Title: Bebtelovimab for high-risk outpatients with early COVID-19 in a large US health system

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Abstract:

There are limited data for the clinical efficacy of bebtelovimab in preventing severe COVID-19. Among outpatients unable to take nirmatrelvir-ritonavir at a large health system, 10 of 377 (2.7%) patients who received bebtelovimab and 17 of 377 (4.5%) matched untreated patients were hospitalized or died. The 43% observed risk reduction with bebtelovimab was not statistically significant (p = 0.14).

Introduction:

Prompt treatment of COVID-19 with monoclonal antibodies binding to the SARS-CoV-2 protein has been found to reduce hospitalization in clinical trials of unvaccinated patients and observational studies of vaccinated patients.[1] However, ongoing SARS-CoV-2 evolution with

substantial amino acid substitutions and deletions in the spike protein have reduced neutralizing activity,[1] and clinical effectiveness,[2] of monoclonal antibodies authorized by the Food and Drug Administration (FDA). In February 2022, the FDA authorized bebtelovimab,[3] a novel monoclonal antibody with retained neutralization activity against Omicron and Omicron subvariants, based on non-clinical data and a trial observing faster nasopharyngeal viral clearance but unable to assess efficacy in preventing severe disease.[4] In April 2022 with the predominance of the Omicron variant BA.2, bebtelovimab became the only SARS-CoV-2 monoclonal antibody authorized for treatment of COVID-19 in the United States.

In response to an Omicron BA.2 wave, Mass General Brigham, a large healthcare system in Massachusetts and New Hampshire, began providing intravenous antiviral remdesivir or bebtelovimab to high-risk COVID-19 outpatients with contraindications to oral antiviral treatment with nirmatrelvir plus ritonavir. Remdesivir was preferred in accordance with national and local guidance; however, providing the required 3 daily infusions became impracticable in the context of an intense wave among vulnerable patients and frequent patient refusal due to cost and logistical concerns. Consequently, we sought to understand the clinical effectiveness of bebtelovimab in preventing hospitalization and death to inform approach to the ongoing BA.5 wave.

Methods:

Patients

We utilized electronic health records (EHR) from the seven Mass General Brigham hospitals and associated ambulatory care centers for adult patients with incident COVID-19 diagnosis between March 16 and May 31, 2022. We excluded patients at lower risk of severe disease (Monoclonal Antibody Screening Score [MASS], a comorbidity index predictive COVID-19 hospitalization, of 3 or less),[5] patients diagnosed in the context of hospital admission, patients who received an alternate recommended outpatient therapy for COVID-19 (nirmatrelvir plus ritonavir, remdesivir, or molnupiravir), patients who received bebtelovimab outside of Mass General Brigham, and patients who were not residents of Massachusetts or New Hampshire. All potentially eligible records were individually reviewed by two investigators prior to inclusion.

Analysis

We performed a retrospective matched analysis of high-risk patients that did and did not receive bebtelovimab for outpatient treatment of early COVID-19 to estimate the average treatment effect. Initially we attempted exact matching on age, vaccination status, recent vaccination, and transplant status. However, the resulting cohort was imbalanced by race and ethnicity and treated patients could not be fully matched. We subsequently utilized exact matching on history of solid organ or stem cell transplant followed by 1:1 nearest neighbor propensity score matching without replacement, which successfully matched all bebtelovimab treated patients and yielded sufficient balance (Supplementary Table 1). A logistic model included age (18 to 49, 50 to 64, 65 to 79, or 80 and older), MASS score (4 and 5 or 6 or

greater), vaccination status (unvaccinated, partially vaccinated, vaccinated, or vaccinated and boosted), timing of most recent vaccination (within last 20 weeks or more than 20 weeks), self-reported race and ethnicity (White non-Hispanic/Latinx or all other races and ethnicity), known contraindication for nirmatrelvir plus ritonavir, and history of solid organ or stem cell transplant.

