COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19)

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Abstract

Background

Italy was one of the first countries significantly affected by the coronavirus disease 2019 (COVID-19) epidemic. The Italian Society for Rheumatology promptly launched a retrospective and anonymised data collection to monitor COVID-19 in patients with rheumatic and musculoskeletal diseases (RMDs), the CONTROL-19 surveillance database, which is part of the COVID-19 Global Rheumatology Alliance.

Methods

CONTROL-19 includes patients with RMDs and proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) updated until May 3rd 2020. In this analysis, only molecular diagnoses were included. The data collection covered demographic data, medical history (general and RMD-related), treatments and COVID-19 related features, treatments, and outcome. In this paper, we report the first descriptive data from the CONTROL-19 registry.

Results

The population of the first 232 patients (36% males) consisted mainly of elderly patients (mean age 62.2 years), who used corticosteroids (51.7%), and suffered from multi-morbidity (median comorbidities 2). Rheumatoid arthritis was the most frequent disease (34.1%), followed by spondyloarthritis (26.3%), connective tissue disease (21.1%) and vasculitis (11.2%). Most cases had an active disease (69.4%). Clinical presentation of COVID-19 was typical, with systemic symptoms (fever and asthenia) and respiratory symptoms. The overall outcome was severe, with high frequencies of hospitalisation (69.8%), respiratory support oxygen (55.7%), non-invasive ventilation (20.9%) or mechanical ventilation (7.5%), and 19% of deaths. Male patients typically manifested a worse prognosis. Immunomodulatory treatments were not significantly associated with an increased risk of intensive care unit admission/mechanical ventilation/death.

Conclusion

Although the report mainly includes the most severe cases, its temporal and spatial trend supports the validity of the national surveillance system. More complete data are being acquired in order to both test the hypothesis that RMD patients may have a different outcome from that of the general population and determine the safety of immunomodulatory treatments.

Key words

rheumatic diseases, immunosuppression, COVID-19, health surveys

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is responsible for a Coronavirus Disease 2019 (COVID-19) pandemic, which arose in late 2019 in the Chinese city of Wuhan (1). COVID-19 is characterised by a significant clinical heterogeneity, which can range from asymptomatic to life-threatening conditions (2). The individual characteristics of infected patients can partly explain the clinical heterogeneity; from the first published data, age and comorbidities are the most relevant risk factors, which can lead to a more severe disease course (3, 4).

Immunosuppression states (including those of iatrogenic origin) are also reported as risk factors, since the susceptibility and the course of the infection by SARS-CoV-2 may be more severe in subjects with a high degree of immunosuppression (5).

However, other evidence would support the feasibility to modulate the patients' immune response, and limit both the development of COVID-19 and the severity of its manifestations, through those drugs commonly used in patients with immune-mediated rheumatic and musculoskeletal diseases (RMDs) (6, 7).

Hydroxychloroquine and chloroquine are drugs widely used in patients with immune-mediated RMD, such as inflammatory arthropathies and connective tissue diseases, and have been indicated as candidate modulators of the susceptibility to SARS-CoV-2 infection (8). Tocilizumab is an anti-interleukin-6 drug used in rheumatology for the treatment of rheumatoid arthritis and large vessel vasculitis; it has been identified as one of the possible candidates for the control of acute respiratory distress syndrome (ARDS), which represents the most feared complication of COVID- 19 (9).

The outcome of COVID-19 in RMD patients can be affected by several aspects, which can increase or reduce the susceptibility to the disease: demographic factors, multi-morbidity, organ involvement, inflammatory state, functional impairment, and immunomodulatory/immunosuppressive therapies.

The degree of exposure of patients with RMDs to the COVID-19 and the consequences of its contagion in these patients are not yet known. For this reason, in the context of global surveillance on the frequency and outcomes of the patients' population, it is pivotal to collect information on the outcomes of patients with immunosuppression states, in particular for those exposed to iatrogenic immunosuppressive regimens (10). Preliminary data support the hypothesis that immunuppressive drugs are not associated with an increased risk of hospitalisation (11).

Among other epidemiological contexts, Italy was one of the countries hit first and hardest by the COVID-19 epidemic. Taking advantage from a strong network of the rheumatological units across the country – under the aegis of the Italian Society for Rheumatology (SIR) – all the members of SIR were involved in an active surveillance system (the so-called, CONTROL-19 surveillance database). Such initiative was also connected from the earliest phase to the European and Global registries (12).

