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Original Article

Coronavirus Disease 2019 in Rheumatic Patients with Inflammatory Disorders: A Descriptive Study from a High Infection Incidence Region of Northern Spain

Orlando Pompei Fernández[1], Paula García Escudero[2], Marta González Fernández[2], Claudia Stoye[1], César Antonio Egües[3], Jose Francisco García Llorente[4], Itziar Calvo Zorrilla[4], Oihane Ibargüengoitia Barrena[4], Ana Ruibal-Escribano[5], Juan Ramón De Dios[1], Joaquín María Belzunegui Otano[3], Belén Álvarez Rodríguez[1], Susana Gil Barato[1], Elena Garmendia Sánchez[2], Margarida Vasques Rocha[1], Edurne Guerrero[6], Jaime Calvo-Alén[1]

ORCID iDs of the authors:
O.P.F. 0000-0003-4720-1638;
P.G.E. 0000-0001-9323-2537;
M.G.F. 0000-0001-6594-3227;
C.S. 0000-0002-2595-7242;
C.A.E. 0000-0002-3637-1239;
J.F.G.L. 0000-0001-7525-4492;
I.C.Z. 0000-0001-8008-204X;
O.I.B. 0000-0002-7557-0871;
A.R. 0000-0002-4269-1255;
J.R.D. 0000-0002-8242-8742;
J.M.B.O. 0000-0002-8955-6130;
B.A.R. 0000-0002-8475-2263;
E.G.S. 0000-0003-4331-1485;
M.V.R. 0000-0001-7831-5211;
E.G. 0000-0002-0220-319X;
J.C. 0000-0001-9378-8412.

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[1] Department of Rheumatology, Hospital Universitario Araba, Vitoria-Gasteiz, País Vasco, Spain
[2] Department of Rheumatology, Hospital Universitario Cruces, Barakaldo, País Vasco, Spain
[3] Department of Rheumatology, Hospital Universitario Donostia, Donostia-San Sebastián, País Vasco, Spain
[4] Department of Rheumatology, Hospital Galdakao-Usansolo, Galdakao, País Vasco, Spain
[5] Department of Rheumatology, Hospital Alfredo Espinosa, Urduliz, País Vasco, Spain
[6] Department of Rheumatology, Hospital Alto Deba, Arrasate, País Vasco, Spain

Corresponding author:
Orlando Pompei Fernández
E-mail: orlpompei@hotmail.com

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Abstract

Background: Since the first confirmed case of severe acute respiratory syndrome coronavirus 2 in Spain in January 2020, the susceptibility of patients with rheumatic disease has remained unclear. In this report, we will describe the main features of coronavirus disease 2019 (COVID-19) that occurred in rheumatic patients with inflammatory disorders and try to identify features associated with severe disease.

Methods: We included all rheumatic patients with immune-mediated diseases followed at 6 centers belonging to the public healthcare system in the Basque Country (Spain) and diagnosed with COVID-19 from March 1, 2020, to May 31, 2020.

Results: In total, 131 patients were included in this study. The most frequent rheumatic disease was rheumatoid arthritis (46.6%), and the main comorbidities were arterial hypertension (45%). Forty-seven percent were taking glucocorticoids (GC) (62 patients), 61.8% were under treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and 25 patients (19.1%) were receiving targeted therapies (TT). Thirty-eight percent of patients required hospital admission, 2.3% required transfer to intensive care uni, and the rate of mortality was 9.2%. Associated factors in univariate analysis for a bad outcome were older age, use of GC, obesity, previous cardiovascular disease, and lymphopenia. Use of GC and lymphopenia remained within the multivariate model.

Conclusion: The frequency of COVID-19 seems to be similar in rheumatic patients as in the general population. Advanced age, obesity, heart disease, glucocorticoids, and low levels of lymphocytes were more common among the patients with a bad outcome. Neither exposure to csDMARD nor TT was associated with severe cases.

