SARS-CoV-2 infections in patients with autoimmune blistering disorders: A case series and retrospective analysis

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Background: Autoimmune blistering disorders (AIBDs) are rare, potentially life-threatening conditions often requiring immunosuppression. Throughout the SARS-CoV-2 pandemic, infection risk and mortality in patients with AIBDs are unknown.

Objective: We report the outcomes of SARS-CoV-2 infections in patients with AIBDs and determined if patients on rituximab have an increased risk of SARS-CoV-2 infection.

Methods: We examined clinical outcomes in 10 patients with AIBDs who developed SARS-CoV-2 infections at an American hospital. We performed a retrospective analysis of 132 patients with AIBDs enrolled in a clinical trial.

Results: Patients with severe SARS-CoV-2 (n = 4) or death (n = 2) trended to be older. These patients had higher mortality than the national average (20% vs 1.6%). Our cohort included 52 patients with a history of rituximab treatment, 35 of whom were immunosuppressed by rituximab during the pandemic, and 45 patients never treated with rituximab. We found no difference between the rates of SARS-CoV-2 positivity in patients with AIBDs immunosuppressed by rituximab and those not on rituximab (9.1% vs 12.1%).

Limitations: Testing for SARS-CoV-2 was performed on demand rather than surveillance. Overall transmission varied over time, and outcomes depended on accepted treatments. The small sample size of our cohort limits the generalizability of our results.

Conclusion: This study suggests that rituximab does not increase the risk of SARS-CoV-2 test positivity in patients with AIBDs. However, these results should be interpreted with caution due to our relatively small sample size. (JAAD Int 2022;7:38-43.)

Key words: autoimmune disease; bullous disease; covid-19; immunosuppression; infectious diseases; pemphigoid; pemphigus; sars-cov-2.

INTRODUCTION

Infections with SARS-CoV-2 began spreading in the fall of 2019 and arrived in the United States in January 2020. The outbreak was deemed the “COVID-19 pandemic” on March 11, 2020, by the World Health Organization. The SARS-CoV-2 pandemic has brought to light several questions regarding the risk of infection, morbidity, and mortality in patients with comorbid diseases as well as those on systemic immunosuppressants. Autoimmune blistering disorders (AIBDs) are rare, life-threatening conditions that include bullous pemphigoid, pemphigus vulgaris, mucous membrane pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease. These infections cause disruption of the epidermal barrier due to the formation of...
blisters and erosions of the skin and mucosa due to aberrant immune responses against proteins involved in cell-to-cell adhesion. Patients with these rare blistering disorders have an unknown risk of infection from SARS-CoV-2 and are often treated with systemic immunosuppressants, compounding their possible risk of infection. Given the rarity of these conditions, it is imperative to report real-time clinical experiences with these patients in the literature.

The role of immunosuppression in SARS-CoV-2 infections is controversial and complex in regard to the risks of infection and severe infection. Immune-modulating and antiinflammatory drugs have been used in attempts to decrease the body's aberrant immune response to SARS-CoV-2 infection that has been associated with severe disease, including acute respiratory distress syndrome. Corticosteroids were shown to improve outcomes in patients hospitalized with SARS-CoV-2 infections. Furthermore, treatment with tocilizumab and sarilumab, interleukin-6 receptor antagonists, have improved outcomes including survival. While treatment with hydroxychloroquine initially showed promise, it was later determined that it did not prevent death or severe disease. There are several ongoing clinical trials investigating the use of Janus kinase inhibitors and tumor necrosis factor-α inhibitors during SARS-CoV-2 infection.

Patients with AIBDs are often on systemic immunosuppressants, most notably rituximab, which can potentially be lifesaving. There is a single case series reporting 21 patients with autoimmune bullous diseases in Iran, 14 of whom received rituximab in the prior year. The study found a similar relative risk of hospitalization in patients with rituximab prior to the pandemic versus during the pandemic (3.11 vs 3.02). A retrospective cohort study from Israel demonstrated an increased mortality in 36 patients with pemphigus vulgaris or bullous pemphigoid and SARS-CoV-2 infections compared with that of the general population. There are currently no case series reported regarding the outcomes of patients with blistering diseases and SARS-CoV-2 in the United States.

We present a case series of patients with blistering disorders and SARS-CoV-2 infection. In addition, we conducted a retrospective analysis of patients with AIBDs who underwent testing for SARS-CoV-2 infection. Our primary objective in this study was to report the outcomes of patients with AIBD and SARS-CoV-2 to elucidate trends in severity compared with those of the general population. Our secondary objective was to collect and examine existing data regarding rituximab infusions to observe trends in test positivity in severely immunosuppressed patients. One goal was to help clinicians make decisions regarding risks and benefits of starting a rituximab infusion during the pandemic.

