Original article

Clinical course of COVID-19 infection in inflammatory rheumatological patients: a monocentric Belgian experience

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Abstract

Objective. Little is known about the incidence and consequences of coronavirus disease 2019 (COVID-19) infection in patients with rheumatic diseases. To improve our knowledge in this field, we collected data from patients with inflammatory rheumatic diseases who developed COVID-19 infection.

Methods. We performed a monocentric observational longitudinal study and collected data retrospectively from patients with inflammatory rheumatic diseases who developed a confirmed or suspected COVID-19 infection between 3 March and 10 June 2020.

Results. A total of 23 patients developed COVID-19 infection. Seven patients needed hospitalization [female 57%, mean age 59 $+/-$ 9 years], and 16 patients were followed as outpatients [female 80%, mean age 50 $+/-$ 14 years]. All hospitalized patients had more than one co-morbidity. At the time of infection, all patients were on immunosuppressive therapy consisting of either conventional synthetic DMARDs and/or biotherapy, with or without CSs. A minority received Corticoids (CSs) only. The most common symptoms of COVID-19-infected patients were fever, dyspnoea, cough and fatigue. PCR and chest CT were performed in all hospitalized patients to confirm the diagnosis (100% positive PCR, 71% positive CT). All outclinic patients were diagnosed clinically (confirmed by PCR in only one). The mean length of hospital stay was 21 $+/-$ 19 days. Three patients developed an ARDS, including one who died.

Conclusion. A limited number of patients with inflammatory rheumatic diseases suffered from COVID-19 infection. Two patients needed mechanical ventilation and survived, whereas one patient died. All patients with a severe form of infection had at least one co-morbidity.

Key words: COVID-19, autoimmune disease, rheumatic disease, infection, SARS-CoV-2, co-morbidities

<div style="float:right">CLINICAL SCIENCE</div>

Key messages

- All patients with severe a form of COVID-19 infection had co-morbidities.
- No specific clinical pattern was observed in hospitalized COVID-19 patients compared with outpatients.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China at the end of December 2019. In February 2020, coronavirus disease 2019 (COVID-19) was officially related to the virus. This infection is mainly characterized by pulmonary involvement. Within a few weeks, COVID-19 infection spread very rapidly throughout the world to such an extent that

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the World Health Organization (WHO) declared the pandemic state on 11 March 2020 [1]. To date, the COVID-19 pandemic has wreaked havoc, causing the death of >850 000 people worldwide. Belgium, like several European countries, confined its population from 17 March to 11 May 2020 in order to prevent the overburdening of medical departments. The peak rate of new confirmed cases was reached on 9 April 2020. In the last epidemiological report (31 August 2020), the Belgian health institute Sciensano estimated that 85 042 people were infected and 9894 people had died from COVID-19 in Belgium [2].

As such, COVID-19 infection is typically complicated by hypoxaemic interstitial pneumonia that can progress to a severe ARDS requiring intensive care. Several converging lines of evidence suggest that clinical deterioration towards multiple organ failure is related to a cytokine storm [3]. Indeed, after viral infection an inadequate immune response triggers unabated production of pro-inflammatory cytokines, leading to a systemic and fulminant hyper-inflammatory syndrome. Therefore, several immunosuppressive molecules have been proposed in clinical studies for the treatment of life-threatening cases, such as tocilizumab, sarilumab, CSs, anakinra or baricitinib [4].