CONTROL-19 aims to deepen the knowledge about patients with RMDs affected by COVID-19, in order to describe the clinical course of the diseases, compare to the observed outcome in the general population and identify the major factors associated with a detrimental prognosis.

Methods

Data

The CONTROL-19 registry follows a retrospective, multicentre, national, non-profit design. Data collection started on March 26th 2020, and SIR is still recruiting patients at the time of the submission of this paper. The study was approved on March 24th 2020 by the Ethics Committee of Area Vasta Emilia Centrale (288/2020/Oss/AOUFe).

The data collection was carried out by the SIR rheumatologists, who are distributed throughout the national territory and are involved in the care of patients with RMDs and COVID-19. All the demographic and clinical data were collected from the medical records of these patients.

The analysis included only the patients with a molecular diagnosis for SARS-

CoV-2 (determined by real-time polymerase-chain-reaction), clinical diagnosis of RMD and availability of the COVID-19 outcome data.

The following composite endpoint was used as the primary outcome measure: intensive care unit (ICU) admission/mechanical ventilation or death (1).

The following endpoints were analysed as secondary outcome measures: pneumonia, severe respiratory failure, ARDS, hospitalisation, mechanical ventilation and duration, mortality.

The following information, relating to the period prior and during the infection, was retrospectively collected: variables related to the rheumatology centre, general patient variables (gender, age, area of residence), variables related to the course of the infection (outcome and treatments), activity and severity variables of RMD according to a 4 point semiquantitative scale (0–3), treatments for RMD, comorbidity and risk factors.

Anonymised data are being collected in an online database, created on the REDCap platform and hosted at servers of SIR (13). The presence of possible duplicates was probabilistically explored on the basis of sex, age and the province of residence of the reported cases. Integrated controls into the electronic database guaranteed the completeness and quality of the data entry, while the report was filled.

Statistical analysis

The sample size was calculated under the conservative hypothesis of a cumulative incidence of about 40,000 cases in a year on the national territory, estimating an overall frequency of about 1–2% of RMD; overall, 40–500 cases are expected to be collected, based on reporting rates that represent between 10 and 50% of the total cases.

The characteristics of COVID-19 and RMD are presented through descriptive statistics (absolute and relative frequency, mean and standard deviation (SD) or median and interquartile range (IQR) - based on the type and distribution of variables), stratified by gender. To evaluate the differences between male and female patients, categorical variable were analysed using either the Pearson's Chi-squared test or Fisher's exact test, while quantitative variables were examined using either the Mann-Whitney or the t-test. The association between clinical and treatment variables with clinical outcome was assessed by logistic models, either crude or adjusted for prespecified confounders; results are presented as odds ratios (OR) and 95% confidence intervals (CIs). All data were processed and analysed with the statistical analysis software R (Foundation for Statistical Computing, Vienna, Austria).

Table I. Description of the RMD patients' characteristics.

