REGULAR ARTICLE

blood advances

Impact of SARS-CoV-2 infection on bispecific antibody treatment in patients with B-cell lymphoproliferative disorders

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Key Points

- SARS-CoV-2 infection was associated with prolonged viral shedding, causing therapy delays and permanent discontinuations.
- BsAb treatment was associated with negative antispike serostatus for at least 6 months after treatment completion.

Despite advances in vaccination and the use of antiviral treatments, patients with hematologic malignancies, including B-cell lymphoproliferative disorders, are particularly vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The recent introduction of bispecific antibodies (BsAbs) in the treatment algorithm of relapsed/refractory B-cell non-Hodgkin lymphoma (B-NHL) has raised concerns regarding their impact on COVID-19 outcomes. This study aimed to evaluate the impact of SARS-CoV-2 infection on treatment outcomes in patients receiving BsAbs. We assessed the severity of COVID-19 and SARS-CoV-2 serostatus, with antibody titers measured before, during, and after BsAbs administration. A total of 109 patients with B-NHL treated with BsAbs from March 2020 to January 2023 were included. SARS-CoV-2 infection was observed in 56 patients (51%), with 36% experiencing prolonged viral shedding, causing therapy delays in 78% of patients and permanent discontinuations in 19%. Regarding COVID-19 severity, 36% of patients presented moderate, 20% severe, and 12% critical disease. Seven patients (13%) died owing to COVID-19 pneumonia. Similar to observations with anti-CD20 monoclonal antibodies, BsAbs were associated with negative antispike serostatus for at least 6 months after treatment completion. Importantly, this lack of seroconversion was linked with severe disease and increased mortality. These findings underscore important considerations for the management of patients receiving BsAbs.

Introduction

Patients diagnosed as having B-cell non-Hodgkin lymphoma (B-NHL) typically experience poor outcomes in the relapsed/refractory setting.[1,2] Nevertheless, recent advancements in immunotherapy have shifted treatment paradigms.[3,4] CD19-directed chimeric antigen receptor (CAR) T-cell therapy has received regulatory approval for relapsed/refractory patients with large B-cell lymphoma, follicular lymphoma (FL), and mantle cell lymphoma (MCL).[5-8] More recently, off-the-shelf bispecific antibodies (BsAbs) have been approved for the treatment of B-NHL,[3,9-11] which represent a promising

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The full-text version of this article contains a data supplement.

therapeutic approach. However, accumulating clinical data on these therapies have highlighted their toxicity profile, which includes cytokine release syndrome, cytopenias, hypogammaglobulinemia, and infection, including COVID-19.[12-15] Patients with hematologic malignancies are particularly vulnerable and have been severely affected by the COVID-19 pandemic, presenting higher rates of severe disease and mortality.[16-18] Despite the exclusion of the immunocompromised individuals from the pivotal clinical trials that approved the 2 messenger RNA (mRNA)–based vaccines (BNT162b2 and mRNA-1273),[19,20] their use has been extended to this high-risk population. Patients diagnosed as having B-cell malignancies exhibit the lowest rates of seroconversion after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, likely owing to previous or ongoing anti-CD20 monoclonal antibody treatment.[21-25] However, the patterns and risks for infections with novel agents remain unclear, and data regarding the impact of COVID-19 in patients diagnosed as having B-NHL and treated with BsAbs are limited.

The objective of the current study was to assess the impact of SARS-CoV-2 infection on patients with B-NHL receiving BsAbs treatment and to assess the severity of COVID-19 in this context. In addition, we conducted a longitudinal analysis of patients' immunologic status and antispike (anti-S) SARS-CoV-2 seroconversion at the start of BsAbs, during treatment, and after its completion.

Methods

This study included patients diagnosed as having B-NHL and treated with BsAbs at the Vall d'Hebron University Hospital from March 2020 to January 2023, irrespective of treatment line or combination partner.

Data regarding SARS-CoV-2 infections were collected, during and after treatment with BsAbs, immediately after the treatment completion (early posttreatment, <6 months) or after a median of 6 months (late posttreatment, >6 months).

To assess the immunologic status of the patients before the start of BsAbs, the following parameters were measured: absolute lymphocyte count, total serum immunoglobulin levels, and lymphocyte populations using flow cytometry in peripheral blood samples ($CD3^+$, $CD4^+$, $CD8^+$, $CD3^-CD56^+$, and $CD19^+$).

Serologic data for specific antibodies targeting both the nucleocapsid (N) and S antigens of SARS-CoV-2 were assessed using TrimericS, which is a serologic analysis method that is not specific to any of the SARS-CoV-2 variants. Serologic status was also collected before BsAbs treatment initiation, during the course of treatment, and after its completion. In addition, serologic analysis was performed to assess anti-N and anti-S proteins at the time of SARS-CoV-2 infection. Although antibodies against both the N and S proteins are produced after SARS-CoV-2 infection, only anti-S antibodies are developed in response to SARS-CoV-2 vaccination.[26] Patients with detectable anti-N antibodies but without a history of COVID-19 symptoms were classified as asymptomatic COVID-19 cases. We also detected other variants (Omicron and Delta) by sequencing the entire genome of the virus through the respiratory sample.