Keywords: Autoimmune diseases, COVID-19, epidemiology, infection, population studies, statistics

Introduction

The coronavirus disease 2019 (COVID-19) pandemic produced by the novel beta-coronavirus severe acute respiratory syndrome (SARS-CoV-2)[1] has been one of the most important health challenges for humanity in the last centuries. At this moment, more than 770 million people have been affected, and more than 6.9 million deaths have been certified across the world by the World Health Organization . Moreover, this infection has put numerous healthcare systems on the verge of collapse, including those of several developed countries.

The realm of rheumatology has been impacted by this pandemic in 2 ways. First, some of the commonly used rheumatic drugs, such as hydroxychloroquine, colchicine, tocilizumab (TCZ), baricitinib,[2] or anakinra,[3,4] have been utilized in the treatment of this infection.[5] They are especially relevant, as they have been used as targeted therapies (TT) in patients with severe disease course to block the pro-inflammatory cytokine cascade induced by the virus, which may lead to fatal consequences in many cases.[6,7] Due to their skillfulness

in the handling of these therapies, rheumatologists participated quite actively during the first stages of this pandemic in delineating the protocol treatments for these patients.

Furthermore, patients with inflammatory rheumatic conditions are treated frequently with a large spectrum of immunomodulators and immunosuppressive drugs, which might, theoretically, make these patients more susceptible to this infection and even increase the risk of a worse outcome. In this regard, an early report from the Hubei province, the epicenter of the COVID-19 outbreak in China, suggested that patients with autoimmune rheumatic disease might be more susceptible to COVID-19 infection than general population.[8] More recent data coming from a large tertiary center of Madrid (Spain) seemed to confirm this impression.[9] However, there still exists contradictory and confusing data about questions such as whether the disease course is more severe in our patients, which are the specific COVID-related risk factors, and whether or not the use of specific therapies is associated with a higher susceptibility to this infection and a more severe course of the disease.

The Basque Country, Northern Spain, and specifically the province of Alava, suffered one of the first COVID-19 outbreaks in Spain, thereafter having very high rates of infection incidence during the first wave of the pandemic, and our department was highly involved not only in the management of affected rheumatology patients but also in general COVID-19 hospital patients.

The objectives of the present study have been to describe the characteristics of COVID infection in a large sample of rheumatic patients with different inflammatory disorders, to identify the risk factors associated with severe disease, and to analyze the influence of the use of TT (mainly biologics) on the incidence of this infection in relation to the general population.

Main Points

- The susceptibility of patients with rheumatic diseases and the risk or benefits of immunomodulatory therapies for COVID-19 remains unclear.
- The use of glucocorticoids and comorbidities are the main risk factors for a bad outcome.
- The treatment with targeted therapies in these patients does not seem to predict an especially deleterious effect as a result of SARS-CoV-2 infection.

Material and Methods

Four University (Hospital Universitario Araba, Hospital Universitario Cruces, Hospital Universitario Donostia and Hospital Galdakao-Usansolo) and 2 community hospitals (Hospital Alfredo Espinosa and Hospital Alto Deba) covering most of the territory of Basque Country participated in our study; in total, around 1 519 500 people participated.

In the present observational retrospective study, we included all adult patients (>18 years old) with rheumatic inflammatory conditions and COVID-19 infection [confirmed by a nasopharyngeal swab polymerase chain reaction (PCR), serology, or clinical diagnosis, plus typical radiological imaging features of COVID-19], between March 1, 2020, and May 31, 2020, followed at the following centers: Hospital Universitario Cruces in Barakaldo (Biscay), Hospital Alberto Espinosa in Urduliz (Biscay), Hospital Universitario Galdakao in Galdakao (Biscay), Hospital Universitario Donostia in San Sebastián (Gipuzkoa), Hospital Alto Deba in Mondragón (Gipuzkoa), and Hospital Universitario Araba in Vitoria (Alava).

In order to identify all the possible rheumatic patients with COVID-19, we reviewed the electronic hospital registries for all the patients scheduled for follow-up in the first 6 months of 2020 in the different participating centers. In these registries, the patients with certified COVID infection were tagged, according to the health regulations, with a specific red viral icon facilitating the patient identification. In all the cases, the diagnosis was checked through the medical record review. In addition, records of rheumatic patients admitted to the hospital during the inclusion period with a clinical suspicion of COVID-19 but without PCR or serological confirmation, were also reviewed to see if they met the clinical inclusion criterion previously described.

