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BRIEF REPORT

Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data?

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Objective. To describe the incidence and severity of coronavirus disease 2019 (COVID-19) in patients with rheumatic diseases treated with targeted synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) compared with that in the general population living in the same Italian region.

Methods. Patients followed up at 2 rheumatology referral centers in Lombardy from February 25, 2020 to April 10, 2020 were invited to participate in a survey designed to identify patients who had confirmed COVID-19, close contact with others with confirmed COVID-19, or symptoms of the infection, and to detect changes in work, behavior, and disease management made in an attempt to prevent infection. The incidence of COVID-19 in the Lombardy population was obtained from the National Institute of Statistics. COVID-19 cases were confirmed by nasopharyngeal swab.

Results. The survey was given to 955 patients (531 patients with rheumatoid arthritis, 203 patients with psoriatic arthritis, 181 patients with spondyloarthritis, and 40 patients with connective tissue diseases, vasculitides, or autoinflammatory diseases). These patients had a mean age of 53.7 years, and 67.4% were women. The rate of response to the survey was 98.05%, and the incidence of confirmed COVID-19 cases was consistent with that in the general population (0.62% versus 0.66%; $P = 0.92$). None of the patients had severe complications or required intensive care treatment, and all of the patients who tested positive for COVID-19 temporarily discontinued ongoing targeted synthetic drug or biologic DMARD therapy. Almost all patients took precautions to prevent the COVID-19 infection (90.6%), and almost all continued treatment with targeted synthetic drugs or biologic DMARDs (93.2%). Disease activity remained stable in 89.5% of patients.

Conclusion. Our results reflected the attitude of patients with rheumatic diseases regarding the prevention of the infection while maintaining their long-term treatment regimens. The incidence and severity of COVID-19 in patients treated with targeted synthetic drugs or biologic DMARDs was not significantly different from that in the general population in the same region.

INTRODUCTION

The outbreak of an epidemic caused by a new coronavirus of animal origin called severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) in China in December 2019 quickly became a global health emergency declared a pandemic by the World Health Organization (1). The disease generated by SARS–CoV-2, coronavirus disease 2019 (COVID-19), is mainly a respiratory infection ranging from asymptomatic or oligosymptomatic cases to severe and life-threatening forms of interstitial pneumonia, which can develop into acute respiratory distress syndrome (ARDS) and even death (2). Pathogenetically, ARDS is accompanied by a massive immune response characterized by the release of enormous amounts of proinflammatory mediators such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF), known as cytokine storm syndrome (3).

Along with the escalation of the worldwide health emergency, there has been an increasing need to clarify the incidence

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and course of COVID-19 in immunosuppressed patients with rheumatic disease in order to optimize disease management strategy. In fact, many chronic immune-mediated inflammatory diseases are characterized by an overall intrinsic increase in the risk of infectious disease, specifically viral infections such as influenza (4). Interestingly, this risk tends to increase proportionally to the degree of disease activity and is minimal in patients with disease in sustained remission (5). However, use of either conventional or targeted disease-modifying antirheumatic drugs (DMARDs) may be an additional iatrogenic risk factor, although many of these drugs are currently being tested as potential treatments for COVID-19–induced cytokine storm syndrome (6). To date, data on the epidemiology of COVID-19 in rheumatic disease populations are very scarce. For this reason, we have conducted a multicenter, observational study to assess the incidence, the clinical course, and the predictive factors of SARS–CoV-2 infection in a cohort of patients receiving biologic agents for rheumatic diseases managed by 2 rheumatology units located in Lombardy, the main epicenter of the COVID-19 outbreak in Italy. The incidence of COVID-19 observed in our cohort of patients who live in Lombardy was also compared with the data recorded in the overall Lombardy population. The secondary objective of the study was to assess the impact of COVID-19 on this population of patients in terms of changes in behavior and work patterns made to prevent infection.

PATIENTS AND METHODS

Study population. The study included patients age >18 years with rheumatic disease, who had a follow-up visit scheduled between February 25 and April 10, 2020 at the outpatient clinic of the Division of Clinical Rheumatology at the ASST Gaetano Pini-CTO Institute in Milan or in the Rheumatology Department of Policlinico San Matteo in Pavia. The current analysis is part of a study to collect observational data from patients with rheumatic diseases who were followed up at these 2 rheumatology units. The study was approved by the ethics committee at the Gaetano Pini-CTO Institute (approval no. 141/2010) and by the ethics committee in the Rheumatology Department of Policlinico San Matteo (approval no. 31748/2009). All patients provided written informed consent.

