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To cite this version:

Jérôme Avouac, Elodie Drumez, Eric Hachulla, Raphaèle Seror, Sophie Georgin-Lavialle, et al.. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. The Lancet Rheumatology, 2021, 3 (6), pp.e419-e426. 10.1016/S2665-9913(21)00059-X . hal-03365306

HAL Id: hal-03365306

https://hal.science/hal-03365306v1

Submitted on 13 Jun 2023

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Version of Record: https://www.sciencedirect.com/science/article/pii/S266599132100059X
Manuscript_3cf06e4fbcb63a9058b125e3ae14c5e8

Outcome of COVID-19 in patients with rheumatic and inflammatory diseases treated with RITUXIMAB: data from de French RMD COVID-19 cohort

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Abstract word count : 299 Manuscript word count: 2638
Keywords: COVID-19, rituximab, inflammatory rheumatic and musculoskeletal diseases

Abstract

Background: Various observations have suggested that the course of the COVID-19 infection may be less favorable in patients with inflammatory rheumatic and musculoskeletal diseases (iRMD) receiving rituximab (RTX). We aimed to investigate whether treatment with RTX is associated with severe infection and death.

Methods: Observational, multicenter, French national cohort study querying the French RMD COVID-19 cohort, including highly suspected/confirmed iRMD-COVID-19 patients. The primary endpoint was to assess the severity rate of COVID-19 in RTX treated patients compared to all RTX untreated iRMD patients. Severe disease was defined by hospitalization in intensive care unit or death. Secondary objectives were to analyze death rate and length of hospital stay. Adjusting on 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) was performed by inverse probability of treatment weighting propensity score method. Odds-ratio and hazard-ratio and their 95% confidence intervals were calculated as effect size (ES), by dividing the two population mean differences by their standard deviation.

Findings: of the 1,090 patients, 137 developed severe disease (12.6%), and 89 died (8.2%). After adjusting on potential confounding factors, a severe disease was observed more frequently (ES 3.26, 95% confidence interval, CI 1.66-6.40, $p<0.001$) and the length of hospital stay was markedly longer (ES 0.62, 95%CI 0.46-0.85, $p=0.002$) in the 63 patients receiving RTX compared to all non-RTX treated iRMD patients (n=1027).

Death rate was numerically higher in RTX treated patients (13/63, 20.6%) compared to all RTX untreated iRMDs patients (76/1027, 7.4%), but the adjusted risk of death was not significantly increased in RTX-patients (ES 1.32, 95%CI 0.55-3.19, $p=0.532$).

Interpretation: RTX therapy is associated with a more severe COVID-19 infection. RTX will have to be applied with particular caution in patients with iRMDs.

Funding: None

Research in context

Evidence before this study

We searched MEDLINE and Embase from March 1, 2020, to Dec 1, 2020, for studies published in English related to RTX and COVID-19. We found several case reports or small series that have identified Rituximab (RTX) as high risk of severe COVID-19 infection in patients with inflammatory rheumatic and musculoskeletal diseases (iRMD). We also considered the first analysis of the French RMD COVID-19 cohort published in Annals of the Rheumatic Diseases, which identified a potential risk of more severe COVID-19 in patients treated by RTX. 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 multiple factors including a signal for RTX, but this result was preliminary, since it did not take into account the main characteristics and potential confounders of patients receiving this drug (i.e. comorbidities, corticosteroid use). Moreover, we did not find large cohort studies that specifically assessed whether RTX itself adversely impacts COVID-19 outcomes.

