Husni M. Elaine (Orcid ID: 0000-0002-3181-4205)
Fernandez Anthony Patrick (Orcid ID: 0000-0003-4490-8427)
Calabrese Leonard H (Orcid ID: 0000-0002-1789-4923)

Running title: Breakthrough SARS-CoV-2 infections in patients undergoing B cell depleting therapy

Breakthrough SARS-CoV-2 infections in immune mediated disease patients undergoing B cell depleting therapy: A retrospective cohort analysis

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Cassandra M Calabrese DO[1]

Elizabeth Kirchner DNP[1]

Elaine M Husni MD[1]

Brandon P Moss MD[2]

Anthony P Fernandez MD PhD[3]

Yuxuan Jin MS[4]

Leonard H Calabrese DO[1]

1 Department of Rheumatic and Immunologic Diseases, Cleveland Clinic

2 Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic

3 Department of Dermatology, Cleveland Clinic

4 Quantitative Health Sciences, Cleveland Clinic

Corresponding author:

Leonard H. Calabrese, D.O.

Professor of Medicine, Cleveland Clinic Lerner

College of Medicine of Case Western Reserve University

RJ Fasenmyer Chair of Clinical Immunology

Department of Rheumatic and Immunologic Diseases

9500 Euclid Avenue, Desk A50

Cleveland, Ohio 44195

Phone: (216) 444-5258

Fax: (216) 445-7569

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Abstract

Objectives

Patients with immune mediated inflammatory diseases (IMIDs) receiving B cell depleting therapy (BCDT) are among the most vulnerable to severe COVID-19 as well as the most likely to respond sub-optimally to SARS-CoV-2 vaccines. However, little is known about the frequency or severity of breakthrough infection in this population. We retrospectively analyzed a large group of vaccinated IMIDs patients undergoing BCDT in order to identify the presence of breakthrough COVID-19 infections and assess their outcomes.

Methods

In this retrospective cohort study, the pharmacy records and COVID-19 registry at the Cleveland Clinic were searched using specific ICD-10 codes to identify IMIDs patients who (1) were treated with BCDT, (2) were vaccinated against SARS-CoV-2, and (3) experienced breakthrough infections. Each EMR was reviewed to extract clinical data and outcomes. Univariate and multivariable logistic/proportional-odds regression models were used to examine the risk factors for severe outcomes.

Results

Of 1696 IMIDs patients on BCDT, 74 developed breakthrough COVID-19 prior to December 16th, 2021. Outcomes were severe with 29(39.2%) hospitalized, 11(14.9%) requiring critical care, and 6(8.1%) deaths. Outpatient anti-SARS-CoV-2 monoclonal antibodies were used to treat 21 with 1 hospitalization and no deaths. A comparator analysis examining 1437 unvaccinated IMIDs patients on BCDT over the same time period identified 57(3.9%) COVID-19 cases with 28(49.1%) requiring hospitalization including 7(12.3%) deaths.

Conclusions

IMIDs patients on BCDT regardless of vaccine status appear vulnerable to infection with SARS-CoV-2 and are frequently associated with severe outcomes. Outpatient use of anti-SARS-CoV-2 monoclonal antibody therapy appeared to be associated with enhanced clinical outcomes.

Introduction

The deployment of vaccines to both prevent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as limit the severity of coronavirus disease 2019 (COVID-19) has proven efficacious for the general population. However, data on patients with underlying immunocompromising conditions, including those with immune mediated inflammatory diseases (IMIDs), suggest both an increased likelihood for developing breakthrough infections and for experiencing more severe outcomes despite full vaccination status [1-3].

While there is great heterogeneity in the capacity of specific immunosuppressive agents to limit the integrated immune response to both natural infection and vaccines, of particular concern is the class of B cell depleting therapies (BCDTs) widely used to treat an array of IMIDs. Before the introduction of SARS-CoV-2 vaccines, treatment of both rheumatic and neurologic IMIDs with such BCDTs was associated with more severe COVID-19 [4-10]. Furthermore, numerous studies have documented the capacity for certain BCDTs to profoundly impair humoral response to vaccines, including the vaccine against SARS-CoV-2 [11-14]. More recently, however, several studies [15,16] have documented a dichotomy in vaccine responses in IMIDs patients receiving BCDTs, demonstrating suppression of the humoral response while documenting a preserved and robust cell mediated immune response - raising hope that such a pattern of immunity will afford adequate protection. Until now there have been only limited investigations of IMIDs patients on BCDTs examining the frequency and outcomes of breakthrough infections. Using pharmacologic records and the COVID-19 registry at the Cleveland Clinic we have systematically examined a large population of IMIDs patients who received BCDTs and were vaccinated against SARS-CoV-2, and have described the frequency of breakthrough infections and their outcomes.

