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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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ABSTRACT

Objectives: To describe the incidence and severity of coronavirus disease 2019 (COVID-19) in rheumatic patients treated with targeted synthetic or biological anti-rheumatic drugs (ts/bDMARDs) compared with the general population living in the same Italian region.

Methods: Patients followed at two referral rheumatology centres in Lombardy from 25th February to 10th April 2020 were invited to participate in a survey to detect patients with confirmed COVID-19, close contacts with known COVID-19 cases, symptoms of infection, working, behavioural and disease management changes applied to prevent the contagion. The incidence of COVID-19 in the Lombardy population was obtained from the National Institute of Statistics. Confirmed COVID-19 was defined by nasopharyngeal swab.

Results: The survey was circulated amongst 955 patients (531 rheumatoid arthritis, 203 psoriatic arthritis, 181 spondyloarthritis, and 40 of connective tissue diseases/vasculitides/autoinflammatory diseases; mean age 53.7 years; female: 67.4%). The rate of responders was 98.05%. The incidence of confirmed COVID-19 is consistent with the general population (0.62% vs 0.66%; $p=0.92$). None of the patients had severe complications or required intensive care treatment, and all of them temporarily discontinued ongoing ts/bDMARDs therapy. Almost all patients adopted precautions to prevent the contagion (90.6%) and maintained the ongoing treatment with ts/bDMARDs (93.2%). The disease activity remained stable in 89.5% of patients.

Conclusions: Our results highlight the attitude from rheumatic patients to prevent the contagion while maintaining their chronic treatments. The incidence and severity of COVID-19 in patients

treated with ts/bDMARDs was not significantly different from that of the general population in the same region.

1. Introduction

The outbreak in December 2019 in China of an epidemic caused by a new coronavirus of animal origin called severe acute respiratory syndrome coronavirus (SARS-CoV-2) quickly became a global health emergency declared a pandemic by the World Health organization (WHO) (1). The disease generated by SARS-CoV-2 (COVID-19) is mainly a respiratory infection ranging from asymptomatic or oligosymptomatic cases to severe and life-threatening forms of interstitial pneumonia evolving towards 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 pro-inflammatory mediators such as interleukin (IL)-6, IL-1 and TNF, known as cytokine release storm (CRS) (3).

Along with the growth of the worldwide health emergency, there has been an increasing need to clarify the incidence and course of COVID-19 in immunosuppressed rheumatic patients in order to optimize their management strategy. On the one hand, in fact, many chronic immune-mediated inflammatory diseases are characterized by an overall intrinsic increase in infectious risk, demonstrated specifically for viral infections such as influenza (4). Interestingly, this risk tends to increase proportionally to the degree of disease activity and is minimal in patients in sustained remission (5). On the other hand, both conventional and targeted disease-modifying drugs (DMARDs) may be an additional iatrogenic risk factor, although many of them are currently being tested for COVID-19-induced CRS (6). To date, data on the epidemiology of COVID-19 in rheumatic populations are very scarce. For this reason, we have conducted a multicenter observational study with the aim 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 two rheumatology units located in Lombardy, the main epicenter of the COVID-19 outbreak in Italy. The incidence of COVID-19 observed in Lombardy patients in our

cohort was also compared with the data recorded in the overall population of the Lombardy region. Secondary aims were to assess the impact that COVID-19 had on this population of patients in terms of behavioral changes to prevent the contagion and on the working activities.

2. Methods

Study population.

The source for study population encompassed all adult (>18 years-old) rheumatological patients with a follow-up visit scheduled in the period between 25th February and 10th April 2020 at the Biologic outpatient clinic of the Division of Clinical Rheumatology of the ASST Gaetano Pini-CTO Institute in Milan or of the Rheumatology Department of Policlinico San Matteo in Pavia. The current analysis is part of a project to collect observational data from rheumatological patients followed at the two involved Rheumatology Units. The project was approved by the Ethics Committee of the Gaetano Pini Institute with approval number 141/2010 and by the Ethics Committee of the Policlinico San Matteo with approval number 31748/2009. All included patients have signed an informed consent to participate in the data collection. The possibility of including this survey within the abovementioned data collection project has been waived by the same ethics committee.