Added value of this study

We collected and adjusted on the main comorbidities associated with COVID-19 severity and RTX prescription and we used a specific control group of RTX untreated patients eligible for this therapy, which represent added value compared to previous literature. Our findings support that RTX therapy is associated with a more severe COVID-19 infection defined by hospitalization in intensive care unit or death. Time between last infusion of RTX and first symptoms of COVID-19 was significantly shorter in patients who developed a severe form of COVID-19 than moderate or mild forms, which support direct drug accountability. In addition, prolonged hospitalization was observed in RTX treated patients, increasing the risk of morbidity, mortality and potential infection-related sequelae. Death rate was numerically

higher in patients treated with RTX, but the risk of death did not increase significantly compared to RTX untreated patients after adjusting on potential confounders, which emphasizes the weight of associated comorbidities on the risk of death,

Implications of all the available evidence

RTX will have to be applied with particular caution in patients with iRMDs, especially if they suffer from other comorbidities that render them particularly at risk. Future research is now required to confirm this result in independent cohorts from other countries.

Introduction

The COVID-19 pandemic initially raised concerns about the risk of severe infection in patients with inflammatory rheumatic and musculoskeletal diseases (iRMD). First preliminary reported data have been rather reassuring on the risk of severe COVID-19 pneumonia in iRMD patients treated with targeted biologic or synthetic therapy [1-3]. Subsequently, European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) provisional guidelines stated that there was no evidence that patients with iRMD were at higher risk of SARS-CoV-2 infection than individuals without iRMD, nor have a worse prognosis with a diagnosis of COVID-19 [4,5]. These findings were confirmed by the analysis of the French RMD COVID-19 cohort, who included individuals with highly suspected iRMD-COVID-19 [6]. In this cohort, the use of methotrexate, TNFα and IL-6 inhibitors was not related to severe infection and anti-TNFα therapy was associated with less frequent hospitalization. In addition, when matched for common comorbidities, the iRMD population had no more statistically frequent death compared to a non-iRMD population [6]. However, corticosteroids (with a dose >10 mg) were identified as high risk of severe infection, and a potential risk of more severe COVID-19 in patients with interstitial lung disease (ILD) or treated by Rituximab (RTX) has been suspected [6-8]. This finding was supported by several other observations made in severe, sometimes fatal, COVID-19 in patients receiving RTX for the treatment of different conditions, [7] including rheumatoid arthritis (RA) [9] granulomatosis with polyangiitis [10], systemic sclerosis [11,12] and haematological malignancies [13]. These various observations suggest that the course of the COVID-19 infection seems less favorable with RTX than that described with other targeted treatments, with the possibility of severe forms, which may be linked to a defect in the drug-induced antiviral humoral response. On the other hand, it is of note that many non-serious cases of COVID-19 in RTX treated patients have been reported as well [14,15]. Thus, it is crucial to further clarify the risk of severe COVID-19 in

patients receiving RTX, and assess whether RTX itself adversely impacts COVID-19 outcomes, or whether other confounding factors are influential. To that end, our aim was to investigate whether treatment with RTX is associated with severe infection and death in the French RMD COVID-19 cohort, taking into account the main comorbidities associated with COVID-19 severity and RTX prescription, and considering a specific control group of RTX untreated iRMD patients with diseases for which RTX is a recognized therapeutic option.

Patients and Methods

Study design and Patients: This is an observational, multicenter, French national cohort study querying the French RMD cohort, which has been previously described [6]. The study was conducted between April 15th, 2020 to November 20th, 2020. Briefly, it included ≥18 years old patients with confirmed iRMD and highly suspected/confirmed diagnosis of COVID-19. The study was performed in compliance with MR-004, received permission from Lille University Hospital, was declared to the Commission Nationale de l'Informatique et des Libertés (reference DEC20-107), and was registered on ClinicalTrials.gov (NCT04353609).

Data collection: All cases of highly suspected/confirmed iRMD-COVID-19 patients were reported retrospectively. The individual data regarding iRMD diagnosis/specific ongoing treatments were captured from physicians via one national data entry portal. Data collected from the patient's medical record were previously described in detail [6]. Data cutoff was on November 20th, 2020. Before freezing, 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 endpoint was to compare the severity rate in patients treated or not by RTX, 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=ambulatory; moderate=hospitalized out of intensive care unit (ICU); and severe=ICU or deceased. The secondary objectives were to compare death rates and length of hospital stay in patients treated or not by RTX.

