Effectiveness of SARS-CoV-2 vaccination program in systemic sclerosis patients treated by autologous haematopoietic stem cell transplantation: a comparative study on behalf of MATHEC-SFGM-TC group

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Abstract

Objective

This study aimed to evaluate the effectiveness of the SARS-CoV-2 vaccination program in systemic sclerosis (SSc) patients treated by Autologous Hematopoietic Stem Cell Transplantation (AHSCT) compared to non-AHSCT SSc patients.

Methods

A French retrospective case-control study was conducted in SSc patients eligible for SARS-CoV-2 vaccination. AHSCT SSc (cases) were matched 1:1 with non-AHSCT SSc (controls) patients by age, sex, and disease duration. The primary endpoint was to assess the cumulative incidence of COVID-19 infection. Secondary objectives evaluated vaccination acceptance, the onset of severe adverse events after SARS-CoV-2 vaccination, the severity of COVID-19 infection and the serological response after vaccination or not.

Results

Seventy-two SSc patients (36 AHSCT 1:1 matched to 36 non-AHSCT, on age, sex, and disease duration on 1 January 2021) were included. The study showed a higher incidence of COVID-19 infection in AHSCT (p=0.007) versus non-AHSCT SSc patients, with respectively 11 out 36 cases and 2 out 36 controls contracting mild to moderate infections. The vaccine acceptance rate did not differ between AHSCT and non-AHSCT SSc patients, with respectively 5 out 36 cases and 3 out 36 controls who refused vaccination. No severe adverse event was reported after SARS-Cov-2 vaccination. Serological responses did not significantly differ between the two groups.

Conclusion

The incidence of COVID-19 infection was higher in AHSCT-SSc compared to non-AHSCT SSc patients, with no difference in vaccine acceptance rate. COVID-19 vaccination in AHSCT highly fragile patients appeared to provide substantial COVID-19 protection, as shown by their favourable clinical evolution and effective humoral response.

Key words

Covid-19, systemic sclerosis, incidence, vaccination, autologous haematopoietic stem cell transplantation, autoimmune diseases, case-control studies

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Introduction

In France, the first six cases of COVID-19 disease were diagnosed in February 2020, and the government declared a national lockdown in March 2020. Implementation of the SARS-CoV-2 vaccination program began in December 2020 and the French Health Authorities prioritised: a) healthcare providers aged 65 years and over, as well as those with comorbidities, and b) patients who were immunosuppressed, obese, diabetic, or who had specific comorbidities (*e.g.*, heart, lung, kidney failure) due to the risk of developing severe COVID-19 disease (1). In these vulnerable patients, adequate vaccination with mRNA SARS-CoV-2 vaccines (*i.e.*, at least two injections at four-week intervals) was expected to be one of the safest and most effective preventive measures, in addition to the proper use of personal protective equipment (*e.g.*, mask and physical distancing). In April 2021, the updated French national guidelines recommended to perform a third injection of mRNA SARS-CoV-2 vaccination amongst immunosuppressed patients, specifically for those recently treated by haematopoietic stem cell transplantation (HSCT) and/or by anti-CD20 biotherapies (2). In July 2021, the European Bone Marrow Transplantation (EBMT) guidelines recommended vaccination against SARS-CoV-2 as early as three months after HSCT (3), and one study had provided first evidence of the efficacy of SARS-CoV-2 vaccination after autologous HSCT (AHSCT) in seven systemic sclerosis (SSc) patients (4). In November 2021, the French Health Authorities recommended to prospectively follow-up the observed serological responses after vaccination with quantitative measurements of anti-S antibodies (anti-spike S1/S2) one month after the second vaccine injection to help guiding the need for a third vaccine dose (5).

