**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 (TNF, 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 TNF, 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 TNF. 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 TNF. 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 TNF. 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). 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. Addressing the knowledge gaps around the influence of b/tsDMARDs on COVID-19 outcomes is a priority for people with RA and their providers.
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. In addition, among patients with COVID-19, treatment with interleukin 6 inhibitors (IL-6i) and baricitinib led to improved outcomes in some clinical trials. 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.

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. 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. 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. 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. 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. 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. 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). 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. 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. 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%).
Rheumatoid arthritis

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%)
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 1.53, 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 diseases²₂ 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.

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**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)

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

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

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6i</th>
<th>JAKi</th>
<th>TNFi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.88 (1.35 to 2.63)</td>
<td>&lt;0.01</td>
<td>4.63 (3.60 to 5.96)</td>
<td>&lt;0.01</td>
<td>1.00 (0.71 to 1.41)</td>
</tr>
<tr>
<td>Age-adjusted and sex-adjusted</td>
<td>1.40 (0.99 to 1.99)</td>
<td>0.06</td>
<td>4.45 (3.43 to 5.77)</td>
<td>&lt;0.01</td>
<td>1.06 (0.68 to 1.37)</td>
</tr>
<tr>
<td>Multivariable-adjusted (primary analysis)</td>
<td>1.26 (0.88 to 1.80)</td>
<td>0.21</td>
<td>4.15 (3.16 to 5.44)</td>
<td>&lt;0.01</td>
<td>0.81 (0.56 to 1.18)</td>
</tr>
<tr>
<td>Confirmed cases only*</td>
<td>1.14 (0.77 to 1.68)</td>
<td>0.52</td>
<td>4.25 (3.17 to 5.69)</td>
<td>&lt;0.01</td>
<td>0.74 (0.49 to 1.11)</td>
</tr>
<tr>
<td>Excluding patients with ILD or cancer†</td>
<td>1.18 (0.79 to 1.76)</td>
<td>0.43</td>
<td>4.34 (3.23 to 5.82)</td>
<td>&lt;0.01</td>
<td>0.81 (0.54 to 1.21)</td>
</tr>
<tr>
<td>Restricted to USA and additionally adjusted for race‡</td>
<td>1.16 (0.79 to 1.69)</td>
<td>0.45</td>
<td>4.77 (3.57 to 6.38)</td>
<td>&lt;0.01†</td>
<td>†</td>
</tr>
<tr>
<td>Propensity score-matched§</td>
<td>1.60 (1.02 to 2.51)</td>
<td>0.04</td>
<td>4.70 (3.31 to 6.65)</td>
<td>&lt;0.01</td>
<td>0.76 (0.46 to 1.23)</td>
</tr>
</tbody>
</table>

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.

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)

<table>
<thead>
<tr>
<th>COVID-19 outcome</th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
<th>TNFi inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Hospitalised</td>
<td>1.18 (0.76 to 1.82)</td>
<td>0.47</td>
<td>4.53 (3.32 to 6.18)</td>
<td>&lt;0.01</td>
<td>0.84 (0.53 to 1.33)</td>
</tr>
<tr>
<td>Hospitalised with oxygenation/ventilation or death</td>
<td>1.12 (0.70 to 1.81)</td>
<td>0.63</td>
<td>2.87 (2.03 to 4.06)</td>
<td>&lt;0.01</td>
<td>0.72 (0.43 to 1.20)</td>
</tr>
<tr>
<td>Death</td>
<td>1.46 (0.72 to 2.89)</td>
<td>0.30</td>
<td>4.57 (3.32 to 9.01)</td>
<td>&lt;0.01</td>
<td>1.13 (0.50 to 2.59)</td>
</tr>
<tr>
<td>Mechanical ventilation (restricted to only hospitalised patients, n=613)</td>
<td>1.41 (0.94 to 2.10)</td>
<td>0.09</td>
<td>4.05 (3.08 to 5.33)</td>
<td>&lt;0.01</td>
<td>0.75 (0.51 to 1.10)</td>
</tr>
<tr>
<td>Mechanical ventilation or death</td>
<td>1.14 (0.78 to 1.66)</td>
<td>0.50</td>
<td>4.44 (3.29 to 6.82)</td>
<td>&lt;0.01</td>
<td>0.74 (0.50 to 1.09)</td>
</tr>
</tbody>
</table>