The final analysis was limited to patients living in the Lombardy region who had been treated with targeted biologic DMARDs or synthetic DMARDs for at least 6 months. The control group was the overall adult population (age >18 years) of the Lombardy region, stratified by provinces according to data from the National Institute of Statistics (https://www.istat.it). The same period of evaluation (between February 25 and April 10, 2020) was considered for the calculation of COVID-19 incidence in the Lombardy population. Patients were considered to have been in contact with a confirmed case of COVID-19 if the contact occurred over a prolonged period of time or if the patient was in cohabitation with the confirmed case.

Statistical analysis. A survey was designed to investigate the impact of COVID-19 on the study population (Supplementary Methods, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41388/abstract). The survey comprised 2 separate sections, one completed by the rheumatologist and the other by the patient. The first part of the questionnaire evaluated the diagnosis and demographic characteristics of the patient, the ongoing treatment (for both rheumatic and nonrheumatic disease), the presence of comorbidities, and the degree of disease activity (measured by specific composite indices for the different rheumatic disorders, where applicable). The second section of the questionnaire investigated the reported symptoms suggesting viral infection, the eventual confirmed diagnosis of COVID-19 formulated by nasopharyngeal swab, the patient's contacts with subjects diagnosed as having COVID-19, adherence to ongoing antirheumatic therapy, any information received by the patient about COVID-19 from different sources, any precautions taken to prevent infection, and the impact of the COVID-19 outbreak on the underlying disease and on work activity.

All questions in the second part of the survey referred to activity in the 14 days prior to administration of the survey (since 14 days was the length of the COVID-19 incubation period established by the Italian health authorities). The survey was administered to all patients followed up at the 2 participating centers' biological outpatient clinics, either face-to-face during each visit or by telephone for patients who missed a scheduled visit during the reporting period. In order to compare the incidence of COVID-19 with that in the general population, only patients living in the Lombardy region were selected from the overall study cohort. The data in this subgroup were compared with the official number of subjects who tested positive for COVID-19 on nasopharyngeal swab in the overall population living in Lombardy during the same evaluation period (https://www.regione.lombardia.it/wps/portal/istituzionale/).

Descriptive statistics, including the mean ± SD and the median and interquartile range, were calculated. Statistical analyses were performed using SPSS version 20.0. *P* values less than or equal to 0.05 were considered significant.

RESULTS

Clinical characteristics of the study participants. During the study period, 1,225 patients were surveyed. The rate of nonresponders was 1.95% and among them, the vast majority (21 of 24 [87.5%]) could not be reached directly for a telephone interview but were confirmed to be alive and without signs of infection by a relative. These patients were not included in the final study population. After selecting only patients who were currently being treated with targeted synthetic or biologic DMARDs and living in the Lombardy region, the final study population included 955 patients, 67.4% of whom were female (Figure 1). The demographic, clinical, and treatment characteristics of these patients are detailed in