These drugs are well known and largely prescribed by rheumatologists for the treatment of rheumatic inflammatory diseases, such as RA. When the first cases series were published, several concerns cropped up concerning the potential risk of COVID-19 linked to immunosuppression in patients with chronic inflammatory diseases [5–7]. Immunosuppressive therapy as such and disease-induced immunosuppression carry the risk of infection in general [8]. On the contrary, the anti-inflammatory and anti-cytokine action of the immunosuppressive therapies could have curbed the excessive immune response induced by the virus [9]. Few cases of severe COVID-19 infection have been reported in patients with inflammatory diseases treated with immunosuppressant drugs, especially in China [10], but also in Italy [11] and Spain [12, 13]. In each country, the incidence of patients with confirmed COVID-19 and immune-mediated disease was consistent with the general population. The low incidence of severe cases reported among patients with inflammatory diseases receiving immunosuppressive therapy, particularly in areas with a high rate of contamination, suggests that these patients are not at risk of developing SARS-CoV-2 infection [6, 12, 14, 15]. In patients with inflammatory rheumatic diseases who developed the COVID-19, the unfavourable development towards ARDS was associated with the presence of the same co-morbidities as those described in the Chinese and Italian populations [9]. An in-depth analysis of cases that developed in China enabled the delineation of several risk factors for disease severity and prognosis, such as male sex, obesity, the presence of underlying diabetes, arterial hypertension, cardiovascular diseases or cancer [16]. Conversely, the potential efficacy of these immunosuppressive drugs to treat patients with worsened prognosis prompted the rheumatological scholar societies to recommend maintaining immunosuppressive treatments during the pandemic in chronically treated patients without obvious clinical suspicion of COVID-19 infection [17–19].

Currently, there are scant data about the exact prevalence and the specific evolution of COVID-19 infection in patients with immune-mediated inflammatory diseases. The risk of poor disease outcome in this population is unclear, as is their susceptibility related to the underlying disease or the presence of associated diseases and the administration of specific medications.

To improve our knowledge in this new field of clinical disease, we conducted a single-centre observational study to characterize clinically those patients with chronic inflammatory rheumatic diseases who developed symptoms compatible with COVID-19.

Methods

This monocentric observational longitudinal study was performed at the Erasme Hospital in Brussels (Belgium) and was approved by the local Ethics Committee. This study complies with the Declaration of Helsinki, and informed consent has been obtained from the subjects (or their legally authorized representative).

We collected data retrospectively from patients with inflammatory rheumatic diseases who developed a confirmed (by nasopharyngeal swabs and/or chest CT) or suspected COVID-19 infection between 3 March and 10 June 2020. The diagnosis of outclinic patients was based solely on clinical diagnosis. A clinical diagnosis of COVID-19 was established by the general practitioner, if the patient presented either general symptoms (fever and fatigue) associated with pulmonary symptoms (dyspnoea or cough or chest pain) or general symptoms associated with anosmia and/or dysgeusia. The characteristics of patients with severe forms of disease requiring hospitalization were analysed and compared with those who required only outpatient care. No statistical sample size calculation was performed a priori. Continuous variables are presented as the median (interquartile range), and categorical variables as number (percentage).

Results

A total of 26 patients were selected. An alternative diagnosis was found in three patients: a *Pneumocystis jiroveci* infection, an interstitial lung disease and a non-COVID-19 atypical pneumonia. They were therefore excluded from the analysis. Demographics and clinical characteristics of the 23 patients are described in Table 1. Eight patients were diagnosed with RA, three with axial SpA, three with peripheral SpA, six with PsA, two with primary SS and one with SLE. Seven patients needed hospitalization [female 57%, mean age 59 +/−

TABLE 1 Demographic and clinical characteristics of the hospitalized and outpatients

