EPIDEMIOLOGICAL SCIENCE

Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry

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ABSTRACT

Objective To investigate baseline use of biologic or targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) and COVID-19 outcomes in rheumatoid arthritis (RA).

Methods We analysed the COVID-19 Global Rheumatology Alliance physician registry (from 24 March 2020 to 12 April 2021). We investigated b/tsDMARD use for RA at the clinical onset of COVID-19 (baseline): abatacept (ABA), rituximab (RTX), Janus kinase inhibitors (JAKi), interleukin 6 inhibitors (IL-6i) or tumour necrosis factor inhibitors (TNFi, reference group). The ordinal COVID-19 severity outcome was (1) no hospitalisation, (2) hospitalisation without oxygen, (3) hospitalisation with oxygen/ventilation or (4) death. We used ordinal logistic regression to estimate the OR (odds of being one level higher on the ordinal outcome) for each drug class compared with TNFi, adjusting for potential baseline confounders.

Results Of 2869 people with RA (mean age 56.7 years, 80.8% female) on b/tsDMARD at the onset of COVID-19, there were 237 on ABA, 364 on RTX, 317 on IL-6i, 563 on JAKi and 1388 on TNFi. Overall, 613 (21%) were hospitalised and 157 (5.5%) died. RTX (OR 4.15, 95% CI 3.16 to 5.44) and JAKi (OR 2.06, 95% CI 1.60 to 2.65) were each associated with worse COVID-19 severity compared with TNFi. There were no associations between ABA or IL6i and COVID-19 severity.

Conclusions People with RA treated with RTX or JAKi had worse COVID-19 severity than those on TNFi. The strong association of RTX and JAKi use with poor COVID-19 outcomes highlights prioritisation of risk mitigation strategies for these people.

INTRODUCTION

The ongoing COVID-19 pandemic has had a significant impact on people with rheumatoid arthritis (RA), many of whom are treated with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).[1] While b/tsDMARDs are important for controlling RA disease activity, their influence on COVID-19 outcomes in people with RA remains unclear. This uncertainty has led to anxiety, social isolation due to shielding practices and b/tsDMARD discontinuation, which may contribute to RA flares.[2–4] Addressing the knowledge gaps around the influence of b/tsDMARDs on COVID-19 outcomes is a priority for people with RA and their providers.

Key messages

What is already known about this subject?

- A previous international registry study of the COVID-19 Global Rheumatology Alliance (C19-GRA) suggested that people with systemic rheumatic diseases on biologic or targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) had lower odds of hospitalisation than those not using DMARDs.
- Previous studies reported that people with systemic rheumatic diseases using rituximab had higher odds of COVID-19-related mortality than those using alternative DMARDs such as methotrexate.

What does this study add?

- Using the C19-GRA, we analysed people with rheumatoid arthritis (RA) using b/tsDMARD (to limit the potential for confounding) at the time of COVID-19 onset and investigated an ordinal outcome that encompassed a range of COVID-19 outcomes.
- People with RA using rituximab or Janus kinase (JAK) inhibitors at COVID-19 onset were more likely to experience poor COVID-19 outcomes, ranging from hospitalisation to death, compared with use of tumour necrosis factor inhibitors.

How might this impact on clinical practice or future developments?

- People using rituximab or JAK inhibitors for RA are more likely to experience poor COVID-19 outcomes and should be prioritised for risk mitigation strategies.

The impact of b/tsDMARDs on COVID-19 outcomes is of particular interest since some of these medications, such as tocilizumab and baricitinib, have been studied as repurposed treatments for COVID-19. Some evidence suggests that baseline use of certain b/tsDMARDs, like tumour necrosis factor inhibitors (TNFi), for inflammatory disorders may be associated with less severe COVID-19 outcomes.[5] In addition, among patients with COVID-19, treatment with interleukin 6 inhibitors (IL-6i) and baricitinib led to improved outcomes in some clinical trials.[6–9] However, there are also concerns that baseline use of certain b/tsDMARDs, such as rituximab or abatacept, may be associated with worse COVID-19 outcomes due to impaired viral immune defences.[10 11]

Due to sample size limitations, previous studies of b/tsDMARD use and COVID-19 outcomes have combined heterogeneous rheumatic diseases and medications and/or investigated a single outcome, such as hospitalisation.[5 12] Therefore, we used the COVID-19 Global Rheumatology Alliance (C19-GRA) physician registry to evaluate the associations of different classes of b/tsDMARDs with a range of COVID-19 outcomes in people with RA.

