B-cell targeted therapy is associated with severe COVID-19 among patients with inflammatory arthritides: a 1-year multicentre study in 1116 successive patients receiving intravenous biologics

Dear Editor,

A potential association between rituximab and more severe COVID-19 outcomes has been previously raised, based on case reports, retrospective studies and mostly declarative registries.[1–4] To further investigate this association, we focused on patients with inflammatory arthritides (IA) receiving intravenous biological agents at day hospitals to limit selection and recall bias, as well as missing data.

All patients with IA treated in day hospitals with intravenous biological agents (rituximab, abatacept, infliximab or tocilizumab) in seven clinical centres in France (Strasbourg, Colmar, Mulhouse, Nancy, Reims, Clermont-Ferrand and Saint-Antoine hospitals in Paris) were enrolled in the study. Data were collected from 1 September 2019 (5 months before the outbreak of the epidemic in France, so that all enrolled patients had been exposed to a biologic prior to the start of the epidemic) to 1 January 2021.[3] In each centre, we obtained the list of all patients receiving intravenous biological agents from the hospital pharmacist. Therefore, all patients receiving one of the four drugs within the time frame of the study were enrolled in each centre. The occurrence of hospitalised COVID-19 was the primary outcome criterion, that is, SARS-CoV-2 presence confirmed by PCR and resulting in hospitalisation or death. Data were analysed with Bayesian methods in univariate and multivariate analyses using weakly informative prior (specifying that $0.05 < OR_x < 20$ a priori) or priors derived from recently published data.[3] A prior distribution is a probability distribution that expresses what is already known on the parameter of interest, such as the OR, through either theoretical consideration and/or past observations, and is a fundamental part of Bayesian methods and inference. Using a prior distribution allows decreasing, at least partially, concerns about the potential lack of statistical power. In order to ensure that any difference in risk with rituximab was not primarily due to baseline differences between rituximab and other biological groups, we performed multivariate analyses accounting for risk factors of severe COVID-19 based on literature.

A total of 1116 patients receiving intravenous biological agents were enrolled: 449 with infliximab, 392 with rituximab,

Table 1 Univariate and multivariate models assessing the association between the occurrence of hospitalised COVID-19 and each variable

