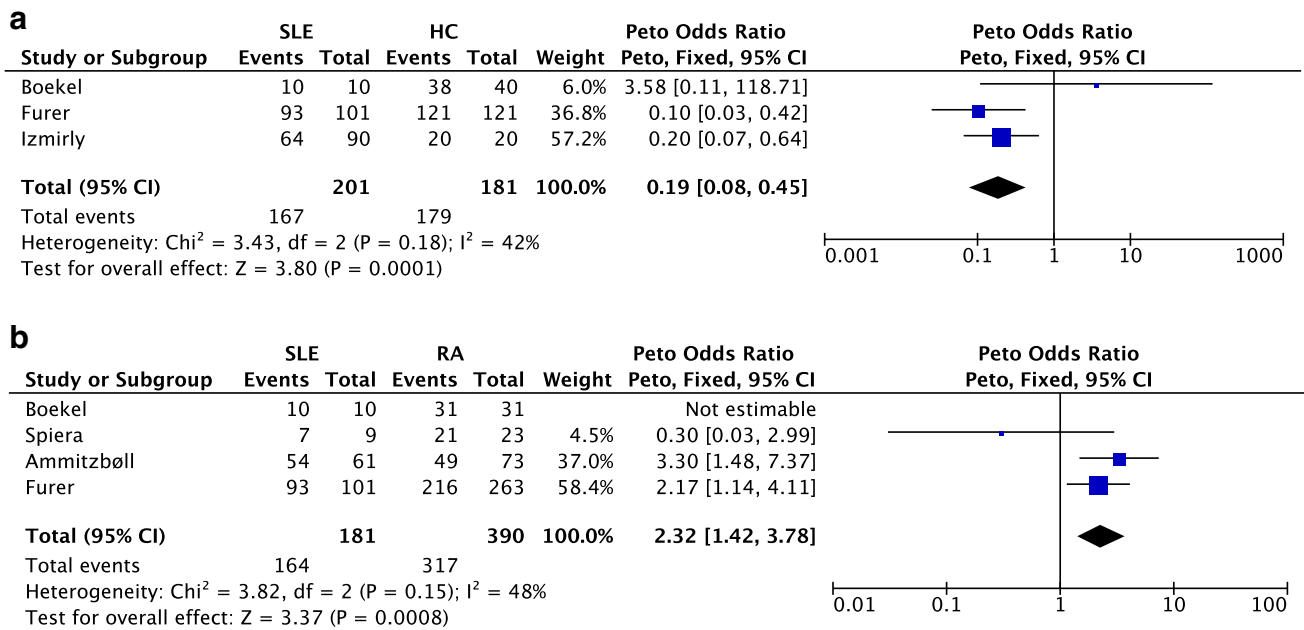
a

Study or Subgroup	SLE Events	Total	HC Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boekel	10	10	38	40	6.0%	3.58 [0.11, 118.71]
Furer	93	101	121	121	36.8%	0.10 [0.03, 0.42]
Izmirly	64	90	20	20	57.2%	0.20 [0.07, 0.64]
Total (95% CI)		201		181	100.0%	0.19 [0.08, 0.45]
Total events	167		179			

Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 3.80 (P = 0.0001)

b

Study or Subgroup	SLE Events	Total	RA Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boekel	10	10	31	31		Not estimable
Spiera	7	9	21	23	4.5%	0.30 [0.03, 2.99]
Ammitzbøll	54	61	49	73	37.0%	3.30 [1.48, 7.37]
Furer	93	101	216	263	58.4%	2.17 [1.14, 4.11]
Total (95% CI)		181		390	100.0%	2.32 [1.42, 3.78]
Total events	164		317			

Heterogeneity: Chi² = 3.82, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 3.37 (P = 0.0008)

Figure 1 **a** Meta-analysis of 3 cohorts studies investigating seroconversion rate following SARS-CoV-2 vaccination in SLE patients versus HC. **b** Meta-analysis of 3 cohort studies investigating seroconversion rate following SARS-CoV-2 vaccination in SLE versus RA patients

vaccination based on the American College of Rheumatology (ACR) COVID-19 vaccine clinical guidance.