METHODS

Data source and study sample assembly

People with rheumatic disease and COVID-19 from the C19-GRA registry and the European Alliance of Associations for Rheumatology (EULAR) COVID-19 database were included in the analyses. We included cases entered between 24 March 2020 and 12 April 2021. The C19-GRA and EULAR databases include people with rheumatic diseases diagnosed with COVID-19, as reported by rheumatology providers via two international data entry portals. The details of these registries have been previously reported.[5 12–17] We analysed people with RA on b/tsDMARD at the time of COVID-19 clinical onset. As of 12 April 2021, a total of 15 127 people with rheumatic diseases and COVID-19 have been reported. We included people with RA who were taking one of the following medication classes: Cytotoxic T lymphocyte-associated antigen immunoglobulin (CTLA4-Ig: abatacept), anti-CD20 (rituximab), IL-6i (tocilizumab, sarilumab), Janus kinase inhibitors (JAKi: tofacitinib, baricitinib or upadacitinib) or TNFi (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab). The drug class of b/tsDMARD was collected, rather than individual drugs. We did not include IL-1 inhibitors since these were infrequently used for RA. Prior studies using the C19-GRA and EULAR databases have included some patients also reported in this study, but the analyses included in this study and observations reported are novel. In addition, follow-up for this study is more current than previous publications using these data.

Data quality was assessed by the University of California, San Francisco and the University of Manchester, UK, which both confirmed that there were no duplicates in the data entries.

Baseline b/tsDMARD exposures

The exposure of interest was baseline use of a b/tsDMARD at the time of COVID-19 clinical onset. As in previous C19-GRA investigations, we included confirmed and presumptive cases of COVID-19.[5 12 14] We limited this analysis to users of abatacept, rituximab, IL-6i, JAKi or TNFi to limit the cohort to people with similar RA disease severity and minimise the impact of confounding by indication. We included b/tsDMARD users regardless of whether they also used a conventional synthetic (cs) DMARD or glucocorticoids, but did not include people on csDMARDs (eg, hydroxychloroquine, methotrexate, sulfasalazine, leflunomide) monotherapy, as monotherapy may indicate less severe RA or be due to care access barriers or socioeconomic factors. TNFi users were the reference group since TNFis are the most frequently used b/tsDMARD in RA. People with RA who were reported to be on more than one b/tsDMARD were excluded from the analysis.

COVID-19 outcomes

The primary outcome of interest was a mutually exclusive ordinal COVID-19 severity outcome: (1) no hospitalisation, (2) hospitalisation with no oxygenation, (3) hospitalisation with any oxygenation or mechanical ventilation, and (4) death. We chose this primary outcome to estimate the association of b/tsDMARD exposure with general odds of worse COVID-19 severity rather than a single outcome. A similar outcome was developed by the WHO to capture the spectrum of disease and is used in clinical trials evaluating COVID-19 therapeutics.[18] If a patient met multiple levels of the outcome, they were only included at the highest level. At the time of analysis, all patients were required to have a resolved clinical course.

Covariates

Details regarding demographics, including age, race/ethnicity and continent, and patient characteristics, including obesity, smoking, comorbidities (interstitial lung disease (ILD), history of cancer, hypertension, cardiovascular disease, chronic kidney disease/end-stage kidney disease, diabetes, non-ILD pulmonary disease), RA disease activity (as judged by the reporting physician), glucocorticoid dose for RA at the time of COVID-19 onset

and use of concomitant csDMARD (methotrexate, sulfasalazine, hydroxychloroquine), were by physician report. For glucocorticoid dose, the amount of prednisone-equivalent glucocorticoid prescribed was treated as a categorical variable (none, >0–5 mg/day, 6–9 mg/day and ≥10 mg/day). Hypertension and cardiovascular disease were collapsed as a single comorbidity due to collinearity.

Statistical analysis

We reported baseline characteristics and outcomes across the exposure categories of baseline b/tsDMARD use with descriptive statistics.

