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Breakthrough SARS-CoV-2 infections among recipients of tixagevimab-cilgavimab prophylaxis: A citywide real-world effectiveness study

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Abstract

There are limited real-world data on the effectiveness of tixagevimab-cilgavimab as pre-exposure prophylaxis of COVID-19. We describe lessons learned when coordinating data collection and identifying breakthrough SARS-CoV-2 infections among patients across indications and institutions in a major US city. The Chicago Department of Public Health requested patient-level tixagevimab-cilgavimab administration data from all prescribing providers in Chicago, for treatments December 8, 2021 through June 30, 2022. Records were matched to COVID-19 vaccinations and laboratory-confirmed SARS-CoV-2 infections through December 31, 2022. Due to difficulty collecting data from all providers, targeted follow-up was conducted to improve completeness on key variables (demographics, vaccination status, clinical indication for prophylaxis). Over half of reported tixagevimab-cilgavimab administrations were to patients residing outside Chicago. Five hundred forty-four Chicago residents who received at least one dose of tixagevimab-cilgavimab were included in this analysis. Most were age 50 years or older (72%), Black non-Latinx (33%) or White non-Latinx (29%), and fully vaccinated (80%). Seventy-five patients (14%) had laboratory-confirmed COVID-19. Patients with and without breakthrough infections were demographically similar. Clinical indication was missing for >95% of cases, improved to 64% after follow-up; the most frequently specified was hematologic malignancy (10%). Severe outcomes were uncommon: 16% had documented COVID-19-related hospitalizations, one death was identified. Tixagevimab-cilgavimab recipients in Chicago had a lower rate of severe SARS-CoV-2 infection than reported among other untreated high-risk patients, including during predominance of non-neutralizing variants. Improving stakeholder collaboration is essential for generation of real-world effectiveness data, informing pandemic preparedness and optimizing use of medical countermeasures.

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Keywords

immunosuppression; monoclonal antibodies; pharmacoepidemiology; real-world effectiveness; SARS-CoV-2

1 | INTRODUCTION

Tixagevimab and cilgavimab (Evusheld, Astra Zeneca) are two long-acting monoclonal antibodies that were granted emergency use authorization (EUA) December 8, 2021 by the Food and Drug Administration (FDA) as co-administered pre-exposure prophylaxis (PrEP) for SARSCoV-2 infection, among individuals with underlying conditions or otherwise not expected to mount a sufficient antibody response after vaccination alone (e.g., those severely immunocompromised or receiving immunosuppressive medications).[1] The initial recommendation was for the administration of a single carton (150 mg each tixagevimab and cilgavimab), with repeat doses every 6 months. In February 2022, in response to findings of reduced activity against certain omicron variants, the FDA issued a revised EUA recommending use of two cartons every 6 months, and additional doses of 150 mg of tixagevimab and 150 mg of cilgavimab to previously treated patients as soon as possible. In late 2022, the FDA noted emergence of omicron variants that tixagevimab-cilgavimab failed to neutralize in-vitro[2]; the EUA was withdrawn on Jan 26, 2023.

Tixagevimab-cilgavimab's authorization was based on trials conducted before the emergence of omicron variants, and among unvaccinated, COVID-naïve participants not representative of the target (immunocompromised) population.[3,4] These and most tixagevimabcilgavimab studies to-date have largely been limited to evaluation of the lower-dose regimen, patients of a single institution or indication,[5–8] and the period before nonsusceptible variants were predominant.[5,6,9–13] There is a lack of real-world effectiveness data comparing the outcomes of tixagevimab-cilgavimab-treated patients across indications,[9] both before and after changes in dosing recommendations, and as variants with reduced susceptibility to tixagevimab-cilgavimab became more prevalent.

We present real-world data on breakthrough SARS-CoV-2 infections in patients who had received PrEP tixagevimab-cilgavimab in the city of Chicago through June 2022, lessons learned during data collection, and future implications for monitoring and tracking drugs approved under EUA and distributed through a public health agency.

2 | METHODS

In December 2021, the Chicago Department of Public Health (CDPH) convened an advisory panel of relevant subject matter experts, including clinical specialists who treat individuals with immunocompromising conditions (e.g., transplant and infectious disease specialists), pharmacists, community health centers, ethicists, policy experts, and local public health leaders to discuss distribution of COVID-19 therapeutics. The panel advised on prioritizing distribution of tixagevimab-cilgavimab to the highest risk patients based on level of immunocompromise. Using those recommendations and estimated numbers of highest risk patients served by healthcare entities (obtained by CDPH through survey),

CDPH worked with the State to identify and prioritize distribution to providers serving tixagevimab-cilgavimab-eligible patients.