*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 inhibitors.
Our findings are of particular interest given recent clinical trials and observational studies suggesting that IL-6i and JAKi 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, 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. 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. 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. 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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Correction notice This article has been corrected since it published Online First. Collaborator names have been updated.

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contributed to data collection, data analysis and interpretation of data. AS, ZSW and JY directed the work, designed the data collection methods, contributed to data collection, data analysis and interpretation of data, and had final responsibility for the decision to submit for publication. All authors contributed intellectual content during the drafting and revision of the work and approved the final version to be published.

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Competing interests JAS is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant numbers K23 AR069688, R03 AR073588, L30 AR066953, P30 AR072523 and P30 AR072577), the Rheumatology Research Foundation (K Supplement Award and R Bridge Award), the Brigham Research Institute, and the R Bruce and Joan M Mickey Research Scholar Fund. JAS has received research support from Amgen and Bristol-Myers Squibb and performed consultancy for Bristol-Myers Squibb, Gilead, Inova, Janssen and Optum, unrelated to this work. ZSW reports grant support from Bristol-Myers Squibb and Prince of Persia; Sano and performed consultancy for Vio Bi and MedFace, outside the submitted work. His work is supported by grants from the National Institutes of Health. MG is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant numbers K01 AR070585 and K24 AR74534). JY has received speaker’s fees from AbbVie and grant income from BMS, UCB and Pfizer, all unrelated to this study. KLH is supported by the NIHR Manchester Biomedical Research Centre. LC has not received fees or personal grants from any laboratory, but her institute works by contract for laboratories such as, among others, AbbVie, Spain, Eisa, Gebo Pharma, Mercel+ & Dompe且 Shiva, Novartis Farmacología, Pfizer, Roche Farmacia, Sanofi Aventis, AstraZeneca, Actelion Pharmaceuticals Farmacia, Greekenthal and UC Pharma. LG reports research grants from Amgen, Galapagos, Janssen, Lilly, Pfizer, Sandoz and Sanofi; consulting fees from AbbVie, Amgen, BMS, Biogen, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Sanofi, BioPelie, Sanofi Aventis and UCB, all unrelated to this work. EFM reports that LPCDR received support for specific activities: grants from AbbVie, Novartis, Janssen-Cilag, Lilly Puerto Rico, Sanofi, Greenenthal, MSD, Celgene, Medac, Pharma Kem and GAIPA; grants and non-financial support from Pfizer; and non-financial support from Grünenthal, outside the submitted work. AS reports grants from a consortium of 13 companies (among them AbbVie, BMS, Celltrion, Fresenius Kabi, Lilly, Mylan, Helsa, MSD, Pfizer, Roche, Sanosan, Sanofi Aventis and UCB) supporting the German RABBIT register, and personal fees from lectures for AbbVie, MSD, Roche, BMS and Pfizer, outside the submitted work. AD-G has no disclosures relevant to this study. His work is supported by grants from the Centers for Disease Control and Prevention and the Rheumatology Research Foundation. KJ has received research support from Amgen and Bristol-Myers Squibb, chugs and Pfizer, and performed consultancy for Biogen, Janssen, Biostil-Mylus Squibb, Lilly, Sanofi, Pfizer, Chugai, Roche and Janssen, unrelated to this work. NS is supported by the RRF Investigator Award and the American Heart Association. MFU-G reports grant support from Janssen and Pfizer; SB reports no competing interests related to this work. He reports non-branded consulting fees for AbbVie, Horizon, Novartis and Pfizer ($<10 000). RG reports no competing interests related to this work. Outside of this work she reports personal and/or speaking fees from AbbVie, Janssen, Novartis, Pfizer and Comerstone, and travel assistance from Pfizer ($<10 000). JH has no competing interests related to this work. His work is supported by grants from the Rheumatology Research Foundation and the Childhood Arthritis and Rheumatology Research Alliance. He has performed consulting for Novartis, Sobi and Biogen, all unrelated to this work ($<10 000). JL has received research funding from Pfizer, outside the submitted work. ES is a Board Member of the Canadian Arthritis Patient Alliance, a patient-run, volunteer-based organisation whose activities are largely supported by independent grants from several pharmaceutical companies. No competing interests related to this work. He reports honorarium for doing social media for American College of Rheumatology journals ($<10 000). PMM has received consulting/fees’ speaker’s fees from AbbVie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche and UCB, all unrelated to this study ($<10 000). PMM is supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC). PCR reports no competing interests related to this work. Outside of this work he had consulting and/or to this work. EL has received research support from Amgen, Janssen, Novartis, Pfizer and UCB, and travel assistance from Roche ($<10 000). JY reports no competing interests related to this work. Her work is supported by grants from the National Institutes of Health, Centers for Disease Control and the...
Rheumatoid arthritis