Methods

Patient Identification and Data Extraction

This study was a retrospective cohort analysis. Pharmacy records from the Cleveland Clinic were electronically searched for patients undergoing BCDT (rituximab, ocrelizumab, ofatumumab) in the year 2020, prior to receipt of SARS-CoV-2 vaccine. Records with ICD-10 codes for IMIDs (see Supplementary Table 1) but not malignancies were identified. Using the Cleveland Clinic COVID-19 Research Registry, which tracks vaccine and COVID-19 data across our system, we cross-referenced these patients to identify those who were vaccinated at least once and experienced breakthrough COVID-19. Only infections confirmed by PCR or rapid test at any time after the first vaccination were included. In addition, patients identified through routine care who fulfilled the above criteria were included. This strategy allowed identification of breakthrough patients who may have received BCDT and/or were diagnosed outside our health care system but who were nevertheless under the care of our providers. Patients who received BCDT during the same time period for the same ICD-10 codes but were never vaccinated were also identified, using the same search strategy.

For the primary analysis cohort of patients with breakthrough COVID-19, additional data on demographics (age, gender, race), weight, comorbidities (heart disease, pulmonary disease, chronic kidney disease, malignancy, smoking history), associated immunosuppressive medications, prednisone use and dosage, timing and duration of BCDT, vaccine type and number of doses, whether or not the patient received outpatient anti-SARS-CoV-2 monoclonal antibody (mAb) treatment, and clinical outcomes were extracted by individual chart review from patient electronic medical records. Each breakthrough infection was classified as complete [i.e. 14 or more days following the second mRNA vaccine (or first J&J)] or incomplete. For an additional exploratory analysis of unvaccinated patients on BCDTs who contracted COVID-19 over the same time period, data were gathered utilizing the same strategy.

Outcome Assessment

Our primary outcome was disease severity; each patient was classified on the 8 point National Institutes of Health (NIH) COVID-19 ordinal scale[17] (Supplementary Table 2). Patients were classified to their highest level of disease severity and grouped as mild (Groups 1-3) or severe (Groups 4-8).

Influence of Delta Variant on Infection Incidence and Classification of Vaccination Status

To account for changes in COVID-19 breakthrough infection rates attributable to the Delta variant, we used June 20th 2021 as the date by which to stratify the follow-up period into pre– or post–Delta phases. The date was based on the Centers for Disease Control and Prevention (CDC) report of Delta being the dominant SARS-CoV-2 strain (>50%) in the US[18]. The end date of the study was December 15th 2021, selected based on the date that the Cleveland Clinic microbiology laboratory monitoring SARS-CoV-2 variants in Northeastern Ohio identified when Omicron became and persisted as the dominant variant.

Because of the timing of Emergency Use Authorizations (EUAs) and EUA amendments for primary vaccination and boosters (see Supplementary Table 3), the most doses any patient in our cohort could have received by our cutoff date of December 15th, 2021, was three – all considered part of the primary series. For the purposes of our analysis, "incomplete" vaccination refers to the receipt of one mRNA vaccine. "Complete" vaccination refers to either the receipt of one dose of the J&J vaccine or two doses of either mRNA vaccine. "Additionally dosed" patients are those who received either 3 doses of mRNA vaccines or one dose of J&J plus one dose of either mRNA vaccine.

The Cleveland Clinic Institutional Review Board approved this study.

Statistical analysis

Continuous variables were summarized using mean and standard deviation, or median and interquartile range (IQR) when appropriate. Categorical variables were summarized using counts and frequencies. For patients who received anti-SARS-CoV-2 mAb treatment versus those who did not, two-sample t-tests (or

Wilcoxon tests) and Pearson Chi-square tests (or Fisher's exact tests) were performed. Person-time (at risk) accrued from the date of the first dose of the vaccine to the date of breakthrough infection or December 15th, 2021, whichever occurred first. Unadjusted Poisson regression was used to calculate the overall incidence rate, and the incidence rates of pre-Delta and post-Delta periods. We then investigated the association between each risk factor and COVID-19 severity outcome using univariate logistic regression. Additionally, we built multivariable logistic regression models to examine the effect of potential risk factors on severity outcome after controlling for confounding variables. The exploratory analysis of outcomes and epidemiologic risk factors in patients on BCDTs who were not vaccinated against SARS-CoV-2 and tested positive for the virus were compared descriptively. Data management and analysis were conducted using R Software (Version 4.0; Vienna, Austria). All tests are two-sided, with an alpha level of 0.05.

Results

Clinical Features of the Primary Cohort

The results of our search revealed 3220 patients with IMIDs (as identified via specific ICD-10 codes) receiving one or more doses of approved BCDT in the year 2020. Of these patients, 1696 received one or more doses of vaccine against SARS-CoV-2. From this vaccinated group, 74 were found to have experienced a breakthrough infection from the time of their first vaccine through December 15th, 2021. The details of these patients are displayed in Table 1. The patients were nearly equally distributed between rheumatic and neuroinflammatory disease with multiple sclerosis the single most common diagnosis. Thirty-four (45.9%) patients were on additional immunosuppressive medications with prednisone being the most common (35.1%). Thirteen patients (17.6%) were on one or more additional disease-modifying anti-rheumatic drugs including six on methotrexate, four on azathioprine and four on mycophenolate. Half of the patients (37, 50.0%) had one or more comorbidities.