Variables	Rituximab (n=392)	Other bDMARDs (n=724)	Univariate OR of hospitalised COVID-19 (95% CrI)	Multivariate OR of hospitalised COVID-19 (95% CrI) Model #1	Multivariate OR of hospitalised COVID-19 (95% CrI) Model #2
bDMARDs (RTX vs other bDMARDs)			**8.5 (2.4 to 38.6) Pr (OR >1)≈1.0**	**7.7 (1.7 to 44.7)**	**4.4 (1.8 to 11.1)**
Median age (years)	64 (56–71)	57.3 (47.0–67.0)	**1.0 (1.0 to 1.1) Pr (OR >1)≈1.0**	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Female	285 (72.7)	426 (58.8)	0.6 (0.2 to 2.0) Pr (OR >1)=0.2	0.5 (0.1 to 2.1)	0.5 (0.2 to 1.0)
IA diagnosis					
RA	366 (95.6)	305 (42.4)	RA versus SPA 0.3 (0.0 to 1.4) Pr (OR >1)=0.06	RA versus SPA 1.0 (0.1 to 7.4)	RA versus SPA 0.6 (0.1 to 3.7)
Spondyloarthritis (including psoriatic arthritis)	0	364 (50.6)	RA versus other 2.2 (0.4 to 8.7)	RA versus other 2.3 (0.3 to 13.2)	RA versus other 2.1 (0.3 to 10.7)
Other*	17 (4.4)	51 (7.1)	Pr (OR >1)=0.8		
Comorbidities†					
Cardiovascular disease	60 (15.4)	167 (23.1)	0.5 (0.1 to 2.1) Pr (OR >1)=0.2	3.6 (0.9 to 16.6)	2.7 (1.3 to 5.8)
Cerebrovascular disease	10 (2.6)	29 (4.0)	0.5 (0.0 to 4.2) Pr (OR >1)=0.3	0.5 (0.0 to 4.0)	0.5 (0.0 to 4.3)
Chronic lung disease	92 (23.5)	84 (11.6)	1.9 (0.5 to 6.4)	1.0 (0.2 to 3.9)	1.8 (0.9 to 3.8)
Diabetes	48 (12.3)	68 (9,4)	2.8 (0.6 to 9.6) Pr (OR >1)=0.8	1.7 (0.4 to 7.4)	2.1 (0.5 to 5.4)
Median BMI (kg/m²) (IQR)	25.8 (23.2–29.4)	27.3 (23.4–31.2)	Normal BMI vs BMI >25 0.2 (0.0 to 1.4) Pr (OR >1)=0.1	Normal BMI vs BMI >25 0.1 (0.0 to 1.0)	Normal BMI vs BMI >25 0.2 (0.0 to 1.1)
BMI >30 kg/m²	67 (24.4)	120 (32.3)	Normal BMI vs BMI >30 0.5 (0.1 to 2.6) Pr (OR >1)=0.2	Normal BMI vs BMI >30 0.4 (0.1 to 2.9)	Normal BMI vs BMI >30 0.4 (0.1 to 2.2)
Treatments					
Conventional synthetic DMARDs	242 (61.7)	374 (51.7)	0.6 (0.2 to 1.9) Pr (OR >1)=0.2	0.6 (0.2 to 2.1)	0.5 (0.2 to 1.0)
Other immunosuppressive agents	7 (1.8)	5 (0.7%)	3.0 (1.4 to 6.5) Pr (OR >1) ≈ 1.0	4.0 (0.5 to 30.4)	2.1 (1.0 to 4.4)
Oral glucocorticoids Median dose (mg/day) — (IQR)	1 (0–5)	0 (0–0)	No steroids vs 0–10 mg/day 3.0 (0.7 to 11.4) Pr (OR >1)=0.9 No steroids vs >10 mg/day 2.9 (0.3 to 20.5) Pr (OR >1)=0.8	No steroids vs 0–10 mg/day 1.7 (0.4 to 7.2) No steroids vs >10 mg/day 1.3 (0.1 to 10.9)	No steroids vs 0–10 mg/day 1.7 (0.4 to 7.5) No steroids vs >10 mg/day 1.5 (0.1 to 11.1)
No steroids	190 (48.5)	486 (37.1)			
0–10 mg/day	114 (29.1)	90 (12.4)			
>10 mg/day	13 (3.3)	10 (1.4)			

Model #1: weakly informative prior (specifying that $0.05<OR_c<20$ a priori).
Model #2: taking into account prior according to a recent publication by Strangfeld *et al*.[3]
Bold indicates statistically significant results.
*Other IA includes vasculitides n=16, juvenile idiopathic arthritis n=12, connective tissue diseases n=11, polymyalgia rheumatica n=10 and others n=19: uveitis, inflammatory bowel disease, stiff-person syndrome, sarcoidosis, inflammatory myositis, calcium pyrophosphate deposition disease, familial Mediterranean fever, Blau syndrome and McCune-Albright syndrome.
†Comorbidities: 'cardiovascular disease' includes abnormal heart rhythms or arrhythmias, aorta disease, coronary artery disease (narrowing of the arteries), heart attack, heart failure, cardiomyopathy, heart valve disease, hypertension, pericardial disease, peripheral vascular disease; 'cerebrovascular disease' includes history of stroke and transient ischaemic attack; 'chronic lung disease' includes asthma, chronic obstructive pulmonary disease, interstitial pneumopathy and pulmonary fibrosis, asbestosis, pneumonitis, obstructive sleep apnea–hypopnea syndrome and history of pulmonary embolism; diabetes includes type I and II diabetes.
bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, Body Mass Index; IA, inflammatory arthritides; RA, rheumatoid arthritis; RTX, rituximab; SPA, spondyloarthr.

