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Effectiveness and Safety of Long-acting Antibody (LAAB) to Prevent COVID-19 among High-risk Population in Thailand: a 6-month Retro-prospective Cohort Study

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Abstract

During COVID-19 pandemic, evidence showed lower immunity after infection and vaccination among immunocompromised individuals. In July 2022, a prophylaxis campaign using long-acting antibodies (LAAB), tixagevimab-cilgavimab was launched in Thailand to decrease hospitalizations among high-risk groups. To evaluate the real-world effectiveness and safety of LAAB for high-risk populations, a 6-month retro-prospective cohort study was conducted starting in March 2023. We included 1,249 participants aged ≥18 years with high-risk conditions who tested negative for COVID-19 using antigen test kits during the campaign in Thailand's central, northern, and northeastern regions. Participants provided blood samples for anti-S and anti-N IgG testing and were monitored weekly by phone for six months for acute respiratory symptoms and were screened if COVID-19 was suspected. Positive cases were further tested with RT-PCR and sequencing. We matched 600 individuals who received the study drug tixagevimab-cilgavimab (exposed) by age and comorbidities to 600 individuals who did not receive the drug (non-exposed). Predominant strain was the omicron sublineage XBB. One participant who did not receive the drug was hospitalized without respiratory failure. Anti-N IgG was positive and high levels of anti-S IgG were observed. The effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections or hospitalizations among high-risk groups was not seen. Existing immunity from previous infections and vaccinations likely influenced these results. No serious adverse events related to the drug were reported. Despite these findings, there is a potential prophylactic role of LAAB for immunocompromised groups in the early phase of a pandemic while effective vaccines and treatments are unavailable.

Keywords: effectiveness, long-acting antibody, COVID-19

Introduction

As of 25 Feb 2024, coronavirus disease 2019 (COVID-19) has contributed to the deaths of more than seven million people worldwide, including nearly 40,000 in Thailand.[1] Vaccination is a key strategy to prevent infections and serious outcomes of COVID-19. In Thailand, in May 2023, the coverage for the primary series was 77.2%, while the coverage of at least one booster dose was 48.9%.[2]

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have evolved, the effectiveness of COVID-19 vaccines has been significantly affected. In Thailand, real-world data indicate that vaccines targeting the original strain are less effective against omicron variants, particularly for preventing infection. This protection varies based on vaccine type, viral strains, and other factors, meaning that immunocompromised individuals, those with chronic kidney diseases, and older adults may have lower immune responses than healthy individuals.[3–5] For these high-risk groups, tixagevimab-cilgavimab, a long-acting antibody (LAAB) used as a pre-exposure prophylaxis, may reduce the incidence and severity of COVID-19. Tixagevimab-cilgavimab neutralizes the SARS-CoV-2 virus by binding to two different epitopes

on the spike protein of the virus. It blocks the virus from binding to angiotensin-converting enzyme 2 receptors on host cells, thus preventing infection.[6]

The US Food and Drug Administration gave authorization for tixagevimab-cilgavimab in December 2021 for emergency use in moderate to severe immunocompromised individuals aged ≥12 years old and recommended a dose of 600 mg against the emergence of omicron BA.1 sub-variants in June 2023.[7]

In June 2022 the Thai Food and Drug Administration approved, under conditional marketing, a 300 mg dose of tixagevimab-cilgavimab, which was subsequently updated to 600 mg in April 2023.[8,9] In addition, the Thai Ministry of Public Health issued guidelines for tixagevimab-cligavimab as prophylaxis in solid organ transplant recipients, patients with end-stage kidney disease, and individuals aged ≥60 years.[10,11]

Thus, we aimed to analyze the real-world effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and severe outcomes among high-risk groups in Thailand.

Methods

Operational Definitions

Prior to April 2023, tixagevimab-cilgavimab 300 mg was the recommended dose according to the Department of Disease Control (DDC). After April, the recommended dose was increased to 600 mg, derived from B cells of COVID-19 survivors and engineered to prolong the half-life by at least threefold.[10] The drug demonstrated efficacy against COVID-19, including original and mutant strains.