In terms of vaccination history and status, 45 patients received the Pfizer mRNA vaccine: 2 patients received only one dose before breakthrough, 39 had two doses, and four patients had an additional third dose. Twenty-three patients received Moderna mRNA vaccine with only 1 having a single vaccination before breakthrough, 17 having two doses, and five an additional third dose before infection. Six patients received a single J&J vaccination before breakthrough. Overall, of those experiencing breakthrough infections defined as 14 days past the second vaccination (or single J&J), 6 of 74 were incomplete in their vaccination status while 68 were either completely vaccinated or completely vaccinated and additionally dosed.

Incidence

Of 1696 patients with any form of vaccination, 74 had breakthrough infection for a raw incidence of 4.4%; 68 (91.9%) occurred after complete vaccination (i.e. 14 days after the final administration). We also examined the crude incidence of COVID-19 breakthrough as a function of the pre-Delta and post-Delta periods in 2021. Prior to June 20th (the date CDC identifies as the onset of the Delta surge) there were 12/74 cases identified while after June 20th there were 62, supporting a seeming acceleration of breakthrough infections with the Delta variant. The total person-time of vaccine exposure for this cohort (1696 patients with at least one vaccine) was 14302.67 months. As a result, the time-adjusted incidence rate of breakthrough infection in the entire group is 5.19 per 1000 person-months (95%CI, 4.13-6.52). The time-adjusted incidence rate of breakthrough infection in the pre-Delta period is 2.48 per 1000 person-months (95% CI, 1.41-4.36). The incidence rate in the post-Delta period is 6.59 per 1000 person-months (95% CI, 5.14-8.45).

Outcomes

Clinical outcomes for the entire group revealed that 45 patients had outpatient-managed disease with 30 (40.5%) in group 1 and 15 (20.3%) in group 2. The remaining 29 (39.2%) patients were hospitalized with 6 (8.1%) not requiring supplemental O_2 (groups 3 and 4) and the remaining requiring some level of O_2 support with 12 (16.2%) (Group 5) requiring any O_2, and 5 (6.8%) (Groups 6 or 7) requiring high flow O_2 or mechanical ventilation. There were 6 (8.1%) deaths. In terms of risk factors for severe outcomes we examined the groups based on clinical grade by ordinal scale, separating the patients into two groups: those with mild disease (groups 1-3), and those with more severe disease (groups 4-8). Univariate and multivariate analyses (Table 2) comparing mild (ordinal scale groups 1-3) to severe (ordinal scale groups 4-8) revealed that only the presence of two or more comorbidities (present in 21 of the 74 breakthrough patients) was associated with disease severity ($P = 0.001$; $P = 0.009$, respectively). Vaccine associated variables (i.e. complete, incomplete, additionally dosed) had no association with severe outcomes nor did the use of concomitant immunosuppressive therapies. Analysis of BCDT-associated variables including duration of therapy and the time interval from most recent BCDT treatment to vaccination demonstrated no statistical effect on risk of severe outcomes in either univariate or multivariate analysis. Four breakthrough patients had experienced a single prior episode of COVID-19 before receiving their first vaccine which had no association with severe outcomes in univariate analysis (Table 2).

Incidence and Severity of COVID-19 among Unvaccinated Patients

An additional exploratory analysis was performed examining the incidence and severity of COVID-19 in 1437 unvaccinated patients identified via the same search strategy as a comparator group. Among these, 57 were diagnosed with COVID-19 for a crude incidence of 3.9% with 27 (47.4%) diagnosed before June 20th and 30 (52.6%) after June 20th. In terms of severity as measured by the NIH ordinal

scale, 29 patients (50.9%) fit the criteria for groups 1-3, and 28 patients were in groups 4-8 (49.1%); 7 (12.3%) patients died. Summaries of the clinical and epidemiologic features for this group are provided in Table 1.

Effects of outpatient therapy with anti-SARS-CoV-2 monoclonal antibodies

Anti-SARS-CoV-2 mAb therapy (casarivimab and imdevimab) within 10 days of symptom onset as outpatient therapy for COVID-19 was employed in 21 patients. No patients in our cohort received any other type of anti-SARS-CoV-2 mAb treatment. In the multivariate model, after controlling for both number of comorbidities and time of first vaccination administration, this therapy was associated with more favorable outcomes with only one out of the 21 patients requiring hospitalization (with O_2 support; ordinal scale 5) and no deaths (p=0.006) (Table 2). The results of this intervention and effects on highest level of ordinal scale severity is displayed graphically in Figure 1. To explore the possibility that those treated with anti-SARS-CoV-2 mAbs differed in some manner that could potentially contribute to their markedly different clinical outcomes we compared a select number of clinical characteristics (age, number of comorbidities, concomitant immunosuppressive therapies, duration of BCDT) between those who received anti-SARS-CoV-2 mAb therapy and the entire breakthrough cohort; none were statistically significant (Table 3). In the exploratory analysis of COVID-19 outcomes in the unvaccinated cohort, 7 of 57 patients received anti-SARS-CoV-2 mAb therapy with 3 of these 7 requiring hospitalization and no deaths (Supplementary Table 4).