Table 2 Informative prior used in multivariate analysis Model #2

Variables	Gaussian prior distribution on log(OR), N(mu, sigma²)	Prior OR (95% CrI)
RTX versus other bDMARDs	N(1.04, 0.281)	2.8 (1.0 to 8.0)
Median age (years)	N(–0.079, 0.0016)	0.9 (0.85 to 1.0)
Gender	N(–0.757, 0.189)	0.5 (0.2 to 1.1)
Cardiovascular disease	N(0.752, 0.191)	2.1 (0.9 to 5.0)
Chronic lung disease	N(0.752, 0.191)	2.1 (0.9 to 5.0)
Conventional synthetic DMARDs	N(–0.757, 0.191)	0.5 (0.2 to 1.1)
Other immunosuppressive agents	N(0.64, 0.145)	1.9 (0.9 to 4.0)
Other variables	N(0, 0.428)	1.0 (0.05 to 20)

bDMARD, biological disease-modifying antirheumatic drug; CrI, credibility interval; DMARD, disease-modifying antirheumatic drug; RTX, rituximab.

170 with tocilizumab and 105 with abatacept. Ten cases of severe COVID-19 occurred: 9 in patients treated with rituximab (2.3% of total patients treated with rituximab) and 1 in a patient treated with infliximab (0.1% of patients treated with biological agents other than rituximab, 0.2% of patients treated with infliximab) (table 1 and online supplemental table 2). Four deaths occurred during follow-up, but none were related to COVID-19 (a dialysed 50-year-old man treated with tocilizumab for systemic sclerosis who developed a serious non-COVID infection, an 86-year-old woman treated with rituximab for rheumatoid arthritis, who developed a serious pulmonary bacterial infection; and a 62-year-old woman and a 70-year-old man treated with infliximab for psoriatic arthritis, who died of unexplained sudden death). In univariate analysis, the proportion of hospitalised COVID-19 was higher for patients receiving rituximab than other biological agents (9/392 vs 1/724, OR=8.5, 95% credibility interval (CrI) 2.6 to 38.6, Pr (OR >1)≈1; tables 1 and 2). Rituximab remained the only factor associated with risk of hospitalised COVID-19 (OR 7.7, 95% CrI 1.7 to

44.7) in multivariate analyses (table 1). In patients with hospitalised COVID-19 (online supplemental table 1), the median delay from last infusion to infection was 3.5 months (IQR 1.8–5.0). One patient was admitted to intensive care. The sensitivity analysis, in patients with moderate-to-severe and critical COVID-19 (ie, individuals who had SpO_2 <94% on room air at sea level and who required oxygen), yielded the same results as the main analysis in patients with hospitalised COVID-19 (online supplemental table 2).

The present work joins previous studies to confirm the risk of B-cell depletion with regard to the development of hospitalised and severe COVID-19.[1–3] Of note, the low number of events and the number of covariates limit the robustness of the statistical analysis, which might explain that classical risk factors such as age, sex, comorbidities, body mass index and corticosteroids were not associated with severe COVID-19 in the present study. In addition, the present study is the first to provide a prevalence of severe SARS-CoV-2 infection in a cohort which includes the totality of patients receiving intravenous biological treatment. In this study, approximately 2% of rituximab-treated patients developed hospitalised COVID-19, compared with only one patient (0.1%) among those treated with infliximab, tocilizumab or abatacept.

These results strongly indicate the increased risk of severe COVID-19 in patients receiving B-cell targeted therapy. Among patients with IA, those receiving rituximab should be prioritised for vaccination against SARS-CoV-2, sufficiently in advance of treatment infusion/reinfusion.

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Supplementary Table 1. Description of patients with hospitalized COVID-19.

