Vaccination Status and Prevalence of SARS-CoV-2 Infection in Immunocompromised Patients Receiving Tixagevimab/Cilgavimab in Minnesota

Sarah Lim[1], Keeley Morris[1], Lydia Fess[1], Miriam Muscoplat[1], Kathryn Como-Sabetti[1], Ruth Lynfield[1]
[1]Minnesota Department of Health, St Paul, MN, USA

Background

- Tixagevimab/cilgavimab (TC) is a combination of two long-acting monoclonal antibodies that inhibit SARS-CoV-2 spike protein attachment.
- TC was authorized for use by the Food and Drug Administration (FDA) in December 2021 for pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in patients with moderate to severe immune compromise who are not expected to develop a strong immune response to COVID-19 vaccination OR COVID-19 vaccination is contraindicated due to a history of severe adverse reaction.
- Additional data from observational studies has supported real-world effectiveness of TC in immunocompromised patients.
- TC is not recommended as a substitute for vaccination.
- We evaluated TC experience in Minnesota, including the incidence of possible breakthrough infections and the vaccination status of those receiving TC.

Methods

- Minnesota Department of Health (MDH) established a voluntary TC patient registry in December 2021 via secure REDCap form.
- In February 2022, FDA recommended increasing TC dose due to decreased neutralization activity against Omicron subvariants (BA.1 and BA.1.1).
- Questions were added to the survey form on whether the administered dose was a first dose or second top-up dose. However, since the survey was voluntary, complete data on all doses received was not available for all patients.
- The survey was closed on June 30th. Patients were matched to state COVID-19 case data on July 27th to examine the occurrence of SARS-CoV-2 infection (defined by a positive test by PCR or antigen) and hospitalization or death following receipt of TC.
- Patients were also matched with the state immunization information system (Minnesota Immunization Information Connection, (MIIC)) to confirm COVID-19 vaccination status, including date, type and number of doses received.

Results

- See Tables 1 and 2 for baseline characteristics and eligibility for TC. All patients were eligible due to underlying immune compromise per FDA criteria.
- 15 patients had a positive SARS-CoV-2 test following receipt of TC. 2 other patients had positive SARS-CoV-2 tests 39 and 60 days before the date of TC receipt, but these were reported as second doses so were included in the analysis for a total of **17 patients (5.7%) with possible breakthrough infection.** See Table 3 for patient details and outcomes.
- By the end of the study period on July 27th**, 9 patients (3.1%) had died.** 2/9 had positive SARS-CoV-2 testing prior to death, however none of the 9 deaths were classified as COVID-19 related.
- Almost **69% of patients were up to date with vaccination recommendations**, including 1 booster dose, at the time of receipt of TC (Figure 1).
- **17 patients were unvaccinated for COVID-19 at the time of receiving TC**. While TC is indicated for patients with a contraindication to COVID-19 vaccination due to a history of adverse reaction**, no patient was reported as being eligible for TC for this reason.**
- A reason for not being vaccinated was reported for 7 patients; one was reported as being 'afraid of adverse events', one was thought to be ineligible for vaccination due to an underlying malignancy, and the other 5 were reported as 'patient choice'.
- Most patients in this study received TC prior to CDC's recommendation for a second booster for immunocompromised patients in March 2022.
- **By the end of the study period in July 2022, only 83 patients (28.9%) had received a second booster.**
- 11 patients were ineligible for a booster as it had been ≤4 months since their first booster, and 2 patients had just received the first dose in the primary series. **At least another 191 patients were theoretically eligible for additional vaccine doses but had not received them.**