**METHODS**

Patients with autoimmune blistering disease and a confirmed SARS-CoV-2 infection who were seen at Duke University and its affiliated clinics since the beginning of the pandemic (from March 1, 2020, to August 31, 2021) were included in the case series. Severe infection was defined as dyspnea, respiratory rate of >30 breaths per minute, blood oxygen of <93%, ratio of PaO₂ to fraction of inspiratory oxygen of <300 mmHg, or infiltrates in >50% of the lung field. Patients with AIBDs currently enrolled in Duke Dermatology Department's autoantibody cohort who underwent SARS-CoV-2 testing during the pandemic were included in the retrospective analysis. Rituximab treatment was considered relevant to the pandemic if it was administered after March 1, 2019, due to the estimated immune recovery of 12 months after rituximab therapy and the World Health Organization declaration of start of the COVID-19 pandemic in March, 2020. Immune reconstitution after rituximab therapy has been noted in approximately 6 months, with recovery to near-normal in approximately 9 to 12 months. Statistics were performed using the chi-square tests. Both the case series and retrospective analyses received Institutional Review Board approval from Duke University School of Medicine.

**RESULTS**

We present 10 cases of patients with AIBDs (4 with pemphigus vulgaris, 5 with bullous pemphigoid, and 1 with mucous membrane pemphigoid) who developed SARS-CoV-2 infections from March 1, 2020, through August 31, 2021. The outcomes of patients with AIBDs and SARS-CoV-2 infections are outlined in Table I. Of those who were infected, 4 had severe infections requiring hospitalization, 2 of whom died. Five patients were symptomatic but did
not require hospitalization. One patient had a positive SARS-CoV-2 test, but no other information regarding their infection was available through chart review. The median age of those who died was 88 years, that of those with severe disease but not death was 61 years, and that of those with mild or asymptomatic disease was 54 years. Only 1 patient had documented vaccination to SARS-CoV-2 (infection approximately 6 months after second vaccination), although the vaccination status of 2 patients is unknown.

Regarding immunosuppression, 1 patient (aged 62 years) had 2 1000-mg rituximab infusions spread 2 weeks apart within 2 months of their SARS-CoV-2 infection and did not require hospitalization. Seven patients were on prednisone (range of 5-10 mg daily) during their SARS-CoV-2 infections. Two patients on prednisone did not require hospitalization for SARS-CoV-2 infections. Two patients on prednisone did not require hospitalization for SARS-CoV-2 (aged 73 and 83 years), and 1 had a positive test with no reported symptoms (aged 45 years). Two patients on prednisone (aged 63 and 59 years) required hospitalization and admission to intensive care unit due to their SARS-CoV-2 infection. The 59-year-old patient was enrolled in a clinical trial for the treatment of pemphigus (NCT03762265) that has not been unblended; therefore, it is unknown whether this patient was taking placebo or the study drug rilzabrutinib, an oral Bruton tyrosine kinase inhibitor. The 63-year-old patient also had comorbid multiple sclerosis and was chronically bedridden. Two patients died from SARS-CoV-2, 1 patient on prednisone only (aged 95 years) and 1 on both mycophenolate mofetil and prednisone who also had comorbid chronic obstructive pulmonary disease (aged 81 years).

To produce a denominator of the number of SARS-CoV-2 tests collected from patients within 12 months of rituximab infusion during the study period, and of those tests, only 1 was positive (9.1%) (Fig 1, A). There were 66 SARS-CoV-2 tests from patients who had not had a rituximab infusion within the prior 12 months of the test, of which 8 were positive (12.1%). A timeline of SARS-CoV-2 positive tests over time in North Carolina is displayed in Fig 1, B, which can be viewed together with the timeline of rituximab infusions displayed in Fig 1, C. The combination of these shows a relatively even distribution of infusions over the course of our study period as cases wax and wane, with the exception of a small gap during the shutdown period in March 2020. Similar to patients with rituximab within the past year, the prevalence of SARS-CoV-2 test positivity did not differ in patients with a history of rituximab infusion ever compared to never (13.7% vs 7.7%, \( P = .44 \)).