	Male (n=83)	Female (n=149)	Total (n=232)	*p*-value
Age, mean (SD)	64.6 (13.4)	60.9 (14)	62.2 (13.9)	0.037
Age 18-40, n (%)	4 (4.9%)	11 (7.4%)	15 (6.6%)	
Age 40-65, n (%)	32 (39.5%)	70 (47.3%)	102 (44.5%)	0.31
Age >65, n (%)	45 (55.6%)	67 (45.3%)	112 (48.9%)	
Smokers, n (%)	11 (14.3%)	11 (8%)	22 (10.3%)	0.008
Comorbidities, median (IQR)	2 (1 - 4)	2 (1 - 3)	2 (1 - 3)	0.042
Major comorbidities, n (%)				
Lung (COPD)	7 (8.6%)	14 (9.5%)	21 (9.2%)	1
Lung (interstitial)	7 (8.6%)	20 (13.7%)	27 (11.9%)	0.292
Lung (other)	7 (9.2%)	14 (10.3%)	21 (9.9%)	1
Hypertension	42 (51.9%)	61 (41.2%)	103 (45%)	0.129
Obesity (BMI>30)	12 (15.4%)	19 (13.3%)	31 (14%)	0.688
Cardiovascular	28 (35%)	22 (15.1%)	50 (22.1%)	0.001
Diabetes	13 (16%)	15 (10.1%)	28 (12.2%)	0.21
RMD, n (%)				
Rheumatoid arthritis	26 (31.3%)	53 (35.6%)	79 (34.1%)	0.61
Spondyloarthritis	34 (41%)	27 (18.1%)	61 (26.3%)	<0.001
Connective tissue disease	6 (7.2%)	43 (28.9%)	49 (21.1%)	<0.001
Vasculitis	8 (9.6%)	18 (12.1%)	26 (11.2%)	0.728
Other	9 (10.8%)	8 (5.4%)	17 (7.3%)	0.204
Disease activity, n (%)				
Remission	29 (34.9%)	42 (28.2%)	71 (30.6%)	
Low	43 (51.8%)	78 (52.3%)	121 (52.2%)	
Moderate	9 (10.8%)	23 (15.4%)	32 (13.8%)	0.614
Severe	2 (2.4%)	6 (4%)	8 (3.4%)	
Functional disability, n (%)				
None	26 (31.7%)	41 (27.7%)	67 (29.1%)	
Mild	39 (47.6%)	74 (50%)	113 (49.1%)	
Moderate	14 (17.1%)	25 (16.9%)	39 (17%)	0.894
Severe	3 (3.7%)	8 (5.4%)	11 (4.8%)	
RMD treatment, n (%)				
Hydroxychloroquine	9 (10.8%)	34 (22.8%)	43 (18.5%)	0.038
Glucocorticoids	42 (50.6%)	78 (52.3%)	120 (51.7%)	0.906
cDMARDs	43 (51.8%)	54 (36.2%)	97 (41.8%)	0.03
Immunosuppressants	6 (7.2%)	19 (12.8%)	25 (10.8%)	0.28
bDMARDs				
TNF-i	26 (31.3%)	29 (19.5%)	55 (23.7%)	0.061
Tocilizumab	0 (0%)	3 (2%)	3 (1.3%)	0.555
Sarilumab	0 (0%)	2 (1.3%)	2 (0.9%)	0.538
Abatacept	1 (1.2%)	4 (2.7%)	5 (2.2%)	0.657
Rituximab	2 (2.4%)	4 (2.7%)	6 (2.6%)	1
Belimumab	0 (0%)	2 (1.3%)	2 (0.9%)	0.538
Other bDMARDs	3 (3.6%)	4 (2.7%)	7 (3%)	0.703
ts-DMARDs				
Baricitinib	0 (0%)	4 (2.7%)	4 (1.7%)	0.3
Tofacitinib	0 (0%)	4 (2.7%)	4 (1.7%)	0.3
Apremilast	1 (1.2%)	0 (0%)	1 (0.4%)	0.358

cs: conventional synthetic; b: biologic; ts: targeted-synthetic; DMARD: disease-modifying anti-rheumatic drugs; SD: standard deviation; IQR: inter-quartile range.

Results

On June 3rd 2020, 232 patients with RMD and confirmed SARS-CoV-2

infection were registered in the CONTROL-19 database.

General and RMD characteristics

The general and RMD clinical characteristics of the included patients are reported in Table I.

The male to female ratio was ~1:2; about half of the patients were over, 65 years of age and suffered from multimorbidity, as more than 50% of the overall sample had at least two comorbid conditions beyond RMD.

Among different comorbidities, 26% of patients showed lung disease.

Most of the patients (60.4%) suffered from chronic inflammatory arthritis and 32.3% from systemic autoimmune diseases, such as connective tissue disease or vasculitis.

The majority of patients showed an active disease and functional impairment; in particular, 17.2% of patients had a moderate or severe activity, and 21.8% had a moderate or severe functional disability.

Most patients were on conventional synthetic (cs)-DMARDs or immunosuppressants (52.6%), such as azathioprine, cyclophosphamide, mycophenolate, cyclosporin or tacrolimus; more than one third on targeted synthetic (ts)- or biologic (b)-DMARDs (36.6%), whilst more than half patients were on corticosteroids (55.2%). The average dose of prednisone equivalent per day was 7.9 mg (SD 8.8).