Agency for Healthcare Research and Quality. She has performed consulting for Eli Lilly and AstraZeneca, unrelated to this project.

Patient consent for publication Not required.

Ethics approval The C19-GRA physician-reported registry was determined ‘not human subjects’ research’ by the UK Health Research Authority and the University of Manchester, as well as under US Federal Guidelines assessed by the University of California, San Francisco Institutional Review Board. Due to the de-identified and non-interventional nature of the study, it was determined to be exempt by each institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Applications to access the data should be made to the C19-GRA Steering Committee.

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REFERENCES

Supplementary Material for “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” by Sparks JA, Wallace ZS, et al.

Supplementary Figure 1: Love plot for abatacept vs. TNF inhibitors.

![Abatacept vs. TNF Love Plot](image_url)
Supplementary Figure 2: Love plot for rituximab vs. TNF inhibitors.
**Supplementary Figure 3:** Love plot for IL-6 inhibitors vs. TNF inhibitors.
**Supplementary Figure 4**: Love plot for JAK inhibitors vs. TNF inhibitors.

**JAK vs. TNF Love Plot**

- Distance
- Europe
- North America
- South America
- Age
- Gender
- Ever Smoke
- Never Smoke
- Other
- Obese
- Disease Activity
- Comorbidity Count 0
- Comorbidity Count 1
- Comorbidity Count >2
- Glucocorticoid Dose 0
- Glucocorticoid Dose 1-4
- Glucocorticoid Dose 6-9
- Glucocorticoid Dose > 10
- Any DMARD

Jan. 1 2020-June 15, 2020
June 16, 2020- April 12, 2021

Absolute Standardized Mean Difference
**Supplementary Figure 5:** Flow diagram illustrating analyzed sample for propensity score matching analyses.

![Flow Diagram of Matched Regression](Image)

- **Total:** N = 2869
  - **Specific Medication Only**
    - Abatacept: N = 237 → N = 236 → N = 1376
    - Rituiximab: N = 364 → N = 364 → N = 1382
    - TR inhibitors: N = 317 → N = 313 → N = 1387
    - JAK inhibitors: N = 563 → N = 560 → N = 1379
    - TNF inhibitors: N = 1388 →
**Supplementary Table 1.** Sensitivity analysis restricting to study period before or after June 16, 2021 and by North America or Europe.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
<th>TNF inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Restricted to North America* (January 1, 2020 to June 15, 2020)</td>
<td>0.94 (0.40, 2.21)</td>
<td>0.89</td>
<td>3.95 (1.93, 8.06)</td>
<td>&lt;0.01</td>
<td>0.59 (0.18, 1.93)</td>
</tr>
<tr>
<td>Restricted to Europe (January 1, 2020 to June 15, 2020)</td>
<td>1.11 (0.55, 2.23)</td>
<td>0.77</td>
<td>5.01 (3.10, 8.09)</td>
<td>&lt;0.01</td>
<td>1.00 (0.52, 1.92)</td>
</tr>
<tr>
<td>Restricted to Europe (June 16, 2020-April 12, 2021)</td>
<td>1.45 (0.50, 4.23)</td>
<td>0.50</td>
<td>7.34 (3.94, 13.85)</td>
<td>&lt;0.01</td>
<td>0.28 (0.08, 1.02)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, region, 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.