SSc is a chronic, severe autoimmune disease characterised by vascular damage, immune system dysregulation, and progressive fibrosis of the skin and internal organs (heart, lung and kidney), which may lead to severe comorbidities (6). It has the highest mortality rate amongst all rheumatic diseases (7). In severe, rapidly progressive SSc, we and others have demonstrated that AHSCT is the only treatment so far with disease-modifying activity that can improve overall and event-free survival up to seven years after AHSCT (8), but only a subgroup of SSc patients are eligible and treated by AHSCT. In addition, during the immune reconstitution period, which duration varies from at least 6 months up to 2 years after AHSCT, SSc patients remain highly vulnerable to infections. Susceptibility to infections also depends on previous treatments, type of chemotherapy and conditioning regimen before transplant, and the individual patient. In non-AHSCT SSc patients, the use of various types of immunosuppressive therapies (*i.e.*, corticosteroids, mycophenolate mofetil, methotrexate, rituximab) is frequent aiming to slow or at least to stabilise SSc disease progression, notably interstitial lung disease (ILD) or the other organs involvement. Consistent with the French Haute Autorité de Santé (HAS) and The French Society of Bone and Marrow Transplantation and Cellular Therapy (SFGM-TC) good clinical practice guidelines (9), SARS-CoV-2 vaccinations were proposed to all SSc patients in France, including to those previously treated by AHSCT as soon as vaccines became available on January 2021.

Several reports have demonstrated the safety and the efficacy of SARS-CoV-2 vaccines in the general population, but a significant knowledge gap remains in vulnerable populations, including patients with systemic autoimmune and inflammatory disorders, those on immunosuppressive medications, and transplanted patients. The exclusion of these patients from the early vaccine safety trials resulted in a paucity of data on SARS-CoV-2 vaccination in SSc patients (10, 11).

We therefore designed this case-control retrospective study to evaluate the effectiveness of the French SARS-CoV-2 vaccination program in terms of risk of infection in SSc patients treated by AHSCT compared to other non-AHSCT SSc vulnerable patients.

Materials and methods

We conducted a retrospective case-control (matched 1:1) study of SSc patients actively followed in two centres: CRMR MATHEC at St-Louis Hospital, AP-HP, Paris for patients who had undergone treatment by AHSCT (cases), and the Department of Internal Medicine and Clinical Immunology at CHU Rangueil, Toulouse for patients not treated by AHSCT (controls). The study included SSc patients (as diagnosed according to the 1980 American College of Rheumatology (ACR) or the 2013 ACR/European League Against Rheumatism (EULAR) criteria), aged 18 years or older who were offered SARS-CoV-2 vaccination as per the ongoing French national guidelines' vaccine protocol between January 1st, 2021 and June 30th, 2022. AHSCT (cases) were matched 1:1 to non-AHSCT (controls) SSc patients based on age on January 1st, 2021 (± 5 years), sex (exact matching), and disease duration since onset of the first non-Raynaud phenomenon (± 5 years). Informed non-opposition from the participants was obtained after sending an information document by regular mail. The local institutional ethics committee IRB 00006477 approved the study (N° CER-2023-213) as per national guidelines.

Statistical justification for sample size

Assuming one-third of patients would have experienced at least one episode of COVID-19 infection over the follow-up period, a sample size of 36 cases for 36 control patients would allow a 32%-wide 95% confidence interval for the cumulative incidence of COVID-19 infection at the end of follow-up in each group, using a conservative exact binomial approach.

Data collection

Clinical and biological data were collected using a standardised clinical report form from the electronic medical files of the included patients at Saint-Louis or CHU Rangueil hospitals, which included demographic details; SSc diagnosis, clinical and biological characteristics; ongoing SSc treatments at study inclusion, SARS-CoV-2 infection history, including symptoms, duration, and complications (hospitalisation and/or need for oxygen therapy or Intensive care); SARS-CoV-2 vaccination details (type of vaccine and number of received injections); post-vaccination serology rate.