This study was approved by the institutional clinical research ethics committee of the Vall d'Hebron Institute (study number: PR (AG)179/2022). All patients provided a written informed consent in accordance with the Declaration of Helsinki.

Assessment of COVID-19 severity

The severity of COVID-19 was categorized following the World Health Organization criteria.[27] They were divided into 2 groups: patients with moderate, severe, and critical infections and those with asymptomatic or mild infections. In our cohort, all patients with moderate COVID-19 required hospitalization and were therefore grouped together with those who had severe or critical disease.

Assessment of humoral immune response

Seroconversion rate was assessed using 2 commercial chemiluminescence immunoassays: (1) Elecsys Anti-SARS-CoV-2 (Roche Diagnostics, Mannheim, Germany) performed on the Cobas 8800 system (Roche Diagnostics, Basel, Switzerland) for the determination of total antibodies (including immunoglobulin G [IgG], IgM, and IgA) against N SARS-CoV-2 glycoprotein (cutoff, 1.0 index); and (2) LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Stillwater, MN) performed on the Liaison XL Analyzer (Diasorin, Saluggia, Italy) for the determination of IgG antibodies against the S glycoprotein of SARS-CoV-2 (cutoff, 33.8 BAU/mL).

Humoral response was assessed before, during, and after completion of treatment based on sample availability. Serologic data were also collected after completing the BsAbs therapy (early posttreatment) and after a median of 6 months after BsAbs therapy (late posttreatment). Seroconversion was defined as the detection of an S glycoprotein level of >33.8 BAU/mL.

Patients were vaccinated in accordance with governmental health guidelines and physician recommendations.

Blood samples from patients who received convalescent plasma, sotrovimab, or AZD7442 (cilgavimab and tixagevimab) were excluded from the seroconversion analysis after the administration of these therapies.

Reinfection, reactivation of SARS-CoV-2 infection, and prolonged viral shedding

Reinfection was defined as the identification of a different SARS-CoV-2 variant from the initial infection, confirmed by genetic sequencing of respiratory samples with a viral load of <31 cycle threshold by real-time polymerase chain reaction (PCR). Reinfection was determined by the presence of 2 consecutive negative real-time PCR results between episodes, with a time interval of >60 days after the first infection.

Reactivation or relapse was defined as a positive retest with the same viral clade after recovering from an infection or the development of clinical symptoms within 60 days of the initial episode.[28-32] Prolonged viral shedding was defined as the detection of SARS-CoV-2 RNA for a period exceeding 3 weeks after symptom onset.[33,34]

Statistical analysis

A descriptive analysis was conducted for all variables included in the study. Continuous variables were represented as median and

interquartile range, whereas categorical variables were presented as absolute values and percentages.

Independent predictors of COVID-19 severity in patients diagnosed with B-NHL and treated with BsAbs were investigated using logistic regression modeling. A univariable model was used with variables suspected to influence COVID-19 severity, aiming to compare patients experiencing mild or asymptomatic COVID-19 with those encountering severe, critical, or moderate cases.

No missing data imputation was performed. Statistical analyses were performed using R software version 4.2.2, with results deemed statistically significant if P value <.05.

Results

Study population

A total of 109 patients treated with BsAbs were included in this study. Patients' baseline demographic and clinical characteristics are presented in Table 1. The median age was 62 years (range, 30-86), and 45 patients (41%) were female. Histological diagnoses were diffuse large B-cell lymphoma (73%), FL (18%), MCL (6%), chronic lymphocytic leukemia (1%), primary mediastinal B-cell lymphoma (1%), and Richter transformation (1%).

Regarding BsAbs constructs, 94 patients (86%) received CD20/CD3, 13 (12%) received CD22/CD3, and 2 (2%) received anti-CD19 BsAbs. The median number of previous treatment lines was 2 (range, 0-9). Within 6 months before BsAbs therapy, 61 patients (56%) had been exposed to anti-CD20 agents, and 15 patients (14%) had received CAR T-cell therapy. Eleven patients (10%) had undergone autologous stem cell transplantation (SCT) as a consolidative strategy, with a median of 34.2 months from autologous SCT to BsAbs therapy.

At the start of BsAbs treatment, 49 patients (45%) had a lymphocyte count of $<1 \times 10^9$/L, 35 patients (32%) had IgG levels of <700 mg/dL, 68 patients (62%) had IgM levels of <40 mg/dL, and 44 patients (40%) had IgA levels of <70 mg/dL.

Immunogenicity

Eighty-six patients (79%) were vaccinated, with a median of 3 doses (range, 0-5 doses). Nevertheless, only 58 patients (53%) had received a SARS-CoV-2 vaccine before initiating BsAbs treatment (median, 1 dose; range, 0-4). Regarding the vaccine type, SARS-CoV-2 mRNA-1273 vaccine was administered to 41 patients (48%), BNT162b2 COVID-19 mRNA vaccine to 11 patients (13%), both mRNA vaccines to 24 patients (28%), and AZD1222 vector-based vaccine to 2 patients (2%), and vaccine information was unavailable for 8 patients (9%).

