Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Disease course in patients with systemic autoimmune diseases: insights on the safety of immunosuppression during the SARS-CoV-2 outbreak in Italy

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Dear Editor,

From December 2019 the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for the Coronavirus Disease 2019 (COVID-19), has caused a pandemic, with over 28 million cases and more than 900.00 fatalities reported worldwide so far [1].

The Marche Region was one of the areas with the highest incidence in Italy, with the first case being reported on February 25th, 2020 [2]. Thereafter, the outbreak peaked as expected after lockdown measures were taken countrywide. A total of 6723 cases were confirmed (as of May 29th), within a total population of 1.525.271 inhabitants [3].

Patients with systemic autoimmune diseases are considered to be at higher risk of developing severe disease because of the risk of infection due to the immunosuppressive treatments [4,5], though many of such treatments have also been investigated for the treatment of COVID-19 [6].

In this work, we report the experience of our tertiary referral center, located in central Italy, during the epidemic of SARS-CoV-2, focusing on the incidence and severity of COVID-19 in a large cohort of patients with systemic autoimmune diseases treated with several immunosuppressive drugs.

A cross-sectional standardized survey including adult patients with systemic autoimmune diseases followed at our tertiary referral center at "Azienda Ospedaliero-Universitaria Umberto I-G.M.Lancisi-G.Salesi", Ancona, Italy has been conducted from May 1st to May 29th. Patients were directly contacted by phone call by the medical personnel, considering that the restrictions to mobility had not been completely dismissed and the admission to the hospital was restricted. Patients were asked to report their health status, with particular regard to the underlying autoimmune disease, their ongoing pharmacological treatments, the presence of symptoms suggesting SARS-CoV-2 infection (from February 14th to date), the working status and the close contacts with infected people and/or relatives. Thereafter, at the end of the lockdown, all the patients have been clinically re-evaluated.

Continuous variables are presented as median (1st-3rd quartiles) and categorical variables as number (%).

All the patients gave oral informed consent to this investigation. The study was carried out in compliance with the Declaration of Helsinki on ethical principles for medical research.

A total of 326 patients with systemic autoimmune diseases were contacted by phone call and 305 (93.5%) answered the call and/or accepted to participate in this survey. Patients' characteristics are described in Table 1.

Most of the patients were women (67.8%), and most of the whole cohort (93%) had inflammatory arthritis: rheumatoid arthritis (RA) n. 43, psoriatic arthritis (PsA) n. 168, spondyloarthritis n. 71, undifferentiated arthritis n. 9), and 7% other connective tissue diseases (vasculitis, SLE).

Among them, at the time of the survey, 72.6% of the patients were taking a biologic DMARD (bDMARD), 88% in monotherapy, and 38.4% a conventional synthetic DMARD (cDMARD; methotrexate, sulphasalazine, hydroxychloroquine) (Table 1).

With regard to comorbidities, 62.7% of the patients had cardiovascular diseases and 10.5% diabetes.

Over the period of the first outbreak in this region of Italy, in our cohort a total of 10 (3.3%) patients reported symptoms suggestive of COVID-19, upon evaluation by the general practitioner. The most common symptoms were fever (80%), shortness of breath (50%), cough (40%), malaise (30%), and diarrhea (20%). Symptoms were generally mild and none of the patients without confirmed COVID-19 had to be hospitalized for severe disease.

Among symptomatic patients, 4 (40%) underwent nasopharyngeal swab and 2 (0.65%%) resulted positive for SARS-CoV-2 and developed COVID-19, an incidence comparable to that reported in the general population of the Marche region (0.53%).

Of the two patients with confirmed COVID-19, one was a 51-year-old overweight male with psoriatic arthritis (PsA) treated with apremilast, working as a nurse. His comorbidities were hypertension and diabetes. He developed fever, shortness of breath, cough, malaise, joint and muscle pain, anosmia and ageusia. These symptoms resolved without treatment within 10 days, and the nasopharyngeal swab was negative after 42 days from the first one.

The second case was a 59-year-old woman with PsA treated with adalimumab. She worked as a cook and had no history of cardiovascular

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Table 1
Baseline characteristics of the patients.