Mycophenolate or Mycophenolic Acid

A 2013 case-control study that investigated the immunogenicity of quadrivalent HPV vaccine in SLE patients reported that patients on MMF had lower seroconversion rates for two genotypes than those on other immunomodulators and anti-HPV titers were inversely correlated with MMF dose [32]. Solid organ transplant recipients treated with MMF-based regimens were reported to have higher incidence of impaired humoral responses to SARS-CoV-2 BNT162b2 mRNA vaccine [33, 34]. In line with these, five cohort studies showed reductions in the seroconversion rate following SARS-CoV-2 vaccination in AIIRD patients treated with MMF-based regimens [14, 19, 21, 24, 35].

Our meta-analysis (Fig 4) including 5 observational studies (pooled n=1330) showed an association between MMF use and a lower seroconversion rate following SARS-CoV-2 vaccination among patients with AIIRDs (pooled OR=0.21 [95% CI 0.13, 0.34]).

Rituximab

RTX depletes CD20+ B cells and diminishes humoral immune responses to vaccination. Substantial reductions in immune responses to SARS-CoV-2 vaccinations have been consistently observed in AIIRD patients treated with RTX across all studies [14, 16, 19, 21, 24, 35–37].

Spiera et al. reported that longer duration from last RTX exposure was associated with higher rates of seroconversion and that even low levels of B-cell reconstitution was sufficient to render more robust immune responses, illustrating the importance of appropriate timing when administering SARS-CoV-2 vaccination in RTX-exposed AIIRD patients [37]. Furthermore, Deepak et al. found that the reduction in antibody titers and neutralization activities were most significant when SARS-CoV-2 vaccination occurred within 6 months of BCDT, with gradual recovery after 9-month post-treatment with RTX [21]. However, Salviani et al. described 2 patients with AAV who failed to develop neutralizing antibodies after SARS-CoV-2 mRNA vaccines even though the most recent RTX infusion was more than 9 months earlier [38]. Furthermore, Ammitzbøll et al. found a strikingly low seroconversion rate in RA and SLE patients (n=17) treated with RTX (4/17, 23%) after two doses of BNTb262 mRNA vaccine. The median time interval between last RTX infusion and vaccination was 187 (IQR 150–245) days, and this time interval did not influence levels of total antibody against SARS-CoV-2 [16].

Our meta-analysis (Fig 5) including 6 observational studies (pooled n=1509) revealed a significant association between RTX use and a lower seroconversion rate following SARS-CoV-2 vaccination among patients with AIIRDs (pooled OR=0.04 [95% CI 0.02, 0.08]).
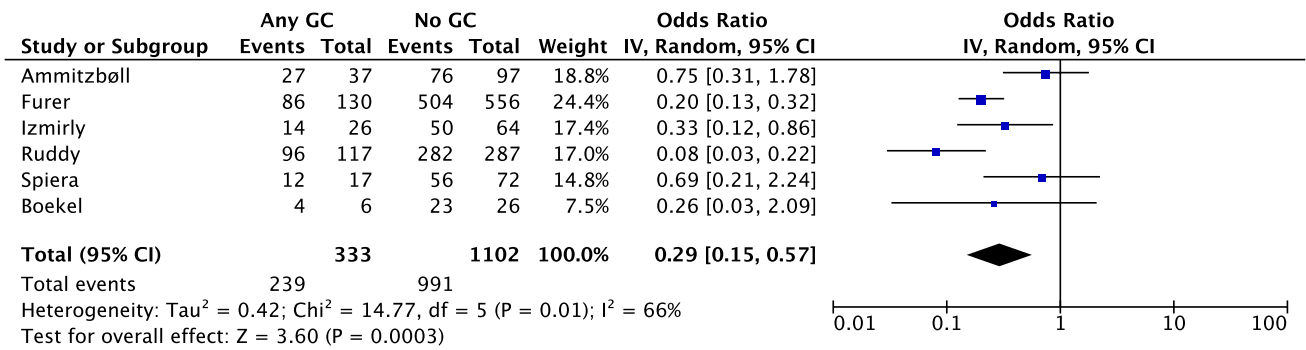
Study or Subgroup	Any GC Events	Total	No GC Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Ammitzbøll	27	37	76	97	18.8%	0.75 [0.31, 1.78]	
Furer	86	130	504	556	24.4%	0.20 [0.13, 0.32]	
Izmirly	14	26	50	64	17.4%	0.33 [0.12, 0.86]	
Ruddy	96	117	282	287	17.0%	0.08 [0.03, 0.22]	
Spiera	12	17	56	72	14.8%	0.69 [0.21, 2.24]	
Boekel	4	6	23	26	7.5%	0.26 [0.03, 2.09]	
Total (95% CI)		333		1102	100.0%	**0.29 [0.15, 0.57]**	
Total events	239		991				