*There were too few cases to analyze North America June 16, 2020-April 12, 2021.
**Supplementary Table 2.** Frequencies and proportions of outcomes using a revised ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at time of COVID-19 onset (n=2,869).

<table>
<thead>
<tr>
<th>COVID-19 severity scale</th>
<th>Overall n=2,869</th>
<th>Abatacept n=237</th>
<th>Rituximab n=364</th>
<th>IL-6 inhibitors n=317</th>
<th>JAK inhibitors n=563</th>
<th>TNF inhibitors n=1388</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Not hospitalized</td>
<td>2256 (78.6%)</td>
<td>181 (76.4%)</td>
<td>210 (57.7%)</td>
<td>271 (85.5%)</td>
<td>409 (72.6%)</td>
<td>1185 (85.4%)</td>
</tr>
<tr>
<td>2) Hospitalized with or without oxygenation (but no mechanical ventilation)</td>
<td>428 (14.9%)</td>
<td>36 (11.0%)</td>
<td>91 (25.0%)</td>
<td>36 (11.4%)</td>
<td>108 (19.2%)</td>
<td>157 (11.3%)</td>
</tr>
<tr>
<td>3) Hospitalized with mechanical ventilation</td>
<td>28 (1.0%)</td>
<td>2 (0.8%)</td>
<td>9 (2.5%)</td>
<td>1 (0.32%)</td>
<td>6 (1.1%)</td>
<td>10 (0.7%)</td>
</tr>
<tr>
<td>4) Death</td>
<td>157 (5.5%)</td>
<td>18 (7.6%)</td>
<td>54 (14.8%)</td>
<td>9 (2.8%)</td>
<td>40 (7.1%)</td>
<td>36 (2.6%)</td>
</tr>
</tbody>
</table>
**Supplementary Table 3.** Associations of b/tsDMARD use with COVID-19 severity using a revised ordinal outcome scale.

<table>
<thead>
<tr>
<th></th>
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<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.87 (1.34, 2.61)</td>
<td>0.25</td>
<td>4.50 (3.50, 5.79)</td>
<td>&lt;0.01</td>
<td>0.99 (0.70, 1.40)</td>
</tr>
<tr>
<td>Multivariable Adjusted</td>
<td>1.24 (0.78, 2.19)</td>
<td>0.36</td>
<td>3.60 (3.40, 3.80)</td>
<td>&lt;0.01</td>
<td>0.83 (0.50, 1.37)</td>
</tr>
</tbody>
</table>

Using different ordinal outcome scale as supplemental analysis

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.
Supplementary Table 4. Associations of b/tsDMARD use with COVID-19 severity using a revised ordinal outcome scale.

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Multivariable adjusted</strong></td>
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<tr>
<td>(primary analysis)</td>
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<td></td>
<td>1.24 (0.78, 2.19)</td>
<td>0.36</td>
<td>3.60 (3.40, 3.80)</td>
<td>&lt;0.01</td>
<td>0.83 (0.50, 1.37)</td>
</tr>
<tr>
<td><strong>Excluding patients with</strong></td>
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<td></td>
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<tr>
<td>ILD or cancer*</td>
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<td></td>
<td>1.24 (0.78, 1.96)</td>
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<td>4.15 (2.95, 5.84)</td>
<td>&lt;0.01</td>
<td>0.66 (0.40, 1.07)</td>
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<tr>
<td><strong>Restricted to US and</strong></td>
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<tr>
<td>additionally adjusted for</td>
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<tr>
<td>race**</td>
<td></td>
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<tr>
<td></td>
<td>1.00 (0.48, 2.12)</td>
<td>0.99</td>
<td>3.82 (2.72, 5.37)</td>
<td>&lt;0.01</td>
<td>0.66 (0.40, 1.07)</td>
</tr>
<tr>
<td><strong>Propensity score</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>matched***</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1.72 (0.99, 2.98)</td>
<td>0.051</td>
<td>3.36 (2.11, 5.34)</td>
<td>&lt;0.01</td>
<td>0.68 (0.35, 1.32)</td>
</tr>
</tbody>
</table>