A completed vaccination protocol was defined as two injections of SARS-CoV-2 vaccine plus 10 days. Patients with post-vaccination SARS-CoV-2 serology <40 BAU/mL were considered "non-responders", those with post-vaccination serology 40-260 BAU/mL were defined as "light responders", and with post-vaccination serology >260 BAU/mL as "good responders" (5). The threshold for a positive immunogenic response was defined by literature findings (12-14). The clinical severity of COVID-19 infection during

Table Ia. Systemic sclerosis (SSc) patients treated by autologous haematopoietic stem cell transplantation (AHSCT) (cases) and non-AHSCT (controls): demographics and clinical characteristics.

Characteristics n. (%) or Med [min-max]	AHSCT-SSc (cases)	Non AHSCT-SSc (controls)
N. pts / females	36/22	36/23
Age	52 [28;71]	52 [27;73]
Diffuse/localised SSc at diagnosis	36 (100)/0 (0)	9 (25)/27 (75)
Disease duration before 1/1/2021 (yrs)	11 [2;34]	11 [4;26]
Organ involvement at inclusion		
Modified Rodnan Skin score	6 [0;37]	4 [0; 30]
Electrocardiogram abnormalities	10 (33)	2 (6)
Left ventricle ejection fraction (%)	65 [48;79]	63 [37;84]
Pulmonary artery systolic pressure (mmHg)	26 [18;50]	29 [9;80]
Pericardial effusion	1 (3)	1 (3)
Interstitial lung disease	24 (86)	8 (23)
Forced vital capacity (% theoretical value)	88 [58;119]	88 [17;123]
Carbon monoxide diffusing capacity (% theoretical value)	49 [24;91]	60 [21;92]
Serum creatinine (mg/l)	68 [6;134]	66 [5;330]
Previous scleroderma renal crisis	3 (8)	5 (15)
Autoantibodies		
Anti-nuclear	26/28 (93)	33/35 (94)
Anti-topoisomerase I (Anti Scl-70)	11/26 (42)	8/35 (23)
Anti-centromere	0/27 (0)	15/35 (43)
Anti-RNA Polymerase III	3/16 (19)	3/35 (9)
Leukocyte count 10^9 cells/L	7 [3;33]	8 [4;11]
Lymphocyte sub-populations		
CD4+ (/mm3)	592 [157;1852]	600 [442;1368]
CD8+ (/mm3)	559 [101;2113]	382 [144; 938]
CD19+ (/mm3)	218 [54;711]	238 [0;395]
Immunosuppressive drugs at inclusion		
Oral steroids	16 (44)	11 (31)
Methotrexate (oral or sub-cutaneous)	1 (3)	3 (8)
Mycophenolate mofetil	**7 (19)**	**6 (17)**
Rituximab	0 (0)	1 (3)
Covid-19 vaccination refusal	5 (14)	3 (8)
No. of vaccine injection(s)		
0	5 (14)	3 (9)
1	1 (3)	0 (0)
2	4 (11)	8 (24)
3	26 (72)	23 (68)
Missing Data	0	2
Covid-19 Vaccine type 1st injection		
BNT162b2-Pfizer®	29 (94)	22 (71)
chAdOx1-S AstraZeneca®	1 (3)	4 (13)
mRNA-1273-Moderna®	1 (3)	5 (16)
Missing Data	0	2
Covid-19 Vaccine type 2nd injection		
BNT162b2-Pfizer®	28 (93)	24 (77)
chAdOx1-S AstraZeneca®	0 (0)	3 (10)
mRNA-1273-Moderna®	2 (7)	4 (13)
Covid-19 Vaccine type 3rd injection		
BNT162b2-Pfizer®	23 (88)	18 (78)
mRNA-1273-Moderna®	3 (12)	5 (22)
Post-vaccination adverse events (≥ grade 3 CTC-AE v5.0)	0 (0)	0 (0)

Table Ib. Characteristics of SSc patients treated by AHSCT are expressed in N. (%) or Med [min-max].