A retrospective review of the medical records of all those included was carried out. The following variables were obtained: demographics, type of rheumatic disorder, comorbidities (obesity, smoking, diabetes, high blood pressure, and previous heart or lung disease), COVID-19-related characteristics, including clinical, radiological, and COVID-19-related laboratory data, and outcome features. Regarding laboratory data, only those considered specifically related to COVID-19, such as lymphocyte counts, C-reactive protein (CRP), ferritin, D-dimer, and IL6 levels, were recorded at the time of diagnosis or in the following days. All

Table 1. Epidemiological and Clinical Characteristics of Patients with Rheumatic Disease with Coronavirus Disease 2019 (n = 131)

	N (%)
Sex	
Female	83 (63.4)
Male	48 (36.6)
Age (years); mean age ± SD: 60.9 ± 15.5 years	
18-29	2 (1.53)
30-49	28 (21.37)
50-64	50 (38.17)
>65	51 (38.93)
Most common rheumatic disease diagnoses	
Rheumatoid arthritis	61 (46.6)
Spondyloarthropathies	23 (17.6)
Psoriatic arthritis	13 (9.9)
Polymyalgia rheumatic	9 (6.9)
Systemic lupus erythematosus	8 (6.1)
Systemic vasculitis	6 (4.6)
Sjögren's syndrome	5 (3.8)
Other seronegative arthritis	4 (3.1)
Scleroderma	1 (0.8)
Antiphospholipid syndrome	1 (0.8)
Rheumatic disease activity	
In remission	104 (79.39)
Active	27 (20.61)
Most common comorbidities	
Arterial hypertension	59 (45)
Lung disease	31 (23.7)
Cardiovascular disease	25 (19.1)
Diabetes mellitus	18 (13.7)
Obesity	13 (9.9)
Medication prior to COVID-19 diagnosis	
NSAIDs	45 (34.4)
Prednisone-equivalent glucocorticoids	62 (47.3)
csDMARD:	81 (61.8)
Methotrexate	56 (42.7)
Leflunomide	*13 (9.9)*
Hydroxychloroquine	*10 (7.6)*
Sulfasalazine	*4 (3.1)*
Tacrolimus	*3 (2.3)*
Azathioprine	*2 (1.5)*
Mycophenolate mofetil	*2 (1.5)*

(*Continued*)

Table 1. Epidemiological and Clinical Characteristics of Patients with Rheumatic Disease with Coronavirus Disease 2019 (n = 131) (*Continued*)

	N (%)
b/tsDMARD:	25 (19.1)
TNFi	*14 (10.7)*
Tocilizumab	*3 (2.3)*
Abatacept	*2 (1.5)*
Rituximab	*2 (1.5)*
Baricitinib	*2 (1.5)*
Ustekinumab	*1 (0.8)*
Anakinra	*1 (0.8)*

b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drugs; COVID-19, coronavirus disease 2019; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; NSAID, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor.

the collected data were entered into a common database, respecting patient anonymity, for further analysis.

For this specific study, we used the following specific definitions. Due to the retrospective character of this study, we considered that a patient's rheumatic disease was a non-active disease if, in the 2 monitoring visits prior to the index day (the day of COVID-19 diagnosis), no clinical or laboratory data of disease activity were present. On the other hand, and as far as COVID-19 is concerned, severe disease was defined when the patient required hospital admission or the outcome was fatal.

The number of patients on treatment with TT including biologics and JAK inhibitors was obtained from the hospital pharmacy records. The data regarding COVID-19 incidence and mortality rate in the general population of Basque Country was obtained from the Statistics Office of the Health Department of Autonomic Government of the Basque Country.

The study was carried out according to the principles of the Declaration of Helsinki. It was approved by the Autonomic Ethics Committee of the Basque Country (Approval No: PI2020126, 07/22/2020). Due to the unidentified and non-interventional nature of this study, patient consent was not required.