This panel also developed a process for supplying CDPH with patient-level data enabling city-level analyses of the tixagevimabcilgavimab-treated population. Chicago healthcare providers were required to report aggregate tixagevimab-cilgavimab administration data into the federal Tiberius platform,[14] which CDPH leveraged to identify prescribers and inform quarterly outreach. CDPH developed a secure, REDCap-based datasharing portal ("ChiRx"), through which individual-level data including demographics and vaccination status were requested on all patients receiving at least one dose of tixagevimab-cilgavimab through June 30, 2022. Providers were also specifically asked to report cases of SARS-CoV-2 infection after partial or full tixagevimab-cilgavimab dosing; partial dosing was defined as 150 mg each, full dosing was defined as 300 mg each. (This definition was kept uniform through the study period, despite changes in dosing recommendations.) While the provider advisory panel was instrumental in facilitating responses, outreach was discontinued in July of 2022, following a consensus that data requests were too effort-intensive. Due to high rates of overall missingness for key variables of interest (e.g., clinical indication), CDPH conducted targeted follow-up with four high-volume academic medical centers to help complete data for patients with identified breakthrough infections.

All data were housed at CDPH, where treatment records were matched to those of COVID-19 vaccinations and (postdose) laboratory-confirmed SARS-CoV-2 infections among Chicagoans, and cleaning and descriptive analyses were conducted using SAS version 9.4 (SAS Institute Inc). This investigation was determined to be nonresearch as public health surveillance and exempt from Instutitional Review Board review.[15] Data were requested under City of Chicago Public Health Order 2020–4,[16] which required City of Chicago healthcare providers who provided COVID-19 care or treatment to send CDPH demographic and clinical data, as deemed relevant and necessary. Given limited access to COVID-19 case data for residents outside Chicago, analyses excluded patients reported to live outside Chicago (n = 980/1,639 or 60% of those with individual data). As birthdate was required for matching to case and immunization records, city residents missing date of birth (n = 115/659, or 17%) were also excluded, resulting in a sample of n = 544 tixagevimab-cilgavimab recipients followed for incident COVID-19 through December 31, 2022.

3 | RESULTS

Among 544 Chicago residents with at least one reported dose of tixagevimab-cilgavimab from December 2021 through June 2022, most (72%) were age 50 years or older, Black, non-Latinx (33%) or White, non-Latinx (29%) (Table 1). Eighty percent were fully vaccinated and 64% received at least one booster dose.

Seventy-five patients (14%) had corresponding records of laboratory-confirmed SARS-CoV-2 infection occurring after their treatment dates (Table 2). These patients were demographically comparable to those without record of infection, although rates of full vaccination and boosting were higher among those with COVID-19 (88% and 81%) than

without (79% and 63%). Sixty-four percent of cases were diagnosed within 6 months of full tixagevimab-cilgavimab dosing, 12% within 6 months of partial tixagevimab-cilgavimab dosing, and 25% more than 6 months from tixagevimab-cilgavimab dosing. Indications for PrEP were reported for 36% of cases across providers, with hematologic malignancy the most frequently specified (10%); others included solid organ transplant and stem-cell transplant (9% each) and multiple sclerosis (3%). Twelve cases (16%) had documented COVID-19-related hospitalizations; one COVID-19-related death was identified.

4 | DISCUSSION

Emergency-authorized COVID-19 therapeutics were used extensively in populations different from the one in which they were initially studied. Increases in non-neutralizing variants raised questions among providers and healthcare systems about the utility of SARS-CoV-2 monoclonals. Despite their necessity for informing both policy and practice, real-world effectiveness data for tixagevimab-cilgavimab have been relatively sparse. In this report, we describe challenges and successes in data sharing between public health and multiple healthcare providers in a major US city. We also provide unique real-world evidence of the clinical efficacy of tixagevimab-cilgavimab. Although prevalence of nonneutralizing variants was increasing, only 14% of treated patients developed breakthrough SARS-CoV-2 infections through December 2022, and infections had a low case-fatality rate (<2%). Our observed hospitalization and case-fatality rates are markedly lower than those reported among other immunosuppressed populations (i.e., transplant recipients) during omicron predominance.[17–20] Our data support PrEP for prevention of severe COVID-19 among high-risk patients.