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= 2,704 1,563 in the analysis excluding ILD and cancer.
**n=622 868 in the US-only analysis.
***n for each pair of propensity-score matched analyses: ABA: 236 TNF: 1376; RTX: 364 TNFi: 1382;
 IL6i: 313 TNFi: 1387; JAKi: 560 TNFi: 1379
CI, confidence interval; COVID-19, Coronavirus Disease 2019; IL-6, interleukin-6; ILD, interstitial lung disease; JAK, Janus kinase; OR, odds ratio; TNFi, tumor necrosis factor inhibitors.
Supplementary Material for “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” by Sparks JA, Wallace ZS, et al.

**Supplementary Figure 1**: Love plot for abatacept vs. TNF inhibitors.
**Supplementary Figure 2**: Love plot for rituximab vs. TNF inhibitors.
Supplementary Figure 3: Love plot for IL-6 inhibitors vs. TNF inhibitors.
**Supplementary Figure 4**: Love plot for JAK inhibitors vs. TNF inhibitors.
**Supplementary Figure 5**: Flow diagram illustrating analyzed sample for propensity score matching analyses.

![Flow Diagram of Matched Regression](image_url)
Supplementary Table 1. Sensitivity analysis restricting to study period before or after June 16, 2021 and by North America or Europe.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
<th>TNF inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Restricted to North America*</td>
<td>0.94 (0.40, 2.21)</td>
<td>0.89</td>
<td>3.95 (1.93, 8.06)</td>
<td>&lt;0.01</td>
<td>0.59 (0.18, 1.93)</td>
</tr>
<tr>
<td>(January 1, 2020 to June 15, 2020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted to Europe</td>
<td>1.11 (0.55, 2.23)</td>
<td>0.77</td>
<td>5.01 (3.10, 8.09)</td>
<td>&lt;0.01</td>
<td>1.00 (0.52, 1.92)</td>
</tr>
<tr>
<td>(January 1, 2020 to June 15, 2020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted to Europe</td>
<td>1.45 (0.50, 4.23)</td>
<td>0.50</td>
<td>7.34 (3.94, 13.85)</td>
<td>&lt;0.01</td>
<td>0.28 (0.08, 1.02)</td>
</tr>
<tr>
<td>(June 16, 2020-April 12, 2021)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, region, 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.

*There were too few cases to analyze North America June 16, 2020-April 12, 2021.
Supplementary Table 2. Frequencies and proportions of outcomes using a revised ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at time of COVID-19 onset (n=2,869).

