COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study

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Summary

Background Various observations have suggested that the course of COVID-19 might be less favourable in patients with inflammatory rheumatic and musculoskeletal diseases receiving rituximab compared with those not receiving rituximab. We aimed to investigate whether treatment with rituximab is associated with severe COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases.

Methods In this cohort study, we analysed data from the French RMD COVID-19 cohort, which included patients aged 18 years or older with inflammatory rheumatic and musculoskeletal diseases and highly suspected or confirmed COVID-19. The primary endpoint was the severity of COVID-19 in patients treated with rituximab (rituximab group) compared with patients who did not receive rituximab (no rituximab group). Severe disease was defined as that requiring admission to an intensive care unit or leading to death. Secondary objectives were to analyse deaths and duration of hospital stay. The inverse probability of treatment weighting propensity score method was used to adjust for potential confounding factors (age, sex, arterial hypertension, diabetes, smoking status, body-mass index, interstitial lung disease, cardiovascular diseases, cancer, corticosteroid use, chronic renal failure, and the underlying disease [rheumatoid arthritis *vs* others]). Odds ratios and hazard ratios and their 95% CIs were calculated as effect size, by dividing the two population mean differences by their SD. This study is registered with ClinicalTrials.gov, NCT04353609.

Findings Between April 15, 2020, and Nov 20, 2020, data were collected for 1090 patients (mean age 55·2 years [SD 16·4]); 734 (67%) were female and 356 (33%) were male. Of the 1090 patients, 137 (13%) developed severe COVID-19 and 89 (8%) died. After adjusting for potential confounding factors, severe disease was observed more frequently (effect size 3·26, 95% CI 1·66–6·40, p=0·0006) and the duration of hospital stay was markedly longer (0·62, 0·46–0·85, p=0·0024) in the 63 patients in the rituximab group than in the 1027 patients in the no rituximab group. 13 (21%) of 63 patients in the rituximab group died compared with 76 (7%) of 1027 patients in the no rituximab group, but the adjusted risk of death was not significantly increased in the rituximab group (effect size 1·32, 95% CI 0·55–3·19, p=0·53).

Interpretation Rituximab therapy is associated with more severe COVID-19. Rituximab will have to be prescribed with particular caution in patients with inflammatory rheumatic and musculoskeletal diseases.

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Introduction

The COVID-19 pandemic initially raised concerns about the risk of severe infection in patients with inflammatory rheumatic and musculoskeletal diseases. Preliminary data were reassuring about the risk of severe COVID-19 pneumonia in patients with inflammatory rheumatic and musculoskeletal diseases treated with targeted biological or synthetic disease-modifying antirheumatic drugs (DMARDs).[1–3] Subsequently, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) provisional guidelines stated that there was no evidence that patients with inflammatory rheumatic and musculoskeletal diseases were at higher risk of infection with SARS-CoV-2, and did not have a worse prognosis with a diagnosis of COVID-19, than individuals without such diseases.[4,5] These findings were supported by an analysis of the French RMD COVID-19 cohort, which included individuals with inflammatory rheumatic and musculoskeletal diseases and highly suspected or a confirmed diagnosis of COVID-19.[6] In this cohort, the use of methotrexate, tumour necrosis factor (TNF), and interleukin (IL)-6 inhibitors was not related to severe COVID-19 outcomes, and anti-TNF therapy was associated with less frequent hospital admission. In addition, when matched for common comorbidities, there was no difference in the frequency of

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Research in context

Evidence before this study

We searched MEDLINE and Embase for studies published in English between March 1, 2020, and Dec 1, 2020, using the search terms "rituximab" and "COVID-19". We found several case reports and small series that suggested a possible association between rituximab and a severe COVID-19 in patients with inflammatory rheumatic and musculoskeletal diseases. We also considered the first analysis of the French RMD COVID-19 cohort, which identified a potential risk of more severe COVID-19 in patients treated with rituximab. However, the objective of this first study was to identify epidemiological characteristics associated with severe disease in patients with inflammatory rheumatic and musculoskeletal diseases. This analysis detected several factors, including a signal for rituximab, but this result was preliminary, since it did not take into account the main characteristics and potential confounders of patients receiving this drug (ie, comorbidities and corticosteroid use). Moreover, we did not find any cohort studies that specifically assessed whether rituximab itself adversely affects COVID-19 outcomes.