Ordinal logistic regression models were used to assess the association between each b/tsDMARD compared with TNFi use and the severity of COVID-19 on an ordinal scale in unadjusted and multivariable analyses to estimate ORs and 95% CIs. The effect size of the ordinal outcome can be interpreted as the odds of being one level higher on the ordinal COVID-19 severity scale than the reference group. We assessed the proportional odds assumption for the ordinal regression model using the Brant test.[19] Models in which the proportional odds assumption was not met were refitted using the partial proportional odds model which relaxes the assumption of proportionality for offending predictors.[20] We considered potential confounders known to be associated with either b/tsDMARD use or COVID-19 severity. Covariates included in multivariable models included sociodemographic features (age, sex), obesity, smoking status (ever vs never), concomitant csDMARD use (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide), categorical glucocorticoid use/dose, categorical comorbidity count (0, 1, 2 of the following: chronic kidney insufficiency/end-stage kidney disease, diabetes, non-ILD pulmonary disease), other key comorbidities as individual variables (hypertension/cardiovascular disease, ILD and cancer), disease activity (moderate/high vs remission/low), continent (Europe, North America, South America, other) and calendar time (January–15 June 2020 vs 16 June 2020–12 April 2021).[21] These time periods were selected based on the initial publication of the RECOVERY trial, which reported a survival benefit associated with dexamethasone and influenced subsequent practice.[22] We assumed that missing data were 'missing at random'. We then performed multiple imputation five times to get pooled estimates to impute missing values for disease activity, race/ethnicity, glucocorticoid dose, smoking, hypertension/cardiovascular disease and comorbidity count. After imputation, we compared the distribution of imputed values with the distribution of variables before imputation to confirm that distributions were similar before and after imputation.

To confirm the robustness of our findings, we performed several sensitivity analyses. First, we excluded patients with ILD or cancer from the analysis since rituximab is commonly used in these patients, who may also be susceptible to poor COVID-19 outcomes. Second, given data showing a strong association between race/ethnicity and COVID-19 outcomes in the USA, we performed an analysis adjusting for this variable among US patients in the registry. The race/ethnicity variable was categorised as white, black, Hispanic, Asian or other/mixed race. However, for the model with IL-6i, there were few outcomes within the race/ethnicity variable so we were unable to perform the model. Third, we used propensity score matching to further address potential confounding by indication. We estimated propensity scores for b/tsDMARD use based on age, sex, obesity, smoking, concomitant csDMARDs, glucocorticoid use/dose, number of comorbidities, disease activity, region and calendar time. Covariate balance between each b/tsDMARD drug class and TNFi was assessed using Love plots (online supplemental figures 1–4), which showed that most of the covariates were matched with an absolute standardised mean difference less than 0.1, denoting sufficient matching performance.[23] Ordinal logistic regression was then performed after matching. Fourth, we repeated our primary analysis after excluding patients with a presumptive diagnosis of COVID-19. Presumptive cases were those that lacked one of the following: positive PCR or antigen test for SARS-CoV-2 or typical chest imaging findings. Fifth, we repeated the analysis but stratified by calendar time (before or after 15 June 2020 when RECOVERY trial's results were announced) and by continent (North America or Europe) in case calendar time and geography may have influenced the results. Sixth, we used a revised version of the ordinal COVID-19 severity outcome that considered mechanical ventilation as its own category.

We then repeated our primary analyses using dichotomised outcomes rather than the ordinal COVID-19 severity scale to investigate whether there were particular outcomes driving the associations we observed. For example, we investigated whether each b/tsDMARD was associated with hospitalisation (yes/no) compared with TNFi use.

We used the Brant test to assess whether the observed deviations from the ordinal logistic regression are larger than what could be attributed to chance alone. If the p values are greater than the alpha level of 0.05, then the covariates satisfy the proportional odds assumption. This assumption states that the estimate between each pair of outcomes across the response levels regardless of the partition that we consider. For abatacept and JAKis, both age and glucocorticoid dose violated the assumption, and for IL-6is and rituximab, age, gender and glucocorticoid dose violated the assumption. In order to address the lack of proportionality for these covariates, partial proportional odds models were run to relax this assumption for the respective covariates for each medication category (online supplemental table 1). We found that the estimates were similar when comparing the proportional odds models and the non-proportional odds model, so we reported the model without relaxing the assumption.

Results were considered statistically significant at two-sided $p<0.05$. Analyses were conducted in R V.4.0.2.

RESULTS

Study sample and baseline characteristics

From a total of 6132 RA cases reported to the registry, we identified 2869 who were on abatacept (n=237), rituximab (n=364), IL-6i (n=317), JAKi (n=563) or TNFi (n=1388) at the time of clinical COVID-19 onset. The baseline clinical characteristics are shown in table 1. The sample was predominantly female (80.8%) and the mean age was 56.7 years (SD 13.4). Most patients were from Europe (51.8%) and North America (35.0%). Overall, 354 (12.3%) were obese, 582 (20.3%) were ever smokers, 810 (28.2%) were on glucocorticoids, 1409 (49.1%) were on concomitant csDMARDs, and 510 (17.8%) had moderate/high RA disease activity. Among b/tsDMARD users, rituximab users were more likely than TNFi users to have ILD (11.0% vs 1.4%) or a history of cancer (7.4% vs 0.9%); JAKi users were slightly more likely than TNFi users to be obese (15.1% vs 10.3%).

