Multicenter case-control study evaluating the safety of anti-SARS-CoV-2 vaccines in a cohort of patients with systemic vasculitis

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Research Article

Keywords: Systemic vasculitis, vaccination, SARS-CoV-2, adverse events, disease flare.

Posted Date: May 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1630470/v1

Abstract

Objective: Data on the safety of anti-SARS-CoV-2 vaccines in patients with rare rheumatic diseases, such as systemic vasculitis (SV), are limited. Aim of this study was to evaluate the occurrence of a disease flare and the appearance of adverse events (AEs) following administration of anti-SARS-CoV-2 vaccine in a multicenter cohort of patients with SV.

Methods: Patients with SV and healthy controls (HCs) from two different Italian rheumatology centers were asked to complete a questionnaire assessing disease flares occurrence, defined as new onset of clinical manifestations related to vasculitis needing an implementation of therapy, and local/systemic AEs appearance following anti SARS-CoV-2 vaccination.

Results: 107 patients with SV (57 ANCA-associated) and 107 HCs were enrolled. A disease flare occurred in only one patient (0.93%) with microscopic polyangiitis after the first dose of an mRNA vaccine. Both after the first and the second vaccine dose administration, no significant differences in AEs between patients with SV and HCs were observed; no serious AEs were reported as well.

Conclusions: This data suggest a good risk profile for anti-SARS-CoV-2 vaccine in patients with systemic vasculitis.

Introduction

Systemic vasculitis is a group of rare rheumatic diseases characterized by the primary inflammation of wall blood vessels and a large spectrum of systemic manifestations, in some cases with potential life-threatening complications (1, 2). Due to the disease itself or the ongoing immunosuppressive treatment (i.e., rituximab), patients with systemic vasculitis seem more prone to develop infections (3). At the end of 2019, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a new, single positive-stranded RNA coronavirus identified in Wuhan that can lead to a severe respiratory syndrome in humans, began spreading worldwide causing the Coronavirus disease 2019 (COVID-19) pandemic (4). Patients with rare rheumatic diseases such as systemic vasculitis, especially older than 35 years, seems to be at higher risk of death caused by COVID-19 compared to healthy subjects and other rheumatic musculoskeletal disorders (5, 6). By the end of 2020 different vaccines against SARS-CoV-2 infection have been developed and they quickly became one of the most important tools in preventing virus spreading and the development of fatal complications. Considering the higher risk to develop more aggressive forms of COVID-19, patients with systemic rheumatic diseases were prioritized in the vaccination campaigns. Over the last year, several studies evaluated the efficacy and safety of anti-SARS-CoV-2 vaccines in patients with systemic rheumatic diseases with evidence of an acceptable safety profile and a lower immunogenicity compared to the health population (7, 8). However, the studies evaluating vaccine response in rheumatic patients included only few cases of systemic vasculitis; thus, data on vaccine efficacy and safety in this specific subgroup of patients are still limited. This retrospective case-control study aimed at evaluating the safety of SARS-CoV-2 vaccines in a large

multicenter cohort of patients with systemic vasculitis with a particular focus on disease flares occurrence and the development of local and systemic adverse events (AEs) following vaccination.

Materials And Methods

Patients’ enrollment

After providing consent to participate, patients diagnosed with systemic vasculitis (SV) undergoing SARS-CoV-2 vaccination were retrospectively enrolled at the Rheumatology Units of the University of Rome Sapienza and the University of Siena (Italy). Inclusion criteria included a follow up within 6 months before the administration of at least one dose of an anti-SARS-CoV-2 vaccine (Comirnaty-BNT162b2, Spike Vax-mRNA-1273 or Vaxzevria-ChAdOx1-S). The main demographic, clinical and therapeutic features were collected on a dedicated electronic database. Healthy subjects were recruited among members of the healthcare staff of the University hospital Policlinico Umberto I in Rome and used as controls (HCs).

