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ABSTRACT

Objective: COVID-19 outcome may be less favourable in patients with inflammatory rheumatic and musculoskeletal diseases (RMD) receiving immunosuppressive therapy. We aimed to investigate whether RMD patients on anti-IL6 therapy prior to SARS-CoV-2 infection have less severe disease and better outcomes of COVID-19.
Methods: We conducted a retrospective national, multicentre cohort study using data from the French RMD COVID-19 cohort. We compared the severity and outcome of highly suspected or confirmed COVID-19 infection in RMD patients previously treated with tocilizumab or sarilumab (anti-IL6 group) with patients who did not receive anti-IL6 therapy (no anti-IL6 group).
Results: Data were collected for 1883 patients with mean age of 55.2 years [SD 16.7] and 1256 (66.7%) female. Two hundred ten (11.1%) developed severe COVID-19 and 115 (6.4%) died. After adjusting for potential confounding factors, severe COVID-19 was less frequent in the anti-IL6 group compared with the no anti-IL6 group (aOR for moderate vs. mild severity, 0.23 [95% CI, 0.10 to 0.54], $p \leq 0.01$ and aOR for severe vs. mild, 0.29 [95% CI, 0.10 to 0.81], $p \leq 0.01$). No significant differences were found for the evolution of COVID-19 between

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the anti-IL6 group and the no anti-IL6 group (aOR for recovery with sequelae vs recovery without sequelae, 0.78 [95% CI, 0.41 to 1.48] and aOR for death vs recovery without sequelae, 0.29 [95% CI, 0.07 to 1.30]).
Conclusion: RMD patients receiving anti-IL6 therapy prior to SARS-CoV-2 infection have less severe forms of COVID-19. No difference was observed in COVID-19 evolution, i.e., sequelae or death, between the groups.

Introduction

The clinical spectrum of SARS-CoV-2 infection is quite broad, ranging from asymptomatic to life-threatening or fatal disease. Older age, male sex, obesity, hypertension, diabetes, and immunocompromised status linked to malignancy or transplantation are considered risk factors for developing severe forms of COVID-19. Immunosuppression due to immunosuppressors increases the incidence and severity of many infectious diseases [1–3].

The course of COVID-19 may be less favourable in patients with inflammatory rheumatic and musculoskeletal diseases (RMD) who are receiving immunosuppressive therapy such as biologics or DMARDs prior to SARS-CoV-2 infection [4]. Information on the clinical outcomes of COVID-19 in RMD patients receiving anti-IL6 therapy prior to SARS-CoV-2 infection remains limited, but there does n–ot seem to be an association with COVID-19-related death, as opposed to rituximab and sulfasalazine [5]. Rituximab used in patients with RMD is associated with severe COVID-19 outcomes and impaired humoral anti-SARS-CoV-2 vaccine response [6,7]. For these reasons, during the COVID-19 pandemic some physicians and RMD patients may have decided to discontinue immunosuppressive therapy, although the need for their continued use remains a challenging question. A growing body of evidence shows that patients on long-term immunosuppressive therapy do not fare worse than their counterparts in terms of COVID-19 outcomes [8]. Direct correlation between the cytokine storm resulting from a sudden acute increase in circulating levels of various pro-inflammatory cytokines and disease severity with lung injury and poor prognosis is reported in patients with COVID-19 [9]. Due to their anti-inflammatory effects, immunosuppressive drugs have been broadly used as a treatment for COVID-19 to reduce the cytokine storm, a major cause of COVID-19 mortality [10,11]. For example, dexamethasone reduced progression to respiratory failure and death in hospitalised COVID-19 patients receiving respiratory support [12]. Tocilizumab improved outcomes and survival in critically ill patients with COVID-19 receiving organ support in the intensive care unit [13–15]. Inversely, tocilizumab was not effective for preventing intubation or death in moderately ill hospitalised patients with Covid-19 [16]. The possibility of a "protective" effect of anti-IL6 drugs prior to SARS-CoV-2 infection remains an unanswered question. We retrospectively compared COVID-19 severity and outcomes in the French RMD COVID-19 cohort according to whether RMD patients had received or not anti-IL6 therapy prior to SARS-CoV-2 infection.