When comparing general and RMD characteristics between male and female patients, male patients showed an older mean age, manifested a higher comorbidity burden – particularly cardiovascular diseases – and a greater frequency of current smokers than females (14.5% *vs*. 7.4%). Males also presented a different distribution of RMD diagnoses associated treatments, when compared to females.

COVID-19 characteristics and outcome

The typical clinical presentation of COVID-19 in RMD patients included systemic features, such as fever, asthenia, and respiratory symptoms (cough, dyspnea, and tachypnoea). Musculoskeletal symptoms ranged from 42.2% for myalgia to 28.2% for arthralgia. Table II reports the frequency of the clinical features in descending order.

A high proportion of patients were diagnosed with pneumonia (64.1%), with high-resolution computerised tomography showing ground-glass opacities (71.4%). Among the severe respira-

Table II. COVID-19 characteristics in RMDs.

	Male (n=83)	Female (n=149)	Total (n=232)	*p*-value
Clinical features, n (%)				
Fever	75 (90.4%)	124 (84.4%)	199 (86.5%)	0.232
Asthenia/Fatigue	61 (77.2%)	110 (76.9%)	171 (77%)	1
Cough	55 (67.9%)	81 (56.2%)	136 (60.4%)	0.091
Dyspnoea	50 (60.2%)	79 (55.2%)	129 (57.1%)	0.489
Myalgia	26 (33.8%)	66 (46.8%)	92 (42.2%)	0.085
Tachypnoea	29 (38.2%)	42 (30.4%)	71 (33.2%)	0.289
Joint pain	15 (19.5%)	47 (32.9%)	62 (28.2%)	0.041
Dysgeusia	14 (23%)	36 (31.9%)	50 (28.7%)	0.292
Anosmia	10 (16.4%)	33 (28.9%)	43 (24.6%)	0.096
Diarrhoea	11 (13.9%)	40 (28.8%)	51 (23.4%)	0.013
Headache	14 (18.9%)	35 (25.5%)	49 (23.2%)	0.309
Nausea/vomiting	9 (11.8%)	31 (22.1%)	40 (18.5%)	0.069
Nasal congestion	10 (13.5%)	28 (21.2%)	38 (18.4%)	0.194
Sore throat	10 (13.3%)	30 (22.4%)	40 (19.1%)	0.142
Chest pain	10 (13.2%)	20 (14.3%)	30 (13.9%)	1
Abdominal pain	7 (9%)	20 (14.3%)	27 (12.4%)	0.29
Irritability	9 (12.2%)	17 (12.6%)	26 (12.4%)	1
Conjunctivitis	5 (6.7%)	8 (5.9%)	13 (6.2%)	0.775
Complications, n (%)				
Pneumonia	57 (73.1%)	84 (59.2%)	141 (64.1%)	0.041
Serious acute respiratory failure	16 (20.8%)	36 (24.8%)	52 (23.4%)	0.618
Secondary infection	13 (17.6%)	18 (13.7%)	31 (15.1%)	0.543
ARDS	10 (12.8%)	16 (11.3%)	26 (11.9%)	0.828
Macrophage activation syndrome	6 (8%)	8 (6.2%)	14 (6.9%)	0.775
Sepsis	2 (2.7%)	11 (8.4%)	13 (6.3%)	0.14
COVID treatment				
Oxygen	55 (67.1%)	72 (49.3%)	127 (55.7%)	0.014
Antiviral	48 (60%)	55 (38.5%)	103 (46.2%)	0.003
Hydroxychloroquine	53 (66.2%)	80 (55.2%)	133 (59.1%)	0.14
Tocilizumab	6 (7.8%)	13 (9.4%)	19 (8.8%)	0.891
Outcomes				
Hospitalisation, n (%)	67 (80.7%)	95 (63.8%)	162 (69.8%)	0.011
Non-invasive ventilation	17 (21.5%)	30 (20.5%)	47 (20.9%)	1
Mechanical ventilation*	6 (7.6%)	11 (7.5%)	17 (7.5%)	1
Death*	20 (24.1%)	24 (16.1%)	44 (19%)	0.266
Combined outcome**	22 (26.8%)	27 (18.1%)	49 (21.2%)	0.167

Table III. Rheumatic disease medications prior to COVID-19 diagnosis and risk of ICU/mechanical ventilation or death.

