Clinical Rheumatology (2023) 42:1695–1700
https://doi.org/10.1007/s10067-023-06512-z

BRIEF REPORT

Predictors of low spike antibody response in patients with systemic rheumatic disease after an initial course of COVID-19 vaccination

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Received: 11 July 2022 / Revised: 19 December 2022 / Accepted: 9 January 2023 / Published online: 19 January 2023

Abstract

Background Patients with rheumatic disease may mount a suboptimal serologic response to COVID-19 vaccination. We evaluated predictors of low antibody response in a clinic-based cohort.

Methods We conducted a cross-sectional study using electronic health record (EHR) data at Brigham and Women's Hospital, Boston, MA. Patients with systemic rheumatic disease that had SARS-CoV-2 spike antibody (Ab) tested using the Roche Elecsys immunoassay, February–August 2021, after 2 doses of mRNA vaccine or 1 dose of adenovirus vector vaccine were identified. Demographics, systemic rheumatic disease, vaccination dates, and disease-modifying antirheumatic drugs (DMARDs) were extracted. The primary outcome was low spike Ab (≤ 200 U/mL). Logistic regression models estimated predictors of low spike Ab.

Results Among 382 patients, the mean age was 57 years, 77% were female, and 37% had low spike Ab. Older age (OR 1.03, 95% CI [1.02, 1.05]), SLE (OR 4.81 [2.08, 8.43], reference: inflammatory arthritis), prednisone (OR 1.67 [1.03, 2.74]), and rituximab (OR 22.91 [9.85, 53.29]) were significantly associated with higher odds of low spike Ab. Use of csDMARD monotherapy (OR 0.12 [0.04, 0.33]) and JAK inhibitors (OR 0.41 [0.18, 0.92]) were associated with significantly lower odds for low spike Ab. After adjusting for systemic rheumatic disease and DMARDs, SLE and rituximab remained significantly associated with low spike Ab.

Conclusions Over a third of patients with systemic rheumatic disease with spike Ab tested in routine care had low spike Ab after 2 doses of mRNA or 1 dose of adenovirus vector COVID-19 vaccine. SLE and rituximab were significant risk factors for low spike Ab.

Key Points:
- *More than one-third of patients with systemic rheumatic disease that had spike Ab tested in routine care had low spike Ab after 2 doses of mRNA or 1 dose of adenovirus vector COVID-19 vaccine.*
- *Diagnosis of SLE, use of prednisone, and use of rituximab were significantly associated with greater odds of low spike antibodies.*
- *These data underscore the importance of additional doses of COVID-19 vaccine and prophylactic Evusheld in immunosuppressed patients with systemic rheumatic disease as recommended by the US Centers for Disease Control.*

Keywords COVID-19 vaccine · Low antibody response · Rheumatic disease

Introduction

Vaccination against COVID-19 reduced the incidence of severe COVID-19 infection in two large randomized trials among non-immunosuppressed adults [1, 2]. Patients with systemic rheumatic diseases represent a particularly at-risk population for severe COVID-19 infection for a number of reasons, including the use of immunosuppressive disease-modifying anti-rheumatic drugs (DMARDs), comorbidities, and underlying abnormal immune responses due to the autoimmune disease itself [3, 4]. A growing body of literature

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suggests that COVID-19 vaccines are safe in persons with systemic rheumatic disease [5–8], and the American College of Rheumatology recommends COVID-19 vaccination for persons with systemic rheumatic disease [3].

Antibody response following vaccination against COVID-19 is less robust among immunosuppressed organ transplant recipients and persons using B cell-depleting therapies [9, 10]. However, the serologic response following an initial course of COVID-19 vaccination in persons with systemic rheumatic disease using a range of DMARDs has been less widely studied.

We evaluated predictors of low antibody response following an initial course of COVID-19 vaccination in a clinic-based cohort of patients with rheumatic disease.

Methods

Study design and study population

We performed a retrospective cross-sectional study of patients with systemic rheumatic disease treated at Brigham and Women's Hospital (BWH), Boston, USA. We queried the electronic health record (EHR) for patients that had been seen at least twice at the BWH Arthritis Center, January 2019–December 2020, and had at least 2 diagnosis codes for rheumatoid arthritis (RA), psoriatic arthritis (PsA), spondylarthritis, scleroderma, systemic lupus erythematosus (SLE), inflammatory myositis, or vasculitis. We reviewed the EHR to verify that each patient had a rheumatologist-confirmed diagnosis of systemic rheumatic disease.