According to the DDC's Disease Surveillance Definition and Reporting Manual for COVID-19, a person was defined as being infected if he or she developed at least two of the following symptoms: fever, cough, nasal congestion, sore throat, or phlegm; or one of these symptoms plus additional signs such as loose stools, muscle pain, headache, nausea/vomiting, fatigue, rash, or shortness of breath, difficulty breathing, olfactory or gustatory changes, confusion, decreased consciousness; or severe respiratory illness (e.g., pneumonia or chest x-ray abnormalities of unknown cause), and was confirmed by antigen test kit (ATK) or reverse transcription-polymerase chain reaction (RT-PCR) testing for COVID-19 viral genetic material.[12]

An adverse event was defined as an illness after receiving the study drug regardless of the causal relationship. A serious adverse event was defined as death, having a life-threatening illness such as anaphylaxis, and prolonged hospitalization after receiving the drug within 30 days, regardless of the causal relationship, and was reported to the DDC adverse events following immunization reporting system.[13]

Study Design

A retro-prospective matched cohort study was conducted, considering an individual pair matched in the same period by age and comorbidity. Matching age groups were 18–30, 31–40, 41–50, 51–60, 61–70, 71–80, and over 80 years. Comorbidity was prioritized based on its association with COVID-19 severity, including chronic kidney disease stages 3–5, diabetes mellitus, chronic lung disease, cancer with chemotherapy/ radiation therapy within two years, autoimmune disease, heart disease, cerebrovascular disease, and obesity (body mass index ≥30 kg/m^2). Participants aged 60 years and older without underlying diseases were matched with others of the same age group.

Participants were enrolled in two phases. During the retrospective phase, hospital-based patients who received tixagevimab-cilgavimab from January to February 2023 had their medical records reviewed and consented for a 6-month prospective observation period. In the prospective phase, participants eligible for the study were recruited from the standard LAAB campaign in the hospital and community during March to July 2023.

Study Site and Population

Both hospital and community settings were chosen purposively, considering the geographic distribution, internal management, and network collaboration. Patients without a history of acute respiratory symptoms in Pranangklao Hospital, Samutprakarn Hospital, Nakhonpathom Hospital in the central region of Thailand were selected to represent hospital-based participants. High-risk individuals residing in provinces covered by the Office of Disease Prevention and Control (ODPC) Regions 3 Nakhon Sawan, ODPC 9 Nakhon Ratchasima, and ODPC 4 Saraburi were selected to represent community-based participants from Thailand's northern, northeastern, and central regions.

We targeted high-risk individuals susceptible to severe COVID-19 infection adhering to DDC's guideline for LAAB administration to establish our study inclusion and exclusion criteria.[10,11] Study participants without COVID-19 infection based on interviews, without any history of acute respiratory symptoms, and who tested negative on ATK screening at enrollment and after seven days

High-risk groups were defined as individuals aged 60 years and older or those with any of the seven specified

chronic diseases used for matching. High-risk groups with low immunity or an inadequate vaccine response included organ or bone marrow transplant recipients on immunosuppressive drugs, patients with hematologic malignancies or solid tumors who are undergoing or have recently completed treatment, HIV-positive individuals with compromised immunity (e.g., CD4 <200 cells/mm^3) who are not on anti-HIV therapy, those with a history of opportunistic infections or ongoing HIV symptoms, patients with end-stage renal disease on kidney replacement therapy, and individuals on immunosuppressive drugs or with immune system impairment as determined by a physician.

Sample Size Assumptions and Calculation

The sample size calculation applied a vaccine effectiveness of 83% as a proxy for LAAB effectiveness with a desired precision width of 20%.[14,15] The attack rate among the unexposed population was estimated at 8%.[16] This yielded a minimum sample size of 1,035 participants. Accounting for a 20% compensation for loss of follow-up, the total sample size was determined to be 1,200.

Sampling Methods

The eligible participants were enrolled through consecutive sampling based on underlying disease records in hospital databases and villagers' family folders. Participants were informed that their participation and treatment choice was entirely voluntary. Those opting for the study drug (exposed) underwent at least one hour of post-injection observation. Participants declining the drug (non-exposed) who were matched by age and comorbidity (Table 1) were also invited to join the study during the same period and within the same region as the LAAB campaign until either there were no more eligible participants in the site or the sample size was reached. Exposed participants were matched with the non-exposed on the same comorbidity if possible, otherwise other chronic diseases were used instead.

Data and Specimen Collection

Participants consented to undergo nasopharyngeal swabs for COVID-19 antigen testing and venipuncture for immune testing before drug administration. Data collected included demographics, risk behaviors, health status, and expenses related to LAAB. Participants were monitored for adverse events at one hour, one day, seven days, and four weeks after injection.

Trained research assistants checked for COVID-19 symptoms and collected nasopharyngeal samples for RT-PCR and whole genome sequencing if symptoms developed. Hospitalizations were reported by hospitals and medical records were reviewed. Weekly follow-up assessments were conducted by phone for six months with additional checks against the DDC COVID-19 database and ongoing monitoring for outbreaks and mutations in Thailand.