	Crude OR [95% CI]		Adjusted§ OR [95% CI]	
No DMARD	reference		reference	
b/ts DMARD only	0.29[0.09-0.87]	0.031	0.50[0.13-1.81]	0.298
cs-DMARD only	0.54[0.22-1.37]	0.188	0.62[0.20-1.97]	0.419
b/ts DMARD + cs-DMARD	0.59[0.19-1.74]	0.342	0.97[0.22-4.22]	0.970
Hydroxychloroquine	1.16[0.50-2.48]	0.716		
NSAIDs	0.57[0.19-1.46]	0.278		
No prednisone	reference		reference	
prednisone 1-9 mg/day	3.05[1.50-6.45]	0.003	1.73[0.68-4.43]	0.244
prednisone >10 mg/day	2.45[0.78-7.06]	0.107	1.60[0.40-5.86]	0.488

cs: conventional synthetic; b: biologic; ts: targeted-synthetic; DMARDs: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence intervals; § adjusted for sex, age >65, comorbidities (hypertension or cardiovascular disease, lung disease, diabetes).

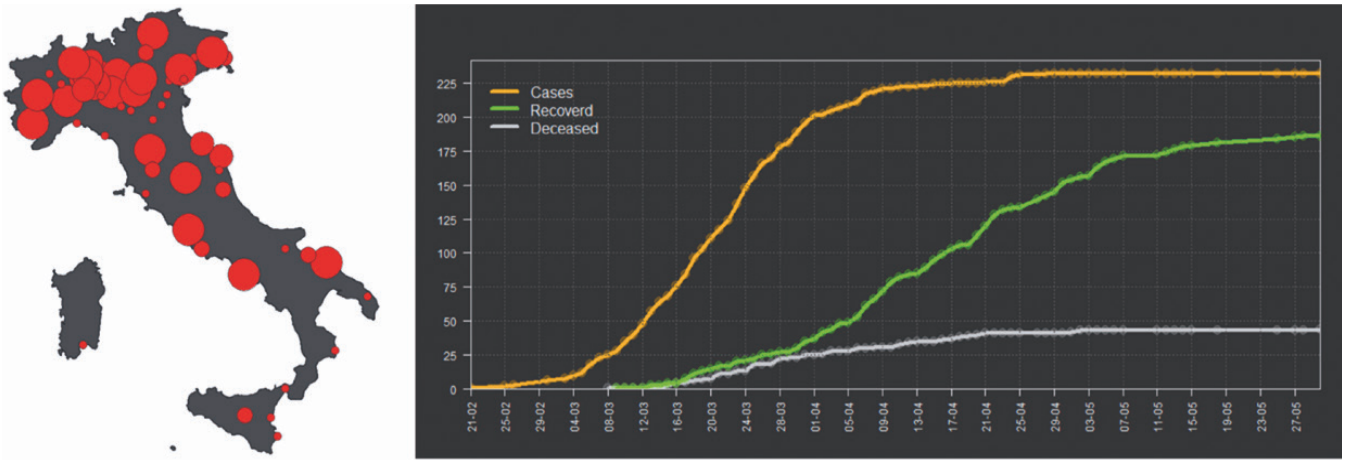

Fig. 1. Geographical and temporal distribution of the first 232 COVID-19 cases in the CONTROL-19 registry.

tory complications, severe acute respiratory illness and ARDS, respectively involved 23.4% and 11.9% of patients.
The majority of patients required hospitalisation (69.8%), and many of them respiratory support: oxygen (79.2%), non-invasive ventilation (30.3%) or mechanical ventilation (10.9%). In addition to supportive care (antibiotics, antipyretics, corticosteroids, and low-molecular-weight heparin), both non-specific anti-viral therapy (48.7%) and immunomodulating drugs (hydroxychloroquine, 61.8%, and tocilizumab, 10.1%) were extensively used.
The outcome of COVID-19 was generally severe in the included population, with 19% of death and 21.2% of the combined outcome ICU/mechanical ventilation or death.
By comparing COVID-19 characteristics and outcomes between male and female patients, male patients had a higher proportion of pneumonia and hospitalisation.