The final analysis was limited to patients living in Lombardy who had been treated with targeted biologic or synthetic DMARDs for at least 6 months. The background group was the overall adult (>18 years-old) population of the Lombardy region stratified by provinces according to data from the National Institute of Statistics (ISTAT, last update on 1st January 2019) (<https://www.istat.it>. Accessed 25th March 2020). The same period of evaluation as above (25th February and 10th April 2020) was considered for the calculation of COVID-19 incidence in the Lombardy population. The contact with a confirmed case of COVID-19 was considered if it was prolonged and in cohabitation with the infected case.

Outcomes and statistical analysis.

A survey was designed to investigate the impact of COVID-19 on the study population (see Supplementary Files). The survey comprised two separate sections, one filled in by the rheumatologist and one by the patient. In the first part of the questionnaire, the diagnosis and

demographic characteristics of the patient, the ongoing treatment (both rheumatological and non-rheumatological), the presence of comorbidities, and the degree of disease activity (measured by specific composite indices for the different rheumatologic disorders, where applicable) were evaluated. In the second section, the areas investigated were the reported symptoms suggesting viral infection, the eventual confirmed diagnosis of COVID-19 formulated by nasopharyngeal swab, the patient's contacts with subjects diagnosed with COVID-19, the adherence to the ongoing rheumatological therapy, any information received by the patient about COVID-19 from different sources, any precautions taken to prevent contagion, and the impact of the COVID-19 outbreak on the underlying disease and on work activity.

All the information in the second section has been referred to the period between 14 days before the start of the survey (the length of the incubation period established by the Italian health authorities) and the end of the data collection. The survey was administered to all patients followed-up at the biological outpatient clinic of the two involved centers, either face-to-face during each visit or by telephone to all patients who missed a scheduled visit during the reporting period. In order to compare the incidence of COVID-19 with 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 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/>. Accessed 10th April 2020).

Descriptive statistics was used to calculate mean and standard deviation, median and interquartile range. Statistical analyses were performed using SPSS statistical software, version 20.0 (SPSS, Chicago, IL, USA). P values equal to or less than 0.05 were considered statistically significant.

3. Results

Study population.

During the investigated period, 1225 patients were surveyed. The rate of non-responders was 1.95% and among them, the vast majority (21 out of 24, 87.5%) could not be reached directly for a telephone interview but were confirmed to be alive and without signs of infections by a

relative. These patients were not included in the final study population. After selecting only patients currently treated with b/tsDMARDs and living in the Lombardy region, the final study population included 955 patients (67.4% females) (Figure 1), whose demographic and clinical features are detailed in Table 1. Briefly, most patients (95.8%) were diagnosed with inflammatory arthritis (rheumatoid arthritis [RA] 531, psoriatic arthritis [PsA] 203, spondyloarthritis [SpA] 181), 1.8% with connective tissue diseases (systemic lupus erythematosus [n=13], systemic sclerosis [n=3], Sjögren syndrome [n=2]), and 2.5% with other diseases (Behçet disease [n=6], giant cell arteritis [n=3], sarcoidosis [n=1], and adult-onset Still disease [n=3], juvenile idiopathic arthritis [n=5], autoinflammatory diseases [n=4]). Mean age (\pm standard deviation) was 53.7 (\pm 14) years, mean disease duration 13.9 (\pm 9.9) years. The vast majority of patients were on anti-TNF therapy (55.8%). The remaining population was treated with abatacept (11.8%), interleukin-6 inhibitors (10.3%), small molecules (10.1%), secukinumab (4.7%), rituxumab (1.7%), ustekinumab (1.5%), belimumab (1.3%), as shown in Table 1.

Approximately half of the patients (47.3%) were receiving a bDMARD as monotherapy. More than 43% of patients carried at least one comorbidity, especially high blood pressure (20.2%).

The background general population included 8,687,083 people aged over 18 years (51.1% females, mean age 51.4 years) living in Lombardy (7).