Discussion

The current study examines a large cohort of patients exposed to BCDT in 2020, a time frame that began nearly 12 months before introduction of the SARS-CoV-2 vaccine, all of whom received one or more vaccinations for COVID-19 and developed breakthrough infection. Breakthrough occurred in 74 (4.4 %)

or nearly 1 in 20. Our data clearly show that breakthrough infection in this population is associated with severe outcomes, as 39.2% required hospitalization, 14.8% required critical care, and 8.1% died. Thus we confirm that IMIDs patients on BCDTs appear vulnerable to breakthrough infections and, most importantly, are attended by severe outcomes.

While patients with IMIDs on BCDTs have been recognized to be vulnerable to severe COVID-19 infections,[5,7,8,19] relatively scant data exist regarding their risks for and outcomes of breakthrough infections[20,21]. The current cohort of breakthrough patients consisted of nearly equal numbers of patients with rheumatic and neuro-inflammatory disease and most (91.9%) were either fully vaccinated or additionally dosed, with only 6 (8.1%) with incomplete vaccination. Of note is that the group as a whole was heavily exposed to BCDTs with 27.0% on therapy for one to three years and 45.9% for more than three years. More importantly, 86.3% of patients received their last BCDT less than six months before their first vaccine, a time point that several studies have demonstrated is critical for any reasonable chance of developing a humoral response[11,13,15].

Although our study lacked comparator groups of healthy or immunocompromised patients not on BCDTs to appraise breakthrough frequency and severity, indirect comparisons to previously reported studies provide some perspective for interpreting our findings. In terms of severity of breakthrough infections, Sun et. al.[1] retrospectively examined 664,772 patients in the National COVID Cohort Collaborative with a variety of disorders sharing varying degrees of immune dysfunction but not broken down by therapies. This study reported an overall rate of serious disease (as determined by need for hospitalization) of 20.7%, far less than the 39.2% observed in our cohort. Another study by Shen and colleagues[22] examined a large population of immunocompromised patients over a similar time frame as our investigation in a single health system. Patients were identified as taking any one of a number of classes of immunosuppressants including conventional, synthetic or targeted disease modifying therapies and/or glucocorticoids; only 0.35% required hospitalization. A study by Di Fusco et. al.[3]

utilizing the HealthVerity national database examined breakthrough infections from December 2020 through July 2021 among a broad spectrum of immunocompromised patients (n= 1,277,747). This cohort consisted of patients with malignancies, solid organ transplants, HIV infection, and rheumatic/autoimmune disease; among 950 breakthrough patients only 12.7% required hospitalization, and 0.2% resulted in inpatient deaths - far below the severity observed in our study. A recent study from the Netherlands by Boekel et.[al.23] examining breakthrough infections during the Delta epoch in a large cohort of 3207 patients with IMIDs on various immunosuppressants observed, in a post hoc analysis, that severe outcomes appeared to be more frequent in the subset on BCDTs; 3 of 16 patients on BCDTs (19%) required hospitalization versus only 5 of 132 (4%) using other immunosuppressives. On the basis of these published studies, vaccinated patients receiving BCDTs for immune mediated diseases appear to have particularly severe outcomes within the spectrum of immunosuppressed patients.

As opposed to breakthrough infection severity (which can be determined by hospitalizations and death), it is more problematic to examine breakthrough infection frequency via indirect comparisons given differences in study durations, epochs of investigation and thus the influence of viral variants, as well as differences in detection vigilance. In terms of our overall rate of breakthrough infection, a study by the CDC in the general population estimated a breakthrough rate of 2.8% per six month period on September 30, 2021, which is somewhat lower than our observed crude rate of 4.4% over nearly 12 months of observation[24]. In terms of our time adjusted incidence rate of 5.19 per 1000 person-months it appears comparable to the overall rate of 5.0 per 1000 person-months (95%, CI 2.9-2.9) found in immunocompromised patients in the study by Sun et. al.[1]. Another study of breakthrough infections by Ahmed et. al., [25] conducted in India from March to October 2021, found an overall rate of breakthrough infection of 7.5%. This rate is higher than noted in our study, but included two vaccines not used in the United States, limiting comparability. In the study by Shen et. al. [22] of a heterogeneous population on a wide range of immunosuppressive drugs which was conducted over the same time period as ours found

a breakthrough rate of 1.3% among immunocompetent and 2.8% in immunocompromised subjects. Thus it appears that breakthrough infection rate in patients on BCDTs may be higher than in immunocompetent individuals and in the range of other studies examining immunocompromised patients; again, direct comparator studies are needed.