<table>
<thead>
<tr>
<th>COVID-19 severity scale</th>
<th>Overall n=2,869</th>
<th>Abatacept n=237</th>
<th>Rituximab n=364</th>
<th>IL-6 inhibitors n=317</th>
<th>JAK inhibitors n=563</th>
<th>TNF inhibitors n=1388</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Not hospitalized</td>
<td>2256 (78.6%)</td>
<td>181 (76.4%)</td>
<td>210 (57.7%)</td>
<td>271 (85.5%)</td>
<td>409 (72.6%)</td>
<td>1185 (85.4%)</td>
</tr>
<tr>
<td>2) Hospitalized with or without oxygenation (but no mechanical ventilation)</td>
<td>428 (14.9%)</td>
<td>36 (11.0%)</td>
<td>91 (25.0%)</td>
<td>36 (11.4%)</td>
<td>108 (19.2%)</td>
<td>157 (11.3%)</td>
</tr>
<tr>
<td>3) Hospitalized with mechanical ventilation</td>
<td>28 (1.0%)</td>
<td>2 (0.8%)</td>
<td>9 (2.5%)</td>
<td>1 (0.32%)</td>
<td>6 (1.1%)</td>
<td>10 (0.7%)</td>
</tr>
<tr>
<td>4) Death</td>
<td>157 (5.5%)</td>
<td>18 (7.6%)</td>
<td>54 (14.8%)</td>
<td>9 (2.8%)</td>
<td>40 (7.1%)</td>
<td>36 (2.6%)</td>
</tr>
</tbody>
</table>
Supplementary Table 3. Associations of b/tsDMARD use with COVID-19 severity using a revised ordinal outcome scale.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
<th>TNF inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Using different ordinal outcome scale as supplemental analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>1.87 (1.34, 2.61)</td>
<td>0.25</td>
<td>4.50 (3.50, 5.79)</td>
<td>&lt;0.01</td>
<td>0.99 (0.70, 1.40)</td>
</tr>
<tr>
<td><strong>Multivariable Adjusted</strong></td>
<td>1.24 (0.78, 2.19)</td>
<td>0.36</td>
<td>3.60 (3.40, 3.80)</td>
<td>&lt;0.01</td>
<td>0.83 (0.50, 1.37)</td>
</tr>
</tbody>
</table>

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.
**Supplementary Table 4.** Associations of b/tsDMARD use with COVID-19 severity using a revised ordinal outcome scale.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>IL-6 inhibitors</th>
<th>JAK inhibitors</th>
<th>TNF inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Multivariable adjusted (primary analysis)</td>
<td>1.24 (0.78, 2.19)</td>
<td>0.36</td>
<td>3.60 (3.40, 3.80)</td>
<td>&lt;0.01</td>
<td>0.83 (0.50, 1.37)</td>
</tr>
<tr>
<td>Excluding patients with ILD or cancer*</td>
<td>1.24 (0.78, 1.96)</td>
<td>0.36</td>
<td>4.15 (2.95, 5.84)</td>
<td>&lt;0.01</td>
<td>0.66 (0.40, 1.07)</td>
</tr>
<tr>
<td>Restricted to US and additionally adjusted for race**</td>
<td>1.00 (0.48, 2.12)</td>
<td>0.99</td>
<td>3.82 (2.72, 5.37)</td>
<td>&lt;0.01</td>
<td>0.66 (0.40, 1.07)</td>
</tr>
<tr>
<td>Propensity score matched***</td>
<td>1.72 (0.99, 2.98)</td>
<td>0.051</td>
<td>3.36 (2.11, 5.34)</td>
<td>&lt;0.01</td>
<td>0.68 (0.35, 1.32)</td>
</tr>
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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= 2,704 1,563 in the analysis excluding ILD and cancer.

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***n for each pair of propensity-score matched analyses: ABA: 236 TNF: 1376; RTX: 364 TNFi: 1382; IL6i: 313 TNFi: 1387; JAKi: 560 TNFi: 1379
CI, confidence interval; COVID-19, Coronavirus Disease 2019; IL-6, interleukin-6; ILD, interstitial lung disease; JAK, Janus kinase; OR, odds ratio; TNFi, tumor necrosis factor inhibitors.
Medication use for rheumatoid arthritis affects COVID-19 outcomes

People with rheumatoid arthritis treated with rituximab or JAKi have worse COVID-19 severity than those on TNFi.

INTRODUCTION
COVID-19 is the disease caused by a new type of coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was declared a pandemic by the World Health Organization on 11 March 2020. COVID-19 has forced people to change their behaviours to try to limit the spread of infection.