Anti-S levels were available for 76 patients (88%) with samples determined before, during, and after BsAbs treatment. Of these, 28 patients (37%) had negative serology despite being vaccinated, with only 4 of them being vaccinated before BsAbs treatment (the median dose of vaccine administration for patients with negative serology was 3). In contrast, 48 patients (63%) had positive serology (the median vaccine dose for patients with positive serology was 3).

A higher seroconversion rate was observed after a median of 6 months after BsAbs therapy (late posttreatment; Figure 1A), with higher S glycoprotein levels than the seroconversion rate in the early posttreatment setting. No differences regarding anti-S levels were observed based on recent exposure (within the last 6 months) to an anti-CD20 agent, either alone or in combination with chemoimmunotherapy (Figure 1B).

Table 1. Main baseline demographic and clinical characteristics of the patients treated with BsAbs from the total cohort

	% (range)	Total (N = 109), n/N
Age, median (range)	61.83 (30-86)	
Sex		
Male	58.7	64/109
Female	41.3	45/109
Diagnosis		
Diffuse large B-cell lymphoma	73.4	80/109
FL	18.3	20/109
MCL	5.5	6/109
Chronic lymphocytic leukemia	0.9	1/109
Primary mediastinal B-cell lymphoma	0.9	1/109
Richter syndrome	0.9	1/109
No. previous lines, median (range)	2.0 (0.0-9.0)	
Previous rituximab or in combination <6 months		
No	44.0	48/109
Yes	56.0	61/109
Previous CAR T-cell therapy <6 months		
No	79.8	94/109
Yes	13.7	15/109
Previous ASCT		
No	89.9	98/109
Yes	10.1	11/109
BiTE combination agent		
No combination	57.8	63/109
Chemotherapy	11.0	12/109
Immunotherapy	31.2	34/109
Vaccination		
Unknown	0.9	1/109
No	20.2	22/109
Yes	78.9	86/109
No. of doses, median (range)	3.0 (0.0-5.0)	
AZD7442 administration		
No	79.8	87/109
Yes	20.2	22/109
Seroconversion		
Not available	30.3	33/109
No	25.7	28/109
Yes	44.0	48/109
Follow-up, median (range), months	34.3 (1-35.3)	

ASCT, autologous SCT; BiTE, bispecific T-cell engager.