Statistical analysis:

Categorical variables were expressed as numbers (percentage), and quantitative variables as mean ± standard deviation (SD).

Two control groups were considered for comparison with RTX treated patients: a first group including all RTX untreated iRMD patients (n=1027) and a second consisting on RTX untreated iRMD patients with diseases for which RTX is a recognized therapeutic option (n=495) (**Appendix p1**).

Comparison in outcomes between groups (RTX vs. non-RTX treated patients in overall population and in eligible patients for RTX) were made using multinomial logistic regression model for severity outcome measure (a 3-level categorical variable), using binary logistic regression model for binary outcomes (death) or using Fine and Gray regression model for length of hospital stay, with discharge alive as event of interest and hospital death as competing event [16]. Odds-ratio (OR) and hazard-ratio (HR) and their 95% confidence intervals (CIs) were calculated as effect size using non-RTX treated patients as reference groups. To consider the potential confounding factors, comparisons were done by using inverse probability of treatment weighting (IPTW) propensity score (PS) method (using stabilized inverse PS as weighs in regression models) [17], as primary analysis and by using PS matching method as secondary analysis. The PS was estimated using a multivariable logistic

regression model, including pre-specified confounding factors (namely, 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, RTX cases and non-RTX controls were matched using an optimal algorithm with caliper width of 0.2 standard deviation of logit for propensity score [18], without replacement and a maximum ratio of 1:4. To evaluate the bias reduction, absolute standardized differences were calculated before and after applying PS methods. An absolute standardized difference >10% was interpreted as a meaningful difference [19]. The absolute standardized differences between RTX treated patients and non-treated patients in both cohorts before and after applying propensity score methods are presented in **Appendix p 4 and 5**. 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 [20]. The imputation procedure was performed 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 length of hospital stay, all analyses were done in hospitalized patients and therefore we calculated a specific propensity score.

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

All statistical tests were performed at the two-tailed α level of 0.05 using SAS software, release 9.4 (SAS Institute, Cary, NC).

Role of the funding source

This study was not supported by research funding but FAI2R is funded by "le ministère des solidarités et de la santé". The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Study population

We collected a total of 1090 records, all with available final evaluation of COVID-19 severity (primary endpoint). Patients were mainly females (67.3%, 734/1090) with a mean age of 55.2±16.4 years, and 51.1% (557/1090) were over the age of 55. Almost 70% of the population had at least one comorbidity (756/1089), with hypertension (n=271/1089, 24.9%), obesity with a BMI over 30 kg/m2 (n=199/969, 20.5%), respiratory disease (n=145/1089, 13.3%), and cardiovascular disease (n=131/1089, 12.0%) as the most common (**Table 1**).

A total of 63 patients were treated with RTX, mainly for rheumatoid arthritis (RA) (31/63, 49.2%), vasculitis associated with cytoplasmic antineutrophil antibodies (11/63, 17.5%) and systemic sclerosis (7/63, 11.1%). RTX treated patients were more likely to be males, with older age, higher prevalence of comorbidities and corticosteroid use (**Table 1**).

Detailed disease characteristics of Rituximab treated patients and controls (all non-RTX treated iRMD patients, n=1027, and RTX untreated iRMD patients with diseases for which RTX is a recognized therapeutic option, n=495) are provided in **Table 1**.

Primary outcome: development of severe disease

The frequency of severe COVID-19 in patients with iRMD was 12.6% (137/1090). RTX treated patients were more likely to develop severe disease compared to all RTX untreated

iRMDs patients (34.9% vs. 11.2%) (**Table 2**) and the subgroup of untreated RTX patients with diseases eligible for RTX therapy (34.9% vs. 14.3%) (**Table 3**).

After adjusting on potential confounding factors by IPTW PS method, severe disease was confirmed to be observed more frequently in patients receiving RTX compared to all RTX untreated iRMD patients (effect size, ES 3.26, 95% confidence interval, CI 1.66 to 6.40, p<0.001) (**Table 2**) and the subgroup of untreated RTX patients with diseases eligible for RTX therapy (ES 2.62, 95% CI 1.34 to 5.09, p=0.005) (**Table 3**). The adjustment using the PS matching method did not change the sense of the results (**Appendix p 2 and 3**).