The breakthrough rate in our study is higher than in previous studies conducted among immunosuppressed cohorts, with shorter follow-up and earlier in the pandemic (i.e., during dominance of more susceptible subvariants),[5,6,8,12,13] although comparable to rates observed among partial-dose recipients.[7,10] These findings may be attributable to, in addition to Omicron's reduced susceptibility: our inclusion of more unvaccinated patients, patients with multiple immunocompromising conditions, and patients whose last doses were more than 6 months before infection (25% of all breakthrough cases in our report).

This analysis was greatly facilitated by a city-level public health data sharing mandate, which obviated the need for institution-based regulatory approvals. However, CDPH had little ability to enforce this mandate, and could not extend it to out-of-jurisdiction providers. Moreover, CDPH has limited access to surveillance and immunization records among patients who reside out of jurisdiction, and over half of tixagevimab-cilgavimab administrations described by City providers were to patients living outside Chicago. Data sharing initiatives at the state and federal level would have enabled more representative, comprehensive analyses of the treated population.

CDPH dedicated time and personnel to facility outreach which, along with sharing findings back to providers, likely improved reporters' engagement and response. While the minimum requested data and system for collection (a common and secure upload portal for all providers) were straightforward, this project was subject to other logistical limitations,

which also help explain the relative lack of real-world effectiveness studies to date. Aggregation of individual-level patient data across providers required continued cooperation at multiple levels: between stakeholders (i.e., Public Health and provider institutions) and within institutions (i.e, clinical, informatics, and records/administrative teams within one hospital). Furthermore, while queries from electronic health records helped expedite provider responses to requests for information, customized reports were both time and resource-intensive; frequent data omission and systematic reporting limitations reduced utility of the resulting data. Complete analyses often required chart extraction for patients across multiple care teams within an institution. In many cases this was untenable, and some high-volume providers could not fulfill CDPH's data request. Indication for treatment was missing for >95% of all records sent to CDPH, presumably due to limited capacity of provider teams to extract diagnosis codes or other comorbidities data to accompany injection drug orders. Therefore, we could not compare patients who did and did not contract COVID-19 within 6 months of tixagevimab-cilgavimab dosing.

Because data on other COVID-19 interventions (i.e., antiviral treatments or monoclonal antibodies) were not collected through the full study period, case outcomes among tixagevimab-cilgavimab recipients could not be compared by treatment group. Without data on COVID-19 incidence among eligible but untreated patients, we could not evaluate associations between PrEP and SARS-CoV-2 infection. Exclusion of unreported cases, including those detected only through home-based testing, underestimated true incidence among our cohort. At the same time, detection (especially of mild or asymptomatic infection) was probably more common among these treatment-eligible patients than the general population, due to increased healthcare access. The few laboratory-confirmed infections, lack of sequencing data and limited follow-up time preclude comparisons of incidence and outcomes through changes in subvariant prevalence; the relative associations between tixagevimab-cilgavimab dosing, host factors (e.g., severe B-Cell depletion, antibody titers), circulating variants and breakthrough SARS-CoV-2 infections are unknown. Such data, along with representative, timely analyses of incident COVID-19 cases, could have helped inform both SARS-CoV-2 PrEP, and management of patients' ongoing treatment regimens over time.[21]

Significant resources are required to successfully implement medical countermeasures, and effectiveness data are critical to optimizing both clinical practice and equity interventions. Despite limitations inherent to a single local health department, we were able to report a comprehensive description of breakthrough tixagevimab-cilgavimab infections among a core group of immunosuppressed patients. Our study speaks to the need for cross-jurisdictional collaboration in data modernization, particularly since expiration of pandemic-era emergency legislation.[22,23] Our learnings are applicable to future pandemic preparedness efforts, and other initiatives to improve generation and sharing of real-world data between clinicians and public health agencies: (1) a public health reporting mandate, (2) provider advisory panel, and (3) dedicated outreach team all helped CDPH gather these important data. Still, infrastructural improvements to de-silo data, such as mutually accessible systems, are needed to reduce the burden of transferring records within and between entities.

In conclusion, our findings suggest that tixagevimab-cilgavimab prophylaxis may be associated with reduced frequency of severe SARS-CoV-2 infections, despite the emergence of nonneutralizing variants. Health departments maintain rich datasources (case and immunization records) that can be utilized to generate valuable real-world effectiveness data. This cannot be achieved without engagement of providers, who must help public health partners identify and describe the treated population. At the same time, providers have limited capacity to fulfill reporting requests made at multiple levels of government (local, state, federal). This study underscores the need for collaboration of stakeholders across all jurisdictional levels, in (1) engagement and support of clinical teams, and (2) provision of resources to improve data sharing between healthcare providers and health departments, including clear public health authority to receive the data and data modernization. Further, it highlights both the challenges and importance of collecting real-world effectiveness data as part of a public health emergency response.

