ACR Open Rheumatology
Vol. 4, No. 3, March 2022, pp 238–246
DOI 10.1002/acr2.11386

American College of Rheumatology
Empowering Rheumatology Professionals

Coronavirus Disease 2019 Outcomes Among Recipients of Anti-CD20 Monoclonal Antibodies for Immune-Mediated Diseases: A Comparative Cohort Study

Naomi J. Patel,[1] Kristin M. D'Silva,[1] Tiffany Y-T. Hsu,[2] Michael Dilorio,[2] Xiaoqing Fu,[1] Claire Cook,[1] Lauren Prisco,[2] Lily Martin,[2] Kathleen M. M. Vanni,[2] Alessandra Zaccardelli,[2] Yuqing Zhang,[1] Jeffrey A. Sparks,[2] and Zachary S. Wallace[1]

Objective. Patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies may have worse coronavirus disease 2019 (COVID-19) outcomes due to impaired humoral immunity, but differences compared with the general population are unknown.

Methods. We identified patients with immune-mediated diseases who received anti-CD20 monoclonal antibodies within 1 year prior to the index date of polymerase chain reaction–confirmed COVID-19 between January 31, 2020, and January 31, 2021. General population comparators with COVID-19 were matched up 5:1 by age, sex, and polymerase chain reaction date. Unadjusted and multivariable adjusted (for age, race, body mass index, and Charlson Comorbidity Index) hazard ratios (HRs) and 95% confidence intervals (CIs) for hospitalization, mechanical ventilation, and death in recipients of anti-CD20 monoclonal antibodies versus comparators were estimated by using Cox regression.

Results. We identified 114 cases patients COVID-19 who had received anti-CD20 monoclonal antibodies for immune-mediated diseases (mean age 55 years, 70% female) and 559 matched comparators with COVID-19 (mean age 54 years, 70% female). Patients treated with anti-CD20 monoclonal antibodies had higher mortality (adjusted HR 2.16; 95% CI: 1.03-4.54) than matched comparators. Risks of hospitalization (adjusted HR 0.88; 95% CI: 0.62-1.26) and mechanical ventilation use (adjusted HR 0.82; 95% CI: 0.36-1.87) were similar. Similar trends were seen in analyses according to type of indication (eg, rheumatic or neurologic disease) and duration of anti-CD20 monoclonal antibody use (<1 or ≥1 year) and after patients with interstitial lung disease, those with cancer, and those on glucocorticoids prior to COVID-19 diagnosis were excluded.

Conclusion. Patients who received anti-CD20 monoclonal antibodies for immune-mediated diseases prior to COVID-19 had higher mortality following COVID-19 than matched comparators, highlighting the urgent need to mitigate excess risks in recipients of anti-CD20 monoclonal antibodies during the ongoing pandemic.

Dr. Patel's work was supported by the NIH Ruth L. Kirschstein Institutional National Research Service Award (T32-AR-007258). Dr. Hsu's work was supported by the NIH Ruth L. Kirschstein Institutional National Research Service Award (T32-AR-007530). Dr. Sparks' work was supported by the NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants K23-AR-069688, R03-AR-075886, L30-AR-066953, P30-AR-070253, and P30-AR-072577), the Rheumatology Research Foundation R Bridge Award, the Brigham Research Institute, and the R. Bruce and Joan M. Mickey Research Scholar Fund. Dr. Wallace's work was supported by the NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants K23-AR-073334 and R03-AR-078938).

[1]Naomi J. Patel, MD, Kristin M. D'silva, MD, MPH, Xiaoqing Fu, MS, Claire Cook, MPH, Yuqing Zhang, ScD, Zachary S. Wallace, MD, MSc: Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [2]Tiffany Y-T. Hsu, MD, PhD, Michael Dilorio, MD, Lauren Prisco, BA, Lily Martin, BS, Kathleen M. M. Vanni, BA, Alessandra Zaccardelli, MS, Jeffrey A. Sparks, MD, MMSc: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Drs. Patel and D'silva contributed equally to this work. Drs. Sparks and Wallace contributed equally to this work.

Dr. Sparks reports research support from Bristol Myers Squibb and consultancy fees from Bristol Myers Squibb, Gilead, and Pfizer. Dr. Wallace reports research support from Bristol Myers Squibb and Principia/Sanofi and consulting fees from Viela Bio and MedPace. No other disclosures relevant to this article were reported.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr2.11386&file=acr211386-sup-0002-Disclosureform.pdf.

Address correspondence to Zachary S. Wallace, MD, MSc, Massachusetts General Hospital, Division of Rheumatology, Allergy, and Immunology, Clinical Epidemiology Program, 16th Floor, 100 Cambridge Street, Boston, MA 02114. Email: zswallace@mgh.harvard.edu.

Submitted for publication November 2, 2021; accepted November 5, 2021.