The SARS-CoV-2 pandemic exceeded 25 new cases per 100,000 people in North Carolina on November 15, 2020, and remained above that threshold until February 26, 2021.\(^4\) With a resurgence of SARS-CoV-2 infections due in large part to the delta virus, North Carolina again exceeded 25 new cases per 100,000 as of August 2, 2021. Given an estimate of rituximab immune suppression for approximately 12 months after infusion,\(^7\)\(^,\)\(^8\) patients with infusions on or after November 15, 2019, were immunosuppressed during the peak of infections in North Carolina. Patients with rituximab infusions prior to November 15, 2019 (\( n = 25 \)), likely had a lower risk of contracting SARS-CoV-2 infection than those with infusions after (\( n = 27 \)).

**DISCUSSION**

In this small case series and retrospective cohort study, we observed that patients with AIBDs with SARS-CoV-2 infections had a higher mortality rate than the general population. We also observed that patients with AIBDs immunosuppressed by rituximab did not have an increased frequency of SARS-CoV-2 test positivity compared with patients with AIBDs not taking rituximab.

Our case series agrees with the literature that the best predictor of mortality from SARS-CoV-2 infection is age. In our 10-patient series of patients with autoimmune blistering disease and positive COVID tests, the oldest 2 patients died from complications surrounding their infections. The mortality rate is estimated at 1.6% across the global US population,\(^1\) which is far from our series’ mortality rate of 20.0%. Given that Duke University Hospital is a large referral facility, the mortality rate of 20.0% is far from our series’ mortality rate of 20.0%. Given that Duke University Hospital is a large referral facility, the mortality rate of 20.0% is far from our series’ mortality rate of 20.0%.
center, there may be a selection bias for patients who have more severe autoimmune blistering diseases. However, Kridin et al. found a 19.4% mortality in patients with either bullous pemphigoid or pemphigus and SARS-CoV-2 infection, which is in keeping with our findings of increased mortality in this patient population. A larger population-based study could determine if this finding is incidental or represents a larger trend.

We did not observe a trend regarding immunosuppressives given our small number of patients; however, our single patient on rituximab who developed SARS-CoV-2 infection did well. Rituximab is a chimeric monoclonal antibody against CD20 that helps target CD20+ B cells for destruction. B cell function is important in the immune response to SARS-CoV-2 as B cells create neutralizing antibodies, kill virally infected cells, and activate T cell cytotoxic function. Given the considerable immunosuppression achieved with rituximab infusion, patients on rituximab may be more susceptible to severe disease with SARS-CoV-2.

### Table I. Summary of patients with autoimmune blistering disorders and SARS-CoV-2 infections.

<table>
<thead>
<tr>
<th>Blistering disorder</th>
<th>Age</th>
<th>Sex</th>
<th>BMI</th>
<th>Current immunosuppressiona</th>
<th>Previous immunosuppression</th>
<th>Severe infection (Y/N)</th>
<th>Death (Y/N)</th>
<th>Vaccination statusb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>62</td>
<td>M</td>
<td>24</td>
<td>Rituximab 1000 mg × 2 (77 days prior)</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>45</td>
<td>M</td>
<td>37</td>
<td>Prednisone 10 mg</td>
<td>Azathioprine</td>
<td>N</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>63</td>
<td>F</td>
<td>30</td>
<td>Prednisone 5 mg</td>
<td>Mycophenolate mofetil</td>
<td>Y</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>73</td>
<td>F</td>
<td>31</td>
<td>Prednisone 10 mg</td>
<td>Methotrexate</td>
<td>N</td>
<td>N</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>81</td>
<td>F</td>
<td>26</td>
<td>Mycophenolate mofetil</td>
<td>Prednisone</td>
<td>Y</td>
<td>Y</td>
<td>No</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>59</td>
<td>M</td>
<td>40</td>
<td>Prednisone, study drug (rilzabrutinib) vs placebo</td>
<td>Mycophenolate mofetil, rituximab</td>
<td>Y</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>95</td>
<td>M</td>
<td>25</td>
<td>Prednisone 5 mg</td>
<td>None</td>
<td>Y</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Mucous membrane pemphigoid</td>
<td>40</td>
<td>F</td>
<td>49</td>
<td>None</td>
<td>Prednisone</td>
<td>N</td>
<td>N</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>46</td>
<td>F</td>
<td>54</td>
<td>None</td>
<td>Prednisone, methotrexate</td>
<td>N</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Bullous Pemphigoid</td>
<td>83</td>
<td>F</td>
<td>24</td>
<td>Prednisone 5 mg</td>
<td>None</td>
<td>N</td>
<td>N</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BMI, Body mass index.

aCurrent treatment counted as rituximab within the prior 12 months or any other immunosuppressive treatment for autoimmune blistering disease that was administered within 2 months prior to SARS-CoV-2 infection.

bVaccination status at the time of infection.