Table 1 Baseline characteristics according to use of biologic or targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis at the time of COVID-19 onset

	Overall N=2869	Abatacept n=237	Rituximab n=364	IL-6 inhibitors n=317	JAK inhibitors n=563	TNF inhibitors n=1388
Demographics						
Mean age (years), SD	56.7 (13.4)	61.4 (14.0)	58.0 (12.9)	56.4 (12.0)	58.0 (12.3)	55.2 (14.0)
Female	2316 (80.8)	188 (79.3)	299 (82.1)	257 (81.3)	470 (83.5)	1102 (79.4)
Race/ethnicity						
White	1670 (69.0)	78 (69.5)	187 (64.5)	169 (67.9)	360 (73.2)	829 (69.3)
Black	113 (4.7)	5 (3.2)	14 (4.8)	11 (4.4)	22 (4.5)	60 (5.0)
Hispanic	472 (19.5)	32 (20.8)	66 (22.8)	46 (18.5)	79 (16.1)	233 (19.5)
East Asian	81 (3.3)	8 (5.2)	10 (3.4)	12 (4.8)	10 (2.0)	37 (3.1)
Other	85 (3.3)	2 (1.3)	13 (4.5)	11 (4.4)	21 (4.3)	38 (3.2)
Continent						
Europe	1486 (51.8)	103 (43.5)	218 (59.9)	183 (57.7)	283 (50.3)	699 (50.4)
North America	1005 (35.0)	105 (44.3)	111 (30.5)	83 (26.2)	208 (36.9)	498 (35.9)
South America	276 (9.6)	20 (8.4)	23 (6.3)	33 (10.4)	55 (9.8)	145 (10.4)
Other	302 (10.5)	9 (3.8)	12 (3.3)	18 (5.7)	17 (3.0)	46 (3.3)
Comorbidity count*						
0	1494 (52.1)	113 (47.7)	161 (44.2)	161 (50.8)	270 (48.0)	789 (56.8)
1	837 (29.2)	70 (29.5)	119 (32.7)	99 (31.2)	176 (31.3)	373 (26.9)
2	538 (18.8)	54 (22.8)	84 (23.1)	57 (18.0)	117 (20.8)	226 (16.3)
Individual comorbidities						
Hypertension	983 (34.3)	91 (38.4)	121 (33.2)	108 (34.1)	221 (39.3)	442 (31.8)
Cardiovascular disease	247 (8.6)	29 (12.2)	36 (9.9)	32 (10.1)	51 (9.1)	99 (7.1)
Diabetes	356 (12.5)	30 (12.8)	54 (14.9)	43 (13.6)	74 (13.2)	155 (11.3)
Chronic kidney disease	98 (3.4)	11 (4.7)	11 (3.0)	14 (4.4)	22 (3.9)	40 (2.9)
Lung disease†	432 (15.2)	41 (17.4)	87 (24.0)	44 (13.9)	92 (16.4)	168 (12.3)
Interstitial lung disease	103 (3.6)	15 (6.3)	40 (11.0)	15 (4.7)	13 (2.3)	20 (1.4)
Cancer	40 (1.5)	5 (2.5)	27 (7.4)	6 (2.2)	5 (1.0)	11 (0.9)
Obesity	354 (12.3)	31 (13.1)	52 (14.3)	43 (13.6)	85 (15.1)	143 (10.3)
Smoking status						
Ever	582 (20.3)	104 (43.9)	70 (19.2)	57 (18.0)	99 (17.6)	300 (21.6)
Never	1369 (47.7)	56 (23.6)	142 (39.0)	152 (47.9)	262 (46.5)	694 (50.)
Missing	918 (32.0)	77 (32.5)	137 (37.6)	107 (33.8)	202 (35.9)	394 (28.4)
Concomitant RA medications						
Any conventional synthetic DMARD	1409 (49.1)	118 (49.8)	194 (53.3)	102 (32.2)	228 (40.5)	767 (55.3)
Methotrexate	1188 (41.4)	92 (38.8)	146 (40.1)	91 (28.7)	188 (33.4)	671 (48.3)
Sulfasalazine	136 (4.7)	9 (3.8)	26 (7.1)	8 (2.5)	18 (3.2)	75 (5.4)
Hydroxychloroquine	260 (9.1)	25 (10.5)	58 (15.9)	18 (5.7)	43 (7.6)	116 (8.4)
Leflunomide	176 (10.5)	26 (11.0)	49 (13.5)	20 (6.3)	29 (5.2)	117 (8.4)
Glucocorticoid dose, median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–5.5)	5.0 (5.0–7.5)	5.0 (4.5–7.0)	5.0 (3.0–5.0)	5.0 (5.0–7.0)
Categorical glucocorticoid use/dose						
No glucocorticoid use	1756 (61.2)	120 (56.9)	186 (51.1)	173 (54.6)	320 (63.5)	957 (76.1)
Glucocorticoid >0–5 mg/day prednisone equivalent	600 (20.9)	68 (32.2)	93 (25.5)	69 (21.8)	149 (29.6)	221 (17.6)
Glucocorticoid 6–9 mg/day prednisone equivalent	68 (2.4)	8 (3.8)	10 (2.7)	15 (4.7)	12 (2.4)	23 (1.8)
Glucocorticoid ≥10 mg/day prednisone equivalent	142 (4.9)	15 (7.1)	28 (7.7)	19 (6.0)	23 (4.6)	57 (4.5)
Missing	303 (10.6)	26 (11.0)	47 (12.9)	41 (12.9)	59 (10.5)	130 (9.4)
RA disease activity by global physician assessment						
Remission or low	1949 (67.9)	147 (74.2)	226 (76.1)	198 (77.3)	388 (78.7)	990 (81.5)
Moderate or high	510 (17.8)	51 (25.8)	71 (23.9)	58 (22.7)	105 (21.3)	225 (18.5)
Missing	410 (14.3)	39 (16.5)	67 (18.4)	61 (19.2)	70 (12.4)	173 (12.5)
Confirmed COVID-19	2333 (81.3)	201 (84.8)	304 (83.5)	244 (77.0)	475 (84.4)	1109 (79.9)