INTRODUCTION

Risk of severe coronavirus disease 2019 (COVID-19) outcomes may vary among patients with immune-mediated diseases as a result of disease activity, use of immunosuppressive medications, and comorbid conditions (1–6). Anti-CD20 monoclonal antibodies, such as rituximab and ocrelizumab, are used to treat immune-mediated diseases, including rheumatoid arthritis, anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis, and multiple sclerosis, among other conditions. Anti-CD20 monoclonal antibodies cause elimination of circulating pre–B cells and B cells, which results in an impaired immune response to COVID-19 (7,8).

Results from multiple disease-specific voluntary registries have shown that, compared with patients with immune-mediated diseases on other immunosuppressive or immunomodulatory medications, patients receiving anti-CD20 monoclonal antibodies have increased odds of severe COVID-19 outcomes and death (5,9–11). The risk of severe disease may be particularly high in patients who receive these therapies shortly before contracting COVID-19 (10). These registry data likely impact clinical practice but have limitations, including reporting bias and missing data regarding details of anti-CD20 monoclonal antibody use (eg, duration of exposure). Additionally, although comparisons of anti-CD20 monoclonal antibody users with patients on other immunosuppressive treatments can address confounding by indication, it is unclear how the treatments used as the reference group in these studies impact the risk of poor COVID-19 outcomes compared with the general population. Therefore, interpretations of estimates generated from prior studies are limited, and the risk of severe COVID-19 outcomes among patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies compared with the general population is poorly understood.

Delays in anti-CD20 monoclonal antibody treatment to minimize COVID-19 risk put patients at risk for disease flare, irreversible organ damage, and disease-related death in some cases. Thus, additional data regarding COVID-19 risks among patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies are needed to inform management decisions during the ongoing pandemic. Here, we evaluate the risk of severe COVID-19 outcomes in patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies compared with general population comparators.

PATIENTS AND METHODS

Study population. Mass General Brigham (MGB) is a large multicenter health care system with 14 hospitals, including two tertiary care hospitals (Massachusetts General Hospital and Brigham and Women's Hospital), and multiple primary and specialty outpatient centers in the greater Boston, Massachusetts, area. Using the MGB centralized data warehouse, Research Patient Data Registry (RPDR) (12), we identified patients seen at MGB who were 18 years of age or older and had a positive electronic health record (EHR) flag for SARS-CoV-2 (determined by positive molecular testing results at MGB or externally, as documented by infection control) between January 31, 2020, and January 31, 2021, and had received an anti-CD20 monoclonal antibody (rituximab, ocrelizumab, ofatumumab, or obinutuzumab) within 1 year prior to the date of the first positive COVID-19 test result (index date). We manually reviewed the EHR to confirm COVID-19 diagnosis and receipt of an anti-CD20 monoclonal antibody prior to COVID-19 diagnosis. Because the RPDR screen only identified patients who received anti-CD20 monoclonal antibodies within MGB, we also included patients from our physician-reported cohort of patients with rheumatic disease and confirmed COVID-19 infection, which we have collected from MGB rheumatologists since March 2020 (Figure 1). Some of the included patients have been included in prior studies, but the observations made in this analysis in comparison with the general population are novel and have not been previously reported (1,2,4,5). Given that our study was focused on patients with immune-mediated diseases, we excluded patients who received anti-CD20 monoclonal antibodies for indications related to malignancy or organ transplantation. This study was approved by the MGB Institutional Review Board (2020P000833). Patients were not involved in the design, conduct, or reporting of this study.

Comparator identification. Each person with an immune-mediated disease treated with an anti-CD20 monoclonal antibody was matched to up to five comparators who had not received anti-CD20 monoclonal antibodies from the same COVID-19-positive MGB population on the basis of age (±5 years), sex, and the index date (±5 days). We matched by date of COVID-19 diagnosis because testing criteria and treatment strategies changed over time.

Covariates. For the anti-CD20 monoclonal antibody users, clinical variables of interest were extracted from the EHR by manual EHR review, including the indication for the anti-CD20 monoclonal antibody and dates of the initial and most recent anti-CD20 monoclonal antibody administration. Other characteristics, including immune-mediated disease diagnosis and duration, concomitant immunomodulatory medications (including specific dose of any glucocorticoid when available), and disease activity level (determined by one of the members of our study team at the time of data entry and based on global assessment as documented in the history, physical examination, and assessment by the treating provider in the EHR), were also obtained from EHR review.

For anti-CD20 monoclonal antibody users and comparators, additional variables were extracted from the COVID-19 Data Mart (13), an EHR-based data enclave established by MGB that includes all patients diagnosed with COVID-19. Covariates