Age at AHSCT (years)	47 [16;61]
Mobilisation	
Patients receiving cyclophosphamide, n (%)	36 (100)
Total dose (g/m2)	4 [1;6]
N. apheresis: 1 /2	31 (86) /5 (14)
CD34+ selection	17 (47)
Conditioning	
Patients receiving cyclophosphamide	36 (100)
Total dose (mg/kg)	200 [60;290]
Patients receiving fludarabine	6 (17)
Total dose (mg/m2)	120 [90;120]
Patients receiving anti-thymocyte globulin (ATG)	32 (88.9)
Total dose (mg/kg)	7.5 [2;7.5]
Patients receiving rituximab	1 (3)
Total dose (mg)	1186
Patients receiving granulocyte-colony stimulating factor (G-CSF)	30 (83)
Total dose (µg/kg)	44 [6;4800]
Missing data: 8	

the study period was defined as "mild" if requiring outpatient care, "moderate" if requiring hospitalisation outside the intensive care unit (ICU), or "severe" if requiring hospitalisation in the ICU or leading to patient death (15).

Outcomes

The primary outcome was the cumulative incidence of COVID-19 infection, that was either symptomatic (positive PCR test and clinical symptoms related to COVID-19 infection) or asymptomatic (positive PCR on routine testing as contact case or fortuitous discovery). Secondary outcomes included: the percentage of SSc patients refusing vaccination, the percentage of patients experiencing grade ≥3 adverse events (according to CTC-AE v5.0) after anti-SARS-CoV-2 vaccination, the time to first COVID-19 infection (after the second vaccine injection), the clinical severity of COVID-19 disease and the hospitalisation rates, the observed SARS-CoV-2 humoral response measured by the IgG anti-Spike (S1/S2) antibody levels, as compared between the two groups of AHSCT- SSc (cases) and non-AHSCT SSc control patients.

Statistical analysis

Nearest-neighbour Mahalanobis distance 1:1 matching was performed to obtain a 1:1 matched case-control sample. Categorical variables are described with counts and percent and compared between cases and controls with McNemar's paired test. Quantitative variables are described with median interquartile range [minimum;maximum] and compared between cases and controls with Wilcoxon's signed-rank test. The cumulative incidence of COVID-19 infection starting from 1/1/2021 was estimated using standard methods, accounting for death without COVID-19 infection as a competing event. It was compared between cases and controls using an approach extending the Fine-Gray model for sub-distribution hazards with clustered data (16). All statistical tests are two-sided at a 5%-significance level. Analyses were performed on R statistical platform, version 4.0.1.

Results

Population characteristics

All consecutive eligible SSc patients agreed to have their clinical data collected for the study, and none was excluded from the analysis. From January 1st 2021 to June 30th 2022, 72 SSc patients were included; 36 were treated by AHSCT (cases), and 36 were non-AHSCT SSc patients (controls). Patients' demographics, including matching criteria (sex, age, disease duration since the first non-Raynaud phenomenon), are summarised in Tables Ia and Ib. The median overall age on 1 January 2021 was 52 years (IQR: 46-62). The median overall SSc disease duration (since the onset of first non-Raynaud symptom) was 11 years (IQR: 7-15). Forty-five patients overall had diffuse skin involvement with a median modified Rodnan Skin Score (mRSS) of 5 (IQR 2-10) at baseline. SSc-related ILD confirmed by high-resolution computed tomography scan was present in 32 (54%) SSc patients, and in respectively 24 (86%) AHSCT SSc (cases) patients and 8 (23%) non-AHSCT SSc (controls) patients. Antinuclear antibodies were present in 59 (94%) SSc patients overall, while 40 (67%) SSc patients overall displayed SSc-specific autoantibodies: 6 (12%) had anti-RNA polymerase III antibodies (3 (19%) AHSCT SSc and 3 (9%) non-AHSCT SSc patients), 19 (31%) had antitopoisomerase I antibodies (11 (42%) AHSCT SSc; 8 (23%) non-AHSCT SSc) and 15 (24%) (all non-AHSCT SSc patients) had anti-centromere antibodies. Fifty-one (71%) of all included patients had a follow-up until June 30th 2022; 11 patients in the AHSCT-SSc (cases) and 10 non-AHSCT SSc (controls) had a shorter follow-up.