Methods

Study design and patients

This multicentre, national cohort study analysed data from the French RMD COVID-19 cohort, which has been previously described [6,17]. Briefly, the French RMD COVID-19 cohort included patients aged 18 years or older with confirmed inflammatory RMD and a confirmed diagnosis of COVID-19 with nasal swabs/serology or highly suspected disease with compatible symptoms (any three or more of the following signs or symptoms: fever, general weakness or fatigue, headache, anosmia, ageusia, cough, chills, diarrhoea, myalgia, shortness of breath, high-risk exposure and close contact, chest CT findings suggestive of COVID-19 pneumonia). The study was done in compliance with the research methodology MR-004 (research not involving humans connected to studies and evaluations in the field of health); it was approved by Lille University Hospital (Lille, France) and was declared to the Data Protection Authority for France (Commission Nationale de l'Informatique et des Libertés) (reference DEC20-107).

Data collection

All cases of patients with inflammatory rheumatic and musculoskeletal diseases and highly suspected or confirmed COVID-19 were reported retrospectively. Individual data regarding diagnosis of or specific ongoing treatments for inflammatory rheumatic and musculoskeletal diseases were captured from physicians via a single national data entry portal. Data collected from patients medical records have been previously described in detail [6,17]. The data cut-off date was June 15, 2021. Before dataset lock, the final database was monitored to collect missing data, validate the evolution of COVID-19, remove duplicate or erroneous reports, and check data consistency.

Severity and outcomes of COVID-19

The primary objective of the study was to compare the severity of COVID-19 disease between RMD patients treated with tocilizumab or sarilumab (anti-IL6 group) prior to SARS-CoV-2 infection and RMD patients who did not receive anti-IL6 therapy but might have received various biologics or immunosuppressors at the time of SARS-CoV-2 infection (no anti-IL6 group). The severity of COVID-19 illness was defined according to the care required by each patient: mild COVID-19 required ambulatory care; moderate COVID-19 required non-intensive hospital treatment; and severe COVID-19 required admission to an intensive care unit (ICU) or led to death.

The secondary objective of the study was the outcome of COVID-19 in RMD patients treated with tocilizumab or sarilumab prior to SARS-CoV-2 infection (anti-IL6 group) compared with RMD patients who did not receive anti-IL6 therapy prior to SARS-CoV-2 infection (no anti-IL6 group). The outcome of COVID-19 was defined as recovery without sequelae, recovery with sequelae, or death. The assessment of sequelae was left to the discretion of the clinician. Various sequelae were reported in the completed form of the French RMD cohort: asthenia, weakness, anosmia or hypoonosmia, dysgeusia, persistent dyspnoea.

Statistical analysis

Categorical variables were expressed as numbers (percentage), and quantitative variables as mean ± standard deviation (SD). Comparisons of COVID-19 outcomes were made using a multinomial logistic regression model between RMD patients receiving anti-IL6 therapy prior to SARS-CoV-2 infection and those receiving non-anti-IL6 therapy prior to SARS-CoV-2 infection (control groups). To consider the potential confounding factors, comparisons were made with and without adjustment for pre-specified confounding factors (i.e., age, sex, BMI, hypertension, diabetes, and cardiovascular disease). We used RMD patients not treated with anti-IL6 therapy prior to SARS-CoV-2 infection as a control group (no anti-IL6 group). We also used RMD patients treated with any non-anti-IL6 biotherapy prior to SARS-CoV-2 infection (i.e., anti-TNF, anti-IL17A, anti-IL1, abatacept, JAK inhibitor and rituximab) as a control group (non-anti-IL6 biotherapy group), and there was a sub-group excluding RMD patients treated with rituximab prior to SARS-CoV-2 infection (any non-anti-IL6 biotherapy except rituximab) due to the potential deleterious effect of rituximab on the severity and outcomes of COVID-19 [6]. We used RMD patients treated with anti-TNFα therapy

prior to SARS-CoV-2 infection as a control group (anti-TNF group) due to the potential "protective" effect on COVID-19 severity, similar to that of anti-IL6 therapy.