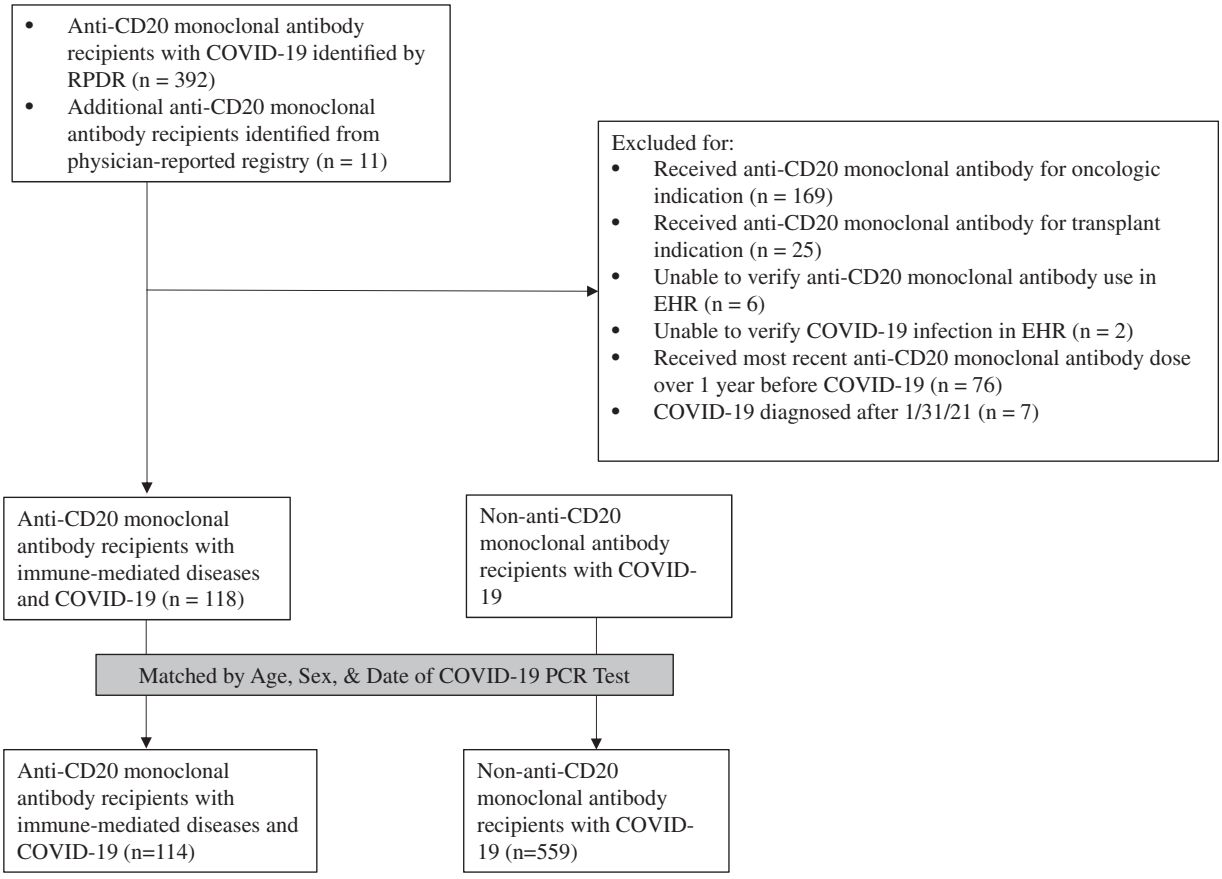

Figure 1. Identification of recipients of anti-CD20 monoclonal antibody with COVID-19. COVID-19, coronavirus disease 2019; EHR, electronic health record; PCR, polymerase chain reaction; RPDR, Research Patient Data Repository;

extracted from the COVID-19 Data Mart included demographics (age, sex, and self-identified race and ethnicity), smoking status, and medical comorbidities. Baseline characteristics, including demographics, comorbidities, smoking history, and body mass index (BMI), were assessed in the 1 year prior to the index date, and the Charlson Comorbidity Index (CCI) (14) was calculated by using all available data prior to the index date.

Outcome assessment. Mortality, the primary outcome, was ascertained from the Data Mart but also confirmed by manual EHR review and online searches of obituaries for all patients and comparators to capture deaths that might have occurred outside the system (15). Secondary outcomes extracted from the Data Mart included hospitalization and mechanical ventilation use.

Subgroup and sensitivity analyses. We performed several subgroup analyses in which we limited patients to those with rheumatic disease or neurologic indications (separate analyses), recent anti-CD20 monoclonal antibody exposure (within 3 months of the index date), short-term duration of anti-CD20 monoclonal antibody exposure (<1 year), and long-term duration of anti-CD20 monoclonal antibody exposure (≥1 year). In sensitivity analyses, we excluded patients with interstitial lung disease or cancer (separate analyses) because these are indications for anti-CD20 monoclonal antibody use in some rheumatic diseases and may be independently associated with COVID-19 severity. We also performed a sensitivity analysis in which we excluded patients who also used glucocorticoids at the time of COVID-19 infection because this may be independently associated with COVID-19 severity. In these subgroup and sensitivity analyses, included patients were compared with their general population comparators.

Statistical analysis. Categorical variables are presented as number (percentage), and continuous variables are presented as mean ± SD or median ± interquartile range (IQR), as appropriate. Continuous variables were compared by using a two-sample *t*-test for continuous normally distributed variables or Wilcoxon rank test for continuous nonnormally distributed variables. Categorical variables were compared by using χ^2 tests.