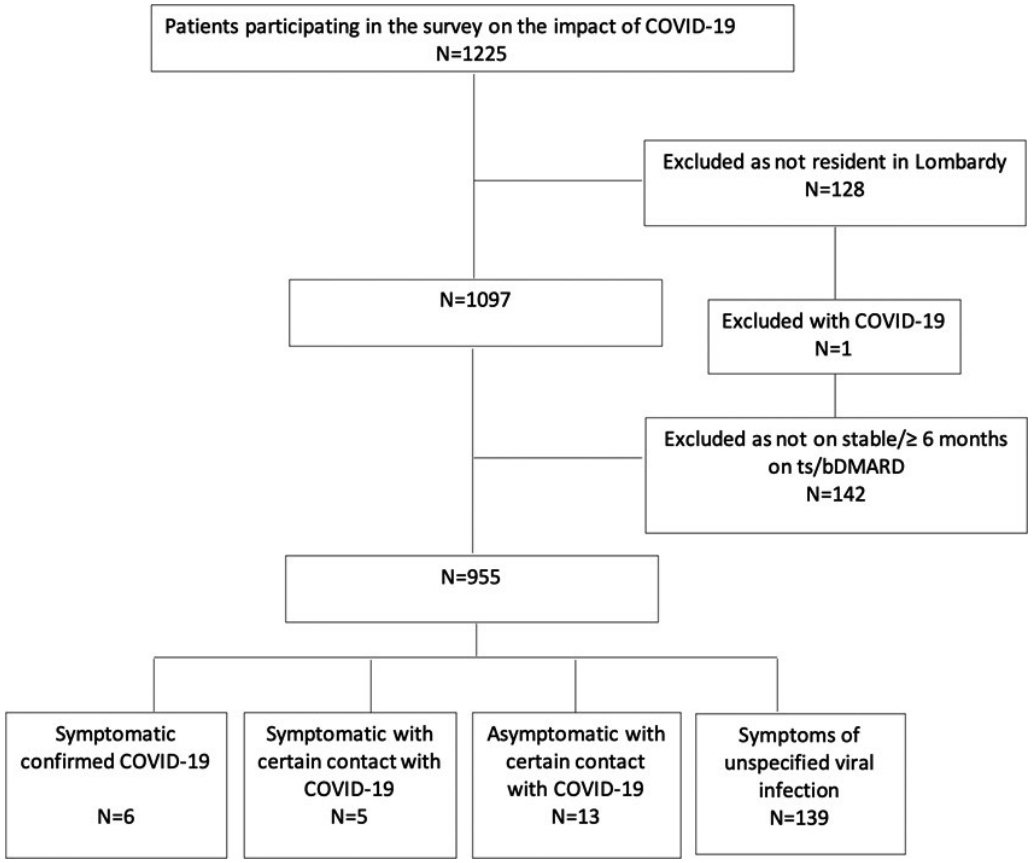

Figure 1. Flow chart showing the disposition of the study patients included in the final analysis of the impact of coronavirus disease 2019 (COVID-19) on patients with rheumatic diseases treated with targeted synthetic or biologic disease-modifying antirheumatic drugs (ts/bDMARDs).

Table 1. Briefly, the majority of the patients (95.8%) were diagnosed as having inflammatory arthritis (531 with rheumatoid arthritis [RA], 203 with psoriatic arthritis [PsA], and 181 with spondyloarthritis [SpA]), 1.8% of the patients were diagnosed as having connective tissue diseases (13 with systemic lupus erythematosus, 3 with systemic sclerosis, and 2 with Sjögren's syndrome), and 2.5% of the patients were diagnosed as having other diseases (6 with Behçet's disease, 3 with giant cell arteritis, 1 with sarcoidosis, 3 with adult-onset Still's disease, 5 with juvenile idiopathic arthritis, and 4 with autoinflammatory diseases). The mean ± SD age of the participants was 53.7 ± 14 years, and the mean ± SD disease duration was 13.9 ± 9.9 years. The majority of the patients were receiving anti–tumor necrosis factor (anti-TNF) therapy (55.8%). The remaining population was treated with abatacept (11.8%), interleukin-6 (IL-6) inhibitors (10.3%), targeted synthetic DMARDs (10.1%), secukinumab (4.7%), rituxumab (1.7%), ustekinumab (1.5%), and belimumab (1.3%) (Table 1).

Approximately half of the patients (47.3%) received biologic DMARDs as monotherapy. More than 43% of patients had at least 1 comorbidity, especially high blood pressure (20.2%). The background general population included 8,687,083 people age >18 years living in Lombardy. These residents had a mean age of 51.4 years, and 51.1% were female (7).

Incidence of COVID-19 and clinical course and characteristics of confirmed COVID-19 cases. In our cohort, we observed 6 cases of COVID-19 confirmed by nasopharyngeal swab, including 3 patients with RA, 2 patients with SpA, and 1 patient with sarcoidosis. Five of these patients were treated with anti-TNF agents (3 with etanercept, 1 with adalimumab, and 1 with infliximab), and 1 patient was treated with abatacept. Only 2 patients received biologic DMARDs as monotherapy, whereas 4 patients were concomitantly treated with methotrexate (n = 2), leflunomide (n = 1), or sulfasalazine (n = 1); 2 patients were also treated with hydroxychloroquine. Three patients were smokers, and 4 had comorbidities (3 had hypertension). None of the patients developed severe respiratory involvement or died. Only 3 patients (ages 26, 56, and 65 years) required hospitalization with low-flow oxygen supplementation, and no patient was admitted to an intensive care unit. All patients who were diagnosed as having COVID-19 temporarily discontinued treatment with conventional synthetic DMARDs or biologic DMARDs, with the exception of hydroxychloroquine. Only 2 of them reported a relapse of rheumatic disease.