Our study also examined the potential impact of the Delta variant on breakthrough incidence and found that the majority of cases were identified during the period of the Delta surge, with 62 of the 74 cases diagnosed between June 20th, 2021 (the date the CDC marked as the onset of the Delta surge[1]) and December 15th, 2021 (the end of our study and the end of the Delta surge in Northeastern Ohio). This observation is consistent with the study of Sun et. al., [1] who described a tripling of incidence in the period following June 20th until the end of their study period of September 16th, 2021. While all of these studies demonstrated an increase in incidence of breakthrough within the time period of the Delta surge the reasons for this remain unclear. Indeed the increased transmissibility of the Delta strain may be one explanation for this rise in incidence, another consideration could be waning vaccine effectiveness as the time from vaccine administration increased. This possibility of waning vaccine effectiveness would seem to be supported by our exploratory analysis of the unvaccinated cohort which over the same time periods demonstrated little change in crude incidence with nearly equal numbers infected over both time periods (i.e. Pre Delta and Delta). Further studies examining biomarker correlates of infection as well as the impact of new variants and the effectiveness of additional doses are needed to increase our understanding of this phenomenon.

Our findings of severe outcomes of COVID-19 in breakthrough infections in patients being treated with BCDTs is important for understanding the implications of the evolving picture of vaccine responsiveness in this population. From early on it has been appreciated that patients on agents such as rituximab and ocrelizumab display severe deficits in their capacity to mount humoral responses to a variety of vaccines and more recently to vaccination against SARS-CoV-2[11]. Our data also helps understand the implications

and clinical limitations of the surprisingly robust T cell response following mRNA vaccines in patients given BCDTs which has been documented in a number of recent studies15,16,26. Further work carefully studying breakthrough infection paired with detailed examinations of biomarkers for humoral and cell mediated immunity are urgently needed.

Given our data indicating breakthrough infection in patients on BCDT appears to be associated with poor outcomes, we conducted an additional exploratory analysis of patients who were unvaccinated with the same diagnoses and use of BCDTs over the same time period to gain insight as to what degree of protection may be afforded by vaccinating such patients. From this analysis we found that the incidence of infection was similar but numerically less in the unvaccinated patients (3.9% vs. 4.4%). In terms of severity both groups had poor outcomes with the distribution of mild and severe cases in the unvaccinated cohort (Ordinal scale categories 1-3 vs 4-8) of 57.9% and 42.1% with 12.3% fatality compared to 63.5% and 36.5% and 8.1% fatality in the breakthrough group. Given that the assignment to these two groups (i.e. no vaccination vs. vaccination) was nonrandom and may indicate differences in health disparities as well as risk behaviors, these small differences should be viewed with caution. At the minimum we must conclude that patients on BCDTs, regardless of vaccine status, are at risk for serious and fatal COVID-19.

Our observation that breakthrough patients receiving anti-SARS-CoV-2 mAbs did extremely well, supported by the fact that only one vaccinated patient who received anti-SARS-CoV-2 mAb treatment required hospitalization, is important yet limited by the nonrandom application of the therapy and the risk of confounding by indication. While anti-SARS-CoV-2 mAbs have been used extensively, their utility at reducing the need for acute care and death is based on clinical trials in patients largely at increased risk based on age and concomitant diseases as opposed to a small minority of patients with immunocompromising conditions and none that we are aware of explicitly recruiting patients on BCDTs such as found in our study[27]. We examined the groups broken down by those treated with anti-SARS-

CoV-2 mAbs versus those who were not, looking for select clinical characteristics with the potential to influence clinical outcomes. We found that the groups were well-matched for traditional risk factors for COVID-19 progression (i.e. age, co-morbidities) as well as concomitant immunosuppression and duration of BCDT. In the unvaccinated cohort anti-SARS-CoV-2 mAbs were used in only 7 patients (12%); 3 of these patients required hospitalization, none died. While intriguing, we would caution against any strong conclusions regarding the efficacy of anti-SARS-CoV-2 mAbs in this population due to limitations including nonrandom allocation and likely residual confounding effects.