Interestingly, patients who developed a severe disease had a more recent rituximab infusion compared to patients with mild or moderate disease. Indeed, 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 1A**).

Secondary outcomes: death and length of hospital stay

Eighty-nine patients in our cohort died, resulting in an overall death rate of 8.2%. Death rate was numerically higher in RTX treated patients (13/63, 20.6%) compared to all RTX untreated iRMDs patients (76/1027, 7.4%) (**Table 2**) and the subgroup of untreated RTX patients with diseases eligible for RTX therapy (49/495, 9.9%) (**Table 3**). After considering potential relevant confounding factors, the risk of death was not significantly increased in patients treated with RTX compared to all RTX untreated iRMDs patients (ES 1.32, 95% CI 0.55 to 3.19, p=0.532) (**Table 2**) and the subgroup of untreated RTX patients with diseases eligible for RTX therapy (ES 1.48, 95% CI 0.68 to 3.20, p=0.317) (**Table 3**).

These results need to be taken cautiously since the adjustment using the PS matching method showed an increased risk of death in RTX treated patients compared to all RTX untreated iRMDs patients (ES 2.43, 95% CI 1.10 to 8.43, p=0.028) (**Appendix p 2**). However, this

finding was not confirmed when considering as control population the subset of patients with diseases eligible for RTX therapy (ES 2.16, 95% CI 0.99 to 4.69, p=0.051) (**Appendix p 3**). Another point to consider was the significantly shorter interval between the last RTX infusion and the first symptoms of COVID-19 in deceased patients (**Figure 1B**) compared to survivors.

In line with a more severe COVID-19 disease, the length of hospital stay was markedly longer in patients treated with RTX compared to both untreated RTX patient groups, independently of the adjustment method (**Tables 2, 3, Appendix p 2 and 3**).

Discussion

Our findings support that RTX therapy is associated with a more severe COVID-19 infection defined by hospitalization in ICU or death, with an effect size of 3.26 compared to all RTX untreated iRMD patients. In addition, prolonged hospitalization was observed in RTX treated patients (median 13 days vs. 9 days in all RTX untreated iRMD patients), increasing the risk of morbidity / mortality and potential infection-related sequelae. One critical concern is to determine whether this worse outcome is related to RTX per se or to the specific population that is treated by this medication. Indeed, RTX is usually used in rheumatic disorders characterized by a higher risk of bad prognosis, including connective tissue disorders, vasculitis or RA with systemic complications, especially ILD. In addition, the profile of patients receiving RTX (older age, male sex, higher rate of comorbidities and corticosteroid use) is more at risk of severe COVID-19 occurrence. Interestingly, RTX therapy remained strongly associated with severe disease after stratification on the main relevant confounders with two complementary methods and the time between last infusion of RTX and first symptoms of COVID-19 was significantly shorter in patients who developed a severe form of COVID-19 than moderate or mild forms, suggesting direct drug accountability. Moreover,

this association further persisted after the analysis of the patient subset with diseases for which RTX would be a recognized therapeutic option.

Death rate was numerically higher in patients treated with RTX, but the risk of death did not increase significantly compared to RTX untreated patients after adjusting on potential confounders by IPTW PS method. This result emphasizes the weight of associated comorbidities on the risk of death, as previously observed in the French RMD cohort [6] and in the general population [6]. Of note, an increased risk of death in RTX treated patients compared to all RTX untreated iRMDs patients was observed after adjustment using the PS matching method, but it was not confirmed when the analysis focused on patients for whom RTX would be a recognized therapeutic option.