Remaining specimens were stored at –70°C at the Thai National Institute of Health and were transferred to a specimen bank where they remain for 10 years for future research and disease control efforts. Participants were informed about the use of their samples in future studies.

Special Laboratory Testing

Baseline antibodies (anti-S and anti-N IgG) against COVID-19 were tested at the Clinical Research Center, Medical Life Sciences Institute, Department of Medical Sciences, Ministry of Public Health using quantitative methods. Serum samples were analyzed for SARS-CoV-2 antibodies to nucleocapsid (N) and spike glycoprotein (S1) proteins using the IgG and Quant IgG-II assay (Abbott Ireland) with the ARCHITECT-i1000SR analyzer (Abbott Diagnostics). Anti-N antibodies were considered negative if the index value was ≤1.40. Anti-S1 antibodies ≥50 AU/mL were considered positive. The reportable range for anti-S1 was 6.8–80,000 AU/mL. For correlation with World Health Organizations international standard, antibodies were converted to binding antibody units (BAU/mL) by multiplying values by 0.142 at the correlation level of 0.999.

CTK-R0182C Onsite COVID-19 Ag rapid tests, were used to screen for SARS-CoV-2 infection during enrollment.

Data Analysis

Categorical variables (gender, age group, underlying diseases, vaccination history including COVID-19, influenza, and LAAB, COVID-19 infection history, risk factors, and prevention behavior in the 14 days before enrollment) were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Baseline COVID-19 antibody concentrations were compared using a t-test on a log scale for geometric mean concentration. A *p*-value <0.05 indicated a significant difference between the two groups.

Effectiveness of Tixagevimab-cilgavimab

The primary outcomes for this study were COVID-19 infection and hospitalization due to COVID-19. Incidence rate ratios were calculated using Poisson regression. Potential confounders and serostatus were

included in the final model. Effectiveness was defined as (1–adjusted incidence rate ratio) × 100.

Ethics

Ethical permission for this study was obtained from the Institute for the Development of Human Research Protections (IHRP). Approval to conduct the study was granted on 28 Mar 2023. The certificate of approval number is IHRP2023040 and IHRP no. 022-2566.

Results

We enrolled 1,249 individuals, of which 49 were excluded (five had COVD-19 infection within seven days after enrollment and 44 exposed could not be matched). Finally, 1,200 participants were included in the analysis, 600 in each group. After the follow-up period, there were 24 COVID-19-infected cases in each group as shown in Figure 1.