All patients had received an initial course of COVID-19 vaccine, defined as 2 doses of mRNA vaccine separated by 3–4 weeks or 1 dose of adenovirus vector vaccine. SARS-CoV-2 spike antibody (Ab) was measured using the Roche Elecsys® anti-SARS-CoV-2 S (receptor binding domain, RBD) immunoassay (range 0 to > 2500 U/mL) as part of routine care from February 17, 2021 (earliest date of spike Ab result in the dataset) through August 13, 2021. The study end date was chosen as the date the Centers for Disease Control and Prevention (CDC) recommended an additional dose of COVID-19 vaccine for immunosuppressed persons (i.e., 3rd dose of mRNA vaccine or 1st dose of mRNA vaccine for those that previously received adenovirus vector vaccine) [11]. We excluded patients with an additional dose of COVID-19 vaccine documented in the EHR before the date of spike Ab assessment.

Outcome

The primary outcome was spike Ab ≤ 200 U/mL. This level was selected based on the definition of "negative serologic or sub-optimal response" in an ongoing NIH-sponsored clinical trial of COVID-19 vaccination in persons with autoimmune disease (clinicaltrials.gov identifier NCT05000216), which also uses the Roche Elecsys® anti-SARS-CoV-2 S (RBD) immunoassay [12].

Covariates

We reviewed the EHR to extract demographics, systemic rheumatic disease diagnosis, vaccine brand and dates, DMARDs at the time of each vaccination, and date of spike Ab assessment. We calculated the interval between completion of the 2nd mRNA vaccine or 1st adenovirus vector vaccine and spike Ab assessment.

Statistical analysis

Descriptive statistics summarized demographics, systemic rheumatic disease diagnoses, and DMARD use. A series of logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for low spike Ab. All models were adjusted for age and interval between completion of vaccination and spike Ab assessment. Subsequent models were additionally adjusted for (1) systemic rheumatic disease, (2) individual DMARDs (separate model for each DMARD), and (3) systemic rheumatic disease and DMARDs (separate model for each DMARD). Analyses were performed using SAS v9.4, and two-sided $p < 0.05$ was considered significant. The Mass General Brigham Institutional Review Board approved all aspects of this study.

Results

Among 382 patients, the mean age was 57.0 (SD 16.1) years, and 76.7% were female. Inflammatory arthritis, including rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis not otherwise specified, was the most common diagnosis (65%) (Table 1). Systemic lupus erythematosus (SLE) (12.3%) and vasculitis (8.4%), including giant cell arteritis, Takayasu arteritis, and ANCA-associated vasculitis, were the next most common diagnoses. The majority received mRNA vaccines (94.5%). Mean interval from vaccination to spike Ab assay was 98.9 days (SD 39.1). Prednisone, conventional synthetic DMARDs, TNF inhibitors, and rituximab were the most common immunosuppressive treatments at the time of vaccination.

Older age (OR 1.03, 95% CI 1.02, 1.05) was associated with higher odds of low spike Ab in a model adjusted for age and interval. Diagnosis of SLE (OR 4.81, 95% CI 2.08, 8.43) was associated with greater odds for low spike Ab (reference group: inflammatory arthritis). Use vs. no use of hydroxychloroquine (OR 2.46, 95% CI 1.37, 4.46), prednisone (OR 1.67, 95% CI 1.03, 2.74), and rituximab

Table 1 Characteristics of systemic rheumatic disease patients

	All subjects $N = 382$	Low spike Ab (≤ 200 U/mL) $N = 143$	Adequate spike Ab (> 200 U/mL) $N = 239$
Age, years	57.0 (16.1)	60.4 (15.5)	55.0 (16.2)
Days from 2nd mRNA vaccine or 1st adenovirus vector vaccine to spike Ab measurement	98.9 (39.0)	96.6 (39.6)	100.4 (38.7)
Female	76.7	76.2	77.0
Vaccine type			
mRNA	94.5	90.2	97.1
Adenovirus vector	5.5	9.8	2.9
Systemic rheumatic disease			
Inflammatory arthritis**	65.1	58.7	69.0
SLE	12.3	18.9	8.4
Vasculitis[+]	8.4	11.9	6.3
Inflammatory myositis	3.9	3.5	4.2
Other[++]	10.2	7.0	12.1
DMARD use at time of initial vaccine dose(s)			
csDMARD[#] only	12.6	18.4	2.8
TNFi	21.7	16.8	24.7
JAKi	10.0	5.6	12.6
Rituximab	16.9	39.2	2.9
Prednisone	23.3	30.1	19.3
1–4 mg/day[##]	29/89 (32.6)	12/43 (27.9)	17/46 (37.0)
5–10 mg/day[##]	36/89 (40.4)	19/43 (44.2)	17/46 (37.0)
> 10 mg/day[##]	24/89 (27.0)	12/43 (27.9)	12/46 (26.1)
Mycophenolate	10.0	12.6	8.4
Hydroxychloroquine	15.7	21.0	12.6
Other[^]	24.9	29.4	22.2
No DMARDs	2.1	0	3.3