Added value of this study

We compared COVID-19 severity in patients with inflammatory rheumatic and musculoskeletal diseases who were treated with rituximab and in those who were not. We collected data on and adjusted for the main comorbidities associated with COVID-19 severity and rituximab prescription, and we used a specific control group of patients who were eligible for rituximab therapy by indication, but did not receive it. Our findings show that rituximab is associated with more severe COVID-19. Time between last infusion of rituximab and first symptoms of COVID-19 was significantly shorter in patients who developed a severe COVID-19 than those with moderate or mild forms, which supports direct drug accountability. In addition, compared with patients who did not receive rituximab, a prolonged hospital stay was observed in patients treated with rituximab, increasing the risk of morbidity, mortality, and potential infection-related sequelae. More patients treated with rituximab died, but the risk of death did not increase significantly compared with patients not treated with rituximab after adjusting for potential confounders, which emphasises the weight of associated comorbidities on the risk of death.

Implications of all the available evidence

Rituximab will have to be prescribed with particular caution for patients with inflammatory rheumatic and musculoskeletal diseases, especially if they have other comorbidities that render them at risk of severe COVID-19 outcomes. Future research is now required to confirm this result in independent cohorts from other countries.

death among people with inflammatory rheumatic and musculoskeletal diseases compared with people without such diseases.[6] However, corticosteroids (at a dose of >10 mg per day) were associated with an increased risk of severe COVID-19, and a potential risk of more severe COVID-19 in patients with interstitial lung disease or those treated with rituximab was observed.[6–8] This finding was supported by several other observations made in patients with severe, sometimes fatal, COVID-19 who received rituximab for the treatment of different conditions,[7] including rheumatoid arthritis[9] granulomatosis with polyangiitis,[10] systemic sclerosis,[11,12] and haematological malignancies.[13] These various observations suggest that the course of COVID-19 seems less favourable with rituximab than that described with other targeted treatments, with the possibility that severe forms of COVID-19 might be linked to a drug-induced defect in the antiviral humoral response. Conversely, non-serious cases of COVID-19 in patients treated with rituximab have also been reported.[14,15] Thus, it is crucial to further clarify the risk of severe COVID-19 in patients receiving rituximab, and to assess whether rituximab itself adversely affects COVID-19 outcomes or whether other confounding factors have an effect. To that end, our aim was to investigate whether treatment with rituximab is associated with severe disease and death in the French RMD COVID-19 cohort, taking into account the main comorbidities associated with COVID-19 severity and rituximab prescription, and considering a specific control group of patients with diseases for which rituximab is a recognised therapeutic option, but who did not receive rituximab.

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] Briefly, the French RMD COVID-19 cohort included patients aged 18 years or older with confirmed inflammatory rheumatic and musculoskeletal diseases and highly suspected or a confirmed diagnosis of COVID-19. 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), received permission from Lille University Hospital (Lille, France), and was declared to the 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. The individual data regarding diagnosis of or specific ongoing treatments for inflammatory rheumatic and musculoskeletal diseases were captured from physicians via one national data entry portal. Data collected from patients'

medical records have previously been described in detail.[6] Data cutoff was on Nov 20, 2020. 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. All participants were followed up until the worst COVID-19 outcome at the time of dataset lock.

Outcomes

The primary outcome was to compare the severity of COVID-19 in patients treated or not treated with rituximab, considered by the clinician as the last ongoing treatment. The severity of COVID-19 was assessed and classified according to the care needed for 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 outcomes were to compare frequency of deaths and duration of hospital stay in patients treated or not with rituximab.

Statistical analysis

Categorical variables were expressed as numbers (percentage), and quantitative variables as mean (SD). Two control groups were considered for comparison with patients in the rituximab group: the no rituximab group included all patients with inflammatory rheumatic and musculoskeletal diseases who did not receive rituximab, and the no rituximab subgroup consisted of patients in the no rituximab group who did not receive rituximab despite having diseases for which rituximab is a recognised therapeutic option (appendix p 1).