Primary endpoint

The cumulative incidence of symptomatic and asymptomatic COVID-19 infections over the 18-month follow-up study period was higher in AHSCT SSc patients (cases) (8% (95%CI 2-20%) *vs*. 0% (0-0%) on July 1st 2021, 14% (5-28%) *vs*. 0% (0-0%) at January 1st 2022, 33% (18-49%) *vs*. 6% (1-19%) on June 30th 2022) compared to controls (p=0.007) as illustrated in Figure 1.

Secondary endpoints

Overall, four AHSCT SSc patients had had one COVID-19 infection before January 1st 2021, and 11 of 36 AHSCT-SSc (cases) patients and 2 of 36 SSc controls, of whom one and one respectively had refused SARS CoV-2 vaccination, experienced one COVID-19 infection between January 1st 2021 and June 30th 2022 (Table II). All SARS CoV-2 infected SSc patients, AHSCT cases and non-AHSCT controls, were symptomatic. Most patients suffered *"mild"* COVID-19 infections and only three AHSCT SSc patients required hospitalisation for *"moderate"* severity COVID-19 infection (Table II). Time, in months, from complete anti-SAR-Cov2 vaccination to COVID-19 infection was 7.2 months (IQR: 6.7-8) for AHSCT SSc patients and 13

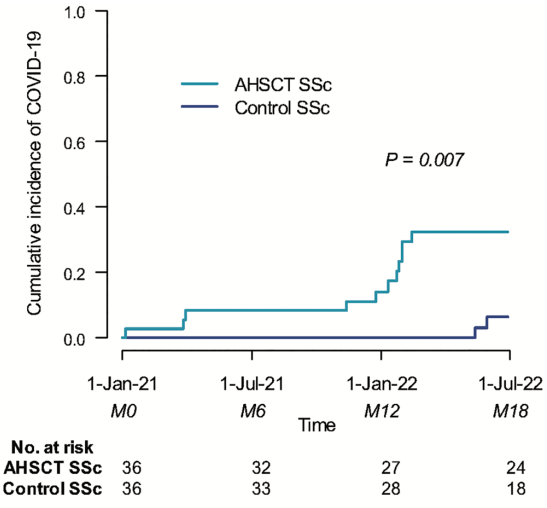

Fig. 1. Cumulative incidence of symptomatic COVID-19 infection in infections in systemic sclerosis (SSc) patients treated by autologous haematopoietic stem cell transplantation (AHSCT) (cases) and non-AHSCT (controls).

Table II. Clinical severity of symptomatic COVID-19 infections in systemic sclerosis (SSc) patients treated by autologous haematopoietic stem cell transplantation (AHSCT) (cases) and non-AHSCT (controls).

Variables	All	AHSCT-SSc	Non AHSCT-SSc
No. of patients with COVID-19 infection	**13**	**11**	**2**
Of whom no. vaccinated	**11**	**10**	**1**
Clinical severity of symptomatic COVID-19 infection			
Mild	**10 (77)**	**8 (73)**	**2 (100)**
Moderate	**3 (23)**	**3 (27)**	**0 (0)**

Table III. SARS-CoV2 serology after vaccine injection in systemic sclerosis (SSc) patients treated by autologous haematopoietic stem cell transplantation (AHSCT) (cases) and non-AHSCT (controls).