Abbreviations: *csDMARDs*, conventional synthetic DMARD; *SLE*, systemic lupus erythematosus; *TNFi*, TNF inhibitor; *JAKi*, JAK inhibitor

Data presented as mean (SD) or percentage. ** Includes rheumatoid arthritis (rheumatoid arthritis, $n = 203$), psoriatic arthritis ($n = 32$), inflammatory arthritis not otherwise specified ($n = 8$), and ankylosing spondylitis ($n = 6$). [+]Includes ANCA-associated vasculitis ($n = 19$) and large vessel vasculitis (giant cell arteritis, Takayasu arteritis, or polyarteritis nodosa) ($n = 13$). [++]Includes polymyalgia rheumatica ($n = 10$), systemic sclerosis ($n = 9$), mixed connective tissue disease ($n = 3$), relapsing polychondritis ($n = 3$), idiopathic recurrent pericarditis ($n = 3$), sarcoidosis ($n = 2$), Still's disease ($n = 2$), IgG4 related disease ($n = 1$), Sjogren's syndrome ($n = 1$), VEXAS syndrome ($n = 1$), undifferentiated connective tissue disease ($n = 1$), subacute cutaneous lupus ($n = 1$), small vessel vasculitis not otherwise specified ($n = 1$), and SAPHO syndrome ($n = 1$). [#]Includes methotrexate, sulfasalazine, and leflunomide; [##]presented as n/N prednisone users and (%) of prednisone users; [^]includes tocilizumab, IL-1 antagonists, IL-17 antagonists, abatacept, azathioprine, belimumab, IVIG, tacrolimus, and cyclosporine

(OR 22.91, 95% CI 9.85, 53.29) were significantly associated with greater odds of low-spike Ab (Table 2). Use of csDMARD monotherapy (OR 0.12, 95% CI 0.04, 0.33) and JAK inhibitors (OR 0.41, 95% CI 0.18, 0.92) were associated with significantly lower odds for low spike Ab compared to nonuse of these DMARDs. In models adjusted for systemic rheumatic disease and individual DMARDs, SLE (OR 4.12, 95% CI 1.94, 8.75) and rituximab (OR 27.23, 95% CI 10.81, 68.62) remained significantly associated with low spike Ab.

Discussion

More than a third of patients had low spike Ab approximately 3 months after the initial 2 doses of mRNA vaccine or 1 dose of adenovirus vector vaccine in a clinic-based cohort of patients with well-defined systemic rheumatic disease. Rituximab use and diagnosis of SLE were associated with significantly greater odds of having a low spike Ab response after mutual adjustment for systemic rheumatic disease and DMARD use. A significant association

Table 2 Adjusted odds ratios and 95% CI for low spike antibody (≤ 200 U/mL)

	Model adjusted for		Model adjusted for systemic rheumatic disease and use vs. nonuse of the following DMARDs						
	Systemic rheumatic disease	DMARD use*	csDMARD only	TNFi	JAKi	Rituximab	Prednisone	Mycophenolate	Hydroxy-chloroquine
Systemic rheumatic disease									
Inflammatory arthritis	1.00 (ref)	--	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
SLE	4.18 [2.08, 8.43]	--	3.37 [1.66, 6.84]	4.00 [1.95, 8.22]	3.79 [1.86, 7.68]	4.12 [1.94, 8.75]	3.89 [1.92, 7.87]	3.77 [1.73, 8.24]	3.33 [1.50, 7.37]
Vasculitis	2.01 [0.93 4.34]	--	1.83 [0.83, 4.07]	1.93 [0.88, 4.23]	1.83 [0.84, 4.98]	1.06 [0.41, 2.77]	1.87 [0.59, 4.08]	1.98 [0.92, 4.29]	2.01 [0.93, 4.34]
Inflammatory myositis	1.06 [0.34, 3.29]	--	0.88 [0.28, 2.77]	1.02 [0.33, 3.20]	0.96 [0.31, 2.99]	0.29 [0.06, 1.40]	0.97 [0.31, 3.02]	1.02 [0.33, 3.21]	1.002 [0.32, 3.13]
Other**	0.70 [0.32, 1.53]	--	0.57 [0.26, 1.25]	0.68 [0.31, 1.50]	0.63 [0.29, 1.39]	0.78 [0.33, 1.81]	0.64 [0.29, 1.42]	0.65 [0.28, 1.48]	0.69 [0.31, 1.51]
DMARDs at the time of vaccination									
csDMARD only	--	0.12 [0.04, 0.33]	0.13 [0.04, 0.37]	--	--	--	--	--	--
TNFi	--	0.67 [0.39, 1.15]	--	0.87 [0.49, 1.54]	--	--	--	--	--
JAKi	--	0.41 [0.18, 0.92]	--	--	0.48 [0.21, 1.13]	--	--	--	--
Rituximab	--	22.91 [9.85, 53.28]	--	--	--	27.23 [10.81, 68.62]	--	--	--
Prednisone	--	1.68 [1.03, 2.74]	--	--	--	--	1.54 [0.92, 2.57]	--	--
Mycophenolate	--	1.90 [0.98, 4.03]	--	--	--	--	--	1.27 [0.55, 2.92]	--
Hydroxychloroquine	--	2.47 [1.3, 4.5]	--	--	--	--	--	--	1.52 [0.76, 3.03]