COVID-19: incidence, clinical course, and patient characteristics of confirmed cases

In our cohort we observed six cases of COVID-19 confirmed by nasopharyngeal swab, three diagnosed with RA, two with SpA, and one with sarcoidosis. Five were treated with anti-TNF agents (3 etanercept, 1 adalimumab, and 1 infliximab) and one with abatacept. Only two patients were receiving bDMARDs as monotherapy, whereas 4 patients were concomitantly treated with methotrexate (n=2), leflunomide (n=1), or sulfasalazine (n=1); two patients were also treated with hydroxychloroquine. Three patients were smokers and 4 carried comorbidities (3 hypertension). None of the patients developed severe respiratory involvement or died. Only three patients (aged 26, 56 and 65, respectively) required hospitalization with low-flow oxygen supplementation, no patient has been admitted to an intensive care unit. All patients diagnosed with COVID-19 temporarily discontinued the treatment with cs/bDMARDs, with the exception of hydroxychloroquine. Only two of them reported a relapse of the rheumatological disease.

The incidence of confirmed COVID-19 observed in our cohort (0.62%; 95% confidence interval 0.25-1.4%) was consistent with that expected in the general population of Lombardy in the same period of observation (57.592 confirmed cases, 0.66%; $p=n.s.$). In our experience the infection was more frequent in females (4 of 6 cases), whereas in the healthy population the ratio observed was the opposite (55% males).

COVID-19: clinically suspected cases

In addition to the 6 cases confirmed with nasopharyngeal swab, 144 patients developed respiratory symptoms compatible with a mild viral infection but had no access to nasopharyngeal swab. Of these patients, 5 (3 females, mean age 52.6 years) also reported definite contact with swab-positive subjects and were therefore highly suspicious (although not confirmed) for COVID-19. Four of the patients highly suspicious of COVID-19 had a diagnosis of RA and one of PsA, two were on treatment with anti-TNF, the other three with tofacitinib, tocilizumab, or secukinumab, respectively. Only one of these patients was on hydroxychloroquine therapy. Another 13 patients reported contact with COVID-19+ subjects but did not develop symptoms suggestive of infection. The proportion of patients treated with hydroxychloroquine was comparable in the group of patients who had experienced ($n=18$) or not ($n=82$) respiratory symptoms (12.5% versus 10.1%, respectively; $p=n.s.$). Thirty-three of the 144 patients who developed respiratory symptoms temporarily suspended biological therapy (on average for 16.9 days) by self-decision ($n=9$) or on indication of the general practitioner ($n=11$) or the rheumatologist ($n=13$). Of these, only 9 patients reported a disease relapse, while in the other 23 disease activity remained stable.

How do patients cope with COVID-19?

About one third of patients (36%) reported having searched for information on how to manage their rheumatological disease in relation to the COVID-19 outbreak. The main source used was contacts with the rheumatologist in 77.8%, the web in 11.3%, the general practitioner in 8.1%, another specialist doctor in 1.7%, or the pharmacist in 1.1% of cases.

Almost all patients (90.6%) took specific precautions to protect themselves against the epidemic, 66.9% adhered strictly to the indications given by health authorities. Home isolation was adopted by 45.9%, the use of face masks by 57.2%, and social distancing by 68.1% of patients. More than

two-thirds of the subjects (70.4%) declared that the outbreak produced a tangible change in work activities shifted to temporally non-working or home-working. Overall, only 6.8% of patients suspended/reduced the dosage of the current disease-modifying therapy, 2.7% because of fear of contagion and 4.1% because of the occurrence of symptoms suggestive of infection, respectively. The underlying disease remained stable in 89.5% of cases, improved in 5.1% and worsened very shortly after the occurrence of infection and the discontinuation of ts/bDMARD in only 5.4% of cases. All this information is summarized in table 2.

4. Discussion

This is the first detailed report on COVID-19 in a cohort of rheumatic patients in an area of high epidemicity 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 biological or targeted synthetic disease-modifying drugs is consistent with the general population in Lombardy. It is known that the risk of infection of all immune-mediated diseases is also increased in relation to the immunosuppressive therapy that is used (7,8). For this reason, in this study, we investigated the frequency of COVID-19 in subjects treated with ts/bDMARDs, which are the pharmacological class used to treat inflammatory arthritis currently assumed to produce the greatest pro-infective iatrogenic effect (9). The results we observed may be useful to optimize the management of our complex patients during the ongoing pandemic and to support rheumatologists in encouraging patients to maintain the ongoing treatment.