Statistical Analysis

The Statistical Package for the Social Sciences Statistics software, version 26.0 was used for computation (IBM SPSS Corp., Armonk, NY, USA). Standard descriptive parameters were used to present the cohort characteristics. Comparisons between those patients with severe and non-severe disease were done. For univariate comparisons, Fisher's exact test and Student's *t*-test were respectively utilized for categorical and continuous variables, setting the significant level at $P < .05$. All the significant variables plus gender and age and those considered to be clinically relevant were entered in a multivariable linear regression model.

Incidence and mortality rates for those patients on treatment with TT in relation to the whole patient population taking these medications were calculated.

Results

Demographics and Rheumatologic Disease-Related Features

Overall, 131 rheumatic patients with different kinds of inflammatory disorders were identified. Of these, 114 patients (87.02%) were diagnosed by SARS-CoV-2 PCR in nasopharyngeal swabs samples. Sixteen patients (2.21%) had positive serology, and only in 1 case (0.76%)

Table 2. Clinical Features, Medical Assistance, Treatments Against Coronavirus Disease 2019 (COVID-19), and Outcomes in Inflammatory Rheumatologic Patients with COVID-19 Infection (n = 131)

Reported days from onset of symptoms until diagnoses of COVID-19	6.8 ± 10.2
Type of COVID 19 manifestations	N (%)
Asymptomatic	21 (16.2)
General symptoms	16 (12.2)
Upper respiratory tract infection	24 (18.3)
Lower respiratory tract infection without pneumonia at chest x-ray	2 (1.5)
Lower respiratory tract infection with pneumonia at chest x-ray	67 (51.1)
Other symptoms	1 (0.8)
Laboratory findings on admission	
Lymphocyte count/μL, mean ± SD	1064.9 ± 795.5
C-reactive protein (mg/L), mean ± SD	89.6 ± 94.4
Procalcitonin (ng/mL), mean ± SD	5.9 ± 18.6
Ferritin (mg/dL), mean ± SD	779.4 ± 891.3
Lactate dehydrogenase mg/dL, mean ± SD	281.6 ± 105.3
D-dimer mg/dL, mean ± SD	1136.8 ± 1334.3
Thrombotic events	3 (2.3%)
Treatment against COVID-19, n (%)	
Hydroxycloroquine	65 (49.6)
Lopinavir/ritonavir	48 (36.6)
Glucocorticoids	19 (14.5)
Azithromycin	18 (13.7)
Tocilizumab	4 (3.1)
Anakinra	2 (1.5)
Remdesivir	1 (0.8)
Baricitinib	1 (0.8)
Disease outcome	
Nonhospitalized patients	81 (61.8)
Hospitalized patients	50 (38.2)
Patients requiring ICU*	*3* (2.3)
Deceased patients**	12 (9.2)

COVID-19, coronavirus disease 2019; ICU, intensive care unit.
*Patients admitted to ICU of the total hospitalized.
**Patients deceased in total (hospitalized and nonhospitalized).

was the diagnosis based only on a clinical basis in addition to typical chest computed tomography findings compatible with COVID-19. The mean age at diagnosis of infection was 60.9 ± 15.5 years, and the majority of the patients were female (63.4%). Seventy-seven percent (77.1%) of the patients were older than 50 years, and only 1.53% were under 30 years.

The distribution of the different underlying diseases was as follows: rheumatoid arthritis 46.6%, spondyloarthropathies 17.6%, psoriatic arthritis 9.9%; other types of inflammatory arthritis 3.1%, polymyalgia rheumatica 6.9%, systemic lupus erythematosus 6.1%, and other autoimmune systemic diseases 9.9%. Twenty-seven patients (20.61%) were considered by their usual rheumatologist to have some degree of activity in their underlying rheumatic disease according to the previously established definition.

The majority of the patients had relevant comorbidities (59.5%), with high blood pressure (45%) and previous lung (23.7%) or heart disease (19.1%) being the most prevalent. Diabetes mellitus and obesity were the next most frequent comorbidities, with 13.7% and 9.9%, respectively.