n (%) presented unless otherwise specified.
*Comorbidity count included diabetes, lung disease and chronic kidney disease.
†Interstitial lung disease, chronic obstructive pulmonary disease, asthma or other lung disease.
DMARDs, disease-modifying antirheumatic drugs; IL-6, interleukin 6; JAK, Janus kinase; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

COVID-19 outcomes

Outcomes according to the COVID-19 severity scale are shown in table 2. The majority of patients (78.6%) were not hospitalised, 137 (4.8%) were hospitalised without oxygenation, 319 (11.1%) were hospitalised with any oxygen or ventilation requirement, and 157 (5.5%) died. Among rituximab users, 80 (22.0%) required hospitalisation with any oxygen or ventilation and 54 (14.8%) died compared with 103 (7.4%)

Table 2 Frequencies and proportions of outcomes in the ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at the time of COVID-19 onset (N=2869)

COVID-19 severity scale	Overall N=2869 n (%)	Abatacept n=237 n (%)	Rituximab n=364 n (%)	IL-6 inhibitors n=317 n (%)	JAK inhibitors n=563 n (%)	TNF inhibitors n=1388 n (%)
Not hospitalised	2256 (78.6)	181 (76.4)	210 (57.7)	271 (85.5)	409 (72.6)	1185 (85.4)
Hospitalised without oxygenation	137 (4.8)	12 (5.1)	20 (5.5)	13 (4.1)	28 (5.0)	64 (4.6)
Hospitalised with any oxygen or ventilation	319 (11.1)	26 (11.0)	80 (22.0)	24 (7.6)	86 (15.3)	103 (7.4)
Death	157 (5.5)	18 (7.6)	54 (14.8)	9 (2.8)	40 (7.1)	36 (2.6)

IL-6, interleukin 6; JAK, Janus kinase; TNF, tumour necrosis factor.

and 36 (2.6%) TNFi users, respectively. Among JAKi users, 86 (15.3%) were hospitalised with oxygen/ventilation and 40 (7.1%) died. Only 9 (2.8%) patients on baseline IL-6i died.

Associations of b/tsDMARDs with COVID-19 severity

The multivariable ordinal logistic regression model is shown in table 3. Compared with TNFi users, rituximab users had 4.15 (95% CI 3.40 to 3.80) greater odds of worse COVID-19 severity as compared with patients taking TNFi, while JAKi users had 2.06 (95% CI 1.60 to 2.65) greater odds of worse COVID-19 severity. No significant associations were found with respect to abatacept or IL-6i compared with TNFi in the primary analysis.