Patient	1	2	3	4	5	6	7	8	9	10
Gender	Male	Male	Female	Male	Female	Female	Female	Male	Male	Female
Age (years)	67	74	52	46	67	49	81	90	81	63
Biologic treatment	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Infliximab
Associated csDMARDs	No	MTX 10 mg/sem (Oral)	Cellcept 3g/day	No	MTX 15 mg/sem (SC)	MTX 15 mg/sem (SC)	No	No	No	MTX 25 mg/sem (SC)
Associated glucosteroids	No	Prednisone 2 mg/day	Prednisone 7 mg/day	No	No	No	Prednisone 3.5 mg/day	No	Prednisone 20 mg/day	No
IAs	Rheumatoid arthritis	Rheumatoid arthritis	Necrotizing myositis	Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Granulomatosis with polyangiitis	Spondyloarthritis
IAs disease activity before COVID-19	DAS28-CRP= 1.74 (remission)	DAS28-CRP= 3.18 (low disease activity)	NA but in a control state	DAS28-CRP= 1.64 (remission)	DAS28-CRP= 1.48 (remission)	DAS28-CRP= 5.3 (high disease activity)	DAS28-CRP= 4.73 (moderate disease activity)	DAS28-CRP= 3.35 (moderate disease activity)	NA but in a controlled state	ASDAS= 3.7 (high disease activity)
Known risk factor for severe COVID-19	Ischemic cardiopathy, hypertension	Diabetes, rhythmic cardiopathy	Obesity, chronic lung disease (interstitial pneumopathy)	Chronic lung disease (bronchiolitis, pulmonary embolism)	No	No	Hypertension, chronic lung disease (obstructive sleep apnea-hyponea syndrome)	Diabetes, hypertension, pacemaker	Cerebrovascular event, chronic lung disease (alveolar hemorrhage)	Cerebrovascular event, obesity
BMI (kg/m²)	26.1	34.5	47.0	20.0	24.1	17.6	23.6	21.7	24.7	40.8
Date of COVID-19	December 2020	November 2020	October 2020	August 2020	April 2020	October 2020	March 2020	December 2020	November 2020	April 2020
Hospitalization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Length of hospitalization (days)	17	19	12	22	66	10	48	18	27	15
Oxygenation	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Admission in an ICU	No	No	No	No	Yes	No	No	No	No	No
Mechanical oxygenation	No	No	No	No	Yes	No	No	No	No	No

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Specific COVID-19 treatment	Dexamethasone	No	No	Remdesivir and convalescent plasma	No	Convalescent plasma	No	No	Dexamethasone and convalescent plasma	No
Death	No	No	No	No	No	No	No	No	No	No
Recovery	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time between last infusion and COVID-19 (months)	3	4	2	1	5	1	4	5	5	2
IgG level (g/L) at the time of COVID-19 [last IgG level before COVID-19]	NA [10.1]	NA [6.6]	IV Ig supplementation	7.4 [12.9]	6.1 [5.6]	11.2 [11.9]	6.4 [7.4]	NA [9.1]	4.5 [NA]	NA [NA]
Lymphocytes count (/µL) (B/TCD4$^+$/ TCD8$^+$)*	0 / 437 / 287	NA	NA	1 / 303 / 144	0 / 607 / 175	1 / 282 / 96	NA	NA	0 / 87 / 266	NA

IA, inflammatory arthritides; BMI, Body Mass Index; ICU, intensive care unit; MTX, methotrexate; NA not available

The median delay from last infusion to confirmation of severe COVID-19 was 3.5 months (IQR [1.8-5.0]). No death was reported, but one patient was admitted to intensive care. Patients were hospitalized for a median of 18.5 days (IQR [14-32]). A minority of patients received specific COVID-19 treatment (n=6), 3 received convalescent plasma, 2 received dexamethasone and 1 received remdesivir. At last follow-up, all patients had recovered. The last immunoglobulin G (IgG) level recorded before infection was normal for all patients (median 7.4, IQR [5.6-10.1] g/L). In patients for whom IgG level was measured at the time of COVID-19, IgG level was at the lower limit of normal (median 6.4, IQR [5.3-9.3] g/L). B-cell counts were available for 5 patients at the time of COVID-19, all of whom presented complete B-cell depletion.