Characteristic	All patients	Hospitalized patients	Outpatients
Number of patients	23	7	16
Age, years, mean (S.D.)	53 (13)	59 (9)	50 (14)
Female, n (%)	12 (52)	4 (57)	8 (80)
Co-morbidities, n (%)			
Obesity (BMI >30 kg/m^2)	9 (39)	3 (43)	6 (38)
Hypertension	7 (30)	3 (43)	4 (25)
Cardiopathy	2 (9)	1 (14)	1 (6)
Dyslipidaemia	2 (9)	0	2 (13)
Diabetes	4 (17)	2 (29)	2 (13)
COPD/asthma	4 (17)	2 (29)	2 (13)
Hepatitis B	1 (4)	1 (14)	0
Fatty liver	1 (4)	0	1 (6)
Neoplasia	2 (9)	1 (14)	1 (6)
Active haematological cancer	1 (4)	1 (14)	0
Solid cancer in remission	1 (4)	0	1 (6)
Renal disease	1 (4)	1 (14)	0
Hypothyroidism	2 (9)	0	2 (13)
Number of co-morbidities, n (%)			
≥ 1	16 (70)	7 (100)	9 (56)
≥ 2	10 (62)	4 (57)	6 (36)
≥ 3	5 (22)	3 (43)	2 (13)
Race, n (%)			
Caucasian	12 (52)	3 (43)	9 (56)
North African	11 (48)	4 (57)	7 (44)
Smoking, n (%)			
Active smoker	3 (13)	1 (14)	2 (13)
Previous smoker	5 (22)	1 (14)	4 (25)
Rheumatological diagnosis, n (%)			
RA	8 (35)	2 (29)	6 (38)
Axial SpA	3 (13)	2 (29)	1 (6)
Peripheral SpA	3 (13)	0	3 (19)
PsA	6 (26)	2 (29)	4 (25)
Primary SS	2 (13)	1 (14)	1 (6)
SLE	1 (4)	0	1 (6)
Associated disease, n (%)			
Psoriasis	2 (9)	0	2 (13)
Sarcoidosis	1 (4)	1 (14)	0
Secondary SS	0	0	0
Crohn's disease	1 (4)	0	1 (6)
Polychondritis	1 (4)	0	1 (6)
VICD	1 (4)	0	1 (6)
Behçet's disease	1 (4)	0	1 (6)
Rheumatological treatment, n (%)			
Glucocorticoids[a] (alone/combined)	5 (22)	2 (29)	3 (19)
Dosage equivalent prednisone, mg, mean (S.D.)	5 (2.5)	7.5 (2.5)	4 (1)
csDMARDs	15 (65)	4 (57)	11 (69)
MTX	13 (57)	3 (43)	10 (63)
SSZ	1 (4)	0	1 (6)
HCQ	3 (13)	1 (14)	2 (13)
AZA	1 (4)	1 (14)	0
bDMARDs	16 (70)	4 (57)	12 (75)
Adalimumab	1 (4)	0	1 (6)
Infliximab	1 (4)	1 (14)	0
Golimumab	4 (17)	1 (14)	3 (19)
Certolizumab	1 (4)	1 (14)	0
Etanercept	1 (4)	0	1 (6)
Secukinumab	1 (4)	0	1 (6)
Abatacept	1 (4)	0	1 (6)
Tocilizumab	1 (4)	0	1 (6)