Heterogeneity: Tau² = 0.42; Chi² = 14.77, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 3.60 (P = 0.0003)

0.01   0.1   1   10   100

Fig 2 Meta-analysis of 6 observational studies investigating glucocorticoid use and seroconversion following SARS-CoV-2 vaccination in AIIRD patients

Safety of COVID-19 Vaccine in Patients with Systemic Lupus Erythematosus

The pathogenesis of SLE and COVID-19 rely on the activation of similar molecular networks, including type I interferon and proinflammatory cytokine pathways [39, 40]. The nucleic acid-based vaccines used for COVID-19 can activate these pathways by signaling through endosomal toll-like receptors (TLRs) and cytosolic RNA and DNA sensors (such as MDA5, RIG-I, and cGAS) that trigger inflammasome activation and type I interferon production, raising initial concern that such approaches could induce disease flares [41]. In addition, we previously speculated that the mRNA vaccines may interact with cytoplasmic RNA-binding proteins involved in the post-translational regulation of inflammatory mediators, thus triggering autoimmune disease activity [9]. Transient elevations of various autoantibodies were observed in patients with SLE following influenza vaccinations though these elevations were not consistently associated with increase in disease activity [42, 43]. Felten et al. conducted a web-based survey in December 2020 on the expectations and concerns regarding SARS-CoV-2 mRNA vaccines in patients with AIIRD (n=1266). Roughly half of the participants expressed unwillingness (13.2%) and uncertainty (32.2%) to get vaccinated; scarcity of vaccine safety profiles and possible induction of a disease flare were identified among the main concerns leading to vaccine hesitancy [44].

Despite all the above theoretical concerns, current data on the safety of COVID-19 vaccines in patients with AIIRDs have been reassuring albeit scarce (Table 2).

Concerns for Disease Flare

Two studies focused on the adverse events following the first dose of COVID-19 vaccine in patients with AIIRD [36, 45]. Reassuringly, both reported that side effect profiles in patients with AIIRD were comparable to data generated from the general population and to large-scale vaccine trials, with high prevalence of reactogenicity, among which pain and fatigue were the most common local and systemic symptoms, respectively. Conolly et al. did note one case of peripheral neuropathy during the 1-week follow-up of 325 patients [45]. Boekel et al. did, however, report a small proportion of 26 patients (5%) with AIIRD that experienced worsening of their underlying disease up to 2 months after vaccination.
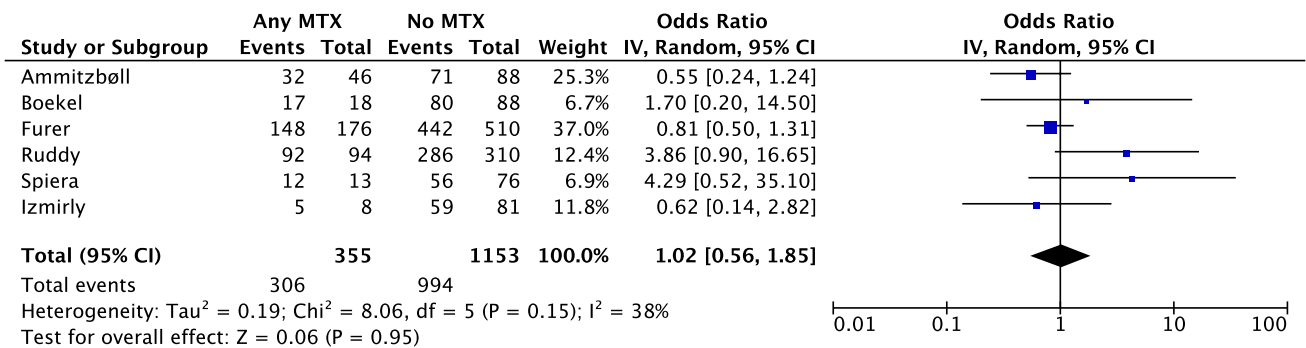
Study or Subgroup	Any MTX Events	Total	No MTX Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Ammitzbøll	32	46	71	88	25.3%	0.55 [0.24, 1.24]	
Boekel	17	18	80	88	6.7%	1.70 [0.20, 14.50]	
Furer	148	176	442	510	37.0%	0.81 [0.50, 1.31]	
Ruddy	92	94	286	310	12.4%	3.86 [0.90, 16.65]	
Spiera	12	13	56	76	6.9%	4.29 [0.52, 35.10]	
Izmirly	5	8	59	81	11.8%	0.62 [0.14, 2.82]	
Total (95% CI)		355		1153	100.0%	**1.02 [0.56, 1.85]**	
Total events	306		994				

