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COVID-19 Breakthrough Infections in Vaccinated Patients With CLL in Israel

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Patients with chronic lymphocytic leukemia (CLL) are more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and increased risk of death from coronavirus disease 2019 (COVID-19).[1] These poor outcomes relate to inherent immune defects associated with the CLL itself and due to anti-CLL therapy administered.[2] Furthermore, it has been suggested that CLL is associated with a reduced immune response to COVID-19 vaccination that depends on disease activity and treatment.[3,4] The pivotal BNT162b2 mRNA COVID-19 vaccine phase III trial excluded patients treated with immunosuppressive therapies and those with immunocompromised disorders.[5,6] In this study, we investigated the clinical efficacy of primary BNT162b2 mRNA COVID-19 vaccination in patients with CLL in a real-world setting, using a large health provider database.

Maccabi Healthcare Services (MHS) is a nationwide state-mandated health provider representing a quarter of the population in Israel, with similar demographics to the national population. The MHS database contains longitudinal data on a stable population of 2.5 million members since 1993, including around 200,000 infected with SARS-CoV-2 and 1.4 million vaccinated members, as of March 31, 2021. We used this well-established database to assess the clinical effectiveness of BNT162b2 mRNA COVID-19 vaccination in patients with CLL who received the first dose between December 19, 2020, and February 28, 2021. We included SARS-CoV-2 infections up to March 31, 2021, when the alpha variant was found in the most of sequenced SARS-CoV-2 in Israel, in order to include in the study only infected patients from the specific variant. We excluded CLL patients who had a documented positive SARS-CoV-2 before December 1, 2020, and CLL patients who were diagnosed after November 2020 or joined MHS after February 2020, due to the inability to determine whether they were infected before joining MHS. The primary outcome was the incidence rate of a SARS-CoV-2 infection confirmed by a positive reverse transcription-polymerase chain reaction (RT-PCR) assay on nasopharyngeal swabs. During the study period, all patients were tested for COVID-19 by RT-PCR, while antigen tests were not available in Israel. The RT-PCR tests were performed either in the community clinics of Maccabi HMS or in hospitals. All RT-PCR results were reported centrally to the database of Maccabi HMS. Patients were stratified by CLL treatment status before vaccination: treatment naive, on-therapy (at the time of SARS-CoV-2 infection or within the prior 3 months, except for anti-CD20 within the last 12 months) and previously treated (off-therapy). Disease severity (hospitalization or intensive care unit [ICU] admission within 1 month from the positive RT-PCR test) and mortality in CLL patients within 3 months from the positive RT-PCR test and until April 30, 2021, were also collected. The primary outcome of number and incidence density rate per 10,000 person-day (PD) of SARS-CoV-2 infections was evaluated according to periods. To mitigate threat of biases and unmeasured confounders between vaccinated and unvaccinated patients, we have utilized the risk-interval cohort study design where time intervals within the same individual are used to classify a person as exposed or unexposed. In this risk-interval design analysis, incidence rates for risk and reference time periods are compared.[7] The reference period was determined from December 1, 2020, until the sixth day after first dose administration or until March 31, 2021, for vaccinated and unvaccinated patients, respectively. This is based on the results of the phase III trial that found no vaccine effectiveness in the week after first dose.[5] The protection period was defined as days 7–28 after the second dose, or until March 31, 2021. Patients with a positive RT-PCR during the reference period and until the sixth day after the second dose were excluded from the protection period (Suppl. Figure S1).

A total of 2282 patients with CLL were included in the study; 2067 (90.6%) were vaccinated with at least 1 dose and 2030 (89.0%) were vaccinated with 2 doses during the study period (Suppl. Figure S1). In accordance with the guidelines of the Israeli Ministry of Health, none of the patients received a booster or 3-shot primary vaccination during the study period. All patients were included in the reference period, 1004 were female (44%), mean aged 70.7±13.0, and 2028 (88.9%) patients were included in the protection period (patients' baseline demographic and clinical characteristics are summarized in Suppl. Table S1). There were no differences in the baseline complete blood counts, creatinine, lactate dehydrogenase, albumin, β-2-microglobulin, and serum immunoglobulin levels between the reference and protection period (Suppl. Table S1). Other

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comorbidities at index date included hypertension (n = 1272, 55%), chronic kidney disease (n = 1057, 46.3%), obesity (n = 672, 29.4%), diabetes mellitus (n = 597, 26.2%), and cardiovascular disease (n = 466, 20.4%) (Suppl. Table S2). At the date of first dose, most of the patients were treatment naive (n = 1669, 73.1%), 329 (14.4%) off-therapy, and 284 (12.4%) on-therapy (10 were treated with chemotherapy, 37 with chemotherapy plus anti-CD20 antibodies, 168 with Bruton tyrosine kinase inhibitors [BTKis], 21 with venetoclax monotherapy, and 48 with venetoclax plus anti-CD20 antibodies, Suppl. Table S3).

In the reference period, 28 SARS-CoV-2 infections were observed (2.65 per 10,000 PD), compared with 6 SARS-CoV-2 infection cases during the protection period (1.44 per 10,000 PD). The protective effect of vaccination was 46%, but not reached a statistical significance (95% confidence interval, 31%-78%). Overall, 21 were symptomatic (1.99 per 10,000 PD) in the reference period compared with 5 cases (1.20 per 10,000 PD) in the protection period (Table 1).