Unadjusted and adjusted multinomial odds-ratios (OR/aOR) and their 95% confidence intervals (CIs) were calculated as effect size using non-anti-IL6 treated patients as reference groups. To avoid case deletion in analyses, missing data for outcomes and pre-specified confounding factors were imputed by simple imputation using the regression-switching approach. The imputation procedure was performed under the missing-at-random assumption, with the predictive mean-matching method for continuous variables and logistic regression (binary, ordinal, or multinomial) models for categorical variables. All statistical tests were performed at the two-tailed α level of 0.05 using SAS software, 9.4 release (SAS Institute, Cary, NC, USA).

Results

Data were collected between April 15, 2020, and June 15, 2021 from 1883 patients with RMD (mean age 55.2 years [SD 16.7]); 1256 (66.7%) of them were female. Seventy-three (3.9%) of the 1883 patients were treated with anti-IL6 therapy, mainly for chronic inflammatory arthritis (52 [71.2%] of 73), and large-vessel vasculitis (16 [21.9%]; Table 1). Of the 73 RMD patients treated with anti-IL6 therapy, 6 were treated with sarilumab and 67 with tocilizumab. Of the anti-IL6 patients, 30 were treated with intravenous anti-IL6 therapy, 41 were treated with the subcutaneous form, and 2 were unknown. Patients who received anti-IL6 therapy were more likely to be female, and showed higher prevalence rates of cardiovascular diseases, BMI (kg/m^2) ≥40, hypertension and corticosteroid use than those who did not receive anti-IL6 therapy. The details of the diagnoses are given in Supplemental Table 1.

Anti-IL6 treatment and COVID-19 severity

In the overall population, 1263 (67.1%) of the 1883 patients with RMD developed mild COVID-19, 410 (21.8%) moderate COVID-19 and 210 (11.1%) severe COVID-19 (Table 2). The distribution of COVID-19 severity was significantly different according to the use or non-use of anti-IL6 treatment ($p < 0.001$), with less frequent severe disease in the anti-IL6 group compared with the no anti-IL6 group (aOR for moderate vs. mild, 0.23 [95% CI, 0.10 to 0.54], $p = 0.01$ and aOR for severe vs. mild, 0.29 [95% CI, 0.10 to 0.81], $p \leq 0.05$; Fig. 1A). Using patients treated with any non-anti-IL6 biotherapy as the control group, we also found a significant difference in COVID-19 severity in favour of anti-IL6 treated patients (aOR for moderate vs mild, 0.35 [95% CI, 0.15 to 0.83], $p \leq 0.05$), although the difference did not reach statistical significance for severe versus mild COVID-19 disease (aOR, 0.40 [95% CI, 0.14 to 1.15]). The use of glucocorticoids (GC) in anti-IL6 and non-anti-IL6 treated patients seemed worse COVID-19 infection severity and outcome (data not shown). When patients treated only with rituximab were used as a control group, the distribution of COVID-19 severity was also significantly different ($p < 0.001$), with a greater effect size in favour of anti-IL6 treated patients (aOR of moderate vs mild, 0.12 [95% CI, 0.04 to 0.32] and aOR for severe vs mild, 0.08 [95% CI, 0.03 to 0.26]). When using anti-TNF-treated patients as controls, no significant difference in the distribution of COVID-19 severity was found. Finally, when patients treated with any non-anti-IL6 biotherapy except rituximab were used as a control group, the difference in COVID-19 severity grade was not significant, although a lower risk of moderate infection relative or mild infection was found (aOR, 0.40 [95% CI, 0.16 to 0.97], $p \leq 0.05$). COVID-19 severity according to the underlying disease showed that patients with vasculitis seemed to have more severe SARS-CoV-2 infection compared to patients with chronic inflammatory arthritis. No difference of mortality was observed according to the underlying disease, except in non-anti-IL6 group with higher mortality in patients with vasculitis (data not shown).

