Long-term outcomes of COVID-19 vaccination in patients with rare and complex connective tissue diseases: The ERN-ReCONNET VACCINATE study.

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ABSTRACT

Background: Vaccination is one of the most important measures to contain the COVID-19 pandemic, especially for frail patients. VACCINATE is a multicentre prospective observational study promoted by the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) aimed at

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assessing the long-term outcomes of COVID-19 vaccination in patients with rare and complex connective tissue diseases (rcCTDs) in terms of efficacy and safety.

Methods: Adult rcCTDs patients were eligible for recruitment. Demographic, clinical and vaccination data were collected at enrolment. Follow-up visits were scheduled 4, 12, 24, 36 and 48 weeks after completion of the first vaccination cycle; data on adverse events, disease exacerbations and the occurrence of new SARS-CoV-2 infections were collected at these time-points.

Findings: 365 rcCTDs patients (87 % female, mean age 51.8 ± 14.6 years) were recruited. Overall, 200 patients (54.8 %) experienced at least one adverse event, generally mild and in most cases occurring early after the vaccination. During follow-up, 55 disease exacerbations were recorded in 39 patients (10.7 %), distributed over the entire observation period, although most frequently within 4 weeks after completion of the vaccination cycle. The incidence of new SARS-CoV-2 infections was 8.9 per 1000 person-months, with no cases within 12 weeks from vaccine administration and an increasing trend of infections moving away from the primary vaccination cycle. Only one case of severe COVID-19 was reported during the study period.

Interpretation: COVID-19 vaccination seems effective and safe in rcCTDs patients. The rate of new infections was rather low and serious infections were uncommon in our cohort. No increased risk of disease flares was observed compared to previous disease history; however, such exacerbations may be potentially severe, emphasising the need for close monitoring of our patients.

1. Introduction

Patients with rheumatic diseases have poorer COVID-19 outcomes as compared to the general population, including higher rates of hospitalisation, oxygen support, intensive care unit (ICU) admission and mortality [1,2]. In addition to the clinical outcomes, COVID-19 has a significant personal and social impact especially on people living with rare rheumatic diseases as it exacerbates the many difficulties that the patients must face in their daily living [3,4], as well as it creates several organizational challenges on the health systems that take care of such fragile patients [5].

Vaccinations are among the most important public health interventions to fight against infectious diseases. In the last three years, several vaccines were developed and approved to prevent COVID-19; they demonstrated effectiveness in preventing severe COVID-19 cases, hospitalisations, and deaths in the general populations. Current evidence suggests that the benefits of vaccination outweigh the potential risks of adverse events in patients with rare and complex connective tissue diseases (rcCTDs). However, there is a paucity of long-term safety data regarding COVID-19 vaccination in these patients. On the other hand, there is a big concern around the possibility of reduced effectiveness of vaccines induced by the concomitant use of immunosuppressive therapies in these patients, which could leave them vulnerable to breakthrough COVID-19 infections [6–8].

This issue was addressed within the European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) [9], by designing and promoting the VACCINATE study. ERN ReCONNET is one of the 24 ERNs launched by the European Commission in 2017 with the aim of tackling low prevalence and rare diseases that require highly specialised treatment and promoting concentration of knowledge and resources through virtual networks involving healthcare providers (HCPs) across the European Union (EU). In this framework, the VACCINATE study was designed as a multicentre international prospective study aimed at assessing the long-term outcomes of COVID-19 vaccination in patients with rcCTDs in terms of both efficacy and safety.

The present work reports the long-term results of the VACCINATE study.

2. Methods

VACCINATE (Protocol Number: NCT04702295, Clinicaltrial.gov: NCT04702295) is a multicentre, prospective observational study of 30 months duration.

The study was conducted in European centres of the ERN ReCONNET network; all the centres involved have a well-established experience in the treatment of rcCTDs.

Patients were eligible to be included in the study if they (i) were at least 18 years of age, (ii) had an established diagnosis of rcCTDs among the following: antiphospholipid syndrome (APS), Ehlers-Danlos syndromes (EDS), idiopathic inflammatory myopathy (IIM), IgG4-related disease (IgG4-RD), mixed connective tissue disease (MCTD), relapsing polychondritis (RP), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), undifferentiated connective tissue disease (UCTD), (iii) received the vaccine against COVID-19 between February 2021 and February 2022, and (iv) signed the informed consent.