Questionnaire administration

After at least two and within four months after the last dose of vaccine patients with systemic vasculitis and HCs were asked to complete a questionnaire evaluating the following items: 1) previous diagnosis of SARS-CoV-2 infection; 2) completed cycle of anti-SARS-CoV-2 vaccination; 3) type of vaccine; 4) occurrence of a disease flare following vaccination; 5) occurrence of AEs following vaccination; 6) time to the AEs (days); 7) type of AEs defined as local and/or systemic; 8) ongoing treatment; 9) withdrawal of therapy prior to vaccination. The questionnaire was proposed during a follow-up visit or by means of a telephone call.

A previously used definition of disease flare was adopted: new onset of signs and symptoms related to vasculitis lasting at least 2 days and occurring within 2 months from the last dose of vaccination requiring treatment modifications (9). AEs were defined as local, in case of occurrence of reaction in the site of injection (pain and/or swelling and/or redness and/or itching), or systemic, in case of occurrence of one of the following symptoms: anaphylaxis, fever, arthromyalgia, fatigue, malaise, lymphadenopathy and others as specified by the patients among which headache, diarrhea, dizziness; systemic symptoms were selected among those more frequently reported in literature (7, 8, 10).

Statistical analysis

Medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann-Whitney and Chi-square tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively, between SV and HCs. To account for baseline clinical differences among SV and HCs, multivariable logistic regression analysis was used to assess the impact of the presence of SV on the above-mentioned items (see the 9 domains questionnaire). Covariates were selected according to a clinical criterion and included age and sex. Kaplan-Meier method was used to evaluate the 7-day survival rate, meaning as survival the intercurrent period between vaccine administration and AEs appearance. All

statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2. All tests were two-sided with a significance level set at $p < 0.05$.

Results

Features of enrolled patients with systemic vasculitis and HCs

We selected 107 patients with SV (women n = 67, men n = 40) and 107 HC (women n = 62, men n = 45), with a median age of 68 (1st Qu. 56, 3rd Qu. 77) and 63 (1st Qu. 60, 3rd Qu. 68.5) years, respectively. Among the SV group, 57 were ANCA Associated Vasculitis (AAV): 22 Granulomatosis with Polyangiitis (GPA), 16 Eosinophilic Granulomatosis with Polyangiitis (EGPA), 19 Microscopic Polyangiitis (MPA). Forty-four patients had Giant Cell Arteritis (GCA), 4 Polyarteritis Nodosa (PAN) and 2 Takayasu's Arteritis (TAK). No patient refused to participate with a response rate of 100%. The main demographic, clinical and therapeutic features of enrolled patients and HCs are reported in **table 1**.

In patients with SV the occurrence of a disease flare following anti-SARS-CoV-2 vaccination is a rare event

A disease flare following vaccination with Comirnaty-BNT162b2 vaccine was detected in only one case of SV. Specifically, this patient was a 77-year-old male with a diagnosis of MPA treated with methotrexate. This patient developed a pulmonary disease flare seven days after the first dose of the vaccine, the flare started as a moderate-severe dyspnea and evolved into respiratory failure leading to patient's hospitalization. Nasopharyngeal swabs for SARS-CoV-2 were negative. Diffuse "ground-glass" opacities with superimposed septal thickening and subpleural consolidations emerged at the high-resolution computed tomography (HRCT). During hospitalization, the patient required high-flow oxygen and was treated with high dose intravenous glucocorticoids with benefit. Details on clinical and laboratory features of this patient were recently described in our previous publication (11).

AEs following SARS-CoV-2 vaccination are similar between patients with SV and HCs

The proportion of AEs is reported in figure (Fig. 1a-b). Following the first and the second dose administration of anti-SARS-CoV-2 vaccine, no significant differences in AEs were detected between patients with SV and HCs (first dose: OR = 1.11 IC 0.63–1.95, p = 0.708; second dose: OR = 0.70 IC 0.39–1.24, p = 0.226) (**table 2**). In both groups, higher age was associated with a reduced risk of developing AEs. Both in the SV group and in the HCs group, the survival analysis demonstrated a major occurrence of AEs within 1–2 days from vaccine administration (Fig. 1c-d). All reported AEs were mild with malaise and arthromyalgia being the most frequently reported in the group of patients with SV; no systemic anaphylaxis and no severe AEs were reported in both groups. No significant differences in AEs occurrence were detected according to the ongoing therapy (**table 2**).