This is the first study that investigates in detail the impact of COVID-19 on rheumatic patients. Only a minority of patients have reduced or discontinued the ongoing therapy with biological or 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 contagion were much less frequent. Almost 90% of patients maintained a good control of the rheumatic disease and only 5% experienced a relapse. All of them experienced the disease flare-up after stopping the ongoing therapy with ts/bDMARDs (9 of 33 patients, 27.2%). 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 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 rheumatologic disease. Beyond the apparently reassuring absence of severe complications in patients receiving ts/bDMARDs, this is also the result of the high adherence of our cohort to infection prevention standards, which have been adopted by more than 90% of the patients since the beginning of the epidemic. In particular, since the 9th of March 2020 in Lombardy health authorities imposed the lockdown including compulsory measures such as social distancing, wearing face masks and implementing home-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 use masks, social distancing and home working. 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 rheumatological patients, who often receive these drugs as anti-rheumatic chronic 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 suspected respiratory symptoms for COVID-19 was observed also in patients taking antimalarials, leaving the question of the actual preventive role of these products open.

A possible limitation of the study inherent in the nature of a cross-sectional survey administered also by telephone is the possibility of having missed all those patients who could not respond to the survey due to the infection (because they were hospitalized or died). However, the rate of non-responders 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 we observed may have been facilitated by the lockdown imposed by health authorities in Lombardy since 9th March 2020, as it was easier to contact patients confined at home. Amongst these few non-responders,

the almost totality of patients who did not respond directly to the survey were confirmed alive and without symptoms of infection by a relative who answered our phone call. These patients were not included in the study population but were certainly not contributing to a distortion of the COVID-19 frequency in our cohort.

Another potential weakness of our analysis is to have considered only those cases of COVID-19 confirmed with nasopharyngeal swab, excluding from the incidence calculation all those who had definite contact with COVID+ subjects or those who developed respiratory symptoms during the observation period. In view of the low number of positive patients observed in our cohort, the incidence rate could also be significantly modified by a few additional subjects with COVID-19 but 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 amongst patients treated with ts/bDMARDs was calculated from patients followed at two referral centres for the management of these drugs, and did not include cases occurring in other smaller rheumatologic centres in Lombardy, nevertheless, the large number of patients, including several diagnoses and types of ts/bDMARDs use is likely to provide an accurate picture of the infection in this type of rheumatologic 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 our patients with confirmed or highly suspicious COVID-19 had a mild course of the infection, that only in rare cases required hospitalization but never in the intensive care unit. Compared with the high number of hospitalized patients (more than 35,000) and deaths observed in the Lombardy population due to COVID-19 (10,511) in the same period (<https://www.regione.lombardia.it/wps/portal/istituzionale/>. Accessed 10th April 2020), our findings may be considered reassuring and are in line with the previously cautiously optimistic observation 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 towards an ARDS generated by an immune-based hyperinflammatory condition such as CRS (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, amongst the older group (≥ 60 years old) of our patients, representing the 34% of our population, there were no severe cases nor fatalities due to COVID-19.

5. Conclusions

In conclusion, the use of biological or targeted synthetic drugs in rheumatic patients has proven safe during the COVID-19 epidemic. Maintaining the ongoing chronic treatment for the underlying rheumatologic disease has minimized the number of disease flare-ups, 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 on rheumatic patients, who must be encouraged to apply even more rigorously all the prevention rules for contagion that are already recommended for the general population.