Variables	AHSCT-SSc	Non AHSCT-SSc
No. of vaccinated Pts	31	33
Serology after 2 inj. (BAU/mL)	682 [0;250000]	1000 0; 1984]
<40	2 (14)	1 (20)
40-260	1 (7)	0 (0)
>260	11 (79)	4 (80)
Missing data	17	28
Serology after 3rd inj. (BAU/mL)	501 [1; 5632]	2179 [0;3702]
<40	2 (12)	1 (33)
40-260	5 (29)	0 (0)
>260	10 (59)	2 (67)
Missing data	14	30

months for the only non-AHSCT SSc infected control. Among the 11 AHSCT patients who experienced at least one COVID-19 infection after vaccination, the clinical severity of COVID-19 disease did not differ according to the elapsed time between AHSCT and the first vaccine injection (p=0.52).

Overall, five AHSCT SSc patients and three non-AHSCT SSc control patients refused vaccination (p=0.68). The patient acceptance rate of SARS-CoV-2 vaccination was comparable between AHSCT (cases) and non-AHSCT (controls) SSc patients. Vaccination characteristics are reported in Table Ia. Both groups predominantly received the Pfizer-BioNTech® vaccine: 94% AHSCT SSc (cases) and 71% non-AHSCT SSc (controls) patients for the first injection, 93% AHSCT SSc (cases) and 77% non-AHCST SSc (controls) for the second injections, 88% AHSCT SSc (cases) and 78% non-AHSCT SSc (controls) for the third injections. The serological response to vaccination did not differ significantly between the two patients' groups. The distribution of serology rate did not differ between cases and controls after the second injection (p=0.62), nor after the third injection (p>0.99), and the majority of SSc patients in both groups still exhibited positive antibody responses at that time (Table III). No severe (≥ grade 3 CTC-AE v5.0) adverse event related to COVID-19 vaccination was reported in either cases or controls group.

Discussion

Five years have passed since COVID-19 was declared a worldwide pandemic by the World Health Organization in March 2020, and COVID-19 continues to significantly affect immunocompromised individuals, including those with autoimmune rheumatic diseases (ARDs), especially those who have undergone AHSCT (17). SSc patients treated by AHSCT remain highly fragile and at higher risk of any bacterial, viral or fungal infections (18) during the immune reconstitution period. In addition, they might have received anti-CD20 antibodies (rituximab), as more recently used for a "cardiac safe" conditioning regimen (19, 20) or in case of Epstein Barr virus infection (18). During longer term follow-up after AHSCT (21), SSc patients may also receive additional immunosuppressive or immunomodulatory drugs, such as mycophenolate mofetil or less frequently methotrexate for maintenance therapy or in case of relapse. In such cases, they face a higher risk of COVID-19 morbidity and mortality (17, 22, 23) depending on the age of vaccination, the type of received vaccines, and previous exposure to SARS-CoV-2 (24-26).

To date, vaccination remains the cornerstone of prevention to decrease COVID-19-related hospitalisation and mortality rates (27). For these reasons and regardless their prior vaccine status, the all vaccination program should be repeated after AHSCT in this patients category (27). The COVID-19 antibody levels do not necessarily correlate with neutralising power and efficacy may be impaired against new variants of the virus (28). In non-AHSCT treated patients, several studies, focused on SARS-CoV-2 antibody response to the receptor binding domain (RBD) or spike protein (29) after vaccination, have shown that ARDs patients

have lower SARS-CoV-2 vaccine seropositivity rates compared to the general adult population (30, 31). Three studies so far have analysed the effect of Covid-19 mRNA vaccines in SSc patients (32-34). Another one was exclusively focused on SSc patients undergoing inactivated SARS-CoV-2 vaccine (35) and one study analysed the efficacy of vaccination against SARS-CoV-2 after AHSCT in 7 SSc patients (4). The SFGM-TC guidance recommends that immunocompromised patients undergo serological testing with quantitative anti-Spike antibody (IgG S1/S2) testing one month after completing their primary vaccination series to assess vaccine response (9). The antibody levels from these serological results, expressed in international units (BAU) according to WHO international standards, define the absence of serological response for anti-S<30 BAU/mL and low serological response for anti-S<250 BAU/mL (SFGM-TC Recommendations on monoclonal antibodies) and a threshold serum level of 264 BAU/mL is considered as the correlate of clinical protection (12). In our study, after two doses of the anti-SARS-Cov2 vaccine, a similar proportion (about 80%) of cases and controls achieved a response of anti-S IgG ≥260 BAU/mL (standard WHO units). After the third anti-SARS-Cov2 vaccine dose in 26 patients of the AHSCT-SSc group, sustained antibody response was found in 15 out of 17 patients with available serological assessment (5 patients at 40-260 BAU/mL and 10 patients >260 BAU/mL).