![Fig 1. Rituximab infusions in patients with autoimmune blistering disorders during the SARS-CoV-2 pandemic.](image-url)

(A) Patients with rituximab infusions in the past 12 months were not more likely to have a positive SARS-CoV-2 test than patients with autoimmune blistering disorders who had not been recently treated with rituximab. Dark green represents test positivity; light green represents test negativity. (B) This graphic demonstrates incidence of positive SARS-CoV-2 tests per 100,000 people throughout the pandemic in the state of North Carolina. This image is a reprint from www.covidactnow.org and used with permission. (C) A timeline of individual rituximab infusions throughout the pandemic. Each green dot represents 1 infusion.
infection. A descriptive study demonstrated high rates of severe disease and death related to SARS-CoV-2 in patients on rituximab with rheumatologic disease. More patients are needed to determine if rituximab influences the severity of SARS-CoV-2 infections. Recently published recommendations conclude that a risk-benefit analysis is the best approach when initiating rituximab or immunoadsorption/plasmapheresis in these patients.

Our patients on rituximab did not have an increased frequency of positive SARS-CoV-2 tests compared with patients with AIBDs not on rituximab, despite the significant immunosuppression of rituximab. The overall prevalence of positive SARS-CoV-2 tests was slightly above the prevalence over the lifetime of the pandemic for the general population in the state of North Carolina, although these include surveillance tests and the patients with AIBDs did not undergo serial testing. In our cohort, patients were given more infusions later in the pandemic, which coincided with increased case numbers in this state. Given the continued high prevalence of SARS-CoV-2 infections, more data are likely forthcoming regarding infection trends in autoimmune blistering patient population. The shorter follow-up time for patients with recent rituximab infusions is a weakness in our study; however, we felt the need to publish our results given the immediate implications for treatment as we enter another wave of SARS-CoV-2 infections.

Our study has several limitations. As discussed earlier, this is a small case series owing to AIBD encompassing relatively rare diseases. These SARS-CoV-2 cases occurred at a single quaternary care center, and, thus, there may be referral bias for more severe cases. Many of these patients developed SARS-CoV-2 infections prior to the development of vaccines specific for SARS-CoV-2; therefore, data on outcomes of infections in vaccinated patients with AIBDs are not presented here. As discussed, patients with recent rituximab infusions did not undergo surveillance testing longitudinally. The SARS-CoV-2 tests included in this study were only those performed at Duke University Hospital, clinics, and testing sites. We were unable to include data from the many other sources of tests including local pharmacies and health departments. Although the ideal study would include a longitudinal component, the unknown duration of the pandemic has made it difficult to plan these types of research projects as case numbers wax and wane. The changes in case numbers over time also add to the uncertainty of rituximab’s effects on SARS-CoV-2 infection, as a patient may by chance be most immunosuppressed during a time of low case prevalence. Nevertheless, we feel strongly that the importance of reassuring physicians caring for patients with AIBDs receiving rituximab therapy that our patients have done well is extremely valuable clinical information.

There are several questions that remain regarding patients with autoimmune blistering diseases and SARS-CoV-2 infection. The risk of developing infection from a single exposure remains unknown. While previous research has not demonstrated an increased risk of SARS-CoV-2 infection based on AIBDs, the studies fail to account for risk modulation in this population. Adults with chronic diseases have been shown to be more likely to adhere to risk modulating behaviors to prevent exposure to SARS-CoV-2 including wearing a mask and avoiding crowds. Although most patients were ineligible for vaccination at the time of infection, there were several patients who had deferred vaccination. It is difficult to estimate by incidence alone the risk of exposure leading to SARS-CoV-2 disease in this population, especially with the development of effective vaccination.

Patients with AIBDs have significant morbidity and mortality associated with their blistering disease and are often on immunosuppressive medications, including systemic steroids, rituximab, and other biologic agents. These medications, most notably rituximab, are responsible for improvements in morbidity and mortality in this patient population. In our small retrospective cohort study, rituximab within the prior year does not appear to increase the frequency of a positive SARS-CoV-2 test, although our case numbers are small given the relative rarity of patients with autoimmune blistering disease on rituximab infusions. A better understanding of SARS-CoV-2 outcomes and risk factors for severe disease is necessary in this special population to inform treatment decisions, especially as infection rates surge in the general population in several countries.

Data availability statement
The data for this project can be made available upon request to the corresponding author.

Conflicts of interest
None disclosed.

REFERENCES