We compared outcomes between groups (rituximab group *vs* no rituximab group and rituximab group *vs* no rituximab subgroup) using a multinomial logistic regression model for severity outcome measures (a three-level categorical variable), a binary logistic regression model for binary outcomes (death), and a Fine and Gray regression model for duration of hospital stay, with discharge alive as event of interest and death in hospital as competing event.[16] Odds ratios (ORs) and hazard-ratios (HRs) and their 95% CIs were calculated as effect size using the no rituximab group and subgroup as reference groups. To consider the potential confounding factors, we made comparisons by using inverse probability of treatment weighting (IPTW) propensity score method (using stabilised inverse propensity score as weights in regression models)[17] as the primary analysis and by using propensity score matching method as the secondary analysis. We estimated the propensity score using a multivariable logistic regression model, including prespecified confounding factors (ie, age, sex, arterial hypertension, diabetes, smoking status, body-mass index (BMI), interstitial lung disease, cardiovascular diseases, cancer, corticosteroid use, chronic renal failure, and the underlying disease [rheumatoid arthritis *vs* others]). In propensity score matching analyses, patients in the rituximab group and those in the no rituximab group were matched using an optimal algorithm with caliper width of 0·2 SD of logit for propensity score,[18] without replacement and a maximum ratio of 1:4. To evaluate the bias reduction, we calculated absolute standardised differences before and after applying propensity score methods. An absolute standardised difference of more than 10% was interpreted as a meaningful difference.[19] To avoid case deletion in analyses, we imputed missing data for outcomes and prespecified confounding factors by simple imputation using the regression-switching approach.[20] The imputation procedure was carried out under the missing-at-random assumption, with predictive mean-matching method for continuous variables and logistic regression (binary, ordinal, or multinomial) models for categorical variables. For duration of hospital stay, all analyses were done in patients admitted to hospital, and therefore we calculated a specific propensity score.

Finally, in the rituximab group, we compared the lag time between last infusion of rituximab between the disease severity using Kruskal-Wallis test (followed by Dunn's pairwise post-hoc comparisons) and between alive and deceased patients using the Mann-Whitney *U* test.

All statistical tests were performed at the two-tailed α level of 0·05 using SAS software (version 9.4).

This study is registered with ClinicalTrials.gov, NCT04353609.

Role of the funding source

There was no funding source for this study.

Results

Between April 15, 2020, and Nov 20, 2020, we collected records for 1090 patients (mean age 55·2 years [SD 16·4]), all of which were included in the analysis of COVID-19 severity (primary endpoint). Of 1090 patients, 734 (67%) were female, and 557 (51%) were older than 55 years. 756 (69%) of 1089 patients had at least one comorbidity, with hypertension, obesity with a BMI of more than 30 kg/m², respiratory disease, and cardiovascular disease as the most common (table 1).

63 (6%) of 1090 patients were treated with rituximab, mainly for rheumatoid arthritis (31 [49%] of 63), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (11 [17%]), and systemic sclerosis (seven [11%]; table 1). Patients who received rituximab were more likely to be male, with older age, and higher prevalence of comorbidities and corticosteroid use than those who did not receive rituximab (table 1).

The absolute standardised differences between the rituximab group and no rituximab group and subgroup before and after applying propensity score methods are presented in the appendix (pp 4–5).

137 (13%) of 1090 patients had severe COVID-19. Patients in the rituximab group were more likely to develop severe disease than patients in the no rituximab group (table 2) and those in the no rituximab subgroup (table 3).