A more practical question perhaps should be posed: why only 21 of 74 breakthrough patients (28.4%) received anti-SARS-CoV-2 mAb therapy. The seeming underutilization of these treatments in our patients is both important and disappointing. There are a number of possible explanations for this underutilization of early and aggressive outpatient therapy. First, during various surges of COVID-19 there were periods of time when these therapies had limited availability. However, upon individual examination of the medical records, this was not explicitly noted as a limitation in any case. A more likely cause of lack of outpatient therapy was patients failing to connect with their providers within the ten day window of eligibility (23). Numerous reasons could cause such a delay including the failure of the provider to educate patients on the time urgency to seek care if they suspected COVID-19 infection. This education must include how to recognize the often subtle symptoms of breakthrough infection[28] as well as how to promptly self-test or obtain testing within the important time window for the given treatment. Also plausible and anecdotally noted in our chart review were uncertainties on behalf of the patients who were diagnosed promptly as to which provider to contact (i.e. primary care or specialist), at times leading to delays caused by caregivers who were unfamiliar with rapidly changing care pathways. The even lower use of anti-SARS-CoV-2 mAbs in the unvaccinated cohort is of great concern and may reflect disparities in health care access and/or belief in health care resources. Moving ahead practitioners caring for immunocompromised patients will need to stay knowledgeable about standards

of care and fill any outstanding deficits in declarative or procedural knowledge on how to manage COVID-19 in their patients.

Our study has several important limitations. First, we have no direct comparator group of immunocompromised patients based on therapy; it would be of interest to compare severity and outcomes to other patients on different immunosuppressive therapies. For now unfortunately large studies such as these have not been reported. Second, it is likely that unknown cases of mild or even asymptomatic infection may have been unreported or missed and certain data fields extracted from the chart review may have been missing, especially from patients receiving their BCDT outside of our health care system. Third, while we chose to examine patients given BCDTs in the year 2020, we did not account for ongoing BCDT through the end of the study which may have further contributed to immunosuppression. A recent study of rituximab in vasculitis patients demonstrated that antibody levels to S protein fell by greater than 50% within 4 weeks of drug administration [29]. Finally, it would clearly be of interest to examine breakthrough infections in concert with the status of patients' integrated immune responses by assessing serologic responses, especially anti-Spike antibody titers, which have been associated with breakthrough infections in IMIDs patients[23 25], as well as B cell numbers and cell mediated immune responses. Unfortunately this was not possible in this retrospective study where such data were not gathered or were missing on the vast majority of patients.

In terms of practical implications our study should serve to highlight the plight of this important segment of the immunocompromised patient population who are likely to face ongoing and formidable risks despite aggressive vaccination if, as many observers predict, an ensuing endemic phase of the pandemic lies ahead with future variants of unknown pathogenicity. For now enhanced non-pharmacologic measures (masking, social distancing, etc.) will remain important; expanded access to pre-exposure prophylaxis with anti-SARS-CoV-2 mAbs effective against prevalent variants and access to emerging antiviral therapies will be vital[28,30,31]. Enhanced education of both patients and the providers who care

for them to increase their awareness and utilization of current and future outpatient therapies is urgently needed.

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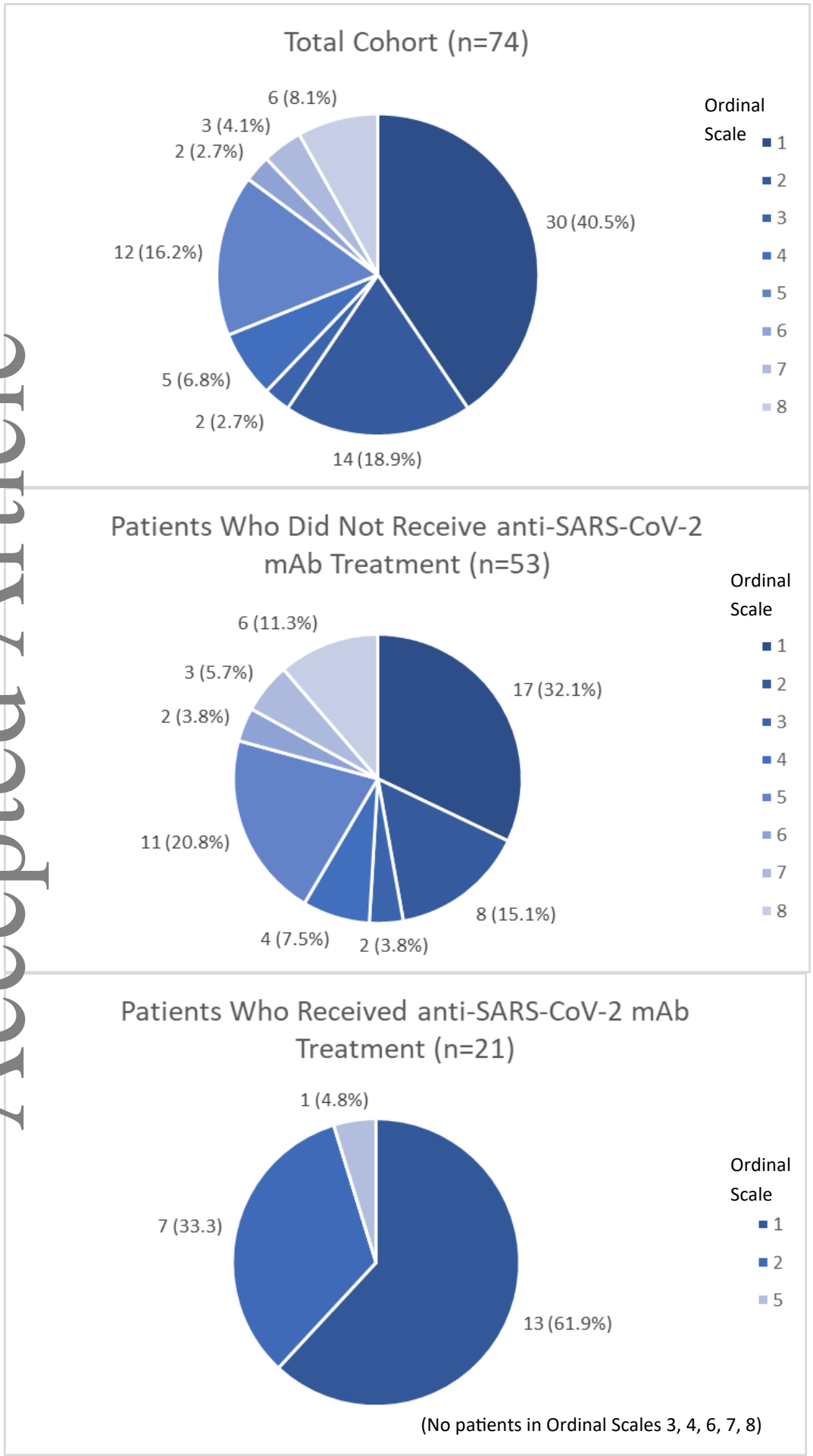
Figure 1. COVID-19 Outcomes by NIH Ordinal Scale