Regarding the treatment for the rheumatic disease prior to infection, 45 patients (34.4%) were regularly taking nonsteroidal anti-inflammatory drugs (NSAIDs), and 62 patients (47.3%) were on glucocorticoid (GC) therapy. The mean time taking the latter treatment was 40.3 months with a mean dose of 3.1 ± 2.4 mg per day of prednisone, ranging from 1.25 mg to 15 mg per day. Out of studied 131 patients, 81 (61.8%) were under treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), and 25 patients (19.1%) were on TT, most of them biologics, 14 in combination with a csDMARD, and the rest in monotherapy. Thirty-nine patients were not taking any DMARD (conventional or TT), although 17 of them were on GCs. These demographics, as well as the main rheumatologic disease-related features, are summarized in Table 1.

Coronavirus Disease 2019-Related Features

As depicted in Table 2, the mean time from the symptom onset to the moment of diagnosis was 6.8 ± 10.2 days. Lower respiratory tract infection with pneumonia was the most frequent clinical picture among these patients, followed by upper respiratory tract infection (18.3%), no symptoms (16.2%), and only general symptoms (12.2%) such as low-grade fever, asthenia, or ache and pains. Only 3 cases (2.3%) presented thrombotic events during the course of the SARS-CoV-2 infection.

Fifty patients (38.2%) required hospital admission and 3 of these (2.3%) were transferred to the intensive care unit. The hospital admission rate of the rheumatic patients was almost 70% higher than that observed in the general population from the same territory, namely 20.6% [RR (95%CI): 1.67 (1.31-2.13)]. In total, there were 12 deceased patients (9.1%), this being a slightly higher mortality rate than that observed in the general population in the Basque Country during this first pandemic wave [8.2%; RR (95%CI): 1.11 (0.65-1.92)] during the same period of time. Of the 12 deceased patients, 11 died whilst in hospital and the others died before being admitted. Salient clinical features of the deceased patients are described in Table 3.

Overall, patients presented a compatible COVID-19 laboratory profile with mean elevations of CRP, lactate dehydrogenase, ferritin, D-dimer, and descended count of lymphocytes. In Table 2, numerical laboratory data are shown.

During the hospital stay of those admitted patients, high-dose intravenous or oral GCs for respiratory were administered to 13 (26%) patients, lopinavir/ritonavir to 29 patients (58%), whereas hydroxychloroquine and azithromycin were used in 42 cases (84%; 30 alone and 12 combined) and 14 (28%) (2 alone and 12 combined), respectively. Additionally, 3 cases (6%) were treated with TCZ, 2 (4%) with anakinra (1 of them in combination with TCZ), and 1 (2%) with baricitinib due to a worsening in their respiratory condition. Of these 6 cases, 5 had a diagnosis of rheumatoid arthritis and 1 had a diagnosis of polymyalgia rheumatica.

Comparison of Patients with Severe and Non-severe Disease

Among 131 rheumatic patients with COVID-19 infection, 51 patients (38.9%) with a mean age of 66.8 ± 13.2 years were defined as severe cases who required admission or who were deceased.

When these severe and non-severe subsets of patients were compared, it was observed that patients with severe disease were older (66.2 ± 12.9 vs. 57.03 ± 16.1 years, respectively; $P = .006$) and had a greater incidence of comorbidities, specifically obesity (16.4% vs. 5.3% respectively; $P = .043$) and previous heart disease (29.1% vs. 11.8%, respectively; $P = .023$). However, no associations with previous lung disease or diabetes mellitus were observed. The only laboratory parameter associated with severe disease was the presence of lymphopenia.

Table 3. Clinical Features of 12 Deceased Patients with Coronavirus Disease 2019 and Rheumatic and Musculoskeletal Diseases