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See **Online** for appendix

	Overall (n=1090)	Rituximab group (n=63)	No rituximab group (n=1027)	No rituximab subgroup* (n=495)
Age, years	55·2 (16·4)	59·1 (15·1)	55·0 (16·5)	58·5 (16·0)
18–54	533 (49%)	22 (35%)	511 (50%)	192 (39%)
55–64	219 (20%)	14 (22%)	205 (20%)	110 (22%)
65–74	182 (17%)	17 (27%)	165 (16%)	104 (21%)
≥75	156 (14%)	10 (16%)	146 (14%)	89 (18%)
Sex				
Female	734 (67%)	38 (60%)	696 (68%)	385 (78%)
Male	356 (33%)	25 (40%)	331 (32%)	110 (22%)
Comorbidities†				
Respiratory disease	145/1089 (13%)	6 (10%)	139/1026 (14%)	85 (17%)
Interstitial lung disease	38/1089 (3%)	4 (6%)	34/1026 (3%)	31 (6%)
COPD	42/1089 (4%)	1 (2%)	41/1026 (4%)	28 (6%)
Asthma	72/1089 (7%)	1 (2%)	71/1026 (7%)	31 (6%)
Cardiovascular disease	131/1089 (12%)	10 (16%)	121/1026 (12%)	75 (15%)
Coronary heart diseases	108/1089 (10%)	9 (14%)	99/1026 (10%)	57 (12%)
Stroke	33/1089 (3%)	2 (3%)	31/1026 (3%)	24 (5%)
Diabetes	110/1089 (10%)	10 (16%)	100/1026 (10%)	57 (12%)
Body-mass index, kg/m²				
<30	741/969 (76%)	54/62 (87%)	687/907 (76%)	327/434 (75%)
30–39	199/969 (21%)	8/62 (13%)	191/907 (21%)	94/434 (22%)
≥40	29/969 (3%)	0	29/907 (3%)	13/434 (3%)
Hypertension	271/1089 (25%)	16 (25%)	255/1026 (25%)	155 (31%)
Cancer	44/1089 (4%)	5 (8%)	39/1026 (4%)	30 (6%)
Smoking	106/1089 (10%)	3 (5%)	103/1026 (10%)	50 (10%)
Chronic renal failure	64/1089 (6%)	7 (11%)	57/1026 (6%)	41 (8%)
Patients with at least one comorbidity	756/1089 (69%)	48 (76%)	708/1026 (69%)	383 (77%)
Rheumatic disease				
Rheumatoid arthritis	334 (31%)	31 (49%)	303 (30%)	303 (61%)
ANCA-associated vasculitis	23 (2%)	11 (17%)	12 (1%)	12 (2%)
Systemic sclerosis	43 (4%)	7 (11%)	36 (4%)	36 (7%)
Primary Sjögren syndrome	33 (3%)	4 (6%)	29 (3%)	29 (6%)
Other vasculitis	15 (1%)	2 (3%)	13 (1%)	13 (3%)
Mixed connective tissue disease	6 (1%)	2 (3%)	4 (<1%)	4 (1%)
Systemic lupus erythematosus	80 (7%)	2 (3%)	78 (8%)	78 (16%)
IgG4-related disease	4 (<1%)	2 (3%)	2 (<1%)	2 (<1%)
Inflammatory myopathy (including dermatomyositis, polymyositis)	17 (2%)	1 (2%)	16 (2%)	16 (3%)
Eye inflammation (including uveitis)	3 (<1%)	1 (2%)	2 (<1%)	2 (<1%)
Others	532 (49%)	0	532 (52%)	0
Treatments				
Corticosteroids	347 (32%)	34 (54%)	313 (30%)	196 (40%)
Systemic corticosteroid doses ≥10 mg	127/345 (37%)	13/34 (38%)	114/311 (37%)	67/195 (34%)
Non-steroidal anti-inflammatory drugs	99 (9%)	2 (3%)	97 (9%)	28 (6%)
Colchicine	38 (3%)	0	38 (4%)	3 (1%)
Hydroxychloroquine	98 (9%)	3 (5%)	95 (9%)	89 (18%)
Methotrexate	393 (36%)	21 (33%)	372 (36%)	233 (47%)
Leflunomide	43 (4%)	5 (8%)	38 (4%)	27 (5%)
Sulfasalazine	12 (1%)	0	12 (1%)	3 (1%)
Mycophenolate mofetil or mycophenolic acid	28 (3%)	1 (2%)	27 (3%)	25 (5%)
Azathioprine	14 (1%)	1 (2%)	13 (1%)	9 (2%)
IgIV	7 (1%)	0	7 (1%)	7 (1%)

(Table 1 continues on next page)