RMD treatment and COVID-19 outcome

The association of the exposure to tretments for RMD and the risk of ICU/mechanical ventilation or death was explored in univariate and multivariable adjusted analyses (Table III).
Compared to patients with no exposure to any DMARD, patients on b-/ts-DMARDs monotherapy showed a lower risk of adverse outcome, while prednisone users showed an increased risk. After adjusting for age, gender and comorbidities both treatments did not resulted significantly associated with the outcome.

COVID-19 course and distribution

The time course and the geographical distribution of the cases are reported in Figure 1.

Discussion

Italy was one of the world countries where the COVID-19 was first noted and manifested with the most dramatic effects. Since the first weeks of the epidemic, SIR has launched a retrospective and anonymous data collection to monitor COVID-19 in RMD patients. This initiative was coordinated with other initiatives at a European and global level to promptly accumulate knowledge as well as inform intervention development and implementation in patients with RMD (12).
The Italian CONTROL-19 registry was mainly based on the SIR's national network of rheumatologists, who guaranteed a widespread national coverage; this preliminary analysis supports the validity of this initiative.
Nonetheless, several aspects should be considered in the interpretation of the report. Firstly, this preliminary analysis included only patients with a molecular diagnosis of SARS-CoV-2 infection. This selection criterion allowed only the inclusion of the ascertained cases, which made the register comparable with the official data that applied the same time horizon; however, the sample was greatly enriched with severe cases, because most of the diagnoses made through nasopharyngeal swab were carried out in a hospital setting, as recommended by Italian health authorities.
The structure of the sample in the Italian register, when compared with the first 110 published cases of the global register (which did not yet include the Italian cases), showed a general greater severity of the Italian cases than the other ones (12). In particular, in the CONTROL-19 register, we found higher frequencies of male patients (36% *vs*. 28%), over-65 patients (48.9 *vs*. 20%), hospitalisation (69.8% *vs*. 35%), steroid therapy (52% *vs*. 25%), and unfavourable outcome (death 21.2% *vs*. 5%).
Even comparing the sample of patients in the CONTROL-19 registry with the first Chinese series, some differences can be noted. Although in the Chinese sample the proportion of hospitalised patients was greater than 90% (*vs*. 69% of the first 232 cases from the CONTROL-19), the patients of the Italian registry had a higher median age (64 *vs*. 47 years) and a more significant prevalence of multi-morbidity. The characteristics of COVID-19 of RMD patients of the CONTROL-19 registry were very similar to the subgroup of patients with a disease defined as 'severe' in the Chinese cohort; although these differences may be primarily related to the different structure for sex, age and pre-existing comorbidities, these preliminary results would suggest a unfavourable progress of the SARS-CoV-2 infection in patients with autoimmune diseases (14, 15).

Our study reported for the first time the impact of pre-existing immunosuppressive treatment in RMD patients on the risk of severe adverse outcome, including ICU/mechanical ventilation or death. In keeping with other results assessing prognostic factors of hospitalisation in COVID-19 RMD patients (11), these preliminary results support a general safety of immunosuppressive treatments including both b-DMARDs and ts-DMARDs, even adjusting for potential confounding.

The temporal and geographical distribution of the sample of RMD patients in the CONTROL-19 registry reflects that of the Italian population reported by official sources (16). Although the data collection is done on a voluntary basis, this result reinforces the validity and the representativeness of the register at a national level as well as the strength of the national rheumatological network. Nevertheless, a more valid and precise estimate of the real frequency and severity of COVID-19 in RMD will be better estimated upon the acquisition of less severe cases, which escaped in the initial identification.

By comparing males and females, the sub-population of males was enriched by subjects with a higher rate of comorbidity, in particular cardiovascular disease. These characteristics are reported among the main risk factors for an unfavourable outcome of COVID-19 (3). As expected, when compared to the female counterpart, male subjects displayed a marginally greater frequency of unfavourable outcomes; for example, male patients had higher hospitalisation and death rates than female patients.

Overall, this first report of the Italian registry of SARS-CoV-2 infection in RMDs (CONTROL-19) demonstrates the validity of a voluntary-based national system of surveillance in mapping the epidemic course of COVID-19 in Italy. This registry together with the COVID-19 Global Rheumatology Alliance (10) will be able to provide evidence of the incidence of COVID-19 in the RMD population compared to the general population; it will also contribute to identify specific risk factors and assess the effects of the anti-rheumatic treatments on the susceptibility and severity of the infection with SARS-CoV-2.

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