Patient, Sex, and Age	Rheumatic Disease/Ongoing Therapy	Comorbidities
1, male, 72 years	Rheumatoid arthritis/NSAIDS, GCs	Lung disease, HBP, DM
2, female, 79 years	SLE/GCs, HCQ	Lung disease, HBP
3, female, 80 years	Rheumatoid arthritis/GCs, MTX	Cardiovascular disease, lung disease, HBP
4, female, 81 years	SLE /GCs, HCQ	Cardiovascular disease, lung disease, HBP
5, male, 65 years	Rheumatoid arthritis/GCs, MTX	Cardiovascular disease, HBP
6, male, 79 years	Rheumatoid arthritis/GCs, LEF	Cardiovascular disease, HBP
7, female, 75 years	Systemic vasculitis/GCs	HBP, DM
8, female, 88 years	Scleroderma*/GCs	none
9, female, 82 years	Spondyloarthropathies/ADA	Obesity, cardiovascular disease, lung disease, HBP
10, female, 84 years	Rheumatoid arthritis*/MTX	Obesity, cardiovascular disease, HBP
11, female, 70 years	Rheumatoid arthritis/GCs, MTX	Cardiovascular disease
12, male, 76 years	Rheumatoid arthritis/anakinra	Obesity, cardiovascular disease, lung disease, DM

ADA, adalimumab; DM, diabetes mellitus; GCs, glucocorticoids; HBP, high blood pressure; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.
*Active disease.

Table 4. Differential Characteristic in Inflammatory Rheumatologic Patients with Severe and Mild Coronavirus Disease 2019 Infection

	Severe	Non-severe	*P*
Age, mean ± SD	66.2 ± 12.9	57.03 ± 16.1	.006
Sex (% female)	60	65.8	.582
Obesity (%)	16.4	5.3	.043
Heart disease (%)	29.1	11.8	.023
High blood pressure (%)	49.1	42.1	.479
Diabetes mellitus (%)	18.2	10.5	.304
Lung disease (%)	29.1	19.7	.221
NSAIDs (%)	26.7	73.3	.015
csDMARD (%)	63.6	57.9	.588
Targeted therapies (%)	21.8	22.4	1
GCs (%)	63.6	35.5	.002
Lymphocytes/µL, mean ± SD	854.2 ± 517.7	1478.9 ± 1057.2	.008
CRP mg/L, mean ± SD	95.44 ± 83.1	78.22 ± 114.2	.435
Procalcitonin ng/mL, mean ± SD	8.25 ± 22.9	1.65 ± 3.3	.159
Ferritin mg/dL, mean ± SD	724.7 ± 739.8	929.7 ± 1245.8	.603
LDH mg/dL, mean ± SD	292.9 ± 119.1	271.3 ± 90.9	.592
D-Dimer mg/dL, mean ± SD	1108.9 ± 1154.8	1188.9 ± 1645.1	.684

P-values less than .05 were considered significant.
CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; GCs, glucocorticoids; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drugs.

As far as the treatments used for their rheumatic disorders are concerned, no differences were observed in disease severity according to the use of csDMARD or TT. Conversely, a significantly higher percentage of patients using GC was seen in those with a severe course (63.6% vs. 35.5%; *P* = .002), and in fact, taking NSAID seems to have a protective role, with a lower number of patients using these medications among those with severe COVID-19 (26.7% vs. 73.3%; *P* = .015) (Table 4).

Analyses were also performed using death as a dependent variable. Although, by and large, the results were comparable with the previous ones, in this case, obesity and lymphopenia were only numerically but not significantly associated with the outcome, and besides previous heart disease, antecedents of lung disease and high blood pressure also showed a significant association with death (data not shown).

Multivariate analysis of those variables found to be significantly associated with severe disease in the univariate analyses showed that only GC use [odds ratio 95% CI: 4.10 (1.32-12.72)] and the presence of lymphopenia were independently associated with a severe course (Table 5).

Coronavirus Disease 2019 Impact in Patients with Targeted Therapies

Overall, 25 patients with COVID-19 were on treatment with TT at the moment of infection diagnosis (mean age 56.8 ± 12.2 years). The large majority of 14 patients were taking tumor necrosis factor inhibitors (TNFi); 3 IL6 blockers (anti-IL6); 2 abatacept, rituximab, and baricitinib; and 1 ustekinumab and anakinra. Fourteen of these patients were taking the targeted therapy in combination: 8 with methotrexate, 3 with leflunomide, and 1 with azathioprine. In 2 cases, they were on combo therapy with more than 1 csDMARD: 1 with methotrexate plus hydroxychloroquine and another with mycophenolate mofetil plus tacrolimus.