The administration of the vaccine (timing, type of vaccine and indications) followed national guidelines for the general population or for high-risk categories.

The baseline assessment coincided with enrolment in the study and was performed during a routine outpatient visit scheduled from one month before until the day of the first vaccine dose administration. After vaccination, each patient was monitored according to a predefined schedule of visits for 12 months; the timetable of the visits and the clinical data collected at baseline and at each monitoring assessment are summarized in Supplementary material (Table S1). Briefly, demographic data, previous clinical history and treatments were collected at baseline from clinical charts; follow-up visits were scheduled 4, 12, 24, 36 and 48 weeks after completion of the first vaccination cycle; at these time-points, ongoing disease activity and therapies, adverse events, potential disease flares, as well as the occurrence of new SARS-CoV-2 infections were collected. For comparison, for each patient the incidence of disease exacerbations during the year before the study entry was retrospectively collected from clinical charts.

Adverse events were categorised as the following: early adverse events (injection site reactions and early systemic events within 7 days from the second injection), late adverse events (any event occurred after the seventh day after last vaccination dose); serious adverse events (SAE) and adverse events of special interest (AESI) were also identified. For definitions of SAE and AESI refer to Supplementary material (Table S2).

Disease flares were defined as at least one of the following: new manifestation attributable to disease activity; increase in Physician Global Assessment (PGA) from previous evaluation; addition of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) or immunosuppressants; hospitalisation. In the group of EDS patients, since no shared guidelines are available for monitoring the disease activity, exacerbations have been determined as worsening of the musculoskeletal complaints and/or increased use of pain medications. Based on these data, disease flares and severe disease flares were distinguished. For a detailed description of the definitions adopted see Supplementary material (Table S3).

SARS-CoV-2 breakthrough infection was defined as a PCR-confirmed

or antigen test-confirmed SARS-CoV-2 infection that occurred at least 14 days after vaccination.

For safety and efficacy endpoints, the incidence of the events was calculated over a 52 weeks period. Demographic and disease characteristics were summarized for all the subject enrolled using descriptive statistics. Logistic regression was used to evaluate the association between predictors (diagnosis) and categorical outcomes (occurrence of flares and breakthrough infections); odds ratio (OR) and 95 % confidence interval (CI) were reported.

Data were recorded on a web-based, electronic collection data form (RedCap) specifically designed for the study.

The VACCINATE study received ethical approval for the coordinating centre by the National Institute for Infectious Diseases Lazzaro Spallanzani (Rome, Italy). The local ethics committees approved the final protocol for each participating centre.

3. Results

A total of 365 patients (87 % female, mean age 51.8 ± 14.6 years, mean disease duration 12.4 ± 10.2 years) were recruited during the period February 2021–October 2021 from 9 ERN ReCONNET centres [AOU Pisan (Pisa, Italy), AO Padua (Padua, Italy), Centro Hospitalar Lisboa Norte (Lisboa, Portugal), IRCCS AOU San Martino (Genoa, Italy), AO San Camillo Forlanini (Rome, Italy), Foundation IRCCS Polyclinic San Matteo (Pavia, Italy), Foundation IRCCS Ca' Granda Ospedale Maggiore Polyclinic (Milan, Italy), Civil Hospital (Brescia, Italy), AOU Careggi (Florence, Italy)].

SLE (168, 46.0 %) was the most frequent diagnosis, followed by SSc (55, 15.1 %), primary SS (40, 11.0 %), IIM (31, 8.5 %), UCTD (29, 8.0 %), MCTD (14, 3.8 %), EDS (14, 3.8 %), APS (7, 1.9 %) and overlap syndromes (7, 1.9 %).

All patients received mRNA vaccines, specifically Pfizer BNT162b2 (Comirnaty, 224/365, 61.4 %) or Moderna mRNA-1273 (Spikevax, 141/365, 38.6 %).

In the whole cohort, 163 patients (44.7 %) were on GCs therapy, 155 (42.5 %) on conventional immunosuppressants and 41 (11.2 %) on biotechnological drugs. A detailed description of clinical characteristics, ongoing therapies at the time of enrolment and comorbid conditions is reported in Table 1. Sixteen patients (4.4 %) had COVID-19 before vaccination, in two cases severe.