The index date was the date of COVID-19 diagnosis by molecular testing. Person-days of follow-up were determined for each patient from the index date to the first of the following: occurrence of the outcome of interest, date of the last encounter

at MGB, or end of the study period (March 2, 2021, to allow at least 30 days of follow-up per person). We calculated incidence rates per 1000 days by dividing the number of events by the number of person-days. Multivariable Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for hospitalization, mechanical ventilation use, and death in separate models, comparing anti-CD20 monoclonal antibody users with nonusers. The first multivariable model was adjusted for age. The second multivariable model was adjusted for age and race. The third multivariable model (the fully adjusted model) was adjusted for age, race, BMI, and CCI (dichotomized as <2 or ≥2). The fourth multivariable model was adjusted for hypertension, heart failure, chronic obstructive pulmonary disease, and chronic kidney disease. Because of a limited number of observed outcomes in some subgroup and sensitivity analyses, only unadjusted or partially adjusted models are reported in some instances (ie, when less than seven outcomes per covariate were present, adjusted models were not performed). For analyses of risk of hospitalization and mechanical ventilation use, death was treated as a competing risk by using a cause-specific model yielding subdistribution HRs (16). The level of significance was set as a two-tailed *P* value less than 0.05, and statistical analyses were completed by using SAS statistical software (version 9.4; SAS Institute, Inc).

RESULTS

We identified 114 patients with COVID-19 who had immune-mediated diseases treated with an anti-CD20 monoclonal antibody within 12 months preceding COVID-19 diagnosis for a nononcologic and nontransplantation indication and 559 matched comparators. The mean age was 55 years in the anti-CD20 monoclonal antibody group and 54 years in the comparator group, and 70% were female in each group (Table 1). The distribution of race and ethnicity was similar between groups. The CCI was higher in the anti-CD20 monoclonal antibody group (median of 1 vs 0, $P = 0.001$).

Among the patients with immune-mediated diseases who received anti-CD20 monoclonal antibodies, 90 (79%) received rituximab and 26 (23%) received ocrelizumab; two patients had received rituximab initially but were later switched to ocrelizumab (Table 2). The most common indication for anti-CD20 monoclonal antibody use was rheumatic disease (54 [47%]), followed by neurologic conditions (43 [38%]) (Table 2). The duration of anti-CD20 monoclonal antibody use was less than 1 year in 33 (29%) patients, 1 to 3 years in 51 (45%) patients, and more than 3 years in 30 (26%) patients. Forty-eight patients (42%) had received their most recent anti-CD20 monoclonal antibody infusion within 3 months of COVID-19 diagnosis.

Table 1. Clinical characteristics of immune-mediated patients with anti-CD20 monoclonal antibodies use prior to COVID-19 and comparators matched by age, sex, and COVID-19 diagnosis date

Characteristic	Patients treated with anti-CD20 monoclonal antibodies (n = 114)	Matched comparators (n = 559)	*P*
Age, years, mean ± SD	55 ± 15	54 ± 15	0.44
Female sex, n (%)	80 (70)	391 (70)	0.96
Race, n (%)			
White	69 (61)	316 (57)	0.43
Black or African American	16 (14)	70 (13)	–
Asian	4 (4)	12 (2)	–
Other	25 (22)	161 (29)	–
Hispanic or Latinx ethnicity, n (%)	6 (5)	46 (8)	0.28
Body mass index, mean ± SD	28.7 ± 6.2	29.7 ± 6.7	0.16
Smoking status, n (%)			
Never	66 (58)	271 (48)	0.06
Former	29 (25)	126 (23)	–
Current	3 (3)	18 (3)	–
Unknown	16 (14)	144 (26)	–
Charlson Comorbidity Index, median (IQR)	1 (0-2)	0 (0-1)	0.001
Comorbidities, n (%)			
Hypertension	45 (39)	120 (21)	<0.0001
Diabetes	13 (11)	56 (10)	0.66
Coronary artery disease	8 (7)	21 (4)	0.12
Heart failure	8 (7)	11 (2)	0.003
Asthma	10 (9)	32 (6)	0.22
Chronic obstructive pulmonary disease	6 (5)	6 (1)	0.002
Obstructive sleep apnea	2 (2)	25 (4)	0.18
Chronic kidney disease	12 (11)	26 (5)	0.01
Interstitial lung disease	25 (22)	55 (10)	<0.001
Malignancy	11 (10)	6 (1)	<0.001

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SD, standard deviation.

Table 2. Immune-mediated disease characteristics of patients with anti-CD20 monoclonal antibody use prior to COVID-19