Table 1
Clinical characteristics of RMD patients receiving and not receiving anti-IL6 therapy prior to SARS-CoV-2 infection.

	Overall (n = 1883)	Anti-IL6 group (n = 73)	Non-Anti-IL6 group (n = 1810)
Age (years)			
18–54	904 (48.0)	33 (45.2)	871 (48.1)
55–64	395 (21.0)	15 (20.5)	380 (21.0)
65–74	326 (17.3)	16 (21.9)	310 (17.1)
≥75	258 (13.7)	9 (12.3)	249 (13.8)
Mean ± SD	55.2 ± 16.7	56.8 ± 15.6	55.2 ± 16.7
Female sex	1256 (66.7)	57 (78.1)	1199 (66.2)
Comorbidities[a]			
Respiratory disease	256 (13.6)	11 (15.1)	245 (13.6)
Interstitial lung disease	90 (4.8)	3 (4.1)	87 (4.8)
COPD	75 (4.0)	4 (5.5)	71 (3.9)
Asthma	110 (5.8)	5 (6.8)	105 (5.8)
Cardiovascular disease	215 (11.4)	13 (17.8)	202 (11.2)
Coronary heart disease	177 (9.4)	10 (13.7)	167 (9.2)
Stroke	55 (2.9)	4 (5.5)	51 (2.8)
Diabetes	188 (10.0)	7 (9.6)	181 (10.0)
BMI (kg/m^2)			
<30	1282 (75.6)	49 (75.4)	1233 (75.6)
30–39.9	368 (21.7)	13 (20.0)	355 (21.8)
≥40	46 (2.7)	3 (4.6)	43 (2.6)
Hypertension	447 (23.8)	25 (34.2)	422 (23.3)
Cancer	67 (3.6)	1 (1.4)	66 (3.7)
Smoking	174 (9.3)	5 (6.8)	169 (9.3)
Chronic renal failure	92 (4.9)	3 (4.1)	89 (4.9)
No. of patients with at least 1 comorbidity	1272 (67.6)	46 (63.0)	1226 (67.8)
Disease History			
Chronic inflammatory arthritis	1250 (66.4)	52 (71.2)	1198 (66.2)
Auto-inflammatory diseases	27 (1.4)	4 (5.5)	23 (1.3)
Vasculitis	180 (9.6)	16 (21.9)	164 (9.1)
Systemic auto-immune diseases	367 (19.5)	1 (1.4)	366 (20.2)
Rheumatic Diseases or AI²D treatments			
Corticosteroid	553 (29.4)	28 (38.4)	525 (29.0)
Systemic corticosteroid doses ≥10 mg	207 (37.7)	10 (35.7)	197 (37.8)
NSAIDs	159 (8.4)	2 (2.7)	157 (8.7)
Colchicine	73 (3.9)	0	73 (4.0)
Hydroxychloroquine	172 (9.1)	0	172 (9.5)
Methotrexate	645 (34.3)	22 (30.1)	623 (34.4)
Leflunomide	72 (3.8)	6 (8.2)	66 (3.6)
Salazopyrine	22 (1.2)	0	22 (1.2)
Mycophenolate Mofetil/ mycophenolic acid	47 (2.5)	1 (1.4)	46 (2.5)
Azathioprine	26 (1.4)	0	26 (1.4)
IgIV	9 (0.5)	0	9 (0.5)
Targeted biologic or synthetic therapies			
anti-TNF	535 (28.4)	0	535 (29.6)
rituximab	100 (5.3)	0	100 (5.5)
anti-IL6	73 (3.9)	73 (100.0)	0
anti-IL17A	58 (3.1)	0	58 (3.2)
anti-IL1	14 (0.7)	0	14 (0.8)
abatacept	41 (2.2)	0	41 (2.3)
JAK inhibitor	70 (3.7)	0	70 (3.9)
Other biologics	36 (1.9)	0	36 (2.0)

Values are presented as frequency (percentage) unless otherwise indicated.
Abbreviations: SD, standard deviation; BMI, body mass index.
[a] 2 missing values for comorbidities except for BMI where 187 values are missing (anti-il6, n = 8; non-anti-il6, n = 179; all biotherapy, n = 91).