Data on the administration of the third dose of the vaccine were available for 168 patients: of these, 160 (95.2 %) received the booster dose during the study period, while a small amount did not.

3.1. Adverse events (not including disease flares)

Globally, a total of 200 patients (54.8 %) experienced at least one adverse event.

Overall, 285 adverse events in 186 patients (51.0 %) were recorded early after the vaccination cycle (within one week after the second dose); 141 (38.6 %) and 144 (39.5 %) after the first and after the second dose respectively, all resolved spontaneously or with symptomatic drugs within a median period of 7 days. They were local reaction in 54 cases (14.8 %) while in the remaining cases were systemic symptoms including fatigue (37.6 %), fever (23.3 %), headache (19.1 %), muscle pain (16.4 %), joint pain (12.8 %), chills (7.7 %), vomiting (2.2 %) and diarrhoea (1.4 %). No serious adverse events were recorded after the first and the second vaccination doses.

In the remaining follow-up period, a total of 14 (3.8 %) events in as many patients were recorded and considered potentially related to the vaccination by the treating physician. Of these, 2 were serious adverse events requiring hospitalisation: a case of pericarditis in a SSc patient between week 12 and week 24 (it should be noted that this patient had received the booster dose a month earlier) and a case of persistent fever and splenomegaly raising the suspicion of a lymphoproliferative disease, later unconfirmed, in a SLE patient between week 36 and week 48.

Table 1
Characteristics of the cohort at enrolment.

N° of patients	365
CUMULATIVE ORGAN INVOLVEMENT	
Musculoskeletal	236 (64.7 %)
Mucocutaneous	186 (51.0 %)
Vascular	145 (39.7 %)
Haematological	103 (28.2 %)
Pulmonary	68 (18.6 %)
Cardiac	52 (14.2 %)
Gastrointestinal	48 (13.2 %)
Renal	93 (25.5 %)
Ocular	7 (1.9 %)
Exocrine glands	86 (23.6 %)
Endocrinological	3 (0.8 %)
Obstetric	12 (3.3 %)
Neurological	34 (9.3 %)
Psychiatric	1 (0.3 %)
ONGOING TREATMENT	
Glucocorticoids	163 (44.7 %)
Mean GCs daily dose (mg) (±SD)	5.5 ± 4.9
Chloroquine/Hydroxychloroquine	221 (60.5 %)
csDMARDs	156 (42.7 %)
Methotrexate	39 (10.7 %)
Azathioprine	25 (6.8 %)
Mycophenolate Mofetil	75 (20.5 %)
Cyclophosphamide	4 (1.1 %)
Cyclosporine	11 (3.0 %)
Tacrolimus	5 (1.4 %)
Leflunomide	5 (1.4 %)
csDMARDs >1	8 (2.2 %)
bDMARDs	41 (11.2 %)
Belimumab	23 (6.3 %)
Rituximab	12 (3.3 %)
Abatacept	2 (0.5 %)
TNF inhibitor	1 (0.3 %)
Tocilizumab	1 (0.3 %)
Ixekizumab	1 (0.3 %)
Baricitinib	1 (0.3 %)
Colchicine	6 (1.6 %)
Immunoglobulins	9 (2.5 %)
COMORBIDITIES	
Diabetes	9 (2.5 %)
Arterial hypertension	68 (18.6 %)
Cardiovascular disease	42 (11.5 %)
Asthma	10 (2.7 %)
Chronic obstructive pulmonary disease (COPD)	9 (2.5 %)
Chronic kidney disease (CKD)	15 (4.1 %)
Osteoporosis	60 (16.4 %)
Malignancy	28 (7.7 %)
Obesity	14 (3.8 %)
Thyroid disease	81 (22.2 %)
Psychiatric comorbidity	18 (4.9 %)

3.2. Disease exacerbations

A total of 55 exacerbations of the underlying disease in 39 patients (10.7 %) were recorded during the entire follow-up; 15 patients (4.1 %) experienced more than one disease flare.

Of these, 21 (38.2 %) occurred early after the vaccination cycle (within four weeks from the second dose); in this period 5 (9.1 %) severe flares were observed, 3 required hospitalisation. In more detail, these last three cases involved an APS patient with severe thrombocytopenia and haemolytic anaemia, a SS patient with exacerbation of cryoglobulinaemic vasculitis and a MCTD patient with digital ulcers and critical ischaemia, while the other two severe flares required a variation of immunosuppressive therapy to control disease activity in a patient with SLE and a patient with overlap syndrome IIM/SSc.