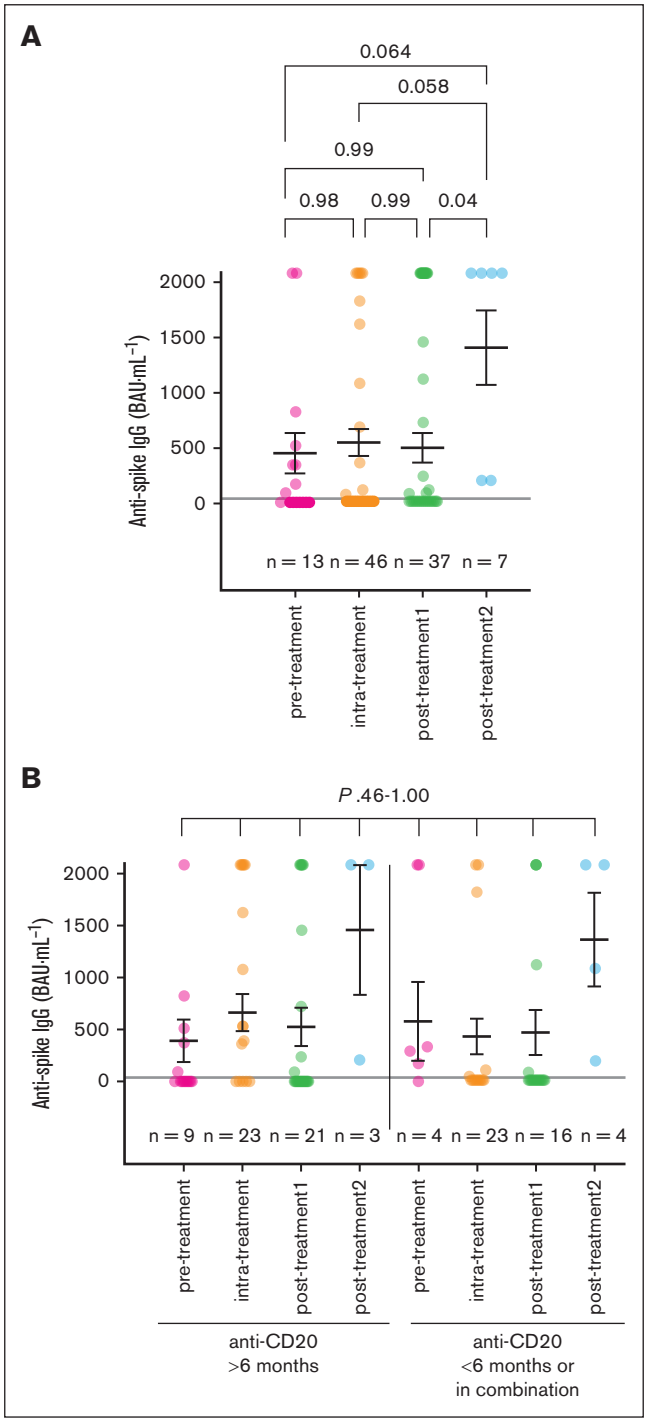

Figure 1. Seroconversion rate based on S glycoprotein levels measured previous, during, and after BsAbs treatment. (A) Seroconversion rate from the overall cohort through BsAbs treatment. (B) Seroconversion rate in patients who received anti-CD20 agent alone or in combination with chemoimmunotherapy >6 months ago and who were exposed to anti-CD20 agent alone or in combination with chemoimmunotherapy in the last 6 months. Posttreatment setting 1 corresponds to early posttreatment, <6 months after treatment with BsAbs. Posttreatment setting 2 corresponds to late posttreatment, >6 months after treatment with BsAbs.

Twenty-four patients (22%) received a median of 2 extra vaccine boosters (range, 1-5) after a median of 5 months (range, 0.3-27.3) after the completion of BsAbs therapy, with a trend to a higher humoral response rate in the available samples (Figure 2).

SARS-CoV-2 infection

SARS-CoV-2 infection was diagnosed in 56 patients (51%; Table 2); 5 patients were diagnosed in 2020, 2 in 2021, and 49 in 2022. Among them, 27 patients (48%) developed the infection during BsAbs treatment (median, 3 months [range, 0-42]; from treatment initiation), whereas 29 patients (52%) developed the infection after treatment completion (median, 12 months [range, 3-12]). SARS-CoV-2 infection was diagnosed by nasopharyngeal swab in 47 patients (84%), whereas 9 patients (16%) were diagnosed as having asymptomatic infection after a positive result for the SARS-CoV-2 N antigen. We identified 21 cases (38%) of the SARS-CoV-2 Omicron variant and 1 case (2%) of the SARS-CoV-2 Delta variant.

At the time of SARS-CoV-2 infection, 21 patients (38%) had a lymphocyte count of $<1 \times 10^9$/L, 11 patients (18%) had IgG levels of <700 mg/dL, 12 patients (20%) had IgM levels of <40 mg/dL, and 7 patients (11%) had IgA levels of <70 mg/dL. Blood samples were available for humoral response evaluation in 43 patients, all of whom had received a median of 3 vaccine doses. Of these, 33 patients (77%) had no detectable antibodies, whereas 10 patients (23%) had anti-S antibodies at the time of infection.

Regarding disease status at the time of SARS-CoV-2 infection, 6 patients (10%) were in a partial response, 27 patients (44%) were in complete remission, 1 patient (2%) had stable disease, and 3 patients (5%) had progressive disease. Response assessment was not available for 24 patients (40%).

Among all patients diagnosed with SARS-CoV-2 infection, the median time to the first negative PCR was 36 days (range, 1-386). Prolonged viral shedding was observed in 20 patients (36%), with a median time to the first negative PCR of 74 days (range, 23-386). Eleven patients with prolonged viral shedding (55%) were diagnosed as having the SARS-CoV-2 Omicron variant. Nine patients (16%) had a second episode of SARS-CoV-2 infection, with sequencing confirming reinfection in 2 patients and reactivation or relapse in 7 patients. Patients who were diagnosed as having reinfection were infected by Omicron variants (BF.1, BA.2.23), and 5 of the 7 cases of reactivation or relapse were caused by SARS-CoV-2 Omicron variants. The median time to first negative PCR was 48 days for those with a second infection (range, 5-180). Reinfection with different Omicron variants (BA.2.23 and BA.5.2) was observed at 3 and 6 months after the initial infection.

In patients undergoing active BsAbs treatment, COVID-19 led to delays in 78% of cases and discontinuations in 19%. Regarding patients diagnosed as having prolonged viral shedding, 5 patients (5/20 [25%]) were diagnosed during BsAbs and interrupted therapy with a median time of interruption of 112 days (range, 70-280) and 2 patients (10%) discontinued BsAbs therapy definitely.