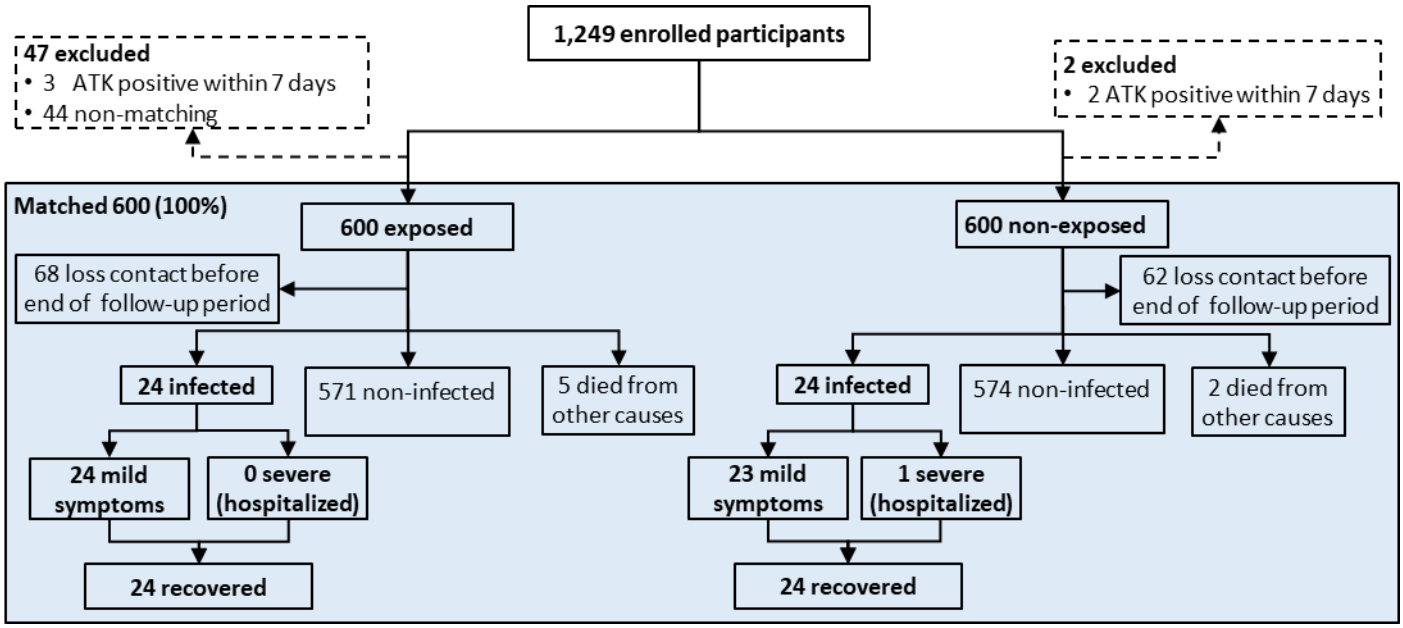

Figure 1. Status of outcomes among enrolled participants with and without long-acting antibody received

Safety Profile or Adverse Event Following LAAB

Among 547 matched pairs who received tixagevimab-cilgavimab 600 mg, 24 exposed and 21 non-exposed were infected. Among 53 matched pairs who received tixagevimab-cilgavimab 300 mg, three non-exposed were infected and no infections were found in the exposed group.

Among seven deaths, the causes, verified through medical records and interviews with hospital staff, were chronic kidney disease with acute renal failure (n=3), hospital acquired pneumonia with negative ATK results (n=2), and heart attack (n=2). Five were from the exposed group who received tixagevimab-cilgavimab for more than 30 days (range 55–166 days), and they did not meet the reporting criteria of serious adverse events. The other two deaths were in the non-exposed group.

Among the 1,200 participants, 972 (81%) were aged 60 years or more. Among these, 220 (23%) had no history of underlying disease (Table 1).

In the non-exposed group, 16 (2.7%) had no prior COVID-19 infection or vaccination, as confirmed by negative anti-S IgG and anti-N IgG results. Of the 24 infected cases, 23 (96%) were vaccinated, and 10 (42%) had a history of prior infection. Only one required hospitalization, and without respiratory failure. The infection, identified as omicron XBB.1.15 by RT-PCR and sequencing, was in a patient who had a prior COVID-19 infection a year earlier and had received three vaccine doses. This patient had positive anti-N IgG (1.87 Index) and anti-S IgG (3,901.3 AU/mL) and eventually recovered.

The effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and hospitalizations was 11% (95% confidence interval NA–51%), as shown in Table 2. The specific effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections by underlying diseases and COVID-19 vaccination is shown in Table 3.

Among 48 infected COVID-19, whole genome sequencing of SARS-CoV-2 was identified in 32 (67%). Of these, 19 (59%) were identified as the omicron B.1.1.529 sublineage: XBB, with 12 cases (38%) specifically being XBB.1.16. Five strains could not be determined by RT-PCR, and the remaining 11 cases did not have respiratory specimens available for RT-PCR testing, as shown in Figure 2.

Table 1. Baseline characteristics (n=1,200)

Characteristics	Received LAAB n=600 n (%)	Did not receive LAAB n=600 n (%)	*P*-value
Gender			
Male	247 (41.2)	194 (32.3)	0.002
Female	353 (58.8)	406 (67.7)	-
Age (mean±SD)	66.2±9.6	66.0±9.5	0.651‡
(Range)	(19–91)	(23–90)	
High-risk groups (n=1,098)	540 (90.0)	558 (93.0)	0.811
Age ≥60 years old	112* (20.7)	108 (19.4)	0.661
CKD (stage 3–4)	18 (3.3)	24 (4.3)	0.345
Diabetic mellitus	226 (41.9)	213 (38.2)	0.365
Chronic lung disease	2 (0.4)	7 (1.3)	0.106
Heart disease	30 (5.6)	39 (7.0)	0.248
Cerebrovascular disease	13 (2.4)	11 (2.0)	0.835
Obesity†	19 (3.5)	20 (3.6)	0.870
Other high-risk groups	154 (28.5)	176 (31.5)	0.711
High-risk groups with low immunity or inadequate vaccine response (n=102)	60 (10.0)	42 (7.0)	0.078
1) ESRD (CKD stage 5)	46 (76.7)	32 (76.2)	0.565
ESRD with hemodialysis	45 (97.8)	30 (93.8)	-
ESRD without hemodialysis	1 (2.2)	2 (6.2)	-
2) Cancer with chemotherapy/radiotherapy	9 (15.0)	6 (14.3)	1.000
3) Autoimmune diseases	5 (8.3)	5 (11.9)	0.737
History of