Anti-IL6 treatment and COVID-19 outcomes

In the overall population, 1353 (75.8%) patients recovered without sequelae from COVID-19, 317 (17.8%) recovered with sequelae, and 115 (6.4%) died (Table 2). No significant differences were found between the anti-IL6 group and each control group for COVID-19 evolution, except with the rituximab group ($p \leq 0.05$). However, anti-IL6 without glucocorticoids (GC) treated patients seemed to have better

Table 2
Description of COVID-19 outcomes according to different study groups.

Severity/Outcome	Overall (n = 1883)	Anti-IL6 group (n = 73)	Non-Anti-IL6 group (n = 1810)	Any non-anti-IL6 biotherapy (n = 854)	Any non-anti-IL6 except rituximab (n = 754)	rituximab (n = 100)	Anti-TNF (n = 535)
Severity							
Mild	1263 (67.1)	61 (83.6)	1202 (66.4)	644 (75.4)	606 (80.4)	38 (38.0)	454 (84.9)
Moderate	410 (21.8)	7 (9.6)	403 (22.3)	140 (16.4)	108 (14.3)	32 (32.0)	65 (12.1)
Severe	210 (11.1)	5 (6.8)	205 (11.3)	70 (8.2)	40 (5.3)	30 (30.0)	16 (3.0)
Outcome [a]							
Recovery without sequelae	1353 (75.8)	56 (80.0)	1297 (75.6)	637 (77.9)	582 (80.5)	55 (57.9)	422 (81.6)
Recovery with sequelae	317 (17.8)	12 (17.1)	305 (17.8)	149 (18.2)	127 (17.6)	22 (23.2)	90 (17.4)
Death	115 (6.4)	2 (2.9)	113 (6.6)	32 (3.9)	14 (1.9)	18 (18.9)	5 (1.0)

Values are presented as frequency (percentage).
[a] 98 missing values for outcome.