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

Consequences for future management of patients with RTX therapy could be a delay in its administration in RA patients whenever RA is in sustained remission or low disease activity. It seems more challenging to postpone RTX 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 to perform a SARS-CoV-2 test before giving RTX, to consider glucocorticoid dose reduction during RTX application (despite SmPC labelled requirement) and to instruct the patient to strictly follow the measures in place to avoid contact for several days following RTX 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 was 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 that missing data could introduce a bias in estimates. Since no formal sample size calculation for primary and secondary objectives was initially performed, we cannot exclude a lack of adequate statistical power to detect significant differences. The number of patients with several diseases of interest (Vasculitis associated with cytoplasmic antineutrophil antibodies, systemic sclerosis, RA with ILD) was too low to be specifically addressed. Moreover, patients with active or very active iRMD 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 RTX could be confounded by indication. Another limitation is the absence of data regarding ethnicity, previous medications (e.g. cyclophosphamide), RTX dose and duration, as well as the presence of associated hypogammaglobulinemia.

In conclusion, the analysis of the COVID-19 RMD cohort suggests the possibility for differential risk of adverse clinical outcomes among patients with iRMD based on the type of biological agents received. In particular, RTX will have to be applied with particular caution

in patients with iRMDs, especially if they suffer from other comorbidities that render them particularly at risk.

Acknowledgements
Muriel Herasse played a major role in collecting the missing data of the cohort.
We thank Julien Labreuche (biostatistician, CHU-Lille) for the help in the statistical analysis.
We thank the pro-bono support of SANOÏA Digital CRO team who provided outstanding eCRF, agile data visualisation and extensive project support.

Declaration of interest
We declare no competing interests

Authors'contributions
JA, EH and CR were responsible for conceptualisation.
RS, SGL, SEM, EP, TP, HM, AS, FD, PC, MD, PC, VG, AM, ATJM, BB, BF, JP, TT and RMF were responsible for data curation.
ED, JA, EH and CR were responsible for formal analysis.
JA, ED, EH, BF, JP, TT, RMF and CR were responsible for methodology and project administration.
EH was responsible for ethics approval.
ED was responsible for software.
JA, EH and CR were responsible for writing the first draft of the manuscript.
ED, RS, SGL, SEM, EP, TP, HM, AS, FD, PC, MD, PC, VG, AM, ATJM, BB, BF, JP, TT and RMF were responsible for writing (review and editing).
ED, EH and CR were responsible for verification of the underlying data. AH and CR were guarantors.

Data availability statement
All relevant anonymized patient-level data is available upon reasonable request to the corresponding author

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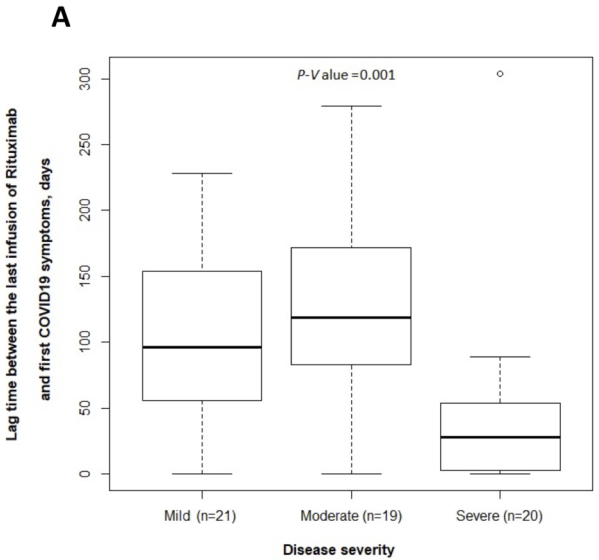
Figure legend:

Figure 1A-B: Distribution (Tukey's box plot) of Lag 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 interquartile range. P-Values for comparison (Kruskal Wallis for comparison between disease severity and Mann-Whitney U test for comparison between alive and died patients) are reported; P-Value<0.002 for either post-hoc comparison of severe disease group with moderate or mild disease group (calculated using Dunn's test).