Table 1: Baseline characteristics

Number of patients	296
• Second dose documented	130 (44%)
Age (median, IQR)	63 (49-70)
Sex	
• Male	156 (53.9%)
• Female	139 (47.1%)
Race/ethnicity	
• White, non-Hispanic	180 (60.8%)
• Black, non-Hispanic	48 (16.2%)
• Asian, non-Hispanic	9 (3%)
• American Indian/Alaskan Native	2 (0.7%)
• Multiple, non-Hispanic	1 (0.3%)
• Other, non-Hispanic	3 (1.0%)
• Hispanic	27 (9.1%)
• Unknown	26 (8.8%)
COVID-19 vaccination status at time of first TC dose	
• No doses	17 (5.7%)
• One dose	13 (4.4%)
• Complete series	49 (16.6%)
• 1 booster	203 (68.6%)
• 2 boosters	12 (4.1%)
• Unknown	2 (0.7%)
COVID-19 vaccination status by Jul 27th, 2022*	
• No doses	14 (4.9%)
• One dose	12 (4.2%)
• Complete series	36 (12.5%)
• 1 booster	140 (48.8%)
• 2 boosters	83 (28.9%)
• Unknown	2 (0.7%)
Type of COVID-19 vaccine as primary series	
• Comirnaty-PFR 30mcg (Pfizer)	175 (62.7%)
• Spikevax-MOD 100mcg (Moderna)	98 (35.1%)
• Janssen (J+J)	6 (2.2%)

**Excluding 9 patients who died prior to July 27th.*

Table 2: Eligibility for treatment with TC

Active treatment for solid tumor malignancy	6 (2%)
Active treatment for hematological malignancy	114 (38.5%)
Receipt of solid organ transplant	45 (15.2%)
Receipt of hematopoietic stem cell transplant	13 (4.4%)
Receipt of (CAR)-T-cell therapy	1 (0.3%)
Moderate or severe primary immunodeficiency	4 (0.7%)
Advanced or untreated HIV infection	0
Active treatment with other immunosuppressant medication	119 (40.2%)
COVID-19 vaccination contraindicated	0

Figure 1: COVID-19 Vaccination Status over Time (%)