Our study, which covered the year 2021 and the first semester of the year 2022, also examined the frequency of severe COVID-19 infections and thereby provided valuable insights into the SARS-CoV-2 vaccination efficacy. Our results appeared consistent with data observed earlier during the COVID-19 pandemic between march and April 2020 in Italy, where a nationwide telephone survey of 1636 SSc patients reported definite COVID-19 in 14 patients and highly suspected COVID-19 in 47 (3 %) with a limited proportion (15%) of infected patients requiring hospitalisation (36). The absence of severe adverse events following vaccination reinforces the vaccine's safety profile in this highly vulnerable SSc population (4, 17).

We aimed at 100% vaccine coverage after AHSCT. Herein, five patients in the AHSCT group refused anti-SARS-CoV-2 vaccination. The reasons for this refusal are unclear. There is limited information about SARS-CoV-2 vaccination acceptance in patients who have undergone AHSCT for autoimmune diseases and, more specifically for SSc. In a cross-sectional UK study of sociodemographic and psychological determinants of influenza vaccine intention in recipients of HSCT, the rate of low intent of vaccination was 23.7%, compared to 14% in the AHSCT in our study, and older age was found to be associated with a low intent toward vaccination (37). Consistently in our sample, the median age of AHSCT patients who refused vaccine was 57 years (range 37-65) compared to 52 (range 28-71) in those who agreed to be vaccinated. In the non AHSCT SSc patients, three of 36 (8%) refused the vaccination. A SPIN study conducted in 2022 revealed that 11% of 489 SSc patients who agreed to participate to an international survey were not fully vaccinated (no injection or incomplete program) (38). This differs from an Italian cohort, where about half of SSc patients completed at least three injections of covid vaccine (34).

There are several limitations to the current study, such as the small sample size, the retrospective scheme, and missing data across the follow-up period. There is a lack of data on other neutralizing antibodies (such as anti-RBD IgG). Given the very low count of SARS-CoV-2 infections (11 in AHSCT cases and 2 in non AHSCT controls), we could not provide a robust assessment of the infection characteristics and outcomes. Serological data after vaccination was very limited, notably after the third vaccine injections and in the control group, which precludes precise conclusions about humoral response and immunogenicity profiles, between the two groups. Furthermore, the study did not analyse the patients long-term outcomes, nor potential disease flares after vaccination, as the risk of increased autoimmunity cases (39).

Conclusions

To our knowledge, this is the first European case-control study that details experiences with SARS-CoV-2 vaccines in systemic sclerosis patients treated by AHSCT. The incidence of COVID-19 infection was higher, as expected, in AHSCT SSc patients compared to non-AHSCT SSc, but the symptomatology remained mild to moderate, and manageable. Notably, this difference was more pronounced during the fifth pandemic wave in late 2021 and early 2022, when social distancing measures were reduced. Vaccination was safe in this group of patients with no serious adverse events and showed comparable acceptance rates to the non-AHSCT SSc population. These findings emphasise the importance of ongoing surveillance and targeted vaccination strategies in AHSCT SSc patients. Further research is necessary to optimise vaccination protocols, explore the long-term implications of vaccination in this vulnerable patient population, and confirm these results. Given the emergence of new variants of concern, these findings, highlight the need for continued vigilance and monitoring in AHSCT SSc patients.

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