The incidence of confirmed COVID-19 cases observed in our cohort (0.62%; 95% confidence interval 0.25–1.4%) was consistent with that expected in the general population of Lombardy

Table 1. Demographic, clinical, and treatment characteristics of the study population*

	Rheumatoid arthritis (n = 531)	Psoriatic arthritis (n = 203)	Spondyloarthritis (n = 181)	Other diagnoses (n = 40)†
Age, mean ± SD years	58 ± 13	52 ± 12	47 ± 13	54 ± 14
Female, no. (%)	429 (45)	104 (51)	78 (43)	32 (34)
Disease duration, mean ± SD years	15 ± 10	12 ± 9	12 ± 9	14 ± 10
Antirheumatic treatment				
Biologic DMARDs, no. (%)	462 (48)	176 (18)	181 (19)	38 (40)
Anti-TNF	230	134	158	11
Abatacept	113	0	0	0
IL-6 inhibitors	98	0	0	6
Anakinra	8	0	0	0
Rituximab	13	0	0	4
Secukinumab	0	25	20	0
Ustekinumab	0	13	1	0
Ixekizumab	0	4	2	0
Canakinumab	0	0	0	4
Belimumab	0	0	0	13
Targeted synthetic DMARDs, no. (%)	69 (7)	26 (3)	0	1 (0.1)
Baricitinib	49	0	0	1
Tofacitinib	20	0	0	0
Apremilast	0	26	0	0
Concomitant csDMARDs, no. (%)	338 (35)	98 (10)	46 (5)	21 (22)
Methotrexate	260	79	29	5
Leflunomide	27	2	0	0
Sulfasalazine	11	12	14	1
Hydroxychloroquine	34	1	2	11
Cyclosporine	6	4	0	0
Azathioprine	0	0	1	2
Mycophenolate	0	0	0	2
Low-dose glucocorticoids, no. (%)‡	201 (21)	27 (28)	18 (19)	24 (25)

* Except where indicated otherwise, values are the number of patients. DMARDs = disease-modifying antirheumatic drugs; anti-TNF = anti–tumor necrosis factor; IL-6 = interleukin-6; csDMARDs = conventional synthetic DMARDs.
† Other diagnoses included systemic lupus erythematosus (n = 13), systemic sclerosis (n = 3), Sjögren's syndrome (n = 2), Behçet's disease (n = 6), giant cell arteritis (n = 3), sarcoidosis (n = 1), adult-onset Still's disease (n = 3), juvenile idiopathic arthritis (n = 5), and autoinflammatory diseases (n = 4).
‡ Prednisone or equivalent <5 mg/day.

during the same period of observation (57,592 confirmed cases, incidence of 0.66%; $P = 0.92$). In our study, the infection occurred more frequently in women (4 of 6 cases), whereas in the healthy population, the opposite was observed, with infection seen more frequently in men (55%).

Clinically suspected cases of COVID-19. In addition to the 6 patients in whom COVID-19 was confirmed with nasopharyngeal swab, 144 patients developed respiratory symptoms similar to those seen in mild viral infection, but they had no access to nasopharyngeal swab. Of these patients, 5 (3 women with a mean age of 52.6 years) also reported having definite contact with swab-positive subjects; therefore, COVID-19 was highly suspected (although not confirmed) in these patients. Four of the patients in whom COVID-19 was highly suspected had a diagnosis of RA and 1 had a diagnosis of PsA. Of the 5 patients who reported having contact with swab-positive subjects, 2 were receiving anti-TNF, and 3 were receiving tofacitinib, tocilizumab, or secukinumab. Only 1 of these patients received hydroxychloroquine therapy. An additional 13 patients reported having contact with subjects who tested positive for COVID-19, but did not develop symptoms suggestive of infection. The proportion of patients treated with hydroxychloroquine was comparable between the group of patients who experienced respiratory symptoms (n = 18) and the group who did not (n = 82) (12.5% versus 10.1%, respectively; *P* not significant). Of the 144 patients who developed respiratory symptoms, 33 temporarily suspended biologic therapy, for an average of 16.9 days, based on self-decision (n = 9) or on the advice of a general practitioner (n = 11) or rheumatologist (n = 13). Of these patients, only 9 reported a disease relapse, while disease activity remained stable in the other 24 patients.

How do patients cope with COVID-19? Approximately one-third of patients (36%) reported having searched for information on how to manage their rheumatic disease in relation to the COVID-19 outbreak. The main source of information for patients was a rheumatologist (77.8%). Other sources were the internet (11.3%), a general practitioner (8.1%), another specialist physician (1.7%), or a pharmacist (1.1%).