Table 5. Risk Factors Associated with Severe Coronavirus Disease 2019 Infection

Variable	Multivariate Odds Ratio	95% CI
Age (years)	0.99	0.95-1.04
Gender	1.91	0.63-5.81
Obesity	4.18	0.48-36.2
Heart disease	0.9	0.19-4.15
Nonsteroidal anti-inflammatory drugs	0.49	0.15-1.59
Glucocorticoids	4.10	1.32-12.72
Lymphocytes count	1.00	1.000-1.002

According to the data given by the pharmacy departments of the different centers participating in the present study, the whole population of rheumatic patients taking this kind of agents at the outset of this pandemic wave was 2355 patients. Therefore, the prevalence of SARS- CoV-2 infection among these patients during this period of time was 1%. In the case of the 2 more commonly used targeted agents, the statistics were similar: among 1622 users of TNFi the infection prevalence was 0.8%, and in 213 anti-IL6 users, 1.4%, bearing in mind that in this latter case we only identified 3 cases. These figures were roughly in the same range as the prevalence in the general population of the Basque Country reported by the Statistics Office of the Health Department of Autonomic Government of the Basque Country during this period of time, namely, 0.9%.

As has been shown before, the use of TT was not associated with disease severity; however, the admission rate in this group was 36%, which was also significantly greater than that reported in the general population [RR (95% CI): 1.75 (1.03-2.96)]. But the mortality rate of 8% was similar to that observed in our region [RR (95% CI): 0.97 (0.26-3.68)].

Discussion

The results of the present report show that overall, the clinical picture of COVID-19 in rheumatic patients resembles, for the most part, that seen in the general population. Given that it was not possible to assure a correct ascertainment of the total population with inflammatory rheumatologic disorders covered by the participating centers at the time the study was carried out, we cannot establish direct comparisons with the rate of seroprevalence observed at that time among the general population. However, according to the data of the subset of patients treated with TT, we can speculate that the incidence of virus infection was probably no higher in the whole population of rheumatic patients. This conclusion is in agreement with data from

studies from other countries,[10,11] although, on the contrary, data from the province of Hubei (China) showed an increased incidence of infection among patients with rheumatic conditions.[8] Finally, in this regard, another study from Spain[12] reported a significant increase in the infection prevalence (around 32% higher than in the general population) in patients with several systemic autoimmune or immune-mediated diseases but not specifically in patients with inflammatory arthropathies or systemic lupus erythematosus, which are largely the most frequent conditions in patients with inflammatory rheumatologic disorders. Nevertheless, this study could be somehow biased due to the fact that it was only based on the analysis of SARS-CoV-2 PCR records of several tertiary centers from different parts of the country.

On the other hand, we observed that the rate of hospital admission was greater in both the whole cohort as well as in the subset of patients taking TT than in the general population at that time, which may be a surrogate for a more severe disease among these patients. However, the rate of mortality for both the whole population of rheumatic patients and for those using TT was not different to that reported for the general population in the Basque Country. These observations are in agreement with data from a large multicenter health electronic record network from the USA. In this study using data from 2379 patients with systemic rheumatic conditions with COVID-19 and 142 750 comparators, the authors found a higher risk of hospitalization but a similar risk of mechanical ventilation or death.[13]

A severe course of COVID infection was observed in almost 40% of patients. We found that older age, comorbidity, specifically previous heart disease and obesity, and low levels of lymphocytes at disease onset were associated with a more severe course of the disease, although only the use of GC and lymphopenia were retained in the multivariate model. By and large, these observations are in line with most of the studies focusing on rheumatic patients and analyzing risk factors for severity.[11,12,14,20,21] In fact, most probably these risk factors are universal and not specific for rheumatic patients.[15,16,17,18,19] Thus, in one of the largest European reported cohort of hospitalized patients with COVID-19, with 2226 cases (including 12% with rheumatological diseases), a poor outcome was associated with a lower lymphocyte count, as well as older age and comorbidities, in addition to oxygen saturation <90% on admission and high CRP[9] However, we have to consider that most of these potential risk factors are clearly more frequent among rheumatic patients than in the rest of the general population. Our patients are frequently taking GC chronically; basal lymphopenia is also common either due to the disease itself or because of the use of certain treatments; and similarly, the prevalence of comorbidities such as obesity or heart and lung disease is higher in comparison with the general population, either as manifestations on their own or as complications of the rheumatic disease.