	N = 307
Sex (female), n (%)	207 (67.86)
Age (years), median (1st- 3rd quartiles)	60 (50-71)
BMI (kg/m2), median (1st-3rd quartiles)	25.9 (23.0-29.4)
Autoimmune diseases, n (%)	
Psoriatic arthritis	168 (55.1)
Spondyloarthritis*	71 (23.3)
Rheumatoid arthritis	43 (14.1)
Undifferentiated oligo-arthritis	9 (2.8)
Vasculitis°	10 (3.3)
Connective tissue disease#	4 (1.3)
Duration of disease (years), median (1st- 3rd quartiles)	3 (2-9)
Ongoing treatments, n (%)	
Secukinumab	58
Adalimumab	48
Apremilast	27
Methotrexate	22
Ustekinumab	20
Etanercept	14
Certolizumab pegol	13
Tocilizumab	6
Baricitinib	9
Infliximab	6
Risankizumab	5
Ixekizumab	6
Golimumab	4
Tofacitinib	3
Sulphasalazine	3
Hydroxychloroquine	3
Guselkumab	2
Vedolizumab	2
Abatacept	1
Rituximab	2
Duration of treatment (months), median (1st- 3rd quartiles)	12 (6 – 24)
Comorbidities, n (%)	
Hypertension	116 (42)
Cardiovascular disease	57 (20.6)
Diabetes	29 (10.5)
Malignancy	19 (7)
COPD	11 (4)
Current tobacco use, n (%)	44 (16)

* i.e. ankylosing spondylitis, non-radiographic spondyloarthritis, inflammatory-bowel disease associated spondyloarthritis.
° i.e. giant-cell arteritis, aortitis, retroperitoneal fibrosis.
i.e. systemic lupus erythematosus and undifferentiated connective tissue disease.

disease. She developed fever, shortness of breath and headache. At the admission to the hospital for interstitial pneumonia adalimumab was discontinued and she was treated with corticosteroids and azithromycin. The hospital course was without complications and she was discharged after 10 days. Importantly, PsA did not relapse during the course of COVID-19, but the patient reported joint symptoms after 2 months of discontinuation of adalimumab.

Among all patients, almost all (97.4%) of those receiving corticosteroids, c- or b-DMARDs continued their treatment without modifying the dose and the autoimmune disease remained stable without significant flares. Conversely, of the eight (2.6%) patients that modified or interrupted the treatment by their initiative, four (50%) experienced a relapse of the autoimmune disease (1 RA, 1 axial spondyloarthritis, 2 PsA) by the time of the survey.

At the beginning of the outbreak, patients with systemic autoimmune disease receiving immunosuppressive therapy were considered at higher risk and it was uncertain whether these treatments should have been continued or not during the pandemic.

As a growing number of studies reported a beneficial effect of drugs that are commonly used in rheumatology, as IL-6 inhibitors, it became clear that the immune system played a major role in the pathogenesis of severe COVID-19 [6]. Subsequently, scientific societies such as EULAR issued recommendations to provide guidance and secure a common behavior across specialists of all countries [7].

In this study, we investigated the frequency and characteristics of COVID-19 in a cohort of patients treated with s/bDMARDs in one of the regions in which the first epidemic outbreak was more severe, as the Marche region (Italy).

During the 3-month outbreak, a low proportion of patients with systemic autoimmune diseases treated with b- or c-DMARDs reported symptoms suggestive of COVID-19, and among them only two (0.65%) had confirmed COVID-19. One patient had to be admitted to the hospital for mild interstitial pneumonia, but she recovered without complications.

The incidence and favorable course of COVID-19 in our cohort of patients with autoimmune diseases are comparable to that observed in other Italian regions [8–10], and similar to those of the general population.

Following the EULAR recommendations, we did not recommend to discontinue or modify the dose of both conventional and biologic DMARDs and we did not observe an increased susceptibility to COVID-19 or a worse outcome in the two confirmed cases. Patients that continued the DMARDs, including those complaining respiratory symptoms, did not experience a more severe course of the intercurrent infection or a flare of the rheumatologic disease. Conversely, half of the patients that spontaneously modified their treatment, as well as one patient that stopped therapy because of COVID-19, experienced a disease relapse.

These observations support the hypothesis that DMARDs do not increase the risk of SARS-CoV-2 infection and that they should not be discontinued.

There are several limitations in this cross-sectional survey administered by phone call, but patients were assessed immediately after the peak of the Italian epidemic. Additionally, as we were not able to contact all the patients, COVID-19 cases could be potentially underestimated.

In conclusion, herein we reported that, in a large cohort of patients affected by several inflammatory rheumatic diseases, the use of biological or targeted synthetic drugs was safe during the COVID-19 epidemic in the Marche region of central Italy and that continuing the immunosuppressive treatment is important to maintain efficacy and avoid flare-ups.

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Declaration of Competing Interest

None declared.

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