Characteristic	Patients treated with anti-CD20 monoclonal antibodies (n = 114)
Indication for anti-CD20 monoclonal antibody, n (%)	
Rheumatic condition only	54 (47)
Inflammatory arthritis[a]	19 (17)
Vasculitis	17 (15)
Systemic lupus erythematosus	7 (6)
Inflammatory myositis	6 (5)
Other rheumatic condition[b]	3 (3)
Multiple primary rheumatic diagnoses[c]	2 (2)
Neurologic condition	43 (38)
Multiple sclerosis	33 (29)
Neuromyelitis optica	4 (4)
Other neurologic condition[d]	6 (5)
Ocular inflammation	3 (3)
Hematologic condition only	5 (4)
Thrombotic thrombocytopenic purpura	3 (3)
Autoimmune hemolytic anemia	2 (2)
Autoimmune hepatitis	3 (3)
Both rheumatic and hematologic conditions[e]	2 (2)
Other miscellaneous conditions[f]	4 (4)
Immune-mediated disease duration, years, median (IQR)	6 (3-15)
Immune-mediated disease status, n (%)	
Remission	26 (23)
Low activity	58 (51)
Moderate/high activity	30 (26)
Type of anti-CD20 monoclonal antibody, n (%)[g]	
Rituximab or biosimilar	90 (79)
Ocrelizumab	26 (23)
Duration of anti-CD20 monoclonal antibody use, n (%)	
<1 year	33 (29)
1-3 years	51 (45)
>3 years	30 (26)
Most recent anti-CD20 monoclonal antibody dose prior to COVID-19 onset, n (%)	
<3 months	48 (42)
3-6 months	44 (39)
6-12 months	22 (19)
Concomitant immunomodulatory medications at COVID-19 onset, n (%)	
Mycophenolate mofetil	8 (7)
Methotrexate	6 (5)
Hydroxychloroquine	5 (4)
Leflunomide	3 (3)
Other immunomodulatory medication[h]	6 (5)
Oral glucocorticoid	35 (31)
Prednisone-equivalent daily dose, mg, median (IQR)	7.5 (5.0-15.0)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.
[a] Includes rheumatoid arthritis, other inflammatory arthritis, and juvenile idiopathic arthritis.
[b] Includes Sjögren syndrome and immunoglobulin G4–related disease.
[c] Includes one patient with both rheumatoid arthritis and vasculitis and one patient with both inflammatory myopathy and inflammatory arthritis.
[d] Includes myasthenia gravis, autoimmune encephalitis, acute disseminated encephalomyelitis, cavernous sinus mass, and small fiber polyneuropathy.
[e] Includes a patient with rheumatoid arthritis and immune thrombocytopenic purpura and a patient with vasculitis and antiphospholipid syndrome.
[f] Includes pemphigus vulgaris, membranous nephropathy, and autoimmune interstitial lung disease.
[g] No individuals were on obinutuzumab or ofatumumab. Two individuals were initially on rituximab and then transitioned to ocrelizumab.
[h] Includes azathioprine (n = 1), cyclophosphamide (n = 2), sulfasalazine (n = 1), and tacrolimus (n = 2).

Patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies had a higher risk of death (12 [11%] vs 21 [4%]; adjusted HR 2.16; 95% CI: 1.03-4.54) than matched comparators. The risks of hospitalization (35 [31%] vs 123 [22%]; adjusted HR 0.88; 95% CI: 0.62-1.26) and mechanical ventilation use (6 [5%] vs 26 [5%]; adjusted HR 0.82; 95%

Table 3. COVID-19 outcomes in immune-mediated patients treated with anti-CD20 monoclonal antibodies versus matched comparators

Outcomes	Patients treated with anti-CD20 monoclonal antibodies (n = 114)	Matched comparators (n = 559)
Hospitalization, n (%)	35 (31)	123 (22)
Total follow-up time (person-days)	11,658	62,942
Incidence rate/1000 days (95% CI)	3.0 (2.0-4.0)	2.0 (1.6-2.3)
Unadjusted HR (95% CI)	1.32 (0.96-1.80)	Reference
Adjusted model 1 HR (95% CI)	1.24 (0.90-1.70)	Reference
Adjusted model 2 HR (95% CI)	1.16 (0.85-1.60)	Reference
Adjusted model 3 HR (95% CI)	0.88 (0.62-1.26)	Reference
Adjusted model 4 HR (95% CI)	1.30 (0.92-1.82)	Reference
Mechanical ventilation, n (%)	6 (5)	26 (5)
Total follow-up time (person-days)	14,755	78,729
Incidence rate/1000 days (95% CI)	0.4 (0.1-0.7)	0.3 (0.2-0.5)
Unadjusted HR (95% CI)	1.10 (0.48-2.52)	Reference
Adjusted model 1 HR (95% CI)	1.18 (0.50-2.79)	Reference
Adjusted model 2 HR (95% CI)	1.49 (0.63-3.49)	Reference
Adjusted model 3 HR (95% CI)	0.82 (0.36-1.87)	Reference
Adjusted model 4 HR (95% CI)	1.21 (0.50-2.89)	Reference
Death, n (%)	12 (11)	21 (4)
Total follow-up time (person-days)	15,818	84,172
Incidence rate/1000 days (95% CI)	0.8 (0.3-1.2)	0.2 (0.1-0.4)
Unadjusted HR (95% CI)	2.86 (1.51-5.41)	Reference
Adjusted model 1 HR (95% CI)	2.86 (1.52-5.37)	Reference
Adjusted model 2 HR (95% CI)	2.42 (1.18-4.93)	Reference
Adjusted model 3 HR (95% CI)	2.16 (1.03-4.54)	Reference
Adjusted model 4 HR (95% CI)	2.98 (1.17-7.58)	Reference

Note: Model 1 was adjusted for age. Model 2 was adjusted for age and race. Model 3 was adjusted for age, race, BMI, and CCI (dichotomized as <2 or ≥2). Model 4 was adjusted for hypertension, heart failure, chronic obstructive pulmonary disease, and chronic kidney disease.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio.