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CONFLICT OF INTEREST STATEMENT

MGI: MGI received research support, paid to Northwestern University Feinberg School of Medicine, from GlaxoSmithKline, royalties from UpToDate and was a paid consultant for Adagio, ADMA Biologics, Adamis, AlloVir, Atea, Cidara, Genentech, Janssen, Roche, Shionogi, Takeda, Telaris and Viracor Eurofins; all of these activities ceased December 4, 2022 with the exception of UpToDate, which is ongoing. GNF: Received research support paid to Rush University Medical Center from the Antibiotic Resistance Leadership Group, NIH Division of Microbiology and Infectious Diseases and Regeneron, Inc. All other authors (FL, LL, LJ, CZ, SRB, JS) have no conflict of interest and nothing to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abbreviations:

CDPH	Chicago Department of Public Health
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
IQR	interquartile range
PrEP	pre-exposure prophylaxis

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TABLE 1

Characteristics of Chicago residents with laboratory-confirmed SARS-CoV-2 infection after receipt of tixagevimb-cilgavimab (*N* = 544).

	All treated (*N* = 544)	**Breakthrough infection (*n* = 75)**	**No record of breakthrough infection (*n* = 469)**
	***n* (%)**	***n* (%)**	***n* (%)**
Age group (years)			
12–17	8 (1.5)	2 (2.7)	6 (1.3)
18–49	147 (27.0)	20 (26.7)	127 (27.1)
50+	389 (71.5)	53 (70.7)	336 (71.6)
Sex			
Female	253 (46.5)	43 (57.3)	210 (44.8)
Male	231 (42.5)	32 (42.6)	199 (42.4)
Unknown	60 (11.0)	0 (–)	60 (12.8)
Race/Ethnicity			
Latinx	88 (16.2)	13 (17.3)	75 (16.0)
Black, non-Latinx	177 (32.5)	27 (36.0)	150 (32.0)
White, non-Latinx	157 (28.9)	27 (36.0)	130 (27.7)
Asian, non-Latinx	28 (5.1)	5 (6.7)	23 (4.9)
Other, non-Latinx	10 (1.8)	1 (1.3)	9 (1.9)
Unknown	84 (15.4)	2 (2.7)	82 (17.5)
Receipt of any COVID-19 vaccine			
Fully-vaccinated[a]	434 (79.8)	66 (88.0)	369 (78.7)
Additional (booster) doses	349 (64.2)	61 (81.3)	293 (62.5)

[a]Fully-vaccinated refers to completion of primary COVID-19 vaccine series according to recommendations at the time of study: two doses of mRNA vaccine or one dose of Johnson & Johnson/Janssen.

TABLE 2

Characteristics of laboratory-confirmed SARS-CoV-2 infections among Chicagoans after receipt of tixagevimab-cilgavimab (n = 75).

	***n* (%)**
Outcomes	
Hospitalization due to COVID-19	12 (16.0)
Deceased due to COVID-19	1 (1.5)
Tixagevimab-cilgavimab exposure at infection [a]	
Partial dose within 6 months (150 mg each)	9 (12.0)
Full dose within 6 months (300 mg each)	48 (64.0)
More than 6 months from treatment	19 (25.3)
Time from dosing to infection, days (median, IQR[b])	
Partial dose within 6 months (150 mg each)	134 (113–175)
Full dose within 6 months (300 mg each)	105 (35–141)
More than 6 months from treatment	107 (61–151)
Overall	138 (89–194)
Indications for treatment [c]	
B-cell depleting agent specified	10 (13.3)
Hematologic malignancy	8 (10.6)
Solid organ transplant	7 (9.3)
Stem cell transplant	7 (9.3)
Multiple sclerosis	2 (2.7)
T-cell depleting agent specified	2 (2.7)
Unspecified condition requiring immunosuppression	7 (9.3)
Unknown	48 (64.0)

[a] The Food and Drug Administration recommended tixagevimab-cilgavimab treatment at 6-month intervals.

[b] IQR: Interquartile range.

[c] Indications reported for 27/75 (36%) of patients, some with multiple indications reported.