Sensitivity analyses

Sensitivity analyses of the drug class comparisons are shown in table 3. After excluding patients with ILD or cancer, the association between rituximab with poor COVID-19 outcomes when compared with TNFi use remained strong (OR 4.34, 95% CI 3.23 to 5.82). Among patients with RA in the USA, results were also similar when additionally adjusting for race/ethnicity. We also performed a propensity score-matched analysis instead of multivariable ordinal logistic regression. The sample for each propensity score-matched analysis is illustrated in online supplemental figure 5. Rituximab users (OR 3.36, 95% CI 2.11 to 5.34) and JAKi users (OR 1.56, 95% CI 1.01 to 2.42) had increased COVID-19 severity compared with TNFi users in this analysis. In the propensity score-matched analysis, abatacept had an OR of 1.60 (95% CI 1.02 to 2.51) for the ordinal COVID-19 severity outcome compared with TNFi. IL-6i use was not associated with COVID-19 severity in any of the analyses. Brant tests indicated that the proportional odds assumption did not hold for propensity score models; therefore, partial proportional odds models were used and confirmed that the effect estimates remained consistent (data not shown).

When stratified by calendar time (before or after 15 June 2020) and restricted to Europe or North America, the results were similar (online supplemental table 2).

Individual COVID-19 outcomes

We also performed analyses for each binary level of the COVID-19 severity scale (table 4). Rituximab and JAKi use were each associated with increased odds for each COVID-19 outcome compared with TNFi use. For example, rituximab use had increased odds for hospitalisation (OR 4.53, 95% CI 3.32 to 6.18) as well as death (OR 4.57, 95% CI 3.32 to 9.01) compared with TNFi use. JAKi use was associated with all outcomes considered, including hospitalisation requiring any oxygen or ventilation or death (OR 1.55, 95% CI 1.04 to 2.18) and death (OR 2.04, 95% CI 1.58 to 2.65) compared with TNFi. In these analyses, there were no statistically significant associations between abatacept or IL-6i use and the dichotomised outcomes when compared with TNFi use.

We considered a revised version of the ordinal outcome that included mechanical ventilation as a separate level. There were relatively few patients who survived after requiring mechanical ventilation (online supplemental table 2). Results were similar using this revised ordinal outcome (online supplemental tables 3 and 4).

DISCUSSION

Among patients with RA on b/tsDMARDs at the onset of COVID-19, rituximab and JAKi users were at increased odds for worse COVID-19 outcomes compared with TNFi users. In contrast, we did not find an association between abatacept or IL-6i use with worse COVID-19 outcomes when compared with TNFi users. These observations can inform decision making for providers and patients during the ongoing COVID-19 pandemic. Given the association between rituximab and JAKi use with poor outcomes, vaccination and public health measures such as mask wearing and social distancing for COVID-19 risk mitigation remain paramount. In addition, other specific interventions (eg, monoclonal antibody treatment) might be considered in these patients with COVID-19 exposure or early infection.[24]

Our observations, which use the largest sample of individuals with RA and COVID-19 assembled to date, regarding rituximab exposure confirm findings from prior studies suggesting an association between baseline use of B cell depleting therapies and worse COVID-19 outcomes in people with rheumatic diseases[12 25 26] and multiple sclerosis.[27] We also expand on prior observations using the C19-GRA and EULAR databases by evaluating the association of rituximab with COVID-19 severity rather than only mortality and by using an alternative reference group (TNFi rather than methotrexate) and performing propensity score analyses to further address confounding by indication. By focusing on a single disease, we also were able to identify a novel association of JAKis with COVID-19 severity. Mechanistically, the impact of B cell depletion on antibody production would be expected to impair the immune system's normal response to a viral infection. Indeed, the antibody response to COVID-19 is critical for controlling the initial infection and preventing reinfection.[28] We lacked details regarding the timing of rituximab exposure in relation to the COVID-19 infection or the duration of B cell depletion at the time of infection, which may be particularly relevant when considering the risk of a poor outcome following rituximab exposure. It is also possible that glucocorticoids given as a premedication to rituximab infusions may have contributed to the increased risk of poor COVID-19 outcomes in patients with RA on rituximab. While the results were robust to several sensitivity analyses, it is possible that the result could be confounded by factors such as unrecognised ILD.