TABLE 1 Continued

Characteristic	All patients	Hospitalized patients	Outpatients
Rituximab	1 (4)	1 (14)[b]	0
tsDMARDs	5 (22)	1 (14)	4 (25)
Baricitinib	3 (13)	1 (14)	2 (13)
Apremilast	2 (9)	0	2 (13)
Glucocorticoids alone	1 (4)	1 (14)	0
csDMARDs alone	4 (17)	1 (14)	3 (19)
bDMARDs alone	5 (22)	2 (29)	3 (19)
tsDMARDs alone	1 (4)	0	1 (6)
csDMARDs + bDMARDs/tsDMARDs	11 (48)	3 (43)	8 (50)
Other treatment, *n* (%)			
IVIGs	1 (4)	0	1 (6)
Azacitidine	1 (4)	1 (14)	0
Colchicine	1 (4)	0	1 (6)
Symptoms, *n* (%)			
Fever	14 (60)	6 (86)	8 (50)
Dyspnoea	14 (60)	4 (57)	10 (63)
Cough	12 (52)	4 (57)	8 (50)
Fatigue	10 (43)	1 (14)	9 (56)
Headache	9 (39)	1 (14)	8 (50)
Myalgia/arthralgia	7 (30)	1 (14)	6 (38)
Anosmia/dysgeusia	7 (30)	1 (14)	6 (38)
Diarrhoea	4 (17)	2 (29)	2 (13)
Chest pain	3 (13)	0	3 (19)
Nausea/vomiting	2 (9)	2 (29)	0
Rhinitis/sinusitis	2 (9)	0	2 (13)
Sore throat	1 (4)	0	1 (6)
Dysphagia	1 (4)	0	1 (6)
COVID-19 diagnosis, *n* (%)[c]			
PCR$^+$		7 (100)	1
Chest CT$^+$		5 (71)	–
PCR$^+$ and chest CT$^+$		5 (71)	–
PCR$^-$ and chest CT$^+$		0	–
PCR$^+$ and chest CT$^-$		2 (29)	1
Clinical suspicion alone		0	15 (94)
COVID treatment, *n* (%)			
HCQ		6 (86)	0
Lopinavir		1 (14)	0
Management			
csDMARDs discontinuation		3/4	2/11
bDMARDs/tsDMARDs discontinuation		5/5	5/12
Duration of hospitalization, days, mean (S.D.)		21 (19)	0
Oxygen therapy, *n* (%)		5 (71)	–
ICU admission, *n* (%)		2 (29)	–
ICU length of stay, days, mean (S.D.)		26.5 (0.5)	–
Endotracheal intubation, *n* (%)		2 (29)	–
Duration of intubation, days mean (S.D.)		19 (0)	–
Non-invasive ventilation, *n* (%)		1 (14)	–
Complications, *n* (%)			
ARDS		3 (43)	–
Bacterial pneumonia post-intubation		2 (29)	–
Death		1 (14)	–
Follow-up			
Time between first symptom and PCR negativity, days, mean (S.D.)		43 (17)[d] Range 20–64	–

[a]With dose range 2.5–10 mg/day. [b]The last dose of rituximab was administrated in 2018. [c]PCR and chest CT were performed on all hospitalized patients but only on a single outpatient. [d]Mean time until PCR negativity in the four patients for whom PCR monitoring was carried out. bDMARDs: biological DMARDs; COPD: chronic obstructive pulmonary disease; csDMARDs: conventional synthetic DMARDs; ICU: intensive care unit; tsDMARDs: targeted synthetic DMARDs; VICD: variable common immune deficiency.

9 years] and 16 patients were followed as outpatients [female 80%, mean age 50 +/− 14 years]. All hospitalized patients presented more than one co-morbidity. At the time of infection, patients were on immunosuppressive therapy with CSs (two hospitalized patients *vs* three outpatients), conventional synthetic DMARDs (csDMARDs; 4 hospitalized patients *vs* 11 outpatients) and/or biotherapy (5 hospitalized patients *vs* 12 outpatients). The most common symptoms of COVID-19-infected patients were, in order of decreasing frequency fever, dyspnoea, cough and fatigue.

PCR and chest CT were performed in all hospitalized patients to confirm the diagnosis (100% positive PCR, 71% positive CT). All outclinic patients were clinically diagnosed (confirmed by PCR in only one). HCQ was administered to 86% of hospitalized patients. At the time of infection diagnosis, all hospitalized patients and 5 of 12 outpatients discontinued biotherapy. The mean length of hospital stay was 21 +/− 19 days. Three patients developed an ARDS and two patients needed invasive mechanical ventilation; hence, admission to the intensive care unit (ICU). These two patients with endotracheal intubation were treated with csDMARDs with biological agents and had an underlying chronic pulmonary disease. The third patient with ARDS also suffered from advanced blood cancer and chronic obstructive pulmonary disease (COPD). Owing to his poor haematological prognosis, this patient was not transferred to the ICU. He received non-invasive ventilation but unfortunately died. All these three patients had general and respiratory symptoms, had been diagnosed by PCR and chest CT, and received HCQ. Only one patient in ICU received lopinavir. The median hospitalization duration was 42 +/− 10 days for patients with mechanical ventilation and 6 +/− 2 days for those without ventilation.