Discussion

This is one of the largest studies investigating the occurrence of disease flares and AEs in patients with SV following SARS-CoV-2 vaccination in a real-world setting.

It is well known that immunological stimuli, including vaccines administration may trigger, in limited cases, a disease flare up in patients with rheumatic diseases (12). The occurrence of disease flares in our cohort was very low with evidence of only one case out of 107 patients. Even though this flare was severe and the patient was hospitalized, he was discharged after one week in good clinical conditions. Our findings, together with the previous demonstration in GCA patients of no significant difference in the rate of flares between patients receiving vaccination for influenza virus and patients receiving vaccination for SARS-CoV-2 (13), look extremely encouraging. As in the general population a great efficacy of SARS CoV2 vaccination has been demonstrated (14.15), our data, along with previous evidence (13), support the safety of these vaccines in SV patients and further encourage their administration in the next future.

It is interesting to note that new cases of SV have been documented following anti-SARS-CoV2 vaccination. We had the opportunity to describe the onset of leukocytoclastic vasculitis following anti-SARS-CoV-2 vaccination with Vaxzevria-ChAdOx1-S (16) and there are a few case reports demonstrating the new appearance of ANCA-associated vasculitis as well as IgA vasculitis and GCA after the administration of anti-SARS-CoV-2 vaccines (17–21). These observations provide interesting insight on the pathogenesis of SV and will surely deserve further investigations in the next future.

In our study the frequency of AEs was similar between patients and controls and generally mild in all of them. In the SV group, no association was found between the ongoing immunosuppressive therapy and the risk of developing AEs. Consistent with our previous findings (22), and as reported in RCTs (14, 15), an inverse association between AEs occurrence and patients' age has been detected. Specifically, a higher age appears as associated with a lower risk of developing AEs; this finding is not surprising as immunosenescence is known to contribute to a reduced vaccine response in older patients and, eventually, a lower occurrence of AEs (23).

Our findings are in line with previous studies demonstrating a low rate of disease flare and an overall good risk profile in patients with rheumatic diseases (8, 10, 13). Interestingly, in one of these studies a lower occurrence of disease flare up was observed in patients with connective tissue diseases and vasculitis compared to other rheumatic conditions such as inflammatory joint diseases (10). Thus, the similar tolerance profile of these vaccines between patients with SV and HCs, as well as the rarity of disease flares, is a reassuring result useful for physicians to encourage patients with SV to undergo vaccination. This topic is particularly relevant as a remarkable vaccine hesitancy has been documented in our patients during COVID-19 pandemic (24)

This study has some limitations, specifically, its retrospective nature did not allow to calculate the exact disease activity at the time of vaccination. However, as suggested by currently available recommendation on vaccine administration in patients with rheumatic diseases (25, 26), vaccines should be administered

only in patients with inactive disease. As included SV patients were strictly monitored in our dedicated outpatient clinics, they were vaccinated only if the referring physician considered them in an inactive phase of disease.

Being SV a rare disease, strength of this study is represented by the large sample size. Additionally, its multicenter nature allowed us to include different types of SV referring to two major dedicated rare disease clinics in our country.

Conclusions

To conclude, this is one of the largest studies investigating the safety of anti-SARS-CoV-2 vaccines in patients affected by SV. Taken together, our data strongly support a relatively good safety profile of anti-SARS-CoV2 vaccines in patients with SV and encourage physicians in recommending anti SARS-CoV2 vaccination in patients affected by this rare rheumatic disease.

Abbreviations

AAV
ANCA associated Vasculitis
AEs
adverse events
bDMARDs
biologic Disease Modifying Anti-Rheumatic Drugs
COVID-19
Coronavirus disease 2019
GCA
Giant Cell Arteritis
HRTC
high-resolution computed tomography
HC
healthy controls
IQR
interquartile range
MPA
Microscopic Polyangiitis
OR
odds ratio
PAN
Polyarteritis Nodosa
RCTs
randomized controlled trials

SV
systemic vasculitis
SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus-2
TAK
Takayasu Arteritis
csDMARDs
conventional syntethic disease modifying anti rheumatic drugs
tsDMARDs
target synthetic Disease Modifying Anti-Rheumatic Drugs.