	Overall (n=1090)	Rituximab group (n=63)	No rituximab group (n=1027)	No rituximab subgroup* (n=495)
(Continued from previous page)				
Targeted biological or synthetic therapies				
Anti-TNF	318 (29%)	0	318 (31%)	74 (15%)
Anti-IL-6	35 (3%)	0	35 (3%)	23 (5%)
Anti-IL-17A	38 (3%)	0	38 (4%)	0
Anti-IL-1	9 (1%)	0	9 (1%)	1 (<1%)
Abatacept	24 (2%)	0	24 (2%)	22 (4%)
JAK inhibitor	35 (3%)	0	35 (3%)	30 (6%)
Other biologics	21 (2%)	0	21 (2%)	8 (2%)

Data are mean (SD), n (%), or n/N (%). ANCA=antineutrophil cytoplasmic antibody. COPD=chronic obstructive pulmonary disease. IL=interleukin. JAK=Janus kinase. TNF=tumour necrosis factor. *The no rituximab subgroup included patients in the no rituximab group who did not receive rituximab despite having diseases for which rituximab is a recognised therapeutic option. †Values for all comorbidities were missing for one individual in the no rituximab group; values for body-mass index were missing for one individual in the rituximab group and 120 individuals in the no rituximab group (61 of whom were also in the no rituximab subgroup).

Table 1: **Patient characteristics overall and according to treatment groups**

After adjusting for potential confounding factors by IPTW propensity score method, severe disease was confirmed as more frequent in the rituximab group than in the no rituximab group (effect size 3·26, 95% CI 1·66–6·40, p=0·0006; table 2) and the no rituximab subgroup (2·62, 95% CI 1·34–5·09, p=0·0046; table 3). The adjustment using the propensity score matching method did not change the results (appendix pp 2–3).

Notably, patients who developed severe disease had a more recent rituximab infusion compared with patients with mild or moderate disease. The time between the last infusion of rituximab and the first symptoms of COVID-19 was significantly shorter in patients who developed a severe form of COVID-19 (figure).

89 (8%) of 1090 patients in the cohort died. 13 (21%) of 63 patients in the rituximab group died, compared with 76 (7%) of 1027 patients in the no rituximab group (table 2) and 49 (10%) of 495 patients in the no rituximab subgroup (table 3). After considering potential relevant confounding factors, the risk of death was not significantly increased in the rituximab group compared with the no rituximab group (effect size 1·32, 95% CI 0·55–3·19, p=0·53; table 2) and the no rituximab subgroup (1·48, 0·68–3·20, p=0·32; table 3).

These results need to be taken cautiously since the adjustment using the propensity score matching method showed an increased risk of death in the rituximab group compared with the no rituximab group (effect size 2·43, 95% CI 1·10–8·43, p=0·028; appendix p 2). However, this finding was not confirmed when considering the no rituximab subgroup as the control (effect size 2·16, 95% CI 0·99–4·69, p=0·051; appendix p 3). Another point to consider was the significantly shorter interval between the last rituximab infusion and the first symptoms of COVID-19 in deceased patients than in survivors (figure).

In line with severe COVID-19, the duration of hospital stay was markedly longer in the rituximab group than in the no rituximab group and subgroup, independent of the adjustment method (tables 2, 3; appendix pp 2–3).

	Rituximab group (n=63)	No rituximab group (n=1027)	Effect size (95% CI)*	p value
Severity	..	..	..	0·0018
Mild	21 (33%)	645 (63%)	1 (ref)	..
Moderate	20 (32%)	267 (26%)	1·98 (1·08–3·63)†	0·026
Severe	22 (35%)	115 (11%)	3·26 (1·66–6·40)†	0·0006
Duration of hospital stay, days	13 (7–not reached)	9 (4–17)	0·62 (0·46–0·85)‡	0·0024
Death	13 (21%)	76 (7%)	1·32 (0·55–3·19)†	0·53

Data are n (%) or median (IQR), unless otherwise indicated. *Effect size calculated using a regression models weighted by inverse probability of treatment weighting propensity score with the no rituximab group as the reference group. †Odds ratio calculated using multinomial or binary logistic regression models. ‡The subhazard ratio was calculated among 424 patients (42 in the rituximab group) admitted to hospital; a subhazard ratio of less than 1 indicates an increase in duration of hospital stay in comparison to the reference group.