During hospitalization, biologic therapies [four patients with biological DMARDs (bDMARDs) and one with targeted synthetic DMARDs (tsDMARDs)] and csDMARDs (three patients with MTX) were discontinued in all patients. CSs were continued, in addition to HCQ. AZA was also continued in a patient with sarcoidosis. During the follow-up, negative PCR tests for four previously hospitalized patients under bDMARDs allowed them to restart their treatment. The patient on tsDMARDs did not resume treatment because of stable remission. Indeed, at the beginning of the epidemic of COVID-19, there were several questions that still remained shrouded regarding the safety of biologic therapies in PCR-positive patients and, in particular, in IBD patients [20]. In this context, we decided as a safety measure to check PCR negativity before restarting biologic treatment. The median time between first symptom and PCR negativity was 43 +/− 17 days (range 20–64 days).

Discussion

To our knowledge, this series of cases is the first data collection in Belgium of patients suffering from inflammatory diseases and presenting symptoms compatible with COVID-19 infection. We analysed the clinical characteristics and clinical course of 26 patients who presented with suspected COVID-19 infection, after exclusion of three patients for whom another diagnosis was confirmed. Seven patients needed hospitalization, and SARS-CoV-2 infection was confirmed in 100% by PCR and in 71% by chest CT. At the peak of the epidemic in Belgium, the regulations from the Belgian Ministry of Health allowed the screening by nasopharyngeal PCR and chest CT only for patients with severe symptoms requiring hospitalization. Patients with mild symptoms were not tested and were asked to remain confined at home, to maintain social distance and continue to apply barrier gestures. Therefore, the diagnosis was suspected only on the basis of clinical signs and symptoms in most of the patients followed on an outclinic basis. The symptoms presented in our patients (hospitalized or not) corresponded to the clinical description of confirmed patients both in China and in Italy [21, 22]. The main complaints were, in order of decreasing frequency, pyrexia, dyspnoea, cough and fatigue. Outclinic patients reported less pyrexia but more myalgia and dyspnoea. In particular, the occurrence of anosmia and/or agueusia was reported in 30% of cases. This symptom seems to be specific for COVID-19 infection. It has been reported to be present in nearly 55% of cases and is sometimes the sole clinical feature related to COVID-19 [23, 24]. The difference between clinical symptoms in hospitalized and non-hospitalized patients can be explained by the subjective and retrospective collection of data, especially for the outclinic patients. Objective data, such as pyrexia, might be unreliable. Furthermore, the anxiety-provoking context of the epidemic might have exacerbated the feeling of dyspnoea.

All the hospitalized patients had at least one co-morbidity. Considering all the infected patients, 39% were obese, 30% had arterial hypertension and 17% had diabetes. This feature has been described soon after the beginning of the epidemic in China. The characteristics of patients who progressed to ARDS or died were published to highlight the risk factors for poor outcome. In a series of 191 patients, almost half had co-morbidities, including, in order of frequency, high blood pressure, diabetes and cardiovascular diseases [16]. The COVID-19 Global Rheumatology Alliance registry, including patients with rheumatic diseases, also reported a higher number of co-morbidities in hospitalized patients: hypertension was the most represented, followed by chronic pulmonary diseases, diabetes, cardiovascular diseases and renal insufficiencies [25]. The data from our cohort therefore confirm the same results: most patients with one or more co-morbidity have developed more severe damage. However, it is interesting to note that one-third of the obese patients included in our cohort required hospitalization. Several studies have shown the susceptibility to SARS-CoV-2

of obese individuals, particularly in Europe (Italy, Spain, France and the UK) and in the USA. Being overweight is associated with an increased risk of admission to the ICU [26].

Among the hospitalized patients, one patient died. This patient, aged 71 years, had primary SS complicated by a malignant haemopathy, for which he was undergoing treatment with azacitidine. He developed rapid respiratory failure, which did not respond favourably to non-invasive ventilation. His prognosis was limited and, with the agreement of his family, he did not benefit from intensive care.