Heterogeneity: Tau² = 0.19; Chi² = 8.06, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 0.06 (P = 0.95)

0.01   0.1   1   10   100

Fig 3 Meta-analysis of 6 observational studies investigating methotrexate use and seroconversion following SARS-CoV-2 vaccination
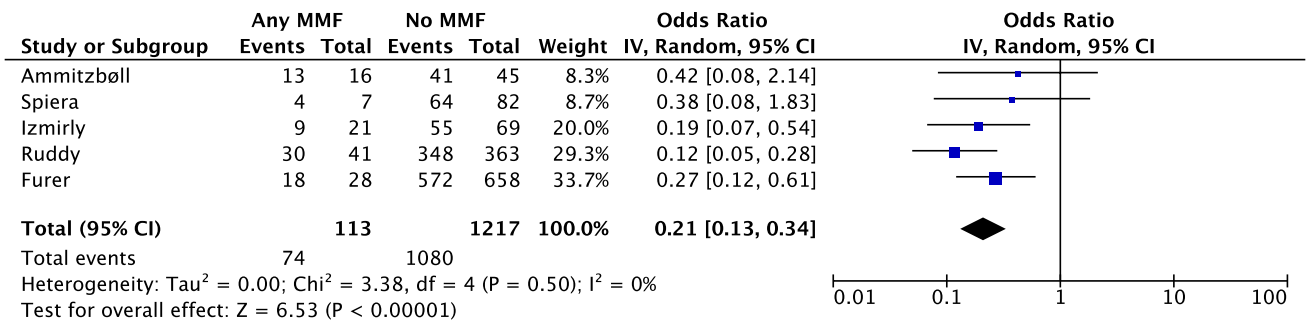
Study or Subgroup	Any MMF Events	Total	No MMF Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Ammitzbøll	13	16	41	45	8.3%	0.42 [0.08, 2.14]	
Spiera	4	7	64	82	8.7%	0.38 [0.08, 1.83]	
Izmirly	9	21	55	69	20.0%	0.19 [0.07, 0.54]	
Ruddy	30	41	348	363	29.3%	0.12 [0.05, 0.28]	
Furer	18	28	572	658	33.7%	0.27 [0.12, 0.61]	
Total (95% CI)		113		1217	100.0%	**0.21 [0.13, 0.34]**	
Total events	74		1080				

Heterogeneity: Tau² = 0.00; Chi² = 3.38, df = 4 (P = 0.50); I² = 0%
Test for overall effect: Z = 6.53 (P < 0.00001)

Fig 4 Meta-analysis of 5 observational studies investigating mycophenolate/mycophenolic acid use and seroconversion following SARS-CoV-2 vaccination in AIIRD patients

A couple of studies evaluated the disease activity of underlying autoimmune disorders in patients with AIIRD before and after two doses of SARS-CoV-2 mRNA vaccines [19, 46]. Geisen et al. monitored disease activity of patients with AIIRD (n=26) by Patient Global Assessment (PGA) plus Physician Global Assessment (PhGA) and additionally monitored patients with inflammatory arthritis (n=8) by Disease Activity Score-28 (DAS-28) [46]. No disease flares were observed following either vaccination time point, and no changes in use of GC or DMARDs were needed during the 6-week trial duration. Similarly, the above cohort study by Furer et al. reported stable post-vaccination indices of disease activity across different disease types, including SLE (measured by SLE Disease Activity Index [SLEDAI]) [19].