Table 3 Results of primary and sensitivity analyses investigating the associations of baseline use of biologic or targeted synthetic disease-modifying antirheumatic drugs with COVID-19 severity (N=2869)

	Abatacept		Rituximab		IL-6i		JAKi		TNFi
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Ref
Unadjusted	1.88 (1.35 to 2.63)	<0.01	4.63 (3.60 to 5.96)	<0.01	1.00 (0.71 to 1.41)	0.99	2.28 (1.80 to 2.88)	<0.01	Ref
Age-adjusted and sex-adjusted	1.40 (0.99 to 1.99)	0.06	4.45 (3.43 to 5.77)	<0.01	1.06 (0.68 to 1.37)	0.84	2.10 (1.64 to 2.68)	<0.01	Ref
Multivariable-adjusted (primary analysis)	1.26 (0.88 to 1.80)	0.21	4.15 (3.16 to 5.44)	<0.01	0.81 (0.56 to 1.18)	0.55	2.06 (1.60 to 2.65)	<0.01	Ref
Confirmed cases only*	1.14 (0.77 to 1.68)	0.52	4.25 (3.17 to 5.69)	<0.01	0.74 (0.49 to 1.11)	0.15	2.05 (1.57 to 2.69)	<0.01	Ref
Excluding patients with ILD or cancer†	1.18 (0.79 to 1.76)	0.43	4.34 (3.23 to 5.82)	<0.01	0.81 (0.54 to 1.21)	0.30	2.14 (1.64 to 2.79)	<0.01	Ref
Restricted to USA and additionally adjusted for race‡	1.16 (0.79 to 1.69)	0.45	4.77 (3.57 to 6.38)	<0.01†	¶	¶	2.86 (1.76 to 4.65)	<0.01†	Ref
Propensity score-matched§	1.60 (1.02 to 2.51)	0.04	4.70 (3.31 to 6.65)	<0.01	0.76 (0.46 to 1.23)	0.26	2.09 (1.50 to 2.90)	<0.01	Ref

The effect size is the odds of being one level higher on the ordinal COVID-19 severity scale than the reference group (TNFi users).
Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity except as otherwise indicated.
*n=2333 in the analysis analysing only confirmed COVID-19 cases.
†n=2704 in the analysis excluding ILD and cancer.
‡n=868 in the USA-only analysis.
§n for each pair of propensity score-matched analyses: abatacept: 236, TNFi: 1376; rituximab: 364, TNFi: 1382; IL-6i: 313, TNFi: 1387; JAKi: 560, TNFi: 1379.
¶Due to the small number of events in the covariate of race, the IL-6i model could not be analysed.
csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ILD, interstitial lung disease; IL6i, interleukin 6 inhibitor; JAKi, Janus kinase inhibitor; Ref, reference; TNFi, tumour necrosis factor inhibitors.

Table 4 Multivariable* OR of biologic or targeted synthetic disease-modifying antirheumatic drugs at each binary level of the COVID-19 severity scale (N=2869)

	Abatacept		Rituximab		IL-6 inhibitors		JAK inhibitors		
COVID-19 outcome	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	TNF inhibitors
Hospitalised	1.18 (0.76 to 1.82)	0.47	4.53 (3.32 to 6.18)	<0.01	0.84 (0.53 to 1.33)	0.45	2.40 (1.78 to 3.24)	<0.01	Ref
Hospitalised with oxygenation/ventilation or death	1.12 (0.70 to 1.81)	0.63	2.87 (2.03 to 4.06)	<0.01	0.72 (0.43 to 1.20)	0.20	1.55 (1.04 to 2.18)	0.01	Ref
Death	1.46 (0.72 to 2.89)	0.30	4.57 (3.32 to 9.01)	<0.01	1.13 (0.50 to 2.59)	0.77	2.04 (1.58 to 2.65)	<0.01	Ref
Mechanical ventilation (restricted to only hospitalised patients, n=613)	1.41 (0.94 to 2.10)	0.09	4.05 (3.08 to 5.33)	<0.01	0.75 (0.51 to 1.10)	0.14	2.03 (1.56 to 2.62)	<0.01	Ref
Mechanical ventilation or death	1.14 (0.78 to 1.66)	0.50	4.44 (3.39 to 5.82)	<0.01	0.74 (0.50 to 1.09)	0.12	2.02 (1.56 to 2.61)	<0.01	Ref

*Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin 6; JAK, Janus kinase; Ref, reference; TNF, tumour necrosis factor.