CI: 0.36-1.87) were similar in both groups (Table 3). Of note, in both groups, more patients died than were mechanically ventilated (Supplementary Table 1). Among recipients of anti-CD20 monoclonal antibodies, six (5%) had a code status that indicated "do not intubate" and ultimately died, compared with 10 (2%) in the comparator group. These differences suggest that the risk of

Table 4. Risk of death following COVID-19 in patients treated with anti-CD20 monoclonal antibodies for rheumatic disease indications versus comparators

	Patients treated with anti-CD20 monoclonal antibodies for rheumatic disease (n = 56)[a]	Matched comparators (n = 276)
Deaths, n (%)	7 (13)	15 (5)
Total follow-up time (person-days)	7917	42,560
Incidence rate/1000 days (95% CI)	0.9 (0.2-1.5)	0.4 (0.2-0.5)
Unadjusted HR (95% CI)	2.52 (1.07-5.90)	Reference
Adjusted model 1 HR (95% CI)	2.42 (1.02-5.74)	Reference
Adjusted model 2 HR (95% CI)	2.02 (0.71-5.80)	Reference
Adjusted model 3 HR (95% CI)[b]	NR	Reference

Note: Model 1 was adjusted for age. Model 2 was adjusted for age and race. Model 3 was adjusted for age, race, BMI, and CCI (dichotomized as <2 or ≥2).
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; NR, not reported.
[a] Rheumatic disease indication includes 54 patients with rheumatic disease indication only and two patients with combined rheumatic and hematologic indications.
[b] Model 3 was NR because of an insufficient number of outcomes (less than seven outcomes per adjusted covariate).

Table 5. Risk of death following COVID-19 in patients treated with anti-CD20 monoclonal antibodies for neurologic disease indications versus comparators

	Patients treated with anti-CD20 monoclonal antibodies for neurologic disease (n = 43)	Matched comparators (n = 211)
Deaths, n (%)	2 (5)	4 (2)
Total follow-up time (person-days)	6551	34,051
Incidence rate/1000 days (95% CI)	0.3 (0.0-0.7)	0.1 (0.0-0.2)
Unadjusted HR (95% CI)	2.41 (0.66-8.77)	Reference
Adjusted model 1 HR (95% CI)	NR	Reference
Adjusted model 2 HR (95% CI)	NR	Reference
Adjusted model 3 HR (95% CI)	NR	Reference

Note: Model 1 was adjusted for age. Model 2 was adjusted for age and race. Model 3 was adjusted for age, race, BMI, and CCI (dichotomized as <2 or ≥2). Adjusted models were NR because of an insufficient number of outcomes (less than seven outcomes per adjusted covariate).
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; NR, not reported.

needing mechanical ventilation among recipients of anti-CD20 monoclonal antibodies is likely an underestimate. No deaths were noted to be directly related to the immune-mediated disease. Among patients with immune-mediated diseases on anti-CD20 monoclonal antibodies who developed COVID-19, nine patients (8%) had COVID-19 antibodies tested after COVID-19 diagnosis (median 70 days, IQR 35-87 days) for clinical indications. Of these nine patients, two had positive COVID-19 antibodies and seven had negative COVID-19 antibodies.

In subgroup analyses, we found that there was a similar trend among patients with rheumatic disease (Table 4) as the indication for anti-CD20 monoclonal antibody use. We found a numerically higher risk of death among patients with neurologic disease as the indication for anti-CD20 monoclonal antibody use, although analysis was limited by a low number of events (Table 5). Similar trends were also observed among short- and long-term anti-CD20 monoclonal antibody users, among those with recent (within 3 months) exposure to an anti-CD20 monoclonal antibody, and after we excluded patients with interstitial lung disease, those with cancer, and those who received glucocorticoids prior to COVID-19 diagnosis (Supplementary Tables 2-6). Our ability to detect significant differences and perform multivariable adjustment in these subgroup analyses was limited by the number of observed events.

DISCUSSION

In this multicenter cohort study, we found an increased risk of death following COVID-19 infection among patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies compared with general population comparators. This association was observed among more recent anti-CD20 monoclonal antibody initiators as well as among patients who had been on long-standing anti-CD20 monoclonal antibody treatment. The results remained consistent in analyses in which we adjusted for comorbidity burden and across sensitivity and subgroup analyses meant to further address potential confounders. These findings raise concern regarding the impact of anti-CD20 monoclonal antibody exposure on COVID-19 risk and the need to investigate strategies to mitigate this potential risk, especially given the poor response to vaccines observed among anti-CD20 monoclonal antibody users (17,18).