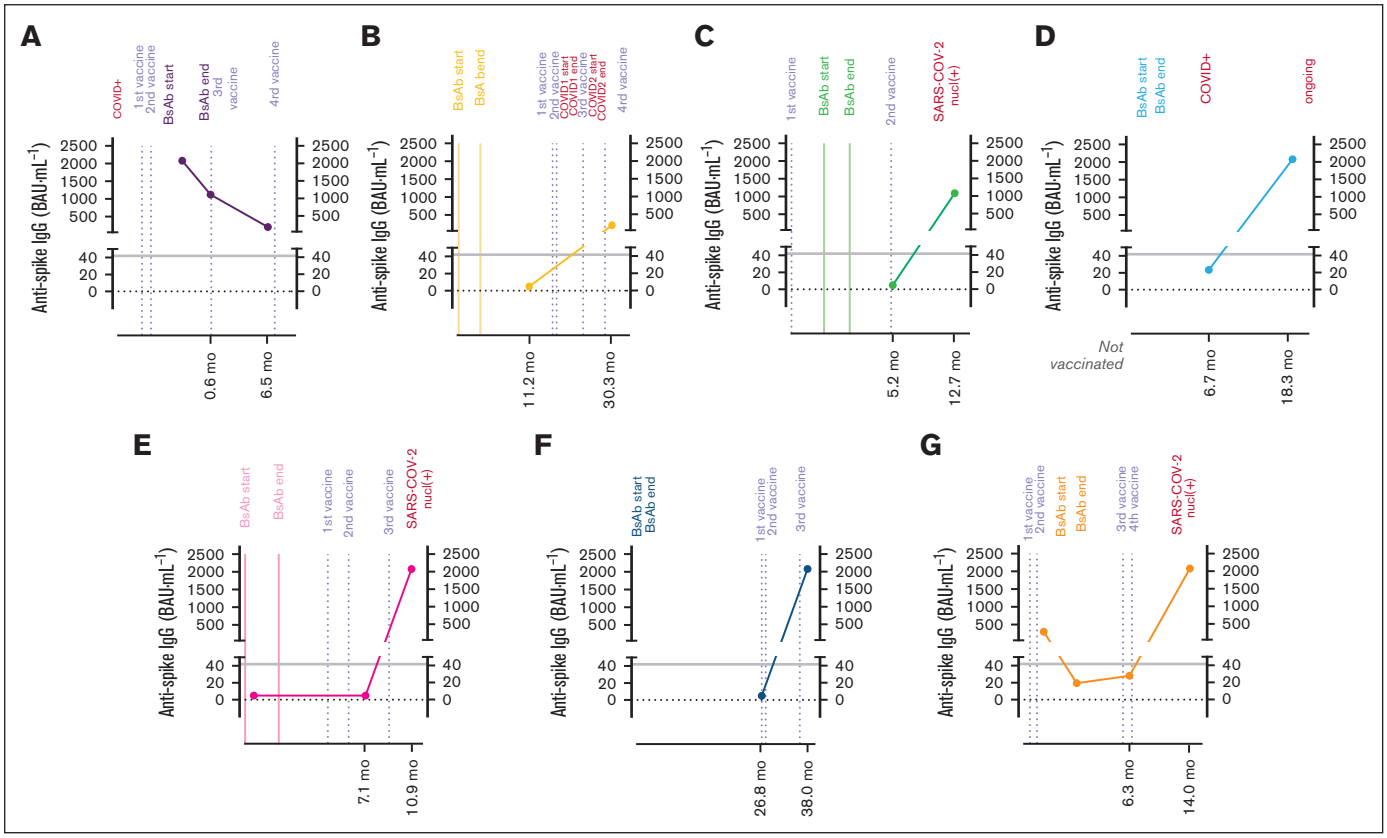

Figure 2. Seroconversion rate evolution of patients with blood samples obtained with a median of 6 months from the end of BsAbs treatment. Posttreatment setting 2 corresponds to late posttreatment (>6 months after treatment with BsAbs), the figure also shows the moment of COVID vaccination, time of administration of BsAbs treatment, titers of seroconversion based on measurement of anti-S protein levels, and the moment of SARS-CoV-2 infection (A-G).

COVID-19 severity

Among the 56 patients diagnosed as having COVID-19, 9 patients (16%) were asymptomatic, 9 patients (16%) had mild symptoms, 20 patients (36%) had moderate symptoms, 11 patients (20%) presented severe symptoms, and 7 patients (12%) experienced critical SARS-CoV-2 infection. All the patients who died had negative serology at the time of infection and had received a median of 3 COVID-19 vaccine doses before or during BsAbs treatment.

The rates of asymptomatic/mild infection were lower among patients diagnosed as having SARS-CoV-2 infection during BsAbs treatment or in the early posttreatment period (33.3% and 23.1%, respectively) than those patients who were infected in the late posttreatment period (37.5%; Figure 3).

Concerning factors influencing COVID-19 severity, no associations were found between lymphopenia, low immunoglobulin levels, or treatment with remdesivir or nirmatrelvir/ritonavir and disease severity in our cohort. Milder infections were significantly related to positive anti-S serology at the time of infection ($P = .01$), administration of more than 3 vaccine doses ($P = .04$), and positive humoral vaccine-induced immunogenicity ($P = .03$; Figure 4). Asymptomatic patients were excluded from this analysis owing to the lack of serologic data at the time of infection.

In the entire cohort, after a median follow-up of 34.3 months, 34 patients had died (31%). The most frequent cause of death was disease progression (n = 20 [59%]). The second cause was COVID-19 pneumonia, responsible for 7 deaths (21%, including 4 patients who were in complete remission). Other causes of death included other infections: 2 cases of enterocolitis and 2 cases of necrotizing fasciitis. In 3 patients, the cause of death remained unknown.