Pie chart of clinical outcomes of 74 cases with COVID-19 breakthrough infection from among 1776 vaccinated patients on BCDTs. Top panel displays clinical status by 8 point ordinal scale. Middle panel displays clinical outcomes in the subset of 53 patients who did not receive outpatient monoclonal antibody therapy while the bottom panel displays clinical outcomes in the subset of 21 patients who received outpatient monoclonal antibody therapy. Ordinal scale categories in inset.

*BCDTs = B cell depleting therapies

Figure 1 COVID-19 Outcomes by NIH Ordinal Scale



Ordinal Scale Legend

1 Ambulatory (no limitation)

2 Ambulatory (with limitation)

3 Hospitalized (no O_2, no medical treatment)

4 Hospitalized (no O_2, but requiring ongoing medical treatment)

5 Hospitalized (any O_2)

6 Hospitalized (NIV or HFNC)

7 Hospitalized (IMV or ECMO)

8 Death

Table 1: Patient Characteristics of vaccinated and unvaccinated

	Vaccinated (N=74)	Unvaccinated (N=57)
	N (%)	N (%)
Median age	53 years	50.3 years
Female	46 (62.2)	42 (73.7)
White race	62 (83.8)	41 (71.9)
Diagnosis		
Inflammatory CNS	34 (45.9)	33 (57.9)
Vasculitis	20 (27.0)	4 (7.0)
RA	9 (12.2)	12 (21.1)
Other	11 (14.9) [1]	11 (19.3)[2]
Comorbidities		
BMI 30+	35 (47.3)	30 (52.6)
Heart Disease [3]	36 (48.6)	24 (42.1%)
Pulmonary [4]	13 (17.6)	17 (29.9)
CKD	8 (10.8)	3 (5.3)
Malignancy	6 (8.1)	3 (5.3)
# of Comorbidities		
0	23 (31.1)	22 (38.6)
1	24 (32.4)	18 (31.6)
2	9 (12.2)	13 (22.8)
3+	18 (24.3)	4 (7.0)
Vaccine		
Pfizer	45 (60.8)	
Moderna	23 (31.1)	
J & J	6 (8.1)	
Duration of BCDT		
< 1 year	20 (27.0)	9 (16.1)
1-3 years	20 (27.0)	27 (48.2)
3+ years	34 (45.9)	20 (35.7)
Immunosuppression		
GC <10 mg/day	20 (27.0)	2 (3.5)
GC ≥ 10 mg/day	6 (8.1)	4 (7.0)
1 DMARD	12 (16.2)	9 (15.7)
2 DMARD	1 (1.3)	3 (5.3)
Time between BCDT & vaccine #1		
<3 months	22 (32.8)	
3-6 months	36 (53.7)	
>6 months	9 (13.4)	
Time between BCDT & COVID-19 diagnosis		
<3 months	36 (48.6)	
3-6 months	21 (28.4)	
>6 months	17 (22.9)	
Received anti-SARS-CoV-2 mAb therapy	21 (31.3)	7 (12.3)

Abbreviations RA: rheumatoid arthritis; CNS: central nervous system; CKD: chronic kidney disease; BCDT: B-cell depleting therapy; GC: glucocorticoid; DMARD: disease-modifying antirheumatic drug (includes hydroxychloroquine, methotrexate, azathioprine, mycophenolate); mAb: monoclonal antibody