Rheumatoid arthritis is a chronic inflammatory disease that affects a person’s joints, and may cause pain and disability. Rheumatoid arthritis can affect people of all ages, but it most often starts between the ages of 30 and 50. Rheumatoid arthritis is more common in women than men. There are many different treatments available for rheumatoid arthritis. The available medications include biologic or targeted synthetic disease-modifying antirheumatic drugs (usually shortened to bDMARD or tsDMARD).

WHAT DID THE AUTHORS HOPE TO FIND?
The authors wanted to see whether using bDMARDs or tsDMARDs for rheumatoid arthritis might affect a person’s chances of COVID-19 outcomes such as hospitalisation, needing oxygen, or dying.

WHO WAS STUDIED?
The study looked at 2,869 people with RA that were taking a bDMARD or tsDMARD when they got COVID-19. Most people were from Europe and North America, and the average age was 57 years.

HOW WAS THE STUDY CONDUCTED?
This was a retrospective observational study, which means that the authors used existing databases of patient records to look back and find people for each group. There was no interventional treatment given.

All the data came from people who took part in the Global Rheumatology Alliance (GRA) Physician Registry. The GRA is an ongoing study that is collecting information on people with systemic rheumatic diseases and COVID-19. Details are entered into the database by a person’s doctor. No identifying information is included, so all the data are anonymous.

In this analysis, the authors used data for people with rheumatoid arthritis who were taking a bDMARD or tsDMARD at the time of COVID-19 onset. The bDMARD drugs being used were abatacept, rituximab, interleukin-6 receptor inhibitors (IL-6Ri), and tumour necrosis factor inhibitors (TNFi). The tsDMARD medicines were all types of janus kinase inhibitors (JAKi).

WHAT WAS THE MAIN FINDING?
The authors found that people with rheumatoid arthritis treated with rituximab or JAKi had an increased risk of worse COVID-19 outcomes compared with people taking TNFi. These poor COVID-19 outcomes included hospitalisation, need for oxygen (including mechanical ventilation), and death. The outcomes for people whose rheumatoid arthritis was treated with abatacept or IL-6Ri were generally similar to those taking TNFi.

ARE THESE FINDINGS NEW?
Some previous studies have found that people treated with rituximab may have poor COVID-19 outcomes. However, those studies included several different types of diseases (not just rheumatoid arthritis), and did not directly compare the results to other drugs that may be considered for a specific disease. In this study, the association of JAKi with poor COVID-19 outcomes was new.
WHAT ARE THE LIMITATIONS OF THIS STUDY?
One limitation is that medications were grouped by class, rather than by individual drugs. It is possible that specific drugs within a class may have differences. For example, tofacitinib, baricitinib, and upadacitinib are all JAKi medications, but may have different biologic effects. While the GRA contains good quality data, some specific information about a person’s rheumatoid arthritis such as duration, severity, and previous medications were not available. Finally, the GRA Registry contains voluntarily entered cases. It is possible that doctors may be more likely to enter more severe cases that come to their attention rather than mild COVID-19 cases that get better quickly. This may affect the results.

WHAT DO THE AUTHORS PLAN TO DO WITH THIS INFORMATION?
The authors plan to replicate the findings and extend to different patient populations. Prospective studies to follow people with rheumatoid arthritis and other rheumatic diseases with COVID-19 are ongoing. Other studies that might be considered include seeing whether antibody levels to COVID-19 vaccines are protective, and whether booster doses may be needed for people who require immunosuppression.

WHAT DOES THIS MEAN FOR ME?
If you have rheumatoid arthritis, these findings suggest that the type of medication you use may affect the severity of COVID-19. Your doctor should be aware that you could be susceptible to poor outcomes, and you may be monitored more closely than usual. Controlling your rheumatoid arthritis is still very important during the pandemic. Do not stop taking any medicines you have been prescribed without talking to your doctor first.

Protect yourself from COVID-19 by following the advice of the government in your country. The best protection is getting vaccinated, but you should also wash your hands regularly, and avoid touching your face. Where recommended, follow social distancing rules, and use protective masks. Maintaining good ventilation may also help stop the virus spreading.

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