Treatments used in immune mediated diseases have been somehow worrisome during this pandemic due to their immune suppressive effects. However, some of them have also been used in the management of this disease. As has been commented above, our results and those from other studies have strongly associated the use of GC with a higher risk for a worse outcome in COVID-19.[20,21,22] In COVID-19 patients, the use of GC has been open to debate. Most experts have advised against of early use of GC for the treatment of infected patients due to its potential delay in the clearance of the virus, and also the increase of the risk of secondary infections and adverse effects (i.e., hyperglycemia, psychosis, and avascular necrosis).[21] Conversely, very recent data from the RECOVERY study have demonstrated that treatment with dexamethasone has benefits in hospitalized COVID-19 patients receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those receiving no respiratory support.[23] In summary, all these data indicate that the GC–COVID-19 interaction is timing dependent. Previous use of GC is not protective. Moreover, it seems to be clearly a risk factor for a more severe course; its therapeutic utility in the early stages of the disease may also be deleterious, although in critically ill hospitalized patients, it might have benefits. Regarding other treatments such as TT, we and others[24] have not found any association with disease incidence or severity. Most of our patients with TT were taking TNFi or anti-IL6 agents, and therefore we cannot establish definitive conclusions for the rest of TT. As far as anti-IL6 agents are concerned, TCZ has also been used in hospitalized patients, and although the data of the COVACTA clinical trial[25] have not been totally positive, the recently published clinical trial EMPACTA[26] has been reassuring in this regard. According to our data, the previous use of TCZ does not seem to be protective against acquiring the infection, although the limited number of patients in our study with this treatment prevents us from drawing strong conclusions. Finally, we observed a negative association between infection and the use of NSAIDs, although this association was not retained in the multivariate analysis. A warning for using NSAIDs (especially ibuprofen) was given at the pandemic outset although finally it was not sustained. Our data seem to go in the opposite direction, but we only recorded previous use of NSAIDs as yes or no, and whether that use was continuous or not was not recorded. As has been mentioned, the association was only seen in the univariate analysis, and therefore the meaning of this finding is unclear.

Our study has several limitations. Retrospective studies are always more prone to potential bias and data loss. However, in this case, the special conditions of this health emergency did not allow for well-designed prospective studies to be set up at that time, and our experience with a sizeable cohort of patients with immune-mediated rheumatic conditions was still valuable. Also, we have mentioned that it was not possible to accurately ascertain the whole population of rheumatic patients with inflammatory conditions covered by the participating centers, and this limited our capacity to perform certain analyses. Finally, SARS-CoV-2 PCR tests were not performed systematically in the population during this stage of the pandemic. The tests were done based on the presence of symptoms compatible with COVID-19 or suspicious contacts. It is possible to hypothesize that the population of rheumatic patients could have had a higher number of tests because they were seen more frequently by their physicians. However, during this time, all face-to-face visits were cancelled or limited to urgent cases, making, under our criteria, the possible effect of greater patient surveillance on the frequency of PCR tests almost negligible.

In conclusion, according to our experience, SARS-CoV-2 infection affects rheumatic patients with inflammatory conditions and the general population to a similar extent, although rheumatic patients require hospital admission more frequently. The use of GC and comorbidities such as obesity and previous heart disease are the main risk factors for a bad outcome. The use of TT in these patients does not seem to predict an especially deleterious effect as a result of SARS-CoV-2 infection.

Ethics Committee Approval: This study was approved by Ethics Committee of the Basque Country (http://euskadi.eus/comite-etico-investigacion-clinica/), (Approval No: PI2020126, Date: July 22, 2020), in accordance with the international standard on

clinical trials: Declaration of Helsinki in its latest revised version (Fortaleza, Brazil; 2013), and Good Clinical Practice Regulations (International Conference for Harmonization).

Informed Consent: Due to the unidentified and non-interventional nature of this study, patient consent was not required.

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