[1] 2 systemic lupus erythematosus, 2 sarcoidosis, 2 solid organ transplant, 2 myositis, 1 interstitial lung disease, 2 hematologic

[2]3 Systemic sclerosis, 2 Pemphigus, 2 Sjögrens, 1 each of autoimmune encephalitis, myasthenia gravis, sarcoidosis, mixed connective tissue disease

[3] Hypertension, coronary artery disease, congestive heart failure

[4] Chronic obstructive pulmonary disease, asthma, interstitial lung disease

[5]Missing data on one patient

Table 2: Univariate and multivariate analysis of clinical variables with potential impact on COVID-19 severity

Variable		NIH COVID-19 ordinal scale				
		Scale: 1-3 (N=47)	Scale: 4-8 (N=27)	P value	Odds Ratio (95% CI)*	P value*
Age at first vaccination, median [25th;75th]		52.3 [40.3;61.9]	60.7 [49.0;71.7]	0.088		
Gender, N (%)	F	30 (63.8%)	16 (59.3%)	Ref		
	M	17 (36.2%)	11 (40.7%)	0.696		
Diagnosis, N (%)	Neuro+Other	25 (53.2%)	15 (55.6%)	Ref		
	Rheum	22 (46.8%)	12 (44.4%)	0.844		
Number of comorbidities (binary), N (%)	0-1	40 (85.1%)	13 (48.1%)	Ref	5.9 (1.56, 22.27)	*0.009*
	>=2	7 (14.9%)	14 (51.9%)	*0.001*		
Vaccination status, N (%)	Complete	29 (61.7%)	16 (59.3%)	Ref		
	Boosted	14 (29.8%)	9 (33.3%)	0.772		
	Incomplete	4 (8.51%)	2 (7.41%)	0.915		
Duration of therapy with BCDT, N (%)	< 1 year	13 (27.7%)	7 (25.9%)	Ref		
	1-3 years	11 (23.4%)	9 (33.3%)	0.519		
	> 3 years	23 (48.9%)	11 (40.7%)	0.842		
Most recent BCDT at time of 1st vaccination, N (%)	<3 months	13 (31.7%)	8 (32.0%)	Ref		
	3-6 months	25 (61.0%)	11 (44.0%)	0.561	0.8 (0.21, 3.07)	0.744
	>6 months	3 (7.32%)	6 (24.0%)	0.159	1.75 (0.28, 10.94)	0.55
Concomitant therapies, N (%)	GC < 10 mg per day	13 (27.7%)	7 (25.9%)	Ref		
	GC > 10 mg per day	2 (4.26%)	4 (14.8%)	0.183		
	Others	32 (68.1%)	16 (59.3%)	0.895		
Prior COVID history, N (%)	No	45 (97.8%)	24 (88.9%)	Ref		
	Yes	1 (2.17%)	3 (11.1%)	0.144		
SARS-CoV-2 mAb treatment, N (%)	No	27 (57.4%)	26 (96.3%)	Ref	0.06 (0.01, 0.57)	*0.006*
	Yes	20 (42.6%)	1 (3.70%)	*0.005*		

*: Results from Multivariable Logistic Regression;
BCDT: B-cell depleting therapy; GC: glucocorticoids; mAb: monoclonal antibody

TABLE 3. Comparisons of clinical features between patients receiving anti-SARS-CoV-2 mAb therapy versus patients not receiving anti-SARS-CoV-2 mAb therapy

		Total (N=74)	(-) anti-SARS-CoV-2 mAb (N=53)	(+) anti-SARS-CoV-2 mAb (N=21)	P value
Age at first vaccination, Median [25th;75th]		55.2 [41.7;65.4]	54.9 [44.0;65.5]	55.5 [37.6;65.1]	0.679
Gender, N (%)	F	46 (62.2%)	34 (64.2%)	12 (57.1%)	0.768
	M	28 (37.8%)	19 (35.8%)	9 (42.9%)	
Concomitant therapies, N (%)	GC < 10 mg per day	20 (27.0%)	11 (20.8%)	9 (42.9%)	0.129
	GC > 10 mg per day	6 (8.11%)	4 (7.55%)	2 (9.52%)	
	Others	48 (64.9%)	38 (71.7%)	10 (47.6%)	
Number of comorbidities (binary), N (%)	0-1	53 (71.6%)	35 (66.0%)	18 (85.7%)	0.160
	>=2	21 (28.4%)	18 (34.0%)	3 (14.3%)	
Duration of therapy with BCDT, N (%)	< 1 year	20 (27.0%)	15 (28.3%)	5 (23.8%)	0.783
	1-3 years	20 (27.0%)	15 (28.3%)	5 (23.8%)	
	> 3 years	34 (45.9%)	23 (43.4%)	11 (52.4%)	