The primary endpoint was composite of all-cause hospital admission within 14 days and/or death within 28 days of their first positive SARS-CoV-2 test (including home antigen tests). We used a modified Poisson model using robust error variance[6] and general estimating equations[7,8] to estimate relative risk reduction with bebtelovimab compared with no treatment. Two-sided tests using a significance threshold of $p < 0.05$ was used. We estimated greater than 80% power to detect an 85% reduction in risk similar to that observed in the trial of sotrovimab.[9]

Results:

Study population and treatment

Between March 16 and May 31, 2022, 5451 outpatients with COVID-19 met study criteria as potentially eligible for bebtelovimab (Supplementary Figure 1). A total of 377 outpatients were treated at Mass General Brigham and were matched 1:1 with 377 patients who were not treated. Treated patients received bebtelovimab a median of 3 days following diagnosis (interquartile range 2 to 3 days). Bebtelovimab was well tolerated and there were no reported adverse events associated with administration of bebtelovimab in this cohort. Characteristics of bebtelovimab recipients and matched non-recipients were similar in comorbidity score,

vaccination receipt, age, race and ethnicity, most individual comorbidities, and date of diagnosis (Table 1). However, patients with heart disease or stroke (p = 0.007) and those with rheumatologic or inflammatory bowel disease (p = 0.06) were relatively under-represented among non-recipients. During the study period, Omicron subvariants BA.2 and BA.2.12.1 accounted for 90% and B.1.1.529 or BA.1 with 9% of sequenced viruses submitted to GISAID from Massachusetts.[10]

Hospitalization and deaths

Among the 754 patients included in the analysis, 24 patients (10 bebtelovimab and 14 untreated) were admitted within 14 days of COVID-19 diagnosis. Admissions occurred a median of 8.5 days (IQR 3 to 12 days) following COVID-19 diagnosis among bebtelovimab treated patients and 2 days (IQR 1 to 4.5 days) among untreated patients. Three patients died within 28 days (all in bebtelovimab untreated group). The primary endpoint of hospitalization or death occurred in 10 (2.7%) bebtelovimab patients and 17 (4.5%) bebtelovimab untreated patients. In the primary analytic model, bebtelovimab was associated with a trend toward decreased risk of hospitalization or death (risk ratio 0.57, 95 CI% 0.28 to 1.19), but this finding was not statistically significant (p = 0.14). The observed magnitude of reduction in risk of hospitalization and deaths was similar across groups of patients (Figure 1).

Discussion:

In this analysis of observational data from high-risk patients with COVID-19, we identified an estimated 43% reduction in risk of hospitalization or death associated with receipt of the

monoclonal antibody bebtelovimab compared with matched patients who did not receive outpatient treatment for COVID-19. Importantly, this observation did not meet the pre-specified threshold for statistical significance and could have been observed by chance in the absence of a true association. The estimated magnitude of protection is similar to the 45% reduction estimated for nirmatrelvir plus ritonavir in another study conducted at Mass General Brigham.[11]

In vitro assays indicate that bebtelovimab effectively neutralizes the currently prevalent Omicron subvariants including BA.4 and BA.5,[1] but the observed risk reduction was lower than observed in trials and observational studies of other monoclonal antibody therapies. Several reasons may account for the observed decreased risk reduction. First, risk of severe COVID-19 is lower in the context of prevalent vaccination and prior infection even among the high-risk population included in this analysis. Hospitalization or death occurred in 4.5% of untreated patients whereas in a largely unvaccinated cohort of high-risk COVID-19 patients from the same hospital system in 2020 to 2021, 12.2% untreated patients were hospitalized or died.[12] The incremental clinical benefit of treatment among lower risk individuals may be smaller, which is similar to the lower risk reduction of oral nirmatrelvir plus ritonavir observed in contemporary contexts.[11,13] One uncontrolled study found similar risk of severe COVID-19 between patients treated with bebtelovimab and those treated with nirmatrelvir plus ritonavir.[14] Second, patients received bebtelovimab a median of 3 days after diagnosis while trial participants received treatment more promptly.[9,15,16] Third, patients with improving COVID-19 symptoms were observed to decline bebtelovimab or cancel infusions, potentially introducing bias. Finally,

bebtelovimab could have lower clinical effectiveness than formerly-authorized monoclonal antibodies due to treatment-emergent resistant variants (5.5% observed in BLAZE-4 trial[3]) or other mechanisms. An observational study among 92 solid organ transplant recipients did not detect reduced clinical effectiveness compared with 269 patients who had received sotrovimab,[17] but the study was not designed to establish equivalence and was conducted during period when efficacy of sotrovimab could have been compromised by resistant variants.