In our series, we identified 18 patients with severe COVID-19, including 11 severe and 7 fatal cases. Among them, 13 patients were diagnosed as having diffuse large B-cell lymphoma, 4 diagnosed as having FL, and 1 diagnosed as having MCL. The median number of previous treatment lines was 2 (range, 0-4). Seven patients received BsAbs as monotherapy, whereas 11 patients received BsAbs in combination with other agents: 5 patients with polatuzumab, 3 with lenalidomide, 2 with atezolizumab and obinutuzumab, and 1 with polatuzumab plus chemotherapy. Regarding vaccination, 10 patients were vaccinated before starting BsAbs therapy, 5 were vaccinated while on treatment with BsAbs, and 3 were vaccinated after completing BsAbs treatment. The median number of vaccine doses was 3 (range, 0-5). Four patients were not vaccinated because they refused vaccination; 2 of them presented a severe disease, and the other 2 a fatal disease.

Table 2. Clinical characteristics of the patients diagnosed as having SARS-CoV-2 infection

SARS-CoV-2 infection	% (range)	Total (N=56), n/N
No	49	53/109
Yes	51	56/109
COVID-19 severity		
Asymptomatic	16.1	9/56
Mild	16.1	9/56
Moderate	35.7	20/56
Severe	19.6	20/56
Critical	12.5	7/56
COVID-19 treatment		
No treatment	30.4	17/56
Treatment	69.6	39/56
COVID-19–specific treatment		
Remdesivir	76.9	30/39
Sotrovimab	51.3	20/39
Tocilizumab	25.6	10/39
Convalescent plasma	33.3	13/39
Paxlovid	28.2	11/39
First SARS-CoV-2 infection, median days for negativization (range)	36.0 (1.0-386.0)	
Second SARS-CoV-2 infection, median days for negativization (range)	47.5 (5.0-180.0)	
SARS-CoV-2 infection during treatment		
No	51.8	29/56
Yes	48.2	27/56
SARS-CoV-2 infection after treatment		
No	48.2	27/56
Yes	51.8	29/56
BsAbs treatment interrupted		
No	22.2	6/27
Yes	77.7	21/27
BsAbs treatment discontinued		
No	81.5	22/27
Yes	18.5	5/27

Among the 11 severe cases, COVID-19 was diagnosed during BsAbs therapy in 3 patients, in the early posttreatment setting in 3 patients, and in the late posttreatment setting in 5 patients. At the time of SARS-CoV-2 infection, only 2 patients had positive serology (1 patient who got infected during treatment and the other one in the late posttreatment). Remdesivir was administered to 8 patients, tocilizumab to 4, and nirmatrelvir/ritonavir to 1 patient. No IV immunoglobulins were administered.

Regarding the 7 fatal cases, COVID-19 was diagnosed during BsAbs therapy in 4 patients, in the early posttreatment setting in 2 patients, and in the late posttreatment setting in 1 patient. All 7 patients had negative serology at the time of SARS-CoV-2 infection. Remdesivir was administered to 5 patients, and tocilizumab to 4. No IV immunoglobulin was administered.

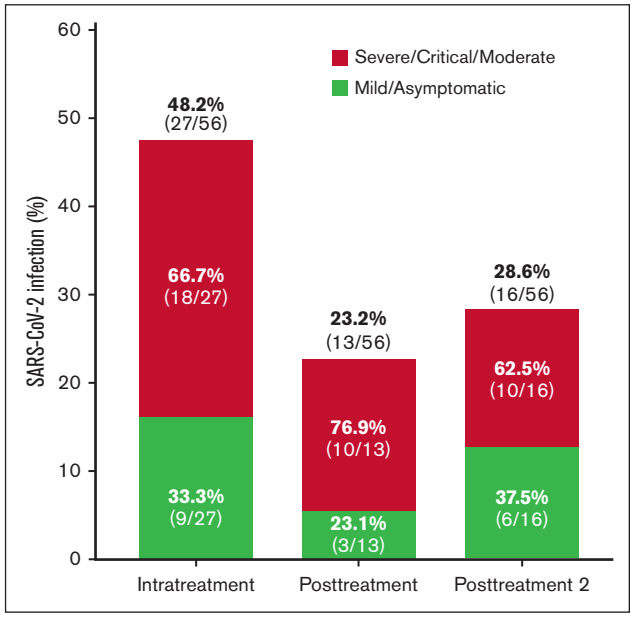

Figure 3. Severity of COVID-19 according to the time of infection of patients treated with BsAbs.