Table 2: **Comparison in outcomes between rituximab and non-rituximab treated patients in inverse probability of treatment weighting propensity score analyses**

Discussion

Our findings support previous studies showing that rituximab therapy is associated with severe COVID-19 (defined in our study as admission to an ICU or death). In addition, a prolonged hospital stay was observed in the rituximab group compared with the no rituximab group (median 13 days *vs* 9 days), increasing the risk of morbidity, mortality, and potential infection-related sequelae. One crucial concern is to determine whether this worse outcome is related to rituximab per se or to the specific population that is treated by this medication. Indeed, rituximab is usually used in rheumatic diseases characterised by a higher risk of poor prognosis, including connective tissue disorders, vasculitis, or rheumatoid arthritis with systemic complications, especially interstitial lung disease. In addition, the profile of patients receiving rituximab (older age, male sex, higher frequency

	Rituximab group (n=63)	No rituximab subgroup* (n=495)	Effect size (95% CI)†	p value
Severity	..	..	..	0·018
Mild	21 (33%)	277 (56%)	1 (ref)	..
Moderate	20 (32%)	147 (30%)	1·47 (0·78–2·74)‡	0·23
Severe	22 (35%)	71 (14%)	2·62 (1·34–5·09)‡	0·0046
Duration of hospital stay, days	12 (6–not reached)	9 (4–19)	0·67 (0·45–0·99)§	0·040
Death	13 (21%)	49 (10%)	1·48 (0·68–3·20)‡	0·32

Data are n (%) or median (IQR), unless otherwise indicated. *The no rituximab subgroup included patients in the no rituximab group who did not receive rituximab despite having diseases for which rituximab is a recognised therapeutic option. †Effect size calculated using a regression models weighted by inverse probability of treatment weighting propensity score with non-rituximab treated patients as reference. ‡Odds-ratio calculated using multinomial or binary logistic regression models. §The subhazard ratio was calculated among 260 patients (42 in the rituximab group) admitted to hospital; a subhazard ratio of less than 1 indicates an increase in duration of hospital stay in comparison to the reference group.

Table 3: **Comparison in outcomes between the rituximab group and the no rituximab subgroup in inverse probability of treatment weighting propensity score analyses**

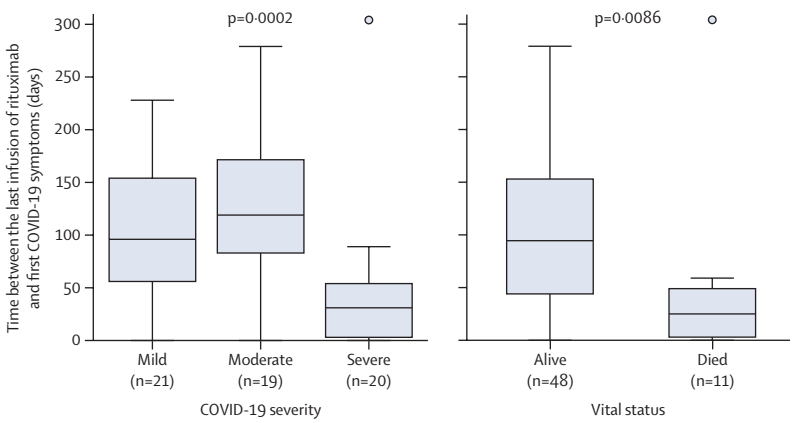

Figure: **Distribution (Tukey's box plot) of time between last infusion of rituximab according to disease severity and vital status**

Boxes show the 25th, 50th, and 75th, and whiskers indicates values outside the lower and upper quartile with a length equal to 1·5 IQR. p values for comparison (Kruskal-Wallis for comparison between disease severity and Mann-Whitney *U* test for comparison between alive and deceased patients) are reported; p=0·0018 for either post-hoc comparison of severe disease group with moderate or mild disease group (calculated using Dunn's test). Five patients with missing data were excluded.

of comorbidities, and corticosteroid use) is associated with increased risk of severe COVID-19. Notably, rituximab remained strongly associated with severe COVID-19 after adjustment for the main relevant confounders with two complementary methods, and the time between last infusion of rituximab and first symptoms of COVID-19 was significantly shorter in patients who developed a severe form of COVID-19 than those with moderate or mild forms, suggesting direct drug accountability. Moreover, this association persisted after the analysis of the subgroup of patients with diseases for which rituximab would be a recognised therapeutic option.

More patients in the rituximab group died than in the no rituximab group, but the risk of death did not increase significantly after adjusting for potential confounders by the IPTW propensity score method. This result emphasises the effect of associated comorbidities on the risk of death, as previously observed in the French RMD cohort and in the general population.[6] Of note, an increased risk of death in the rituximab group compared with the no rituximab group was observed after adjustment using the propensity score matching method, but it was not confirmed when the analysis focused on the subgroup of patients for whom rituximab would be a recognised therapeutic option.

Our findings support the concept that although the innate immune system[21] and T cells[22] are paramount in the early antiviral response, B cells are also crucial. Therefore, long-term administration of rituximab might be associated with decreased antibody production through B-cell depletion and reduced viral clearance, which might impair the priming of antibody responses to neutralise viral replication.[23,24] Rituximab and other B cell-depleting agents, while not alleviating the cytokine storm that causes severe morbidity, might radically inhibit the protective antibody immunity succeeding infection. This process might explain the cases of extended or atypical COVID-19 characterised by a negative or delayed serological response against SARS-CoV-2 in patients with depleted B cells.[25–28] Negative or delayed serological response might also be an issue regarding future COVID-19 vaccination, and plans for further studies on the effect of rituximab on COVID-19 vaccination are required.

Consequences for future management of patients with rituximab therapy during the COVID-19 pandemic could be a delay in its administration in patients with rheumatoid arthritis whenever sustained remission or low disease activity has been achieved. It seems more challenging to postpone rituximab administration in patients with connective tissue disorders or vasculitis considering the potentially increased risk of disease relapse or worsening and of severe organ involvement. Additional protective measures have been proposed, including testing for SARS-CoV-2 before giving rituximab, considering glucocorticoid dose reduction during rituximab application (despite SmPC labelled requirement), and instructing the patient to strictly follow the measures in place to avoid contact for several days following rituximab administration.[9]

The present findings are derived from observational analyses, which are subject to well known limitations. The first is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after propensity score adjustment methods. A second limitation is the presence of missing data in some covariates, including in the propensity score calculation. Although we used multiple imputations to handle missing data as appropriate,[29] we could not exclude the possibility that missing data could introduce a bias in estimates. Since we did no initial formal sample size calculation for primary and secondary objectives, we cannot exclude a lack of adequate statistical power to

detect significant differences. The number of patients with several diseases of interest (eg, ANCA-associated vasculitis, systemic sclerosis, and rheumatoid arthritis with interstitial lung disease) was too low to be analysed separately. Moreover, patients with active or very active inflammatory rheumatic and musculoskeletal diseases tend to be more heavily medicated and, since we were unable to obtain information about disease activity, we cannot rule out that the higher frequencies identified with rituximab could be confounded by indication. Another limitation is the absence of data regarding ethnicity, previous medications (eg, cyclophosphamide), rituximab dose and duration, and the presence of associated hypogammaglobulinaemia.

In conclusion, the analysis of the French COVID-19 RMD cohort suggests the possibility for differential risk of adverse clinical outcomes among patients with inflammatory rheumatic and musculoskeletal diseases based on the type of biological agents received. In particular, rituximab will have to be prescribed with particular caution in patients with inflammatory rheumatic and musculoskeletal diseases, especially if they have other comorbidities that render them particularly at risk of severe COVID-19 outcomes.

Contributors

JA, EH, and CR were responsible for conceptualisation of the study. RS, SG-L, SEM, EP, TP, HM, AS, FD, PCh, MD, PCl, VL, AM, ATJM, BB, BF, JP, TT, and R-MF were responsible for data curation. ED, JA, EH, and CR were responsible for formal data analysis. JA, ED, EH, BF, JP, TT, R-MF, and CR were responsible for methodology and project administration. EH was responsible for obtaining ethics approval. JA, EH, and CR were responsible for writing the first draft of the report. ED, RS, SG-L, SEM, EP, TP, HM, AS, FD, PCh, MD, PCl, VL, AM, ATJM, BB, BF, JP, TT, and R-MF were responsible for writing (review and editing) of the report. ED, EH, and CR were responsible for verification of all the underlying data. AH and CR were guarantors of the study. The corresponding author had the final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

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

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