Almost all patients (90.6%) took specific precautions to protect themselves against the epidemic, and 66.9% adhered strictly to the recommendations given by health authorities. Home

Table 2. Coping strategies of the 955 rheumatic disease patients during the early days of the COVID-19 pandemic*

Adherence to guidelines for the prevention of infection	866 (90)
Social distancing, no.	651
Home isolation, no.	439
Use of mask and/or gloves, no.	429
Modification of antirheumatic treatments	65 (6.8)
Targeted synthetic or biologic DMARDs	60 (5.8)
csDMARDs†	2 (0.4)
Glucocorticoids‡	3 (1.1)
Source consulted for medical advice during COVID-19	344 (36)
Rheumatologists	271 (28.4)
General practitioners	28 (2.9)
Pharmacists	4 (0.4)
Acquaintances/family members	2 (0.2)
Internet	39 (4)
Modification of work activity	387 (70.4)§
Temporary discontinuation	170 (30.9)
Reduction of work hours	66 (12)
Working remotely	146 (26.5)

* Except where indicated otherwise, values are the number (%). COVID-19 = coronavirus disease 2019.
† A total of 512 patients were receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).
‡ A total of 270 patients were receiving glucocorticoids.
§ Information regarding work activity was available for 550 patients.

isolation was adopted by 45.9% of patients, the use of face masks by 57.2% of patients, and social distancing by 68.1% of patients (Table 2). More than two-thirds of the subjects (70.4%) reported that the outbreak produced a shift in work activities to temporarily not working or remote working. Overall, only 6.8% of patients suspended or reduced the dosage of their current disease-modifying therapy; 2.7% of patients did so because of fear of infection and 4.1% did so because of the occurrence of symptoms suggestive of infection. The underlying disease remained stable in 89.5% of cases, improved in 5.1% of cases, and worsened very shortly after the occurrence of infection and the discontinuation of targeted synthetic or biologic DMARDs in only 5.4% of cases.

DISCUSSION

To our knowledge, this is the first detailed report on COVID-19 in a cohort of patients with rheumatic disease in a high pandemic area such as Lombardy. In this phase of extreme health emergency, we have shown that the incidence of COVID-19 confirmed with nasopharyngeal swab in patients treated with targeted synthetic DMARDs or biologic DMARDs is consistent with that in the general population in Lombardy. It is known that the risk of infection associated with all immune-mediated diseases is also increased in relation to the immunosuppressive therapy that is administered (7,8). For this reason, in this study, we investigated the frequency of COVID-19 in patients treated with targeted synthetic or biologic DMARDs, which comprise the pharmacologic class used to treat inflammatory arthritis currently assumed to produce the greatest proinfective iatrogenic effect (9). Our findings may be useful to optimize the management of complex disease during the ongoing pandemic and to support rheumatologists in encouraging patients to continue their long-term treatment regimens.

This study, to our knowledge, is the first to investigate in detail the impact of COVID-19 on rheumatic disease patients. Only a minority of patients have reduced or discontinued ongoing therapy with biologic or targeted synthetic DMARDs. This approach, in most cases, correctly occurred following the onset of suspicious symptoms due to possible infection, while cases of treatment withdrawal due to fear of infection were much less frequent. Good control of rheumatic disease was maintained in almost 90% of patients, and only 5% experienced a relapse. All of the patients who experienced a relapse experienced the disease flare after discontinuing ongoing therapy with targeted synthetic or biologic DMARDs (9 of 33 patients [27.3%]). This rate is certainly higher than expected, but it should be considered that these data are based on a subjective interpretation reported by the patient, and we cannot exclude the possibility that some of the musculoskeletal symptoms might have been related to the infection itself or to the limitations imposed by the lockdown rather than to a real persistent relapse of the underlying rheumatic disease.

Beyond the apparently reassuring absence of severe complications in patients receiving targeted synthetic or biologic DMARDs, this is also the result of the high adherence of our cohort to infection prevention standards, which have been adopted by >90% of the patients since the beginning of the epidemic. In particular, beginning March 9, 2020, health authorities imposed a lockdown in Lombardy, including compulsory measures such as social distancing, wearing face masks, and implementing remote working whenever possible. It is reasonable that the very fact of being affected by an immune-mediated disease treated with potentially immunosuppressive drugs has greatly influenced patients' propensity to wear masks, practice social distancing, and work remotely. Compared to the general population, this could certainly have been a protective factor with a possible role in containing the incidence of COVID-19 in our cohort.