Another two studies investigated the safety profiles of COVID-19 vaccine specifically in patients with SLE [14, 47]. Felten et al. surveyed a group of patients with self-reported medically confirmed SLE (n=696) for the occurrence of side effects. Twenty-one (3%) patients reported a medically confirmed SLE flare after a median IQR of 3 days (0–29) following vaccination, which led to treatment change in 15 (71%) and hospital admission in 4 (19%) patients; notably, the presence of a SLE flare in the year preceding vaccination was identified as a risk factor for

post-vaccination disease flare [47]. In the study by Izmirly et al., SLE patients (n=90) were also assessed for pre- and post-vaccination disease activities by clinical and serological parameters. SLEDAI scores, percentages of patients with abnormal anti-double-stranded DNA (anti-dsDNA) antibodies and/or abnormal complement levels, and levels of C3 and C4 remained similar pre- and post-vaccination. Nine (11.4%) patients had post-vaccination flares, of which only one was severe and characterized by arthritis requiring MTX treatment [14].

Notably, Watad et al. presented a series of 27 cases including 17 disease flares and 10 de novo onsets of AIIRDs following administration of SARS-CoV-2 vaccines. Among them were two SLE flares and one case of discoid SLE that converted to pleuropericarditis [48].

Thrombosis and Thrombocytopenia

Rare development of unusual thrombotic events and thrombocytopenia have been observed within 1–2 weeks of vaccination with adenoviral vector SARS-CoV-2 vaccines, ChAdOx1 nCov-19 (AstraZeneca) and Ad.26.COV2.S (Janssen). The majority of cases occurred in women, predominantly involved cerebral venous sinuses, and presented
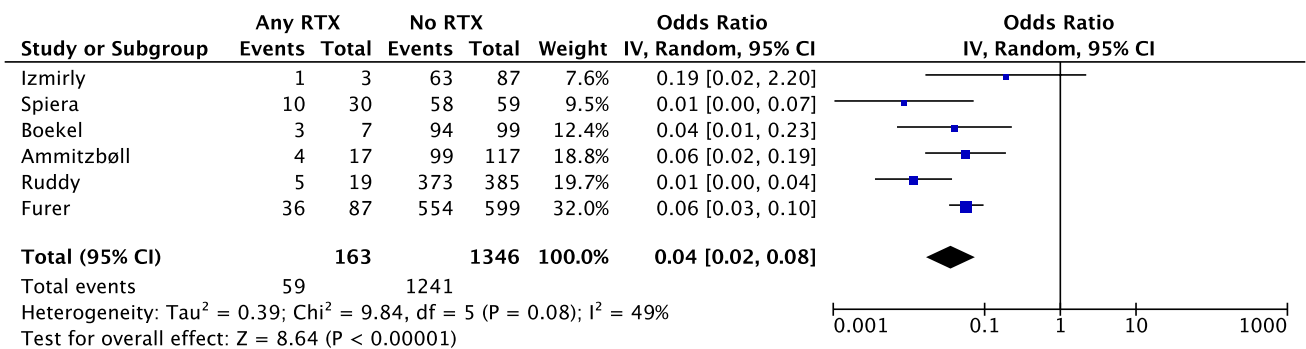
Study or Subgroup	Any RTX Events	Total	No RTX Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Izmirly	1	3	63	87	7.6%	0.19 [0.02, 2.20]	
Spiera	10	30	58	59	9.5%	0.01 [0.00, 0.07]	
Boekel	3	7	94	99	12.4%	0.04 [0.01, 0.23]	
Ammitzbøll	4	17	99	117	18.8%	0.06 [0.02, 0.19]	
Ruddy	5	19	373	385	19.7%	0.01 [0.00, 0.04]	
Furer	36	87	554	599	32.0%	0.06 [0.03, 0.10]	
Total (95% CI)		163		1346	100.0%	**0.04 [0.02, 0.08]**	
Total events	59		1241				