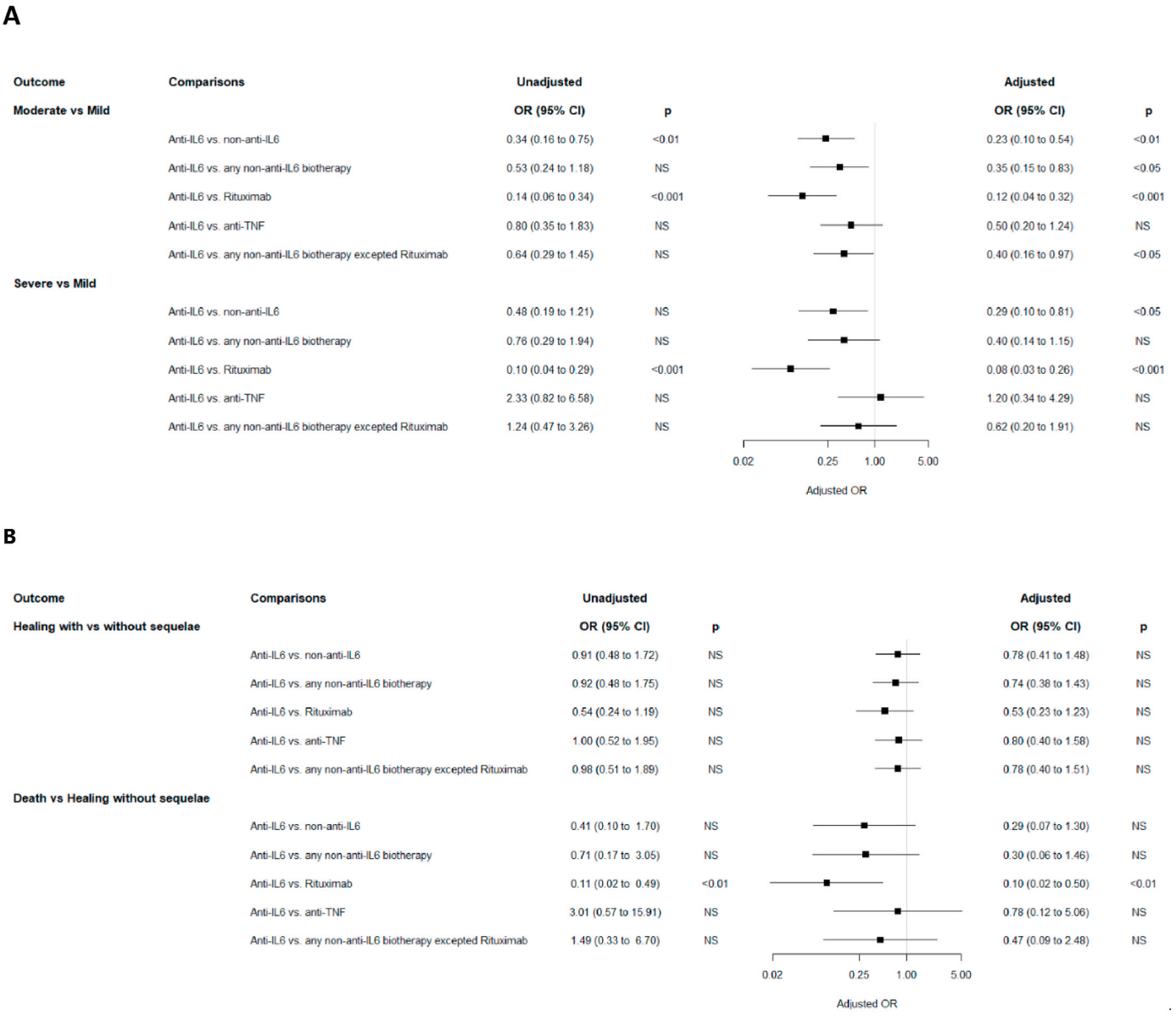

Fig. 1. Effect sizes on COVID-19 severity according to anti-IL6 therapy received prior to SARS-CoV-2 infection and each control group.

outcome than anti-IL6 associated with GC treated patients (data not shown). Relative to recovery without sequelae, recovery with sequelae was not significantly different between these two groups (aOR, 0.53 [95% CI, 0.23 to 1.23], but deaths were more frequent in patients treated with rituximab than in those receiving anti-IL6 therapy (aOR, 0.10 [95% CI, 0.02 to 0.50], $p \leq 0.01$, Fig. 1B). Except for the RMD

patients receiving rituximab before SARS-Cov-2 infection, no difference was observed in COVID-19-related death between the different groups compared to anti-IL6 group: non-anti-IL6 control group, any non-anti-IL6 biotherapy, anti-TNF group, any non-anti-IL6 biotherapy excepted Rituximab.

Discussion

The COVID-19 pandemic continues to cause widespread morbidity and mortality. We examined an important subpopulation of patients with RMD and long-term use of immunosuppressive medications. After adjustment for potentially confounding covariates, the risk of hospitalisation and respiratory support was less frequent among RMD patients receiving anti-IL6 therapy prior to COVID-19 diagnosis than their counterparts. However, no difference was observed for recovery with or without sequelae, except for the rituximab subgroup. In patients with RMD, COVID-19 severity and outcomes were similar between the anti-IL6 group and anti-TNF group. The use of glucocorticoids in anti-IL6 and non-anti-IL6 treated RMD patients prior SARS-Cov-2 infection seemed to worse COVID-19 severity and outcome. Our findings suggest that, unlike with rituximab, anti-IL6 drugs in RMD patients were not associated with more severe presentation or more frequent adverse outcomes of COVID-19 and could be continued during the COVID-19 pandemic. Such results suggest that all immunosuppressive drugs are not equal in the face of SARS-CoV-2 infection.