Our findings are of particular interest given recent clinical trials and observational studies suggesting that IL-6i[6–8 29–32] and JAKi[9] may improve outcomes for patients in the general population with COVID-19. We found no association of baseline IL-6i use in RA with COVID-19 severity compared with TNFi use. In contrast, while baricitinib treatment may have some benefit on time to recovery for patients with more severe COVID-19,[9] we observed worse outcomes associated with baseline use of JAKi. This was also suggested in a recent population-based study investigating RA and other inflammatory joint diseases in Sweden.[25] Glucocorticoids are known to have benefits when initiated for moderate-to-severe COVID-19, but are also associated with worse outcomes among those on baseline glucocorticoids at the time of infection,[5 12] although this may be explained by residual disease activity.[33] Therefore, the timing of JAKi use relative to the COVID-19 disease course may explain our findings. Similar to glucocorticoids, baseline use of JAKi at the time of SARS-CoV-2 infection may enhance viral reproduction and dampen a healthy immune response, while JAKi initiation at clinical deterioration may dampen an aberrant systemic inflammatory response. Alternatively, there may be relevant differences in COVID-19 outcomes depending on the type of JAKi used given that JAKis like tofacitinib, baricitinib and upadacitinib target different Janus kinases. We were unable to perform analyses of each individual JAKi since these were collected as a class. While the primary analysis found no association of abatacept with COVID-19 severity, there was a statistical association in the propensity score-matched analysis. Further research is needed on the safety of abatacept for infection risk and severity since its mechanism of action may impair adaptive immune response.

Our study has a number of strengths, including the international nature of the registry and the large sample size. Additionally, we used an active comparator (TNFi), which was also a b/tsDMARD in a single rheumatic disease, as well as two different modelling approaches (multivariable logistic regression and propensity score matching) among other sensitivity analyses to account for confounding by indication and to confirm the robustness of our findings. Our observations expand on prior general population and RA cohort studies that identified older age, greater comorbidity burden and other factors associated with worse COVID-19 and must also be considered when assessing an individual's risk.

Our study also has certain limitations. First, the Global Rheumatology Alliance and EULAR registries are voluntary and require a provider to submit the details of a case, perhaps biasing our sample towards more severe cases. As such, the proportion of events reported across exposure groups may be an overestimate of that observed among all patients with RA in real-world practice and should be interpreted in that context. However, the effect size estimates do have clinical interpretation in potentially identifying patients with RA who could be susceptible to poor COVID-19 outcomes. While we designed the study to limit the potential impact of selection bias and confounding by indication by examining advanced therapies in a single rheumatic disease, it is possible that selective reporting could have varied across different b/tsDMARD classes as the exposure of interest. This potential bias may have caused an upward deflection in the effect size estimate if more severe cases of a particular b/tsDMARD class were systematically reported compared with others, and this could contribute to the findings that we report. We further mitigated this possibility by adjusting for differences in concomitant medication use, disease activity and comorbidities, as well as performing an analysis removing patients with ILD or cancer. Our findings remained when we excluded presumptive cases of COVID-19. Second, although we were able to adjust for a number of potential confounders of our observed associations, there is the potential for residual unmeasured confounding. Analysing only patients on b/tsDMARD may have helped minimise some unmeasured confounding related to access to care since all analysed patients with RA were able to receive these targeted medications. In addition, the consistent results observed in sensitivity analyses excluding patients with ILD or cancer who may be more likely to receive rituximab support the robustness of our results. However, we did not have data available on RA duration or previous RA medications (eg, previous TNFi use in patients on other classes of b/tsDMARDs), which may have affected the results. Medications were collected by DMARD class, so we were unable to compare individual medications within the same class. However, the goal of the study was to compare different biologic mechanisms of action for COVID-19 severity. Additionally, it is also possible that TNFi use may protect against severe COVID-19 outcomes. Thus, these results should be interpreted cautiously and additional studies are needed to confirm our observed associations. Third, while we leveraged the largest cohort of patients with rheumatic disease with COVID-19, a somewhat small number of outcomes of interest occurred in some subgroups, which may have limited our power to detect significant differences among abatacept users, in particular. In addition, we were unable to investigate individual JAKi or TNFi. Finally, we did not examine medication changes after COVID-19 onset since this occurred after baseline and may have mediated the relationship we report. Most of the drugs have lengthy biologic effects (especially rituximab), while JAKis have short half-lives. Some clinicians may have chosen to continue IL-6is after COVID-19 onset, as suggested by the American College of Rheumatology.[34] Future studies are needed to investigate the association of medication changes with COVID-19 outcomes.

In conclusion, use of rituximab or JAKi, but not abatacept or IL-6i, at the time of COVID-19 infection was associated with worse COVID-19 outcomes compared with TNFi among patients with RA. Additional studies are warranted to confirm these observations. Strategies are needed to improve outcomes following COVID-19 RA on rituximab or JAKis.

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