Declarations

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki. The Local Ethical Committee has approved the research (Sapienza Università di Roma Ethical Committee - protocol 0501/2021). All the subjects gave their informed consent to use their anonymized data for the study.

Consent for publication

Not applicable.

Availability of data and materials

Patients' data are available from the corresponding upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Fundings

This research received no external fundings.

Authors' contributions

Conceptualization, E.S., S.C., and R.P.; manuscript writing and editing, E.S., E.C., F.C. and R.P.; statistical analysis, S.C.; patients' recruitment and data collection, E.S., E.C., F.G., R.I., S.G., A.G., S.T., L.C., and B.F.; healthy subjects' recruitment and data collection, F.R.S., C.G., and E.S.; All authors reviewed the manuscript.

Acknowledgements

Not applicable.

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Tables

Table 1

Demographic and clinical features of subjects participating to the study.

	Vasculitis n= 107	**HC n= 107**
Age, median years (1st Qu., 3rd Qu.)	68 (56, 77)	63 (60, 68.5)
Female, n° (%)	67 (62.6)	62 (57.9)
Previous SARS CoV2 infection, n° (%)	8 (7.4)	5 (4.6)
Vaccine type, n° mRNA - n° viral vector	102 - 5	92-15
AAV, n (%)	57 (53.3)	-
GCA, n (%)	44 (41.1)	-
PAN, n (%)	4 (3.73)	-
TAK, n (%)	2 (1.86)	-
Ongoing therapy with immunosuppressors, n (%)	81 (75.7)	-
Prednisone or equivalent only, n (%)	7 (6.5)	-
csDMARDs, n (%)	36 (33.6)	-
bDMARDs, n (%)	37 (34.5)	-
tsDMARDs, n (%)	1 (0.93)	-
Therapy withdrawal before vaccination, n (%)	15 (14)	-

Legend:

AAV, ANCA-Associated Vasculitis; bDMARDs, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARDs, conventional synthetic disease modifying anti rheumatic drugs; GCA, Giant Cell Arteritis; HC, Healthy Controls; PAN, Polyarteritis Nodosa; Qu, quartile; TAK, Takayasu Arteritis; tsDMARDs, target syntethic Disease Modifying Anti-Rheumatic Drugs.

Table 2

Risk of AEs in patients with SV and HCs.

ENTIRE COHORT					
Adverse events (first dose)			**Adverse events (second dose)**		
	OR	***p value***		***OR***	***p value***
Clinical condition					
SV	1.11 (0.63-1.95)	0.708	SV	0.70 (0.39-1.24)	0.226
HC	*Ref*	-	HC	*Ref*	-
Age and Sex					
Age	0.95 (0.92-0.97)	**0.0002**	Age	0.96 (0.93-0.98)	**0.001**
Female	1.51 (0.85-2.68)	0.154	Female	1.39 (0.77-2.51)	0.262
Male	*Ref*	-	Male	*Ref*	-
SYSTEMIC VASCULITIS					
Adverse events (first dose)			**Adverse events (second dose)**		
	OR	***p value***		***OR***	***p value***
Ongoing therapy with immunosuppressor (IS)					
IS	1.62 (0.63-4.13)	0.307	IS	0.94 (0.36-2.45)	0.905
No IS	*Ref*	-	No IS	*Ref*	-
Category of immunosuppressive drugs					
bDMARDs	1.52 (0.53-4.34)	0.433	bDMARDs	1.04 (0.35-3.02)	0.942
csDMARDs	1.78(0.61 – 5.21)	0.283	csDMARDs	0.79 (0.25-2.40)	0.678
Prednisone only	1.44 (0.25 – 8.06)	0.676	Prednisone only	1.24 (0.20-7.65)	0.815
None	*Ref*	-	None	*Ref*	-
Withdrawal of immunosuppressive therapy					
Withdrawal	0.48 (0.14-1.59)	0.236	Withdrawal	0.44 (0.12-1.59)	0.215
No withdrawal	*Ref*	-	No withdrawal	*Ref*	-