Patients with COVID-19 pneumonia have a deleterious excessive production of pro-inflammatory cytokines, including IL6 [18]. One possible mechanism linking anti-IL6 therapy in RMD patients to less severe COVID-19 disease is blockage of the interleukin 6 pathway, which is involved in slowing down the cytokine storm, systemic inflammatory response syndrome and lung damage. Many survivors of severe COVID-19 disease have long-term residual pulmonary abnormalities on their thoracic CT scans, sometimes referred to as "post--COVID interstitial lung disease" with "fibrotic-like" appearances. Han et al. reported the existence of residual CT abnormalities at 6 months in a large proportion (62%) of patients with severe COVID-19, including 35% of the total cohort (n = 114) with "fibrotic-like" features (the presence of parenchymal bands, irregular interfaces [bronchovascular, pleural, or mediastinal], traction bronchiectasis, and/or honeycombing) [19]. The remaining participants with residual abnormalities had ground-glass opacification and interstitial thickening; 26% of patients had reduced gas transfer levels. These "fibrotic-like" features and residual ground-glass opacities observed in post-COVID interstitial lung disease share radiological similarities with systemic sclerosis-induced interstitial lung disease. Interestingly, subcutaneous injection of tocilizumab has been shown to improve the rate of lung function in patients with systemic sclerosis-induced interstitial lung disease when compared with a placebo. Tocilizumab preserved lung function, slowing decline in the forced vital capacity of patients with systemic sclerosis-induced interstitial lung disease [20,21].

In relation to the benefits of continuing immunosuppressive drugs during the COVID-19 pandemic, it is important to keep in mind that viruses can trigger autoimmune disease, including systemic vasculitis [22]. In severe COVID-19, auto-inflammatory pathways contribute to vascular lesions and organising pneumonia-like changes. A small COVID-19 autopsy study recently documented the existence of inflammatory perivascular lesions distant from sites of epithelial injury, suggesting that direct viral effects as well as perivascular inflammation may contribute to endothelial injury [23]. While the cytokines induced in COVID-19 and released during cytokine storms have been well characterised, the downstream inflammatory pathways spreading the subsequent inflammation are less understood. The efficacy of anti-cytokine therapy such as anti-IL6 on this pathogenic process is largely unknown. Conflicting data persist concerning the efficacy of sarilumab or tocilizumab in the treatment of COVID-19, while the mechanism of action of these two IL6-receptor antagonists is similar regarding inhibition of the IL-6 pathway [15,24,25].

Our study has several limitations inherent to observational research, including the potential for unmeasured confounders. It is unclear whether the pre-existing duration of chronic immunosuppressive use may have affected the COVID-19 outcomes. We were unable to consider certain variables, including the COVID-19 vaccination status, disease activity, duration of immunosuppressive treatment, and level of immunosuppression. The specific management of immunosuppressive drug therapy (duration of withholding, or continuation, or dose reduction) during COVID-19 illness and potential therapy added to the standard of care in the treatment of COVID-19 were unknown.

Our analysis also has many strengths. We reported the real-life experience of COVID-19 disease among a large cohort of patients with RMD receiving immunosuppressive therapy such as biologics or DMARDs.

In summary, RMD patients treated with anti-IL6 therapy prior to COVID-19 diagnosis had less severe COVID-19 disease compared with those without anti-IL6 therapy. Except for the rituximab subgroup, no difference was observed for recovery with or without sequelae. The outcomes of COVID-19 did not differ between patients on anti-IL6 and anti-TNF therapy. Our results provide reassurance to clinicians using anti-IL6 therapy in RMD patients, thereby supporting the recommendation to not discontinue these chronic treatments during the COVID-19 pandemic. We suggest that practitioners not withhold anti-IL6 therapy in RMD patients receiving tocilizumab or sarilumab prior to SARS-CoV-2 infection.

Data sharing

All relevant anonymised patient-level data are available upon reasonable request from the corresponding author.

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Contributors

CC, EH, and PC were responsible for conceptualisation of the study. ED, JL, CC, EH, and PC were responsible for formal data analysis. CC, ED, EH, and PC were responsible for methodology and project administration. EH was responsible for obtaining ethics approval. CC, EH, and PC were responsible for writing the first draft of the report. CC, ED, EH, and PC were responsible for verification of all the underlying data. The corresponding authors had the final responsibility of submission for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2023.100190.

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