Supplementary Table 2. Univariate and multivariate models assessing the association between the occurrence of moderate-to-severe COVID-19 and each variable

Variables	Univariate OR of severe COVID (95% CrI)	Multivariate OR of severe COVID (95% CrI) Model #1	Multivariate OR of moderate-to-severe COVID (95% CrI) Model #2
bDMARDs (RTX vs Other bDMARDs)	**6.6 (1.7-35.0)** **Pr (OR>1) ≈ 1.0**	**6.6 (1.3-43.0)**	**4.1 (1.7-10.4)**
Median age (years)	1.0 (1.0-1.1) Pr (OR>1) = 0.7	1.0 (0.9 -1.1)	1.0 (0.9-1.0)
Female	0.6 (0.2-2.3) Pr (OR>1) = 0.2	0.6 (0.2-2.7)	0.5 (0.2-1.0)
IA diagnosis			
Rheumatoid arthritis	RA vs SPA 0.4 (0.1-1.9) Pr (OR>1) = 0.1	RA vs SPA 1.0 (0.1-7.6)	RA vs SPA 0.6 (0.1-4.0)
Spondyloarthritis (including psoriatic arthritis)			
*Other**	RA vs Other 2.8 (0.5-12.3) Pr (OR>1) = 0.9	RA vs Other 2.7 (0.4-15.5)	RA vs Other 2.4 (0.4-12.3)
Comorbidities			
Cardiovascular disease	**3.7 (1.0-16.9)** **Pr (OR>1) ≈ 1.0**	3.4 (0.8-16.8)	2.7 (1.2-5.7)
Cerebrovascular disease	2.0 (0.9-4.6) Pr (OR>1) = 0.9	0.5 (0.0-5.3)	0.6 (0.0-5.4)
Chronic lung disease	2.4 (0.5-9.3) Pr (OR>1) = 0.9	1.4 (0.2-6.3)	2.1 (1.0-4.4)
Diabetes	2.1 (0.4-8.5) Pr (OR>1) = 0.8	1.4 (0.2-6.9)	1.7 (0.3-8.0)
BMI (kg/m²)	Normal BMI vs BMI > 25 0.2 (0.0-1.7) Pr (OR>1) = 0.1	Normal BMI vs BMI > 25 0.2 (0.0-1.5)	Normal BMI vs BMI > 25 0.2 (0.0-1.7)
	Normal BMI vs BMI > 30 0.7 (0.1-3.9) Pr (OR>1) = 0.3	Normal BMI vs BMI > 30 0.5 (0.1-3.6)	Normal BMI vs BMI > 30 0.5 (0.1-3.1)
Treatments			
Conventional synthetic DMARDs	0.8 (0.2-3.1) Pr(OR>1)= 0.4	1.0 (0.2-4.3)	0.5 (0.3-1.2)
Other immunosuppressive agents	**3.0(1.4-6.6)** **Pr(OR>1) ≈ 1.0**	5.2 (0.6-39.5)	**2.2 (1.1-4.5)**
Glucocorticoids	No Steroids vs. 0 to 10 mg/day 2.9 (0.6-12.9) Pr(OR>1) =0.9	No steroids vs 0 to 10 mg/day 1.6 (0.3-8.3)	No steroids vs 0 to 10 mg/day 1.6 (0.3-8.2)
	No Steroids vs. > 10mg/day 3.4 (0.3-25.1) Pr(OR>1)=0.8	No steroids vs > 10 mg/day 1.7 (0.2-15.0)	No steroids vs > 10 mg/day 1.9 (0.2-15.7)

Model #1: Weakly informative prior (specifying that $0.05<OR_x<20$ a priori)

Model #2: Taking into account prior according to a recent publication by Strangfeld et al. [3] (same as Table 1)

Moderate-to-severe COVID-19 was defined as following: patients who had SpO2 <94% on room air at sea level and who required oxygen.