One of the interesting aspects that emerged in the first months of the pandemic was the potential antiviral effect of chloroquine and hydroxychloroquine, which in vitro appear to be able to counteract the endocytosis of SARS–CoV-2 within alveolar epithelial cells (10). Both drugs are currently being evaluated in randomized clinical trials and have already been included in COVID-19 treatment protocols worldwide. Even though results from large randomized trials are needed to clarify the role of chloroquine and hydroxychloroquine in COVID-19, data from patients with rheumatic diseases, who often receive these drugs as long-term antirheumatic treatment, could provide some suggestions on their potential role in preventing the infection and in making its clinical course milder. In our cohort, confirmed COVID-19 and

respiratory symptoms of suspected COVID-19 were also observed in patients taking antimalarials, leaving the question of the actual preventive role of these products unanswered.

A possible limitation of the study inherent in the nature of a cross-sectional survey, which was administered in part by telephone, is the possibility of having missed patients who could not respond to the survey due to the infection (because they were hospitalized or had died). However, the rate of nonresponders in our analysis was very low (1.95%) and unlikely to significantly modify the overall results. It is reasonable that the high response rate to the survey may have been facilitated by the lockdown imposed by health authorities in Lombardy beginning March 9, 2020, as it was easier to contact patients confined at home. Among the few nonresponders, nearly all of the patients who did not respond directly to the survey were confirmed to be alive and without symptoms of infection by a relative who answered our phone call. These patients were not included in the study population, but their exclusion did not result in an underestimation of the COVID-19 frequency in our cohort.

Another potential limitation of our analysis is that we considered only those cases of COVID-19 confirmed by nasopharyngeal swab, excluding from the incidence calculation all those who had definite contact with subjects who were positive for COVID-19 or those who developed respiratory symptoms during the observation period. In view of the low number of patients who were positive for COVID-19 observed in our cohort, the incidence rate could be significantly modified by the inclusion of a few additional subjects with COVID-19 who were not swabbed. However, the same approach was also used to calculate the incidence of COVID-19 in the general population against which our sample was tested, thus making the comparative data homogeneous. Moreover, the incidence of COVID-19 among patients treated with targeted synthetic or biologic DMARDs was calculated from patients followed up at 2 referral centers for the management of these drugs and did not include cases occurring in other smaller rheumatologic centers in Lombardy. Nevertheless, since the study included a large number of patients who had several different diagnoses and were receiving different types of synthetic or biologic DMARDs, it is likely to provide an accurate picture of the infection in this type of rheumatic disease population. In addition, the aim of the study was to assess the risk of severe and life-threatening infections, which are usually diagnosed by positive real-time polymerase chain reaction for SARS–CoV-2 on nasopharyngeal swabs. It is conceivable that the number of patients who actually had COVID-19 was higher than we estimated, but importantly, all of our patients in whom COVID-19 was confirmed or highly suspected had a mild course of the infection, which in rare cases required hospitalization but not in the intensive care unit. Compared with the high number of hospitalized patients (>35,000) and deaths (10,511) observed in the Lombardy population due to COVID-19 in the same period (https://www.regione.lombardia.it/wps/portal/istituzionale/), our findings may be considered reassuring and are consistent with the previously cautiously optimistic observations from small monocentric case series (11–14). It is still unknown whether this result could possibly be related to the use of immunomodulating therapies that represent one of the main weapons currently used to contain the evolution of COVID-19 toward an ARDS generated by an immune-based hyperinflammatory condition such as cytokine storm syndrome (15).

Another possible explanation for the absence of severe respiratory complications in our population, besides the ongoing immunomodulatory treatments, could be the high prevalence of patients displaying positive prognostic factors for the course of SARS–CoV-2 infection (female sex and relatively younger age). Nevertheless, among our older patients (age ≥60 years), who comprised 34% of the study population, there were no severe cases or fatalities due to COVID-19.

In conclusion, the use of targeted synthetic DMARDs or biologic DMARDs in patients with rheumatic diseases has proven safe during the COVID-19 epidemic. Maintaining the ongoing long-term treatment for the underlying rheumatic disease has minimized the number of disease flares, which are associated with a general deterioration of the patient's condition and must absolutely be prevented in such an emergency period. Obviously, it is essential to maintain a high level of surveillance of patients with rheumatic diseases who must be encouraged to follow even more rigorously all of the guidelines for the prevention of infection that are recommended for the general population.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Favalli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Favalli, Monti, Caporali, Montecucco.
Acquisition of data. Ingegnoli, Balduzzi.
Analysis and interpretation of data. Favalli, Monti, Caporali, Montecucco.

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