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FIGURE LEGENDS

Figure 1: Flow-chart of population included in the final analysis of the impact of COVID-19 on patients with rheumatologic diseases treated with targeted synthetic or biologic disease modifying anti-rheumatic drugs

Competing interests: Authors declare no competing interest

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

| | Rheumatoid arthritis | Psoriatic arthritis | Spondyloarthritis | Other diagnoses* |
|---|---------------------------------|--------------------------------|--------------------------|-----------------------------|
| Number of patients | 531 | 203 | 181 | 40 |
| Age, mean (\pmSD), years | 58 \pm 13 | 52 \pm 12 | 47 \pm 13 | 54 \pm 14 |
| Female, n (%) | 429 (45%) | 104 (51%) | 78 (43%) | 32 (34%) |
| Disease duration, mean (\pmSD), years | 15 \pm 10 | 12 \pm 9 | 12 \pm 9 | 14 \pm 10 |
| RHEUMATOLOGICAL TREATMENT | | | | |
| bdMARD, number (%) | 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 |
| tsDMARD, number (%) | 69 (7%) | 26 (3%) | 0 | 1 (0.1%) |
| -Baricitinib | 49 | 0 | 0 | 1 |
| -Tofacitinib | 20 | 0 | 0 | 0 |
| -Apremilast | 0 | 26 | 0 | 0 |
| Concomitant csDMARD | 338 (35%) | 98 (10%) | 46 (5%) | 21 (22%) |
| -Methotrexate | 260 | 79 | 29 | 5 |
| -Leflunomide | 27 | 2 | 0 | 0 |

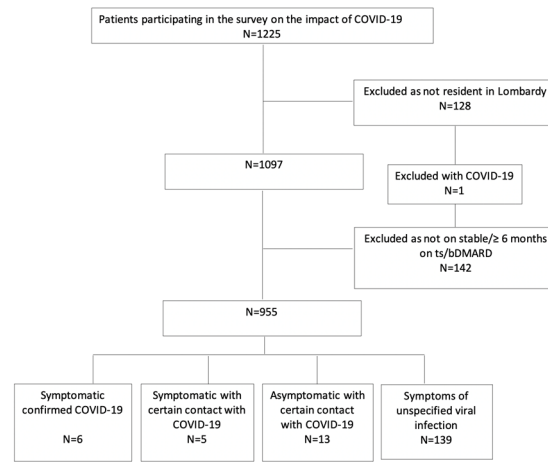
| | | | | |
|----------------------------------|------------------|-----------------|-----------------|-----------------|
| -Sulfasalazine | 11 | 12 | 14 | 1 |
| -Hydroxychloroquine | 34 | 1 | 2 | 11 |
| -Cyclosporine | 6 | 4 | 0 | 0 |
| -Azathioprine | 0 | 0 | 1 | 2 |
| -Mycophenolate | 0 | 0 | 0 | 2 |
| Low-dose glucocorticoids# | 201 (21%) | 27 (28%) | 18 (19%) | 24 (25%) |

*other diagnoses: systemic lupus erythematosus (n=13); systemic sclerosis (n=3); Sjögren syndrome (n=2); Behçet disease (n=6); giant cell arteritis (n=3); sarcoidosis (n=1); adult-onset Still disease (n=3), juvenile idiopathic arthritis (n=5), autoinflammatory diseases (n=4). #below 5 mg/die prednisone. SD, standard deviation; bDMARD: biologic disease-modifying anti-rheumatic drug; tsDMARD: targeted synthetic disease-modifying anti-rheumatic drug; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; TNF, tumor necrosis factor; IL-6, interleukin-6.

Table 2. How do patients cope with the early days of the COVID-19 pandemic.

| | n (%) |
|--|------------------------|
| Adherence to indications to prevent the contagion | 866 (90.6%) |
| Social distancing | 651 |
| Home isolation | 439 |
| Use of mask and/or gloves | 429 |
| Rheumatological treatment modification | 65 (6.8%) |
| ts/bDMARD | 60/955 (5.8%) |
| csDMARD | 2/512 (0.4%) |
| Corticosteroids | 3/270 (1.1%) |
| Information request regarding COVID-19 | 344 (36%) |
| Rheumatologist | 271 (28.4%) |
| General practitioner | 28 (2.9%) |
| Pharmacist | 4 (0.4%) |
| Acquaintances/family members | 2 (0.2%) |
| Web | 39 (4%) |
| Modification of work activity | 387/550 (70.4%) |
| Temporary discontinuation | 170 (30.9%) |
| Reduction | 66 (12%) |
| Home-working | 146 (26.5%) |

bDMARD: biologic disease-modifying anti-rheumatic drug; tsDMARD: targeted synthetic disease-modifying anti-rheumatic drug; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug



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