Heterogeneity: Tau² = 0.39; Chi² = 9.84, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 8.64 (P < 0.00001)

Fig 5 Meta-analysis of 6 observational studies investigating rituximab use and seroconversion following SARS-CoV-2 vaccination in AIIRD patients

Table 2 Summary of studies on COVID-19 vaccine safety in patients with autoimmune inflammatory rheumatic disorders

Author	Design	Vaccine	Cohort	Diseases	Therapy	Time period	Results
Geisen et al.	Cohort	Pfizer, Moderna	26 AIIRDs 42 HCs	SLE 2 (7.7%), RA 8 (30.1%), PsA 6 (23.1%), SpA 3 (11.5%)	GC 7 (26.9%), TNFi 13 (50%), csDMARDs 8 (30.8%)	Pre 1st dose to 14 days post 2nd dose	Stable DAS28, PGA, PhGA pre- and post-vaccine No patient with AIIRDs needed to adjust DMARD or GC therapy in the 6 weeks of trial duration
Izmirly et al.	Cohort	Pfizer, Moderna, J&J	90 SLE 20 HCs	SLE specific	GC 26 (29%), MTX 8 (14.9%), MMF 21 (23%), RTX 3 (3%), BLyS 10 (11%)	Average 23.6 days (range 5–70) post final dose	Similar pre-/post-vaccine SLEDAI 9 (11.4%) patients had a post-vaccination flare; 8/9 mild/moderate and 1/9 severe No changes in % (+) anti-dsDNA and/or low C3/C4
Furer et al.	Cohort	Pfizer	686 AIIRD 121 HC	SLE 101 (14.7%); RA 263 (38.3%), PsA 165 (24.1%)	GC 55 (21%), MTX 116 (44%), TNFi (18%), BCDT 87 (13%), MMF 38 (4%)	Within 2 weeks post 1st dose, within 2–6 weeks post 2nd dose	Stable pre- and post-vaccine disease activity indices
Conolly et al.	Cohort	Pfizer, Moderna	325 AIIRD	SLE 91 (28%), IA 123 (38%), CTDs 62 (19%)	csDMARDs 63 (44%), biologics 62 (19%), combination 120 (37%)	Within 1st week post 1st dose	Peripheral neuropathy—1 case Local side effects—89%, pain most common Systemic side effects—69%, fatigue most common. Similar symptoms to those reported in general population vaccine trials
Boekel et al.	Cross-sectional	Pfizer, AZ, Moderna	505 IMID 203 HC	SLE 25 (5%), RA 204 (40%), PsA 49 (10%); AS 39 (8%), MS 81 (16%), PMR 17 (3%)	No treatment 157 (31%), MTX 169 (33%), other csDMARDs 67 (13%), GC 77 (15%), TNFi 93 (18%), BCDT 35 (7%)	Median of 15 days (IQR 10–25) for AIIRD and 15 days (10–34) for HC post 1st dose	Adverse events of COVID-19 vaccines in patients with IMID are comparable with controls Patients with AIIRD more frequently reported joint pain than controls (10% vs 1%) 26 (5%) patients with AIIRDs self-reported disease worsening up to 2 months post vaccine
Felten et al.	Cross-sectional	Mixed types	696 SLE	SLE specific	GC 373 (53.6%), HCQ 542 (77.9%), MTX/LEF/MMF/AZA/CTX 347 (49.9%), BLyS 76 (10.9%); RTX 22 (3.2%)	Not applicable	21 (3%) self-reported/physician confirmed SLE flares after a median of 3 days (IQR 0–29) post vaccine; 15 treatment change, and 4 admissions for SLE flares. Flare in the year pre-vaccine was associated an increased risk of post-vaccine flare (RR =5.52, 95% CI 2.17–14.03).
Watad et al.	Case series	Pfizer, AZ, Moderna	17 flares, 10 de-novo IMIDs	4 cases in SLE	Not applicable	Not applicable	4 cases of SLE flares