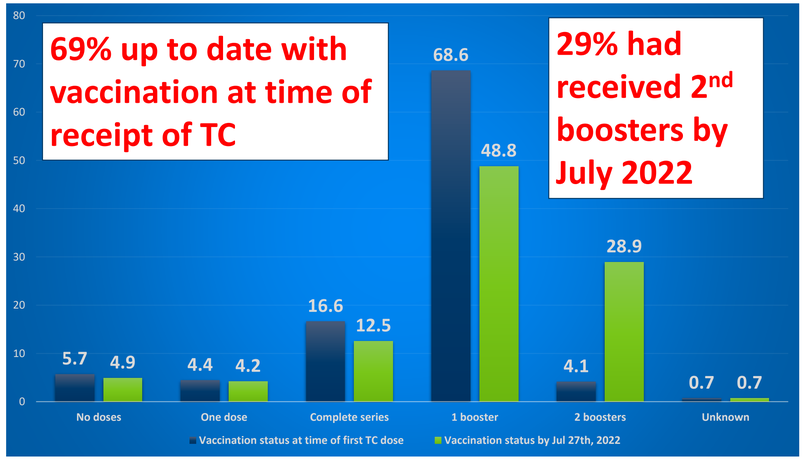

Table 3: 17 patients with positive SARS-CoV-2 tests following receipt of TC

Patient	Eligibility	Vaccination status at time of TC	Dose 1 TC	Dose 2 TC	(+) test	Days from TC to test	Outcome
A	Rituximab	1 Booster	1/3/2022		1/14/2022 (Ag)	11 from dose 1	
B	(CAR)-T-cell therapy	No Doses	1/5/2022		7/25/2022 (Ag)	201 from dose 1	
C	Rituximab	1 Booster	1/12/2022		5/12/2022 (PCR)	120 from dose 1	
D	Hematological malignancy	1 Booster	1/21/2022	3/4/2022	1/28/2022 (PCR)	7 from dose 1	
E	Rituximab	1 Booster	1/25/2022	3/17/2022	6/17/2022 (Ag)	92 from dose 2	
F	Kidney transplant	1 Booster	1/31/2022		5/31/2022 (PCR)	120 from dose 1	
G	Autologous SCT	1 Booster	2/1/2022		6/20/2022 (PCR)	139 from dose 1	
H	Hematological malignancy	1 Booster	2/3/2022	4/21/2022	2/16/2022 (PCR)	13 from dose 1	
I	Rituximab	1 Booster	2/4/2022		2/21/2022 (PCR) **BA.1.1 variant**	17 from dose 1	**Hospitalized** 2/21/2022 **Died** 4/1/22 (not COVID related)
J	Rituximab	1 Booster	2/4/2022		6/25/2022 (PCR)	141 from dose 1	**Hospitalized** 6/25/22
K	Rituximab	1 Booster	2/14/2022	3/8/2022	4/25/2022 (PCR) **BA.1 variant**	48 from dose 2	(SARS-CoV-2 PCR+ 1/12, 2/2, 2/9)
L	Hematological malignancy	1 Booster	2/16/2022	4/1/2022	5/31/2022 (Ag)	60 from dose 2	
M	Hematological malignancy	1 Booster	2/17/2022	3/2/2022	6/1/2022 (PCR)	91 from dose 2	
N	Hematological malignancy	1 Booster	3/1/2022		4/20/2022 (PCR)	50 from dose 1	**Hospitalized** 4/26/22 (ICU) **Died** 4/27/22 (not COVID related)
O	Hematological malignancy	1 Booster		3/1/2022	1/21/2022 (PCR)	Unknown (+) test 39 days before dose 2	
P	Hematological malignancy	Complete Series		3/14/2022	1/13/2022 (PCR)	Unknown (+) test 60 days before dose 2	**Hospitalized** 1/17/22

5.7% tested positive after receipt of TC

Discussion

- In this sample of 296 patients, TC use was consistent with FDA criteria, with most patients eligible for treatment due to use of immunosuppressant medication or with underlying hematological malignancy.
- Rates of **SARS-CoV-2 positivity (5.7%)**, **hospitalization (1.4%)** and **Covid-19-related death (0%)** were low.
- 3 of the patients who tested positive were within the SARS-CoV-2 incubation period (7 days, 11 days, and 13 days), indicating that their infection may have been present at the time of TC receipt and therefore not a true breakthrough infection.
- **Of the 9 deaths that occurred in the total patient sample, none were attributed to COVID-19**, including the 2 patients with positive SARS-CoV-2 testing after receipt of TC. This provides further support for the real-world effectiveness of TC for pre-exposure prophylaxis.
- It is notable that **17 patients were unvaccinated for COVID-19 at the time of receiving TC**. This is inconsistent with the FDA authorization for TC which states ***'Pre-exposure prophylaxis…..is not a substitute for vaccination in…individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise'.***
- **Only about two thirds of patients were up to date with vaccination at the time of receipt of TC and less than a third had received a recommended second booster** by the end of the study period. This is surprising in a high-risk population who are linked to medical care.

Limitations

- As a convenience sample representing a small proportion of patients treated with TC in Minnesota, these results may not be representative of all patients treated with TC.
- Some patients likely received additional doses of TC that were not captured by the survey.
- No clinical information was available for patients with positive tests, such as the presence of symptoms, whether patients received treatment for acute COVID-19 infection, or whether hospitalization was due to COVID-19 vs another condition. Determining whether a positive test represented a true breakthrough infection vs asymptomatic carriage was not possible.
- Our estimate of patients eligible for additional vaccine doses may not be accurate if immunocompromising conditions had resolved by the end of the study period. In addition, it is possible that some patients may have received COVID-19 vaccine doses that were not documented in the state immunization information system, e.g., through the U.S. Dept of Veterans Affairs.
- Finally, given widespread use of at-home tests which are not reportable to MDH, this study may have missed additional patients with positive test results who did not obtain a confirmatory test, such as a PCR test by their provider.

Conclusion

- In a convenience sample of immunocompromised patients receiving TC, **rates of positive SARS-CoV-2 testing, hospitalization and death were low,** supporting its use in this population.
- While pre-exposure prophylaxis with TC is not recommended as a substitute for COVID-19 vaccination, these data suggest that **some health care providers may not be aware of the recommendation to vaccinate immunocompromised patients including those with indications for TC.**
- The slow rate of receipt of second boosters in this patient sample is concerning, given their heightened risk for severe outcomes for COVID-19.
- **Additional provider and patient education is needed regarding pre-exposure prophylaxis with TC as a supplement to, not a substitute for, all recommended COVID-19 vaccine doses.**

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