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Background: At a time when vaccines are being prioritized for individuals most at risk, there is currently no clear evidence that risk of SARS-CoV-2 infection is higher for patients with than without inflammatory arthritides (IA). Biologic use was not associated with worse COVID-19 outcomes for yet but the case of rituximab (RTX) remains an issue, given its immunological long term effect, the role of humoral response against SARS-CoV-2 and its indirect effect on T-cell response. A potential association between rituximab and worse COVID-19 outcomes was raised by case reports and retrospective, declarative studies (with few data on the total number of patients exposed).

Objectives: To address differently the issue of the risk of COVID-19 related to RTX and limit biases, we examined the occurrence of severe COVID-19 in all patients receiving intravenous biologic agents at day-hospitals during the pandemic in France.

Methods: From 1st September 2019 to 1st January 2021, we analyzed patients with IA prospectively treated with intravenous biologic agents (RTX, abatacept, infliximab or tocilizumab) in 7 clinical centers in France. We obtained the list of patients receiving intravenous biologic agents in each center from the pharmacist of the hospitals. Therefore, all consecutive patients receiving 1 of the 4 drugs at the time of the study were included in each center. Patients with no follow-up after September 2020 were systematically contacted by phone. The occurrence of a severe COVID-19 (i.e. resulting in death, hospitalization or increase in length of hospitalization related to COVID-19) was the primary outcome criteria.

Results: In total, 1116 patients receiving intravenous biologic agents were included: 449 with infliximab, 392 RTX, 170 tocilizumab and 105 abatacept. From 1st September 2019, the median follow-up time was 15 months (interquartile range 14-16). In total, 10 cases of severe COVID-19 occurred, 9 treated with RTX and 1 with infliximab (supplementary Table 1). Four deaths occurred in our cohort during follow-up but none was related to COVID-19 (1 patient treated by tocilizumab, 1 by RTX and 2 by infliximab). In univariate analysis, the proportion of severe COVID-19 was significantly higher for patients receiving RTX than other biologic agents (9/392 vs 1/724, $p=0.0003$, OR [95%CI] 17.0 [2.1-134.6]). To take into account potential confounders, we performed multivariate analysis accounting for baseline parameters that differed between RTX and other biologic groups. RTX remained significantly associated with risk of severe COVID-19 ($p=0.019$) (Table 1).

Patient characteristics	Rituximab (n= 392)	Other bDMARDs (n= 724)	Univariate analysis, p-value	Multivariate analysis, p-value
Median age (years), — [IQR]	64 [56-71]	57.3 [47.0-67.0]	< 0.0001	0.51
Female — n (%)	285 (72.7)	426 (58.8)	< 0.0001	0.58
IA diagnosis			< 0.0001	0.12
Median follow-up from 1st September to last news	14 [13-15]	15 [14-16]	< 0.0001	0.86
Confirmed severe COVID-19 cases — n (%)	9 (2.3)	1 (0.1)	0.0003	0.019
Comorbidities** (history of) — n (%)				
Cardiovascular disease	60 (15.4)	167 (23.1)	0.0025	0.77
Chronic lung disease,	92 (23.5)	84 (11.6)	0.0001	0.88
Median BMI (kg/m ²) — [IQR]	25.8 [23.2-29.4]	27.3 [23.4-31.2]	0.015	0.80
Treatments — n (%)				
Methotrexate	179 (45.8)	322 (44.5)	0.71	
Leftunomide	41 (10.5)	39 (5.4)	0.0023	0.43
Hydroxychloroquine	35 (8.9)	24 (3.3)	0.0001	0.15
Glucocorticoids	127 (41.8)	100 (19.4)	< 0.0001	0.36
Median dose (mg/day) — [IQR]	1 [0-5]	0 [0-0]	< 0.0001	

No significant difference in terms of baseline gammaglobulins ($p=0.46$) or number of previous RTX infusions ($p=0.57$) was observed among patients receiving RTX with or without a severe COVID-19.