Among the 28 patients with SARS-CoV-2 infection in the reference period 15 (53.6%) were hospitalized, including 4 (14.3%) in ICU, and 10 (35.7%) died within 3 months from the diagnosis of COVID-19 (all-cause mortality). Among the 6 patients with SARS-CoV-2 infection in the protection period, 3 were hospitalized (50%), of which 1 (16.7%) in ICU, and 1 (16.7%) died (Table 1).

During the reference period, SARS-CoV-2 infections occurred in 21 treatment-naive patients (2.69 per 10,000 PD), in 6 patients on-therapy (4.51 per 10,000 PD) and in 1 patient off-therapy (0.70 per 10,000 PD). Among the patients on therapy infected with SARS-CoV-2 in the reference period, 3 were treated with chemotherapy plus anti-CD20 antibodies (17.33 per 10,000 PD), 2 with BTKis (2.71 per 10,000 PD), and 1 with venetoclax plus anti-CD20 antibody (3.72 per 10,000 PD) (Suppl. Table S4). In the protection period, 4 patients with SARS-CoV-2 infection were treatment-naive, one on-therapy and another off-therapy, with similar rates of 1.32, 1.62, and 1.93 per 10,000 PD, respectively (Suppl. Table S5).

In summary, we evaluated the clinical effectiveness of primary BNT162b2 mRNA COVID-19 vaccination in patients with CLL in a real-world setting and our results indicate that a week after the second BNT162b2 vaccine dose, the risk of SARS-CoV-2 infection and symptomatic COVID-19 decreased by 46% and 40%, respectively. The hospitalization and ICU admission rates were relatively high (~50% and ~15%, respectively), both in the protection and the reference periods, while the COVID-19–related deaths, although not statistically significant, declined from 35.7% in the reference period to 16.7% in the protection period. Patients with CLL infected with SARS-CoV-2 are known to have an increased risk for severe disease and death from COVID-19.[8,9] During the early phase of the pandemic, the reported risk of death in CLL patients with symptomatic SARS-CoV-2 infection ranged between 29% and 33%,[8,9] which is comparable to the mortality rate observed in the reference period. Furthermore, the lower mortality during the protection period reconciles with the 30-day case fatality rate of 12.5% reported in vaccinated patients with hematologic malignancies. Even though the statistical power of our study was limited by relatively low number of events in each cohorts, the clinical protection against COVID-19 after two-BNT162b2 vaccine doses seems to be substantially lower in patients with CLL (40%) compared with the 95% protection reported in the pivotal phase III BNT162b2 vaccine trial.[5] The relatively high rate of SARS-CoV-2 breakthrough infections in patients with CLL is consistent with the poor immune response to COVID-19 vaccination in this population. Recent report[10] showed increased risks of breakthrough SARS-CoV-2 infection, severe disease, hospitalizations, and death among vaccinated patients with hematologic malignancies without a subdivision into lymphomas and CLL. Importantly, active treatment for CLL was particularly associated with increased risk of breakthrough SARS-CoV-2 infections (4.51 per 10,000 PD compared with 2.69 per 10,000 PD for naive patients); this finding, although based only on 6 cases, is consistent with the reduced antibody immune response to COVID-19 vaccination in patients treated with B-cell–targeted therapies.[3,4]

Our study has several limitations; first, this is a retrospective study with a potential bias related to underreporting in the patients' electronic medical records (eg, mild COVID-19 cases) although this is unlikely due to highly accessible PCR testing during the study period. Second, some of the COVID-19 parameters that may affect the patients' outcomes have not been considered, including the serology response to the BNT162b2 mRNA vaccine, COVID-19 severity, and anti-COVID-19 treatments during hospitalization. However, the main strength of our study is relying on a nationwide database, allowing us to investigate a large number of patients compared with other retrospective studies.

In conclusion, primary BNT162b2 mRNA COVID-19 vaccination is significantly associated with a reduced risk of SARS-CoV-2 breakthrough infections among patients with CLL.

Table 1

COVID-19 Outcomes According to Periods

	Reference period n = 2282		Protection period n = 2028	
	Cases	Rate per 10,000 PD	Cases	Rate per 10,000 PD
COVID-19 infection	28	2.65	6	1.44
Symptomatic COVID-19	21	1.99	5	1.20
	Reference period n = 2282		**Protection period n = 2028**	
	n	**% from cases**	**n**	**% from cases**
COVID-19 hospitalization[a]	15	53.6	3	50.0
COVID-19 ICU admission	4	14.3	1	16.7
COVID-19 death[b]	10	35.7	1	16.7

[a]Hospitalization within 1 mo from the positive PCR test or in a COVID-19 ward at any given time after the positive PCR test.

[b]Death within 3 mo from the positive PCR test, relevant only for COVID-19–infected patients.

COVID = coronavirus disease 2019; PCR = polymerase chain reaction; PD= patient days.

AUTHOR CONTRIBUTIONS

All authors participated in the study design or/and in study research and interpretation of data; or/and writing, reviewing, and approving this manuscript for submission.

DISCLOSURES

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