Anti-CD20 monoclonal antibodies have been a particular concern during the COVID-19 pandemic because the humoral immune response plays an important role in the response to SARS-CoV-2 infection (8,19,20). During the early phase of infection, high antibody titers are associated with higher levels of neutralizing antibodies to the receptor binding domain of the spike protein, and antibody titers are significantly higher in patients with shorter duration of SARS-CoV-2 RNA positivity (21,22). To this end, there have been several reports of patients receiving anti-CD20 monoclonal antibodies with subsequent prolonged courses of COVID-19 (22–26). Postmortem studies of lymph nodes from patients with fatal COVID-19 showed the absence of germinal centers and a reduction in germinal center B and T cells, suggesting that a dysregulated adaptive immune response occurs in fatal COVID-19 (27). Lastly, patients treated with anti-CD20 monoclonal antibodies had a 36-fold reduction in humoral responses compared with immunocompetent patients at 1 to 2 weeks after the second dose of SARS-CoV-2 messenger RNA vaccines (17,18,28). Further research is needed to determine whether prophylactic and therapeutic strategies, such as convalescent plasma or SARS-CoV-2 monoclonal antibody therapy, may be beneficial in the prevention and treatment of COVID-19 in patients with B-cell depletion (29,30).

In light of the critical importance of antibody formation for a robust immune response to COVID-19, we had hypothesized that long-term anti-CD20 monoclonal antibody use would be associated with a greater risk of death in recipients compared with the general population because of more sustained B-cell depletion. Instead, we found a similar risk among short- (<1 year) and long-term (≥1 year) anti-CD20 monoclonal antibody users. It is possible that long-term recipients of anti-CD20 monoclonal antibodies are generally healthier and have previously tolerated anti-CD20 monoclonal antibody therapy well without infections or other complications, thus resulting in a similar risk of severe COVID-19 compared with short-term anti-CD20 monoclonal antibody users. However, our observations may suggest that continuous B-cell depletion versus more recent B-cell depletion may not have a differential impact on the critical immediate immunologic response that is blunted by anti-CD20 monoclonal antibodies and needed to control infection (31,32). We cannot rule out the possibility that small sample sizes might have limited the ability to detect a difference when comparing outcomes among short- and long-term anti-CD20 monoclonal antibody users. Similar to Avouac et al (10), we also found a significantly higher risk of death among those who had received their most recent anti-CD20 monoclonal antibody dose close to the time of COVID-19 infection.

Despite the increased risk of death, we did not find any statistical difference in risk of hospitalization or mechanical ventilation use between those who received anti-CD20 monoclonal antibodies and matched comparators. This discrepancy between increased risk of death and not mechanical ventilation use may be explained by the use of "do not intubate" orders. These orders might have led to an underestimate of the effect of anti-CD20 monoclonal antibody use on mechanical ventilation risk if the proportion needing (but not receiving) mechanical ventilation was actually greater among the anti-CD20 monoclonal antibody users, as our findings suggest. We further conducted subgroup analyses to better understand specific factors driving the increased risk of death with anti-CD20 monoclonal antibody exposure and found that the risk was attenuated in multivariable models, but similar trends persisted despite low event rates. Indeed, our findings persisted when we excluded patients with interstitial lung disease and malignancy, two populations commonly prescribed rituximab for immune-mediated conditions who may be at particularly high risk for poor COVID-19 outcomes because of other medical comorbidities.

Our study has multiple strengths. First, we systematically identified patients who received anti-CD20 monoclonal antibodies for a variety of immune-mediated conditions in a large health care system, increasing the generalizability of our observations to the diverse populations who use anti-CD20 monoclonal antibodies. Second, details regarding anti-CD20 monoclonal antibody indication, length of exposure, and COVID-19 outcomes were available, in contrast to prior registry-based studies.

Despite these strengths, our study has certain limitations. First, although our findings persisted after adjustment for covariates, there may be residual confounding by anti-CD20 monoclonal antibody indication, concomitant glucocorticoid use, or disease severity because anti-CD20 monoclonal antibodies are often used as initial induction therapy for severe immune-mediated diseases (eg, ANCA-associated vasculitis) or as treatment for diseases that have been refractory to other therapies (eg, rheumatoid arthritis). However, our findings remained robust in sensitivity analyses and subgroup analyses that addressed the potential impact of residual confounding. Regardless, one should cautiously interpret these results as applying to the population of patients with immune-mediated diseases treated with anti-CD20 monoclonal antibodies in the context of the known effects of anti-CD20 monoclonal antibody therapy on B-cell responses and antibody production. Second, multivariable adjustment was limited in some subgroup and sensitivity analyses because of low event rates. Furthermore, the CCI may not account for all relevant comorbidities, which may subject our results to residual confounding. However, the observed trends remained consistent with those observed in the primary analysis. Last, disease activity as assessed by retrospective medical record review may not be as accurate as a validated, prospectively assessed measure of disease activity; we were not able to draw conclusions regarding the impact of disease activity on COVID-19 outcomes.