Pfizer, Pfizer/BioNTech BNT162b2; Moderna, Moderna mRNA-1273; J&I, Janssen Ad26.COV2.S; AZ, AstraZeneca ChAdOx1 nCoV-19

IMID immune-mediated inflammatory disease, *AIIRD* autoimmune inflammatory rheumatic diseases, *HC* healthy control, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *PsO* psoriasis, *PsA* psoriatic arthritis, *AS* ankylosing spondyloarthritis, *PMR* polymyalgia rheumatica, *MS* multiple sclerosis, *IA* inflammatory arthritis, *CTD* overlap connective tissue disorders, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *HCQ* hydroxychloroquine, *GC* glucocorticoid, *MTX* methotrexate, *AZA* azathioprine, *LEF* leflunomide, *MMF* mycophenolate mofetil, *CTX* cyclophosphamide, *RTX* rituximab, *BCDT* B-cell depletion therapy, *BLyS* belimumab, *TNFi* tumor necrosis factor inhibitor, *%* percentage of patients, *(+)* positive, *Anti-dsDNA* anti-double stranded DNA antibody, *IQR* interquartile range, *RR* relative risk, *CI* confidence interval, *DAS28* disease activity score 28, *PGA* Patients Global Assessment, *PhGA* Physician Global Assessment, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SDAI* Simple Disease Activity Index, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *PASI* Psoriasis Area and Severity Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score

clinical pictures as well as serological reactivity strongly resembling those of autoimmune heparin-induced thrombocytopenia [49].

These cases led to a temporary pause on the administration of Ad.26.COV2.S (Janssen) in the USA, which was later lifted due to the known benefits of protection against SARS-CoV-2 infection outweighing the risks, as determined by FDA and CDC advisory committees. However, no reports of thrombosis and thrombocytopenia were noted in SLE patients.

Discussion

As of September 1, 2021, more than 686 million doses of COVID-19 vaccine have been delivered across the USA, and 61.9% of the total population has received at least one dose of vaccine [50]. Despite limited data on the efficacy and safety profiles in patients with AIIRD, the majority of this population has been fully vaccinated in accordance with ACR COVID-19 vaccine clinical guidance [11]. Our review and analyses show that patients with SLE are less likely to generate adequate immune responses, to COVID-19 vaccines, an effect likely driven by immunosuppressants commonly used to treat SLE, including GC, MTX, MMF, and RTX can further delay or impair vaccine responses. Reassuringly, there is no major safety concern regarding the use of COVID-19 vaccine in patients with AIIRD.

Several critical questions remain unanswered. First of all, previous studies on the efficacy of COVID-19 vaccination in SLE patients invariably focused on the immediate immune response as measured by antibody titers, neutralization activities, and, in some studies, T cell responses. However, no studies have assessed the durability of vaccine responses in SLE patients. Second, emerging SARS-CoV-2 variants, with high transmissibility, extreme virulence, and ability to evade vaccine-induced immunity, have up-trended the COVID-19 case number in recent months with a considerable proportion of fully vaccinated people being re-infected [51]. As a result, over 1 million people chose to get a booster vaccine dose during the period of August 13 to September 1, according to official COVID data tracker [50]. Unfortunately, no evidence exists as to whether fully vaccinated SLE patients are at an increased risk of becoming infected with emerging variants, whether they would benefit from a booster dose, and if so, when is the optimal time to administer the booster and how to adjust the immunosuppressive regimen to optimize booster effects. We are looking forward to the results from the ACV01 study, a randomized clinical trial investigating booster effects with different immunosuppressive regimens in AIIRD patients, to further clarify these critical questions [12].

In sum, as of the date of this review, the benefits of COVID-19 vaccine against SARS-CoV-2 infection far outweighs the risks of side effects or disease flares. Therefore, we stand firmly in line with ACR guidance that all AIIRD patients should receive COVID-19 vaccine and certain immunosuppressive therapies should be modified around the time of vaccination [11].

Declarations

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