In this cohort, the most frequent rheumatic diseases were RA, followed by PsA, axial and peripheral SpA. Five patients were on CS therapy, including one with a dosage >10 mg/day of prednisone equivalent. Seventy per cent of patients received biotherapy, mostly anti-TNF, and 22% were treated by targeted DMARD therapy. Among the most severe cases, we observed that the two intubated patients were treated with infliximab and baricitinib. The deceased patient was treated with CSs alone because of the concomitant haematological complication.

The influence of DMARDs and biotherapies on the severity of COVID-19 infection remains debated [27]. Recent data from the European register suggests that treatments with DMARDs do not increase the risk of hospitalization. The odds of hospitalization would be reduced by the use of anti-TNF treatments but increased by the administration of glucocorticoids with a dosage of >10 mg/day of equivalent prednisone [16]. The mortality in patients with inflammatory diseases treated with bDMARDs or tsDMARDs does not seem to differ from the general population [12]. Rheumatologists were therefore invited to continue rheumatological treatments in their patients as long as they showed no signs of COVID-19 infection and had not been exposed to SARS-CoV-2 [16, 17, 19].

Inhibition of IL-6 via the administration of tocilizumab or sarilumab, or janus kinase inhibitors, such as baricitinib, has been proposed as forays in patients with severe disease. The unfavourable evolution towards an ARDS and/or a multi-organ failure has been attributed to a cytokine storm induced by an unbridled immune response of the host in response to the viral infection [28]. SARS-CoV-2 induces rapid Th1-type lymphocyte activation entailing the production of pro-inflammatory cytokines (TNF and IL-6, but also IL-1, VEGF, monocyte chemoattractant protein-1, IL-8, etc.). The administration of IL-6 receptor antagonists for the treatment of COVID-19 is currently under study. In two small case series, IL-6 inhibition seems to have had a positive effect on survival [29, 30]. The number of patients included was very small; therefore, no conclusion can be drawn. Baricitinib (a janus kinase 1 and 2 inhibitor) has also been assessed as a potential candidate because of its high ability to bind AP2-associated protein kinase 1 (AAK1), one of the regulatory proteins involved in endocytosis. Inactivation of this protein could prevent the virus from entering the lung epithelial cells. However, by its action on the JAK–STAT pathway, baricitinib reduces the production of IFN-α, which is cardinal for viral elimination. Its potential effect is still widely debated [31–33].

Our study has many limitations. The small number of patients included prevents any statistical analysis and does not allow for any conclusions to be drawn. The data were collected retrospectively, which might have led to an under-evaluation of clinical symptoms and chronological inaccuracies. We included patients who reported compatible symptoms during a telephone or physical consultation or after a spontaneous call from them. We therefore probably omitted paucisymptomatic patients or patients who did not inform us about the occurrence of their symptoms. However, the data collection lasted >3 months after the first hospitalization. This time corresponds to the mean time between two successive consultations for the usual follow-up of patients. All patients with an appointment scheduled since the start of Belgian confinement were contacted by telephone. In addition, patients with inflammatory rheumatic diseases followed in our department have been educated to reach our rheumatology nurse by telephone if they have any complication. These measures do not allow us to certify having captured all moderate to severe cases, but it is highly unlikely that a patient with a severe form was missed. All patients who presented symptoms compatible with COVID-19 were included. The patients followed on an outclinic basis did not benefit from PCR screening. However, it was deemed necessary to maintain these patients in our analysis in order to avoid excluding patients with milder features and to have real-life data from patients.

Conclusions

A limited number of patients with inflammatory rheumatic diseases developed COVID-19 infection. Two patients needed intubation and survived, whereas one patient with advanced haemopathy died. All patients with a severe form of infection had co-morbidities. We did not highlight a particular clinical pattern in hospitalized patients or outpatients. This observational study was limited to cases reported to us, probably underestimating the number of patients with SARS-CoV-2 infection.

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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