Discussion

The risk of mortality from COVID-19 among patients with hematologic malignancies is significantly higher than in the general population.[35,36] Despite clinical trials proving the humoral and cellular immunogenicity of various COVID-19 vaccines, the lack of immunocompromised individuals in these studies hinders the capability to predict vaccine efficacy in hematologic patients,[37-41] particularly in the context of novel therapeutic approaches, such as BsAbs and CAR T-cell therapy. A previous study conducted by our group revealed that patients with hematologic malignancies exhibit inferior humoral and cellular responses compared with healthy individuals.[42] In addition, other studies described factors associated with an inferior humoral response, including a diagnosis of lymphoma, previous exposure to anti-CD20 monoclonal antibodies, lymphopenia, and low immunoglobulin levels at the time of vaccination.[43,44]

In this cohort, all patients previously treated with BsAbs treatment for whom assessment of humoral response data was available showed a decline in the anti-S antibody levels during and upon completion of BsAbs treatment. Nevertheless, levels of S glycoprotein increased after a median of 6 months after treatment, suggesting an improvement in humoral immunity after this time point. This amelioration in humoral immunity was further demonstrated by the antibody responses achieved after additional vaccine boosters in the late post-BsAbs treatment phase. The improvement in anti-S levels observed 6 months after treatment completion can be attributed to immune recovery after B-cell-depleting therapies, with a higher humoral response after vaccination and SARS-CoV-2 infection, particularly for these patients who received vaccine boosters or were diagnosed as having SARS-CoV-2 infection after this time point.

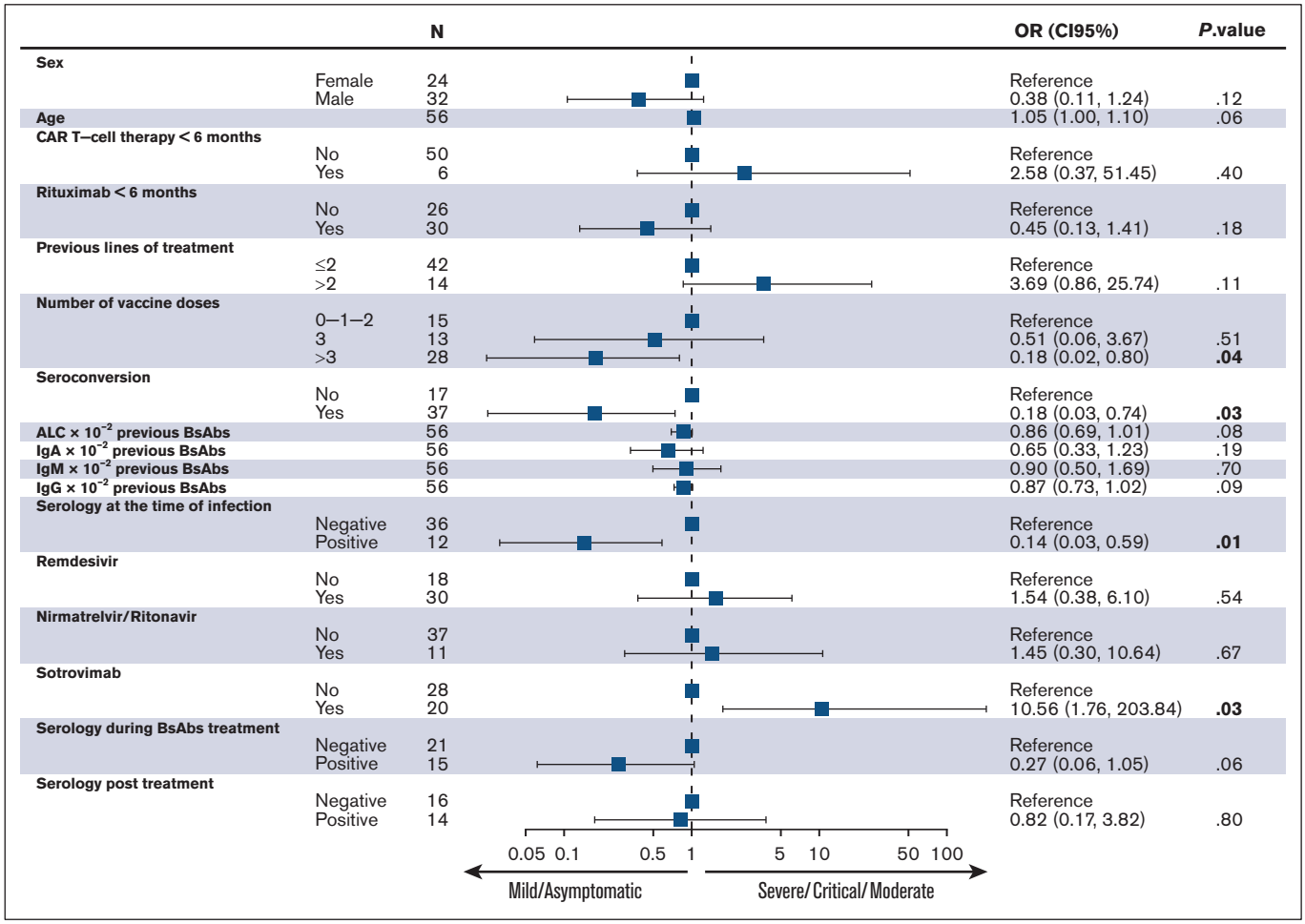

Figure 4. Univariate analysis regarding factors affecting COVID-19 severity. ALC, absolute lymphocyte count; CI, confidence interval; OR, odds ratio.