The findings of this analysis should be considered in the context of the study limitations. While matching resulted in cohorts with balanced predictors of progression to severe COVID-19, the factors guiding clinician decision to recommend monoclonal antibody and the patient's willingness and ability to accept treatment are incompletely captured in available data and may contribute to residual bias. Additionally, receipt of bebtelovimab or hospitalizations outside of Mass General Brigham and not captured in the EHR would contribute to misassignment of exposure and outcome. The sample size was selected with the hypothesis of an 85% reduction in the primary end point, composite of all-cause hospitalization within 14 days and/or death within 28 days. This magnitude of risk reduction was not observed.

In the context of rapid emergence of novel SARS-CoV-2 variants, trials evaluating efficacy of monoclonal antibodies in preventing severe disease are infeasible. Use of observational data to emulate these trials is expected to remain important to direct clinical care, but future analyses should plan for lower incidence of severe disease, and potentially lower risk reduction, when planning sample size.

In conclusion, among high-risk patients unable to receive the recommended oral option for COVID-19, bebtelovimab was safe and appeared to offer a similar level of protection as nirmatrelvir plus ritonavir against hospitalization and death.

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Author contributions. S.D.P. and A.E.W. designed the study. S.D.P., A.K., M.J., and A.E.W. collected and adjudicated the data. S.D.P., J.A.J., A.Y.K., L.R.B., and A.E.W. provided scientific interpretation of the data. S.D.P. and A.E.W. performed the statistical analysis. S.D.P., A.K., M.J., and A.E.W. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S.D.P. and A.E.W. drafted the manuscript. All

authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Patient consent statement. The authors attest that they are in compliance with the ethical standards of the Helsinki Declaration and human studies committees of the authors' institutions. The study was approved by the Mass General Brigham Human Research Committee institutional review board and informed consent was waived.

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Table 1. Baseline characteristics of included COVID-19 cases (March 16 to May 31, 2022)

Characteristic	Bebtelovimab	No bebtelovimab	p
No.	377	377	
Age group (%)			0.937
18 to 49	23 (6.1)	23 (6.1)	
50 to 64	79 (21.0)	72 (19.1)	
65 to 79	185 (49.1)	189 (50.1)	
80 and older	90 (23.9)	93 (24.7)	
Male sex (%)	180 (47.7)	170 (45.1)	0.511
Race and ethnicity (%)			0.404
Asian	6 (1.6)	6 (1.6)	
Black	9 (2.4)	13 (3.4)	
Hispanic or Latinx	14 (3.7)	10 (2.7)	
Other or unavailable	10 (2.7)	4 (1.1)	
White	338 (89.7)	344 (91.2)	
High SES vulnerability of zip code (%)	34 (9.0)	30 (8.0)	0.695
Vaccination status (%)			0.971
Vaccinated and boosted	310 (82.2)	306 (81.2)	
Vaccinated	47 (12.5)	49 (13.0)	
Partially vaccinated	3 (0.8)	4 (1.1)	
Unvaccinated	17 (4.5)	18 (4.8)	
Last vaccine dose more than 20 weeks prior (%)	287 (76.1)	300 (79.6)	0.293
Comorbidity score, MASS (median [IQR])	8 [6, 11]	8 [6, 11]	0.802
Age (median [IQR])	71 [64, 79]	71 [64, 79]	0.694
Solid organ transplant (%)	68 (18.0)	66 (17.5)	0.924
Stem cell transplant (%)	8 (2.1)	11 (2.9)	0.642