Thereafter, 34 (61.8 %) disease exacerbations occurred during the remaining follow-up period: 6 (10.9 %) were recorded within 12 weeks (one severe that required strengthening of immunosuppressant treatment for arthritis in SLE), 10 (18.2 %) between week 12 and 24 (one severe due to lupus nephritis requiring hospitalisation), 8 (14.5 %)

between week 24 and 36 (three severe leading to hospitalisation in a MCTD patient, a SLE patient with renal flare and the same SS patient mentioned above who presented a new exacerbation of vasculitis), and 10 (18.2 %) between week 36 and 48 (none severe).

Of note, in the same study population, in the year before study entry, 56 disease flares were recorded in 51 patients (14.0 %).

Among the different diseases, patients who experienced at least one flare were affected by SLE in 13 cases (7.7 % of total disease diagnosis), SS in 7 cases (17.5 %), EDS in 6 cases (42.9 %), MCTD, SSc and UCTD in 3 cases each (21.4 %, 5.5 % and 10.3 %, respectively), IIM in 2 cases (6.5 %), APS and overlap syndrome (IIM/SSc) in 1 case each (14.3 % both).

A significantly higher rate of flares was found among EDS (OR 7.2, p = 0.001, 95 % CI 2.4–22.1).

The distribution of flares according to rcCTD diagnosis and timing of follow-up is shown in Table 2.

3.3. Vaccine breakthrough infections

Overall, 32 cases of COVID-19 occurred in 31 patients (8.5 %) during the study period for an incidence rate of 8.9 per 1000 person-months.

No new SARS-CoV-2 infections were detected within 12 weeks from vaccination. An increasing trend of new COVID-19 cases occurred moving away from the primary vaccination cycle: indeed 1 case (3.1 %) was recorded at week 24, 8 cases (25.0 %) at week 36, and 23 cases (71.9 %) were registered between 36 and 48 weeks after vaccination.

All new infections generally presented a mild course; only one case of severe COVID-19 was reported, in a patient with overlap syndrome IIM/SSc who experienced severe respiratory symptoms that required hospitalisation.

Only one patient contracted COVID-19 twice during the entire follow-up period.

The distribution of new infections according to rcCTD diagnosis is shown in Table 3.

No differences in gender, type of diagnosis, cumulative dose of GCs and ongoing immunosuppressive treatment at the time of vaccination were found between patients who had breakthrough infections and patients that did not have it.

A total of 160 patients received the booster dose of vaccination within the study period; among those patients, 21 cases of non-severe breakthrough infections were recorded (13.1 %). No differences in breakthrough infections were recorded between patients who received the third dose and patients that did not.

4. Discussion

The VACCINATE study investigated long-term safety and clinical effectiveness of COVID-19 vaccination in a large prospective cohort of patients with rcCTDs.

Overall, the study demonstrated a good short- and long-term safety profile of COVID-19 vaccination in this population. Indeed, almost half of the patients had no adverse event occurring early after each vaccination. Moreover, adverse events were mainly injection site reactions and mild systemic reactions that resolved in a few days, often without any medications, being mainly expression of local and systemic reactogenicity to vaccination instead of true adverse events. No adverse events of special interest or severe adverse events were recorded in this time frame.

In the remaining follow-up period of our study, adverse events were recorded in 4 % of patients and <1 % were severe adverse events, similarly to previous reports.

Data on early safety of vaccination of this cohort are in line with previous reports in clinical trials, in the general population and in other studies on rheumatic diseases [10–13]. Of particular interest, the EULAR COVAX registry reported a 37 % global frequency of adverse events in inflammatory rheumatic diseases; of these, <1 % were serious adverse events and 2.4 % were adverse events of special interest [14].

The higher frequency of early adverse events recorded in our study (51.0 %) could be due to the prospective data collection (adverse events were assessed by telephone call within seven days from the vaccination dose to avoid recall bias).

Thus, patients with rcCTDs should be advised of the high frequency of early side effects of the vaccinations, possibly mimicking disease flare, but they should also be reassured that they are not at increased risk of serious adverse events.