A high rate of moderate, severe, and critical COVID-19 was observed in patients with SARS-CoV-2 infection during or right after BsAbs treatment (early posttreatment setting). This increased susceptibility may be associated with the reduced immunogenicity observed during BsAbs therapy or in the initial months after its completion. Notably, treatment with anti-CD20 agents has been consistently linked with an insufficient humoral response after vaccination, whereas cellular response remains preserved.[45] Patients who received ≥3 vaccine doses and those who presented seroconversion presented a milder infection; noteworthy, all the patients with asymptomatic COVID-19 in our series had a positive serology at the time of infection. In our cohort, 7 patients (6%) died owing to COVID-19, all of them with a negative serology at the time of infection.

Among critical cases, 2 patients diagnosed as having the SARS-CoV-2 Omicron variant and 1 patient with the SARS-CoV-2 Delta variant died. Previous reports have shown that infection with Omicron in patients with hematologic malignancies was associated with considerable mortality.[46,47] However, in our cohort, we did not find differences according to Omicron and Delta variant cases for prolonged viral shedding, COVID-19 severity, and BsAbs discontinuations compared with patients who were not diagnosed as having these specific variants (supplemental Table 1).

In our study, 20 patients (36%) presented prolonged viral shedding, with SARS-CoV-2 RNA detection longer than 3 weeks. This percentage was higher than that observed in other reports.[48,49] Persistent SARS-CoV-2 infection was frequently observed in our cohort, as is common with patients with B-NHL treated with anti-CD20 agents.[50] A recently published series of patients treated with BsAbs and subsequently consolidated with allogeneic SCT showed a high rate of mortality owing to infections, although no COVID-19 was reported in this series.[51] In our series, 5 patients (5/20 [25%]) with prolonged viral shedding during BsAbs interrupted therapy with a median of 112 days of BsAbs interruption, and 2 patients (10%) discontinued BsAbs therapy definitely. It is unclear how to manage these cases, especially for those asymptomatic patients. In our cohort, we stopped BsAbs treatment, and patients received specific therapy for COVID-19. In patients with persistently positive controls, the management was individualized. Initially, we did not recommend restarting BsAbs until viral replication was cleared and assessed with a negative PCR. Discussion is open for those patients who remain asymptomatic and have been vaccinated properly.

A meta-analysis including 27 studies had been recently published evaluating infection outcomes in >2000 patients diagnosed as having B-NHL and treated with BsAbs, which showed 20% of patients presenting grade ≥3 infections. Only 8 studies revealed data regarding severe infections owing to COVID-19. Viral infections were the most common cause of grade 5 infections, largely driven by COVID-19 mortality (91% of viral infections). Nevertheless, in this systematic review, no humoral assessment and immunogenicity analysis were performed. No follow-up of the infections was reported either.[52] Our mortality rate of 6% is consistent with previous death rates related to COVID-19 in other series,[53] which have also evaluated SARS-CoV-2 infection in vaccinated patients with B-cell lymphoma after BsAbs. These rates are lower than other reports,[17,54] and we suggest that this difference in mortality could be explained because our population received a higher median number of vaccine doses administered, facilitated by broader access to vaccines and booster doses. Importantly, in our cohort, 2 patients died owing to SARS-CoV-2 infection and they were not vaccinated, because they refused it. Our results suggest that this population benefits from vaccination, with serologic status being assessed by measuring anti-S titers at the time of infection, one of the most important risk factors for COVID-19 severity. Receiving >2 previous lines of treatment or previous rituximab administration within the last 6 months was not statistically associated with more severe disease, which contrasts with previous reports.[54]

These findings highlight the importance of vaccination in immunocompromised patients undergoing B-cell-depleting therapies. We suggest that vaccination should be mandatory for patients with B-NHL receiving BsAbs. Furthermore, serologic status should be assessed before, during, and after BsAbs treatment to monitor the immune status of these patients and guide the administration of vaccine boosters if needed.

Limitations of this study include its retrospective design and the absence of standardized protocols for determining anti-S titers in routine clinical practice for patients with these characteristics.

In conclusion, we presented a large series of patients treated with BsAbs and evaluated their outcomes related to SARS-CoV-2 infection. COVID-19 had a significant impact on these patients, leading to prolonged viral shedding and causing therapy delays or permanent discontinuations of therapy. As previously observed in patients treated with anti-CD20 monoclonal antibodies, BsAbs treatment was associated with a reduced seroconversion rate for at least 6 months, which was associated with increased disease severity and mortality. SARS-CoV-2 infection must be carefully considered when managing patients receiving B-cell-depleting therapies. It is vital to follow recommendations regarding vaccination and booster doses to mitigate severe COVID-19 in this high-risk population.

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Authorship

Contribution: Á.S., V.N., and P.A. conceived and designed the study; Á.S. and J.I.-T. provided study materials or patients and collected and assembled data; Á.S., V.N., M.J., and P.A. analyzed and interpreted the data; and all authors wrote and gave final approval to the manuscript and are accountable for all aspects of the work.

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