In conclusion, we found an increased risk of death in patients with immune-mediated diseases who had received anti-CD20 monoclonal antibodies prior to COVID-19 diagnosis. Anti-CD20 monoclonal antibodies are the standard of care for induction and maintenance treatment of multiple immune-mediated diseases, some of which have few alternatives. Additional studies are needed to evaluate the potential use of anti-SARS-CoV-2 monoclonal antibodies, booster vaccinations, and other strategies to reduce the risk of poor COVID-19 outcomes in this population. Providers should interpret these results cautiously and weigh the risks and benefits of ongoing anti-CD20 monoclonal antibody use on an individual basis using shared decision-making.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wallace had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Patel, D'silva, Fu, Zhang, Sparks, Wallace.
Acquisition of data. Patel, D'silva, Hsu, Dilorio, Cook, Prisco, Martin, Vanni, Zaccardelli, Sparks, Wallace.
Analysis and interpretation of data. Patel, D'silva, Fu, Zhang, Sparks, Wallace.

REFERENCES

1. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis 2020;79:1156–62.

2. Serling-Boyd N, D'Silva KM, Hsu TY, Wallwork R, Fu X, Gravallese EM, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis 2021;80:660–6.
3. D'silva KM, Jorge A, Cohen A, McCormick N, Zhang Y, Wallace ZS, et al. COVID-19 outcomes in patients with systemic autoimmune rheumatic diseases compared to the general population: a US multicenter, comparative cohort study. Arthritis Rheumatol 2021;73: 914–20.
4. Gianfrancesco MA, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.
5. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930–42.
6. Schäfer M, Strangfeld A, Hyrich KL, Carmona L, Gianfrancesco M, Lawson-Tovey S, et al. Response to: 'Correspondence on 'Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician reported registry" by Mulhearn et al. Ann Rheum Dis 2021. E-pub ahead of print.
7. Jones J, Faruqi AJ, Sullivan JK, Calabrese C, Calabrese LH. COVID-19 outcomes in patients undergoing B cell depletion therapy and those with humoral immunodeficiency states: a scoping review. Pathog Immun 2021;6:76–103.
8. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 2020;183:996–1012.
9. Sormani MP, de Rossi N, Schiavetti I, Carmisciano L, Cordioli C, Moiola L, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann Neurol 2021;89: 780–9.
10. Avouac J, Drumez E, Hachulla E, Seror R, Georgin-Lavialle S, El Mahou S, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol 2021;3:e419–26.
11. Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, et al. 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. Ann Rheum Dis 2021;80:1137–46.
12. Nalichowski R, Keogh D, Chueh HC, Murphy SN. Calculating the benefits of a research patient data repository. AMIA Annu Symp Proc 2006;2006:1044.
13. Mass General Brigham. New COVID-19 tools for researchers. URL: https://rc.partners.org/about/projects-initiatives/new-covid-19-research-tools-researchers.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.
15. Hsu TY, D'Silva KM, Patel NJ, Wang J, Mueller AA, Fu X, et al. Laboratory trends, hyperinflammation, and clinical outcomes for patients with a systemic rheumatic disease admitted to hospital for COVID-19: a retrospective, comparative cohort study. Lancet Rheumatol 2021;3:e638–47.
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
17. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330–8.
18. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. Ann Intern Med 2021;174:1572–85.
19. Zohar T, Alter G. Dissecting antibody-mediated protection against SARS-CoV-2. Nat Rev Immunol 2020;20:392–4.
20. Dispinseri S, Secchi M, Pirillo MF, Tolazzi M, Borghi M, Brigatti C, et al. Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival. Nat Commun 2021; 12:2670.
21. Wu J, Liang B, Chen C, Wang H, Fang Y, Shen S, et al. SARS-CoV-2 infection induces sustained humoral immune responses in convalescent patients following symptomatic COVID-19. Nat Commun 2021; 12:1813.
22. Kos I, Balensiefer B, Roth S, Ahlgrimm M, Sester M, Schmidt T, et al. Prolonged course of COVID-19-associated pneumonia in a B-cell depleted patient after rituximab. Front Oncol 2020;10:1578.
23. Leipe J, Wilke EL, Ebert MP, Teufel A, Reindl W. Long, relapsing, and atypical symptomatic course of COVID-19 in a B-cell-depleted patient after rituximab. Semin Arthritis Rheum 2020;50:1087–8.
24. Yasuda H, Tsukune Y, Watanabe N, Sugimoto K, Uchimura A, Tateyama M, et al. Persistent COVID-19 pneumonia and failure to develop anti-SARS-CoV-2 antibodies during rituximab maintenance therapy for follicular lymphoma. Clin Lymphoma Myeloma Leuk 2020;20:774–6.
25. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med 2020;383:2291–3.
26. Benucci M, Quartuccio L, Li Gobbi F, Damiani A, Grossi V, Infantino M, et al. Persistence of rT-PCR-SARS-CoV-2 infection and delayed serological response, as a possible effect of rituximab according to the hypothesis of Schulze-Koops et al. Ann Rheum Dis 2020. E-pub ahead of print.
27. Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, et al. Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. Cell 2020;183:143–57.
28. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. Ann Rheum Dis 2021;80:1357–9.
29. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238–51.
30. Hueso T, Pouderoux C, Péré H, Beaumont AL, Raillon LA, Ader F, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. Blood 2020;136:2290–5.
31. Harvey RA, Rassen JA, Kabelac CA, Turenne W, Leonard S, Klesh R, et al. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 2021;181:672–9.
32. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27:1205–11.