Legend:

AEs, adverse events; ; bDMARDs, biologic disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti rheumatic drugs; HCs, healthy controls; IS, immunosuppressors; OR, odds ratio; SV, systemic vasculitis; tsDMARDs, target synthetic disease modifying anti-rheumatic drugs

Figures

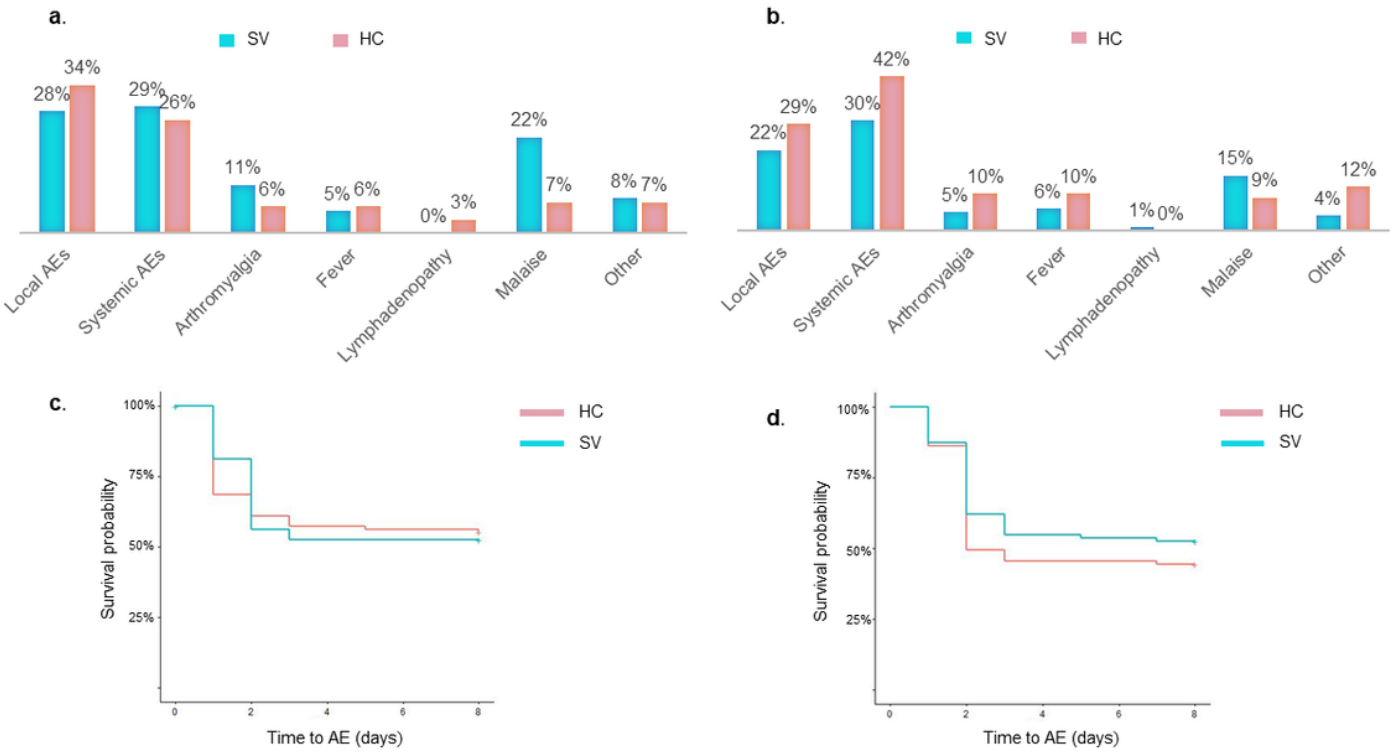

Figure 1

Frequency of local and systemic AEs after the first (a) and the second dose (b). Survival curves of AEs in patients with SV and HCs after the first (c) and second dose (d). HC, healthy controls; SV, systemic vasculitis.