Conclusion: The present results highly indicate increased risk of severe COVID-19 with RTX. Among patients with inflammatory arthritides, those receiving RTX should be prioritized for vaccination against SARS-CoV-2, sufficiently long before infusion/reinfusion and the immunization checked, or an alternative targeted therapy proposed.

Acknowledgements: We thank Dr. Karine Demesmay and all the pharmacists who helped us for this study.

Disclosure of Interests: Renaud FELTEN Speakers bureau: Abbvie, Biogen, BMS, Lilly, Novartis, Pfizer, Pierre-Marie Duret: None declared, Elodie BAUER: None declared, Marc Ardizzone: None declared, H Julien Djossou:

None declared, Jean-Hugues Salmon: None declared, Cassandre Fabre: None declared, Julia Walther: None declared, Isabelle CHARY VALCKENAERE: None declared, marion geoffroy: None declared, Laurent Messer: None declared, Francis Berenbaum: None declared, Martin SOUBRIER: None declared, Jérémie SELLAM Speakers bureau: MSD, Pfizer, Abbvie, Roche, BMS, Lilly, Janssen, Novartis, Galapagos, Sandoz, Fresenius Kabi, Grant/research support from: Roche, MSD, Pfizer, Jacques-Eric Gottenberg: None declared

DOI: 10.1136/annrheumdis-2021-eular.1521

OP0283

DOES TNF-INHIBITION DECREASE THE RISK OF SEVERE COVID-19 IN RMD-PATIENTS?

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Background: Patients with rheumatic and musculoskeletal diseases (RMD) might have an increased risk for infection due to their immunomodulatory treatment, secondary to their disease and comorbidities. Recent studies suggest a decreased risk of severe COVID-19 in RMD-patients treated with biologics.

Objectives: The aim of this study was to assess courses of RMD patients treated with TNF-inhibitors (TNF-I) included in the German COVID-19 registry.

Methods: In the German physician-reported COVID-19-RMD registry, patients with an RMD and confirmed SARS-CoV-2-infection were documented (data entered between March 30, 2020 and January 30, 2021). We analysed TNF-I treated patients, their course and outcome of the infection. Data were compared to RMD-patients treated with other immunomodulatory drugs (OID) than TNF-I.

Results: A total of 269 patients were treated with a TNF-I (57% female) compared to 874 patients who were treated with OID (68% female). Median age was 52 years (range: 19-87) in the TNF-I-group versus 58 years (range: 18-91) in the OID-group. Rheumatoid arthritis was the most common diagnosis (38% in TNF-I-group vs. 52% in the OID-group), followed by ankylosing spondylitis (32% vs. 6%), psoriatic arthritis (22% vs. 11%) and other RMD (9% vs. 31%). Adalimumab (35%) and etanercept (35%) were the most frequently used TNF-I (tab. 1). Glucocorticoids (GC) were used in 22% of TNF-I-treated patients and in 42% of the OID-group.

Under TNF-I, stable disease was reported prior to the SARS-CoV-2-infection in 53% of the patients (OID-group: 47%), followed by low disease activity in 35% (OID: 34%), moderate disease activity in 6% (OID: 12%) and high disease activity in 4% (OID: 3%). Most frequent comorbidities were arterial hypertension (29% under TNF-I vs. 35% under OID), diabetes (8% vs. 11%) and cardiovascular diseases (7% vs. 12%).

The most common reported COVID-19 symptoms were dry cough (57% vs. 55%), fever (53% vs. 61%) and fatigue (50% vs. 49%). Hospitalization due to SARS-CoV infection was required in only 12% of the TNF-I-treated cases vs. in 29% in the OID-group. Oxygen treatment was necessary in 5% of the patients under TNF-I compared to 22% under OID and invasive ventilation in 2% in the TNF-I-group compared to 6% under OID. Most notably, no fatal courses of COVID-19 were reported among the 269 RMD-patients treated with TNF-I versus 49 deaths in the 874 cases (5.6%) treated with OID. Focussing on the hospitalized TNF-I patients, the rate of concomitant GC use ($p<0.001$) and higher disease activity ($p=0.005$) was significant higher (tab. 1).