As far as disease exacerbations are concerned, in our cohort a total of 55 exacerbations of the underlying disease in 10 % of patients were recorded during the follow-up, the majority being within one month after the first vaccination cycle termination. Of note, disease exacerbations were recorded during the entire follow-up period, suggesting the importance of a long-term monitoring of disease activity after vaccination. However, no increased frequency of disease flares was observed compared to the previous disease history of each patient.

The frequency of disease flares recorded in our study is slightly

Table 3
Distribution of new COVID-19 cases in the whole cohort. (The percentage in relation to the total number of new infections is given in brackets.)

	Overall	Week 24	Week 36	Week 48
APS (N = 7)	1 (3.1 %)	0	0	1 (3.1 %)
EDS (N = 14)	0	0	0	0
IIM (N = 31)	3 (9.4 %)	0	0	3 (9.4 %)
MCTD (N = 14)	0	0	0	0
Overlap syndrome (N = 7)	2 (6.2 %)	0	1 (3.1 %)	1[a] (3.1 %)
SLE (N = 168)	17 (53.1 %)	1 (3.1 %)	6 (18.8 %)	10 (31.3 %)
SS (N = 40)	3 (9.4 %)	0	0	3 (9.4 %)
SSc (N = 55)	3 (9.4 %)	0	1 (3.1 %)	2 (6.2 %)
UCTD (N = 29)	3 (9.4 %)	0	0	3 (9.4 %)
Total (N = 365)	32 (100 %)	1 (3.1 %)	8 (25.0 %)	23 (71.9 %)

[a] Severe COVID-19 case in an overlap IIM/SSc.

Table 2
Distribution of rCTD flares according to follow-up period. (The number of severe flares is given in brackets.)

	Overall	Within 7 days after the first dose	From day 8 after the first dose to the day of the second dose	Within 7 days after the second dose	Week 4	Week 12	Week 24	Week 36	Week 48
APS (N = 7)	2 (1)	0	0	0	1 (1)	0	0	0	1
EDS (N = 14)	10 (0)	0	1	0	1	2	3	0	3
IIM (N = 31)	3 (0)	0	1	0	0	1	1	0	0
MCTD (N = 14)	5 (2)	0	0	0	2 (1)	1	0	1 (1)	1
Overlap syndrome (N = 7)	5 (1)	0	0	0	2 (1)	0	1	1	1
SLE (N = 168)	18 (4)	3	1	0	4 (1)	2 (1)	4 (1)	3 (1)	1
SS (N = 40)	6 (2)	1	0	0	1 (1)	0	1	2 (1)	1
SSc (N = 55)	3 (0)	0	0	0	0	0	0	1	2
UCTD (N = 29)	3 (0)	1	1	0	1	0	0	0	0
Total (N = 365)	55 (10)	5 (0)	4 (0)	0 (0)	12 (5)	6 (1)	10 (1)	8 (3)	10 (0)

higher than in other studies. For instance, the EULAR COVAX registry reported in the short-term follow-up a 4.4 % of flares in patients with systemic/inflammatory diseases (0.6 % severe), 1.5 % resulting in medication changes. However, in this study, the duration of follow-up was variable and the mean time between vaccination dose and the flare resulted in 6 days (SD 8), suggesting that only short-term events have been focused [14].

A recent meta-analysis of observational studies reported that the overall random-effect rate of flare after COVID-19 vaccination was 7 % (95 % CI, 5%–9%) in patients with rheumatic diseases with a high level of heterogeneity between the studies [15]. Different methods of ascertainment (e.g. self-reported, physician-reported, survey based) and duration of follow-up seem the major determinants of such a variability.

Concerning this, our study assessed disease exacerbations prospectively, according to predefined criteria, as judged by the clinician at face-to-face follow-up visits over a long period of time, thus providing a high level of accuracy.

Our data also confirmed that COVID-19 vaccination is clinically effective in preventing severe COVID-19 cases; indeed, the rate of new infections is low and severe infections uncommon. Interestingly, these results were similar across different disease groups and medications. However, the infection rate increased significantly after 6 months of follow-up, underlying the importance of the booster dose in patients with immune-mediated inflammatory diseases on immunosuppressive therapy [16].