Abbreviations: *SLE*, systemic lupus erythematosus; *csDMARD*, conventional synthetic DMARD; *TNFi*, TNF inhibitor; *JAKi*, JAK inhibitor

All models are adjusted for age and interval. *Nonuse of each DMARD is the comparator. Odds ratios are from a series of models each adjusted for one DMARD at a time. ++Includes polymyalgia rheumatica, systemic sclerosis, mixed connective tissue disease, relapsing polychondritis, idiopathic recurrent pericarditis, sarcoidosis, Still's disease, IgG4 related disease, Sjogren's syndrome, VEXAS syndrome, undifferentiated connective tissue disease, subacute cutaneous lupus, small vessel vasculitis not otherwise specified, and SAPHO syndrome

between SLE and greater odds of low-spike Ab response has not previously been reported to our knowledge. Notably, this association was still apparent after adjusting for use of DMARDs, including rituximab and mycophenolate mofetil, which might themselves cause low spike Ab.

Our results are consistent with several prior studies on risk factors for low humoral response following COVID-19 vaccination. Rituximab has been associated with diminished humoral response in a number of studies [9, 10]. A recent study by Weiske et al. reported that low spike Ab response persisted in patients using anti-CD20 therapy, such as rituximab, after additional doses (i.e., 3rd dose of mRNA vaccine), though the immunosuppressive effect of other DMARDs could be overcome by an additional dose [10]. Our observation that older age significantly increases odds of low spike antibody response is also supported by prior studies of COVID vaccination in adults with systemic rheumatic disease [8].

In this cross-sectional study, prednisone was associated with significantly greater odds of suboptimal serologic response to COVID vaccination. While prednisone is an immunosuppressive medication, data about the impact of prednisone on vaccine immunogenicity are inconsistent [8, 10, 13]. Hydroxychloroquine use was associated with increased odds of low spike antibody in a model not adjusted for systemic rheumatic disease but was not associated with low spike Ab after adjustment for rheumatic disease, suggesting that diagnosis of SLE and/or concomitant DMARDs or glucocorticoid use confounded this association. In other studies, hydroxychloroquine has not been shown to be associated with responses to COVID vaccination [8, 10].

Prior literature conflicts on the associations of csDMARDs and JAKi with low humoral responses to COVID vaccination. Some studies support our finding that csDMARDs and JAKi allow for robust immune response to COVID vaccination [10, 14]. However, others have reported that methotrexate and JAKi are associated with decreased immunogenicity of the COVID vaccine [13, 15].

Limitations of this study include its cross-sectional nature and relatively small sample size, though we were able to collect detailed data on systemic rheumatic disease and DMARDs by EHR review. Data on disease activity and whether patients temporarily discontinued DMARDs around vaccination were not available. Spike Ab was tested in routine clinical care and may have been more commonly assessed in patients for whom the treating rheumatologist was concerned about low spike Ab. Our primary outcome of low-spike Ab, defined as ≤ 200 U/mL on the Roche Elecsys® assay, was chosen for consistency with an ongoing NIH clinical trial, though an absolute threshold conferring protection against infection has not yet been established and is likely higher than 200 U/mL. Other studies have defined humoral response to COVID vaccines using different definitions of "seroconversion," which makes comparison across studies challenging [8, 10].

Due to mounting evidence that adults with rheumatic disease are at increased risk for insufficient humoral response to the vaccine, additional doses of COVID-19 vaccines are now the standard of care for immunosuppressed patients, according to the US Centers for Disease Control and Prevention (CDC) [16]. Our results suggest that persons with SLE—even if not treated with immunosuppressants—may have low humoral response to the primary vaccine series and should be counseled to take measures to avoid COVID-19 infection, including booster vaccines. Treatment with pre-exposure COVID-19 prophylaxis, such as Evusheld is also increasingly available and recommended, though effectiveness against the current circulating COVID variants is diminished [11]. Data from our study support the need for additional doses to attempt to boost humoral immunity in patients with systemic rheumatic disease, especially those with SLE or using rituximab.

Funding Support for the investigators' time came from the National Institutes of Health (K23 AR075070, L30 AR070514, and K08HS027841).

Declarations

Disclosures None.

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