Conclusion: High or moderate RMD-disease activity is an important factor associated with severity of COVID-19 including mortality. In this large cohort RMD patients treated with TNF-I show a low hospitalisation rate and no fatal course. This is reassuring for patients and treating rheumatologists to use TNF-I to control RMD disease activity. The use of glucocorticoids and high disease activity seem to counteract possible protective effects of TNF-I.

Table 1.

	TNF inhibition (269)		Other immunomodulation (874)	
	Total patients	Rate (%)	Total patients	Rate (%)
Disease activity				
stable	141	53	408	47
low	93	35	299	34
Moderate	15	6	108	12
High	10	4	29	3
Comorbidities				
cardiovascular diseases	18	7	104	12
arterial hypertension	77	29	303	35
bronchial asthma	12	4	65	7
COPD/interstitial lung disease	11	4	86	10
chronic renal failure	9	3	77	9
Osteoporosis	13	5	67	8
Diabetes	22	8	92	11
COVID-19 related symptoms				
Fever	142	53	478	55
dry cough	152	57	530	61
Expectoration	31	12	83	9
muscular pain	97	36	280	32
Fatigue	135	50	424	49
Headache	101	38	237	27
shortness of breath	49	18	245	28
no symptoms	23	9	56	6
COVID-19 outcome				
Outpatients	237	88	619	71
Inpatients	32	12	255	29
need of oxygen treatment	18	7	189	22
invasive ventilation	5	2	49	6
fatal course	0	0	49	6
TNF inhibitors				
Adalimumab	95	35		
Infliximab	23	9		
Certolizumab	33	12		
Golimumab	24	9		
Etanercept	94	35		
GC and disease activity in TNF-I treated patients				
TNF-I inpatients treated with GC	18/32	56	p< 0.001	
TNF-I outpatients treated with GC	42/237	18		
TNF-I inpatients with high disease activity	4/32	13		
TNF-I outpatients with high disease activity	6/237	6	p= 0.005	

Acknowledgements: The authors would like to thank all physicians and personnel involved in the documentation of the cases in our registry.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.4027

OP0284

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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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).

Objectives: To investigate whether treatment with RTX is associated with severe infection and death.

Methods: We performed an 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. Severe disease was defined by hospitalization in intensive care unit or death. The secondary objectives were to analyze death rate and length of hospital stay. Two control groups were considered for comparison with RTX treated patients: a first group including all non-RTX treated iRMD patients and a second consisting on RTX untreated iRMD patients with diseases for which RTX is a recognized therapeutic option. Adjusting on potential confounding factors was performed by using inverse probability of treatment weighting (IPTW) propensity score method.

Results: We collected a total of 1090 records. 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 (756/1090). A total of 63 patients were treated with RTX, mainly for rheumatoid arthritis (RA) (31/63, 49.2%). RTX treated patients were more likely to be males, with older age, higher prevalence of comorbidities and corticosteroid use. The control population consisted on 1027 non-RTX treated iRMD patients, and 495 RTX untreated iRMD patients with diseases for which RTX is a recognized therapeutic option.

Of the 1,090 patients, 137 developed severe disease (12.6%). After 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), 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) 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). 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 1).

Figure 1. Distribution (Tukey's box plot) of Lag time between last infusion of Rituximab according to disease severity. P-Values for comparison between disease severity with Kruskal Wallis test are reported; P-Value<0.001 for either post-hoc comparison of severe disease group with moderate or mild disease group (calculated using Dunn's test).

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%) and the subgroup of untreated RTX patients with diseases eligible for RTX therapy (49/495, 9.9%). After considering the previously described 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=0.53) (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=0.32). 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.

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