Table 1. Baseline characteristics of included COVID-19 cases (March 16 to May 31, 2022)

Characteristic	Bebtelovimab	No bebtelovimab	p
Body mass index (BMI) (%)			0.496
BMI less than 25 or unavailable	100 (26.5)	111 (29.4)	
BMI 25 to 30	129 (34.2)	112 (29.7)	
BMI 30 to 35	80 (21.2)	77 (20.4)	
BMI greater than 35	68 (18.0)	77 (20.4)	
Immunocompromise (%)	298 (79.0)	304 (80.6)	0.650
Diabetes (%)	150 (39.8)	156 (41.4)	0.711
Heart disease or stroke (%)	207 (54.9)	169 (44.8)	0.007
Pulmonary disease (%)	89 (23.6)	97 (25.7)	0.554
Bipolar, schizophrenia, and other disorders (%)	23 (6.1)	17 (4.5)	0.417
Depression and anxiety (%)	120 (31.8)	100 (26.5)	0.128
Hematologic malignancy (%)	38 (10.1)	34 (9.0)	0.710
Solid tumor malignancy (%)	214 (56.8)	226 (59.9)	0.416
Rheumatologic or inflammatory bowel disease (%)	70 (18.6)	50 (13.3)	0.059

Numbers are No. (%) unless otherwise noted. Immunocompromise includes patients with history of malignancy and patients on immunosuppressive medications. SES, socioeconomic status; MASS, Monoclonal Antibody Screening Score

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Subgroup	Bebtelovimab	No bebtelovimab	Hosp. or death rate among untreated	RR (95% CI)	Eff. mod. p-value
All	377	377	4.43%	0.57 (0.28 to 1.19)	
Age					0.336
18 to 49	23	22	15.79%	0.26 (0.03 to 2.15)	
50 to 64	79	73	2.82%	0.46 (0.05 to 4.36)	
65 to 79	185	190	2.15%	1.04 (0.34 to 3.23)	
80 and older	90	92	8.24%	0.29 (0.06 to 1.35)	
Vaccination status					0.977
Incompletely vaccinated or unboosted	67	71	2.9%	0.56 (0.05 to 5.88)	
Vaccinated and boosted	310	306	4.79%	0.56 (0.26 to 1.18)	
Vaccination timing					0.814
Last vaccine < 20 weeks prior	90	78	8.33%	0.58 (0.20 to 1.63)	
Last vaccine > 20 weeks prior	287	299	3.46%	0.51 (0.17 to 1.50)	
Comorbidity score					0.74
MASS 4 and 5	81	79	1.28%	0.98 (0.06 to 16.06)	
MASS 6 or greater	296	298	5.3%	0.55 (0.26 to 1.18)	
Immunocompromise status					0.497
Immunocompromise	298	304	7.14%	0.63 (0.29 to 1.37)	
No immunocompromise	79	73	4.29%	0.29 (0.03 to 2.76)	
Body mass index (BMI)					0.65
BMI less than 30 or unavailable	229	225	5.14%	0.51 (0.19 to 1.40)	
BMI 30 or greater	148	152	3.4%	0.68 (0.20 to 2.29)	

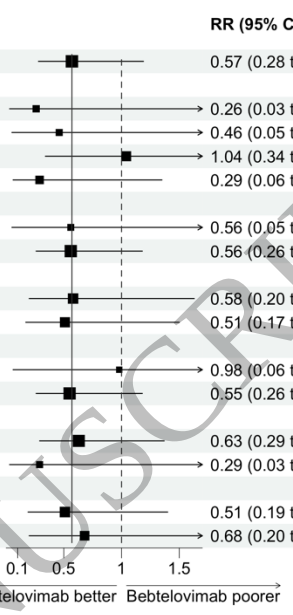

Figure 1
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Figure 1. Subgroup analysis of the risk ratio of hospitalization and/or death comparing patients prescribed and not prescribed bebtelovimab. Estimate and confidence interval calculated from a Poisson model using robust error variance[6] performed within in strata. Effect modification p-value calculated from nested models.