Many data on immunogenicity of SARS-CoV-2 vaccination in patients with systemic autoimmune diseases are reported in the Literature, mainly based on humoral response; there is a general agreement that COVID-19 vaccination elicits a weaker antibody response in patients with systemic autoimmune diseases, especially under certain therapies such as mycophenolate mofetil, rituximab and abatacept. Indeed, the percentages reported of cases with a detectable antibody response range from 62 % to 100 %, while is 96%–100 % in healthy controls [17].

Moreover, studies that measured the level of antibody response demonstrated lower IgG antibody titres or neutralising titres in cases versus controls [18]. Increased age, anti-CD20 therapies, mycophenolate mofetil and glucocorticoids dosage are negatively associated with antibody response in many studies [19–26].

However, while there is a large body of evidence on the humoral immune response elicited by COVID-19 vaccination, few data have been reported on clinical effectiveness of vaccination in systemic autoimmune diseases, especially in rare conditions.

Papagoras C et al. reported a significantly higher risk of poor COVID-19 outcomes (in terms of hospitalisations and death) in unvaccinated patients with systemic rheumatic diseases with respect to fully vaccinated patients [27].

Interestingly, a recent large study on patients with rheumatic and non-rheumatic immune-mediated diseases found no difference in the incidence of breakthrough infections among patients on immunosuppressive therapy, patients not on immunosuppressants and healthy controls, suggesting a comparable effectiveness of the vaccination [28,29].

Similarly, in patients treated with rituximab and fully vaccinated, Md Yusof MY et al. found 30 % of breakthrough COVID-19, but only 4 % of moderate-to-severe breakthrough COVID-19 and no deaths [30].

Conversely, a recent retrospective cohort study on patients with systemic rheumatic diseases found an incidence rate of 2.6 per 1000 person-months of breakthrough infections with a median time from vaccination to infection of 6.3 months. In this study, multiple medications including anti-CD20 monoclonal antibodies, abatacept, mycophenolate mofetil, other csDMARDs, IL-6 inhibitors and TNF inhibitors were associated with higher risk of breakthrough infection [31].

Globally, our study demonstrated the good safety and efficacy profile of COVID-19 mRNA vaccines in patients with rcCTDs over a long-term follow-up period.

Some limitations of the study should be acknowledged. First, no data on transient treatment suspension because of vaccination were collected; this aspect could have an impact on vaccine effectiveness and disease flares [32]. However, while it is reported that some drugs have a major impact on vaccine immunogenicity, we did not observe any differences across different treatments.

Another limitation relies on the fact that no causal relationship can be demonstrated between adverse events and disease flares and COVID-19 vaccination; the putative causal relationship has been based on clinical judgement, but it could be very difficult to be established especially for events that occurred later in the follow-up. Moreover, for disease flares, we have an important comparator represented by the number of flares during the previous year that resulted similar to the number of flares recorded during the study period after vaccination, although it should be considered that this is a comparison between prospectively collected and retrospective data. Furthermore, in the EDS group, most patients, specifically inquired about this argument, did not associate disease worsening with the vaccine, conversely reporting flares as part of their common fluctuating pattern of pain and musculoskeletal complaints, often with a strong seasonal component, that did not significantly differ in their opinion after vaccination.

Lastly, some diseases (especially rarer conditions) were poorly represented in the study not allowing sub-group analysis. This is a common limitation in several studies on rare diseases; however, this study provides a general overview on vaccination safety and effectiveness in these conditions that share several clinical and therapeutic aspects. Additional patient recruitment is ongoing to collect a larger sample of patients with rarer diseases.

Major strengths of the study are the prospective study design that allowed an accurate data collection, limiting, for instance, recall and selection bias, and the long-term follow-up.

Indeed, long-term safety data are essential to reassure patients and clinicians about the clinical utility of the COVID-19 vaccination in a cost-benefit balance.

5. Conclusions

In conclusion, as recommended by the scientific societies [33] and recently highlighted by the ERN ReCONNET points to consider for treating patients living with autoimmune rheumatic diseases [34], COVID-19 vaccination remains one of the main measures to prevent severe disease for patients with systemic autoimmune diseases. Although the number and intervals of additional (booster) vaccinations may differ in the future among countries and depending on the epidemiological situations, the present study confirms and highlights the good safety and efficacy profile of COVID-19 vaccination in rcCTDs patients in the long-term, that can be combined with the use of antiviral agents and anti-SARS-CoV-2 antibody products in the most fragile patients.

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Data sharing

The data underlying this article will be shared on reasonable request to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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