A
P-Value =0.001
Lag time between the last infusion of Rituximab and first COVID19 symptoms, days
0
50
100
150
200
250
300
Mild (n=21)
Moderate (n=19)
Severe (n=20)
Disease severity

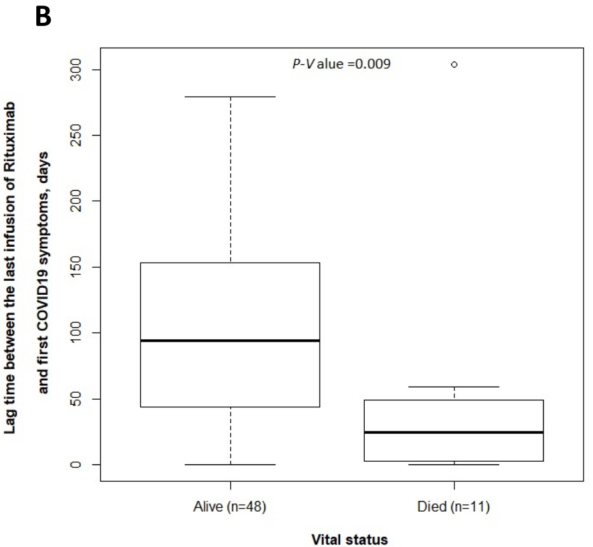

B
P-Value =0.009
Lag time between the last infusion of Rituximab and first COVID19 symptoms, days
0
50
100
150
200
250
300
Alive (n=48)
Died (n=11)
Vital status

Table 1: Patients' characteristics for overall and according to treatment groups

	Overall (n=1090)	Rituximab group (n=63)	Non-Rituximab group (n=1027)	Non-treated but eligible for Rituximab (n=495)
Age (years)				
18-54	533/1090 (48.9)	22/63 (34.9)	511/1027 (49.8)	192/495 (38.8)
55-64	219/1090 (20.1)	14/63 (22.2)	205/1027 (20.0)	110/495 (22.2)
65-74	182/1090 (16.7)	17/63 (27.0)	165/1027 (16.1)	104/495 (21.0)
≥75	156/1090 (14.3)	10/63 (15.9)	146/1027 (14.2)	89/495 (18.0)
Mean ± SD	55.2 ± 16.4	59.1 ± 15.1	55.0 ± 16.5	58.5 ± 16.0
Female gender	734/1090 (67.3)	38/63 (60.3)	696/1027 (67.8)	385/495 (77.8)
Comorbidities[1]				
Respiratory disease	145/1089 (13.3)	6/63 (9.5)	139/1026 (13.5)	85/495 (17.2)
Interstitial lung disease	38/1089 (3.5)	4/63 (6.3)	34/1026 (3.3)	31/495 (6.3)
COPD	42/1089 (3.9)	1/63 (1.6)	41/1026 (4.0)	28/495 (5.7)
Asthma	72/1089 (6.6)	1/63 (1.6)	71/1026 (6.9)	31/495 (6.3)
Cardiovascular disease	131/1089 (12.0)	10/63 (15.9)	121/1026 (11.8)	75/495 (15.2)
Coronary heart diseases	108/1089 (9.9)	9/63 (14.3)	99/1026 (9.6)	57/495 (11.5)
Stroke	33/1089 (3.0)	2/63 (3.2)	31/1026 (3.0)	24/495 (4.9)
Diabetes	110/1089 (10.1)	10/63 (15.9)	100/1026 (9.7)	57/495 (11.5)
BMI (kg/m²)				
<30	741/969 (76.5)	54/62 (87.1)	687/907 (75.7)	327/433 (75.3)
30-39.9	199/969 (20.5)	8/62 (12.9)	191/907 (21.1)	94/433 (21.7)
≥40	29/969 (3.0)	0/62 (0.0)	29/907 (3.2)	13/433 (3.0)
Hypertension	271/1089 (24.9)	16/63 (25.4)	255/1026 (24.9)	155/495 (31.4)
Cancer	44/1089 (4.0)	5/63 (7.9)	39/1026 (3.8)	30/495 (6.1)
Smoking	106/1089 (9.7)	3/63 (4.8)	103/1026 (10.0)	50/495 (10.1)
Chronic renal failure	64/1089 (5.9)	7/63 (11.1)	57/1026 (5.6)	41/495 (8.3)
No. of patients with at least 1 comorbidity	756/1089 (69.4)	48/63 (76.2)	708/1026 (69.0)	383/495 (77.5)
Disease History				
Rheumatoid arthritis	334/1090 (30.6)	31/63 (49.2)	303/1027 (29.5)	303/495 (61.2)
Vasculitis associated with cytoplasmic antineutrophil antibodies	23/1090 (2.1)	11/63 (17.5)	12/1027 (1.2)	12/495 (2.4)
Systemic sclerosis	43/1090 (3.9)	7/63 (11.1)	36/1027 (3.5)	36/495 (7.3)
Primary Sjögren syndrome	33/1090 (3.0)	4/63 (6.4)	29/1027 (2.8)	29/495 (5.9)
Other vasculitis	15/1090 (1.4)	2/63 (3.2)	13/1027 (1.3)	13/495 (2.6)
Mixed connective tissue disease	6/1090 (0.6)	2/63 (3.2)	4/1027 (0.4)	4/495 (0.8)
Systemic lupus erythematosus	80/1090 (7.3)	2/63 (3.2)	78/1027 (7.6)	78/495 (15.8)
IgG4-related disease	4/1090 (0.4)	2/63 (3.2)	2/1027 (0.2)	2/495 (0.4)
Inflammatory myopathy (including dermatomyositis, polymyositis	17/1090 (1.6)	1/63 (1.6)	16/1027 (1.6)	16/495 (3.2)
Eye inflammation (including uveitis)	3/1090 (0.3)	1/63 (1.6)	2/1027 (0.2)	2/495 (0.4)
Others	532/1090 (48.8)	0/63 (0.0))	532/1027 (51.8)	0/495 (0.0)
Rheumatic Diseases or AI²D treatments				
Corticosteroid	347/1090 (31.8)	34/63 (54.0)	313/1027 (30.5)	196/495 (39.6)
Systemic corticosteroid doses ≥10 mg	127/345 (36.8)	13/36 (38.2)	114/311 (36.7)	67/195 (34.4)

NSAIDs	99/1090 (9.1)	2/63 (3.2)	97/1027 (9.4)	28/495 (5.7)
Colchicine	38/1090 (3.5)	0/63 (0.0)	38/1027 (3.7)	3/495 (0.6)
Hydroxychloroquine	98/1090 (9.0)	3/63 (4.8)	95/1027 (9.3)	89/495 (18.0)
Methotrexate	393/1090 (36.1)	21/63 (33.3)	372/1027 (36.2)	233/495 (47.1)
Leflunomide	43/1090 (3.9)	5/63 (7.9)	38/1027 (3.7)	27/495 (5.5)
Salazopyrine	12/1090 (1.1)	0/63 (0.0)	12/1027 (1.2)	3/495 (0.6)
Mycophenolate Mofetil / mycophenolic acid	28/1090 (2.6)	1/63 (1.6)	27/1027 (2.6)	25/495 (5.1)
Azathioprine	14/1090 (1.3)	1/63 (1.6)	13/1027 (1.3)	9/495 (1.8)
IgIV	7/1090 (0.6)	0/63 (0.0)	7/1027 (0.7)	7/495 (1.4)
Targeted biologic or synthetic therapies				
anti-TNF	318/1090 (29.2)	0/63 (0.0)	318/1027 (31.0)	74/495 (14.9)
anti-IL6	35/1090 (3.2)	0/63 (0.0)	35/1027 (3.4)	23/495 (4.6)
anti-IL17A	38/1090 (3.5)	0/63 (0.0)	38/1027 (3.7)	0/495 (0.0)
anti-IL1	9/1090 (0.8)	0/63 (0.0)	9/1027 (0.9)	1/495 (0.2)
abatacept	24/1090 (2.2)	0/63 (0.0)	24/1027 (2.3)	22/495 (4.4)
JAK inhibitor	35/1090 (3.2)	0/63 (0.0)	35/1027 (3.4)	30/495 (6.1)
Other biologics	21/1090 (1.9)	0/63 (0.0)	21/1027 (2.0)	8/495 (1.6)

Values are presented as no./total nol. (percentage) unless otherwise indicated.
[1] 1 Missing values for comorbidities (in non-rituximab group) except for BMI where 121 values are missing (rituximab, n=1; non-rituximab, n=120; non-treated but eligible for rituximab, n=61).
Abbreviations: SD, standard deviation; BMI, body mass index.

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

	Rituximab group (n=63)	Non-rituximab group (n=1027)	Effect size (95% CI)[1]	P-value
Severity				0.002
Mild	21 (33.3)	645 (62.8)	1.00 (ref.)	-
Moderate	20 (31.8)	267 (26.0)	1.98 (1.08 to 3.63) [2]	0.026
Severe	22 (34.9)	115 (11.2)	3.26 (1.66 to 6.40) [2]	<0.001
Length of hospital stay (days), median (IQR)	13 (7 to not reached)	9 (4 to 17)	0.62 (0.46 to 0.85) [3]	0.002
Death	13 (20.6)	76 (7.4)	1.32 (0.55 to 3.19) [2]	0.532

Values are presented as frequency (percentage) unless otherwise indicated.
Values, effect size and p-values were calculated after handle missing data by simple imputation.
[1] Effect size calculated using a regression models weighted by IPTW PS with non-rituximab treated patients as reference. The PS was estimated using a multivariable logistic regression model, including pre-specified confounding factors (namely, 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)).
[2] Odds-ratio calculated using multinomial or binary logistic regression models.
[3] Subhazard ratio calculated among 424 hospitalized patients (n=42 in Rituximab) using Fine and Gray model with discharge alive as event of interest and hospital death as competing event. SHR>1 indicates a decrease in length of hospital stay and an SHR<1 indicates an increase in length of hospital stay by comparison to reference group.
Abbreviation: CI, confidence interval; IQR, interquartile range;; IPTW, inverse probability of treatment weighting; PS, Propensity score; SHR, subhazard ratio.

<u>Table 3:</u> Comparison in outcomes between Rituximab treated patients and non-treated but eligible for Rituximab patients in inverse probability of treatment weighting (IPTW) propensity score (PS) analyses

	Rituximab group (n=63)	Non-treated but eligible for Rituximab (n=495)	Effect size (95% CI) [1]	P-value
Severity				0.018
Mild	21 (33.3)	277 (56.0)	1.00 (ref.)	-
Moderate	20 (31.8)	147 (29.7)	1.47 (0.78 to 2.74) [2]	0.23
Severe	22 (34.9)	71 (14.3)	2.62 (1.34 to 5.09) [2]	0.005
Length of hospital stay (days), median (IQR)	12 (6 to not reached)	9 (4 to 19)	0.67 (0.45 to 0.99) [3]	0.040
Death	13 (20.6)	49 (9.9)	1.48 (0.68 to 3.20) [2]	0.317

Values are presented as frequency (percentage) unless otherwise indicated.
Values, effect size and p-values were calculated after handle missing data by simple imputation.
[1] Effect size calculated using a regression models weighted by IPTW PS with non-rituximab treated patients as reference. The PS was estimated using a multivariable logistic regression model, including pre-specified confounding factors (namely, 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)).
[2] Odds-ratio calculated using multinomial or binary logistic regression models.
[3] Subhazard ratio calculated among 260 hospitalized patients (n=42 in Rituximab**)** using Fine and Gray model with discharge alive as event of interest and hospital death as competing event. SHR>1 indicates a decrease in length of hospital stay and an SHR<1 indicates an increase in length of hospital stay by comparison to reference group.
Abbreviation: CI, confidence interval; IQR, interquartile range; IPTW, inverse probability of treatment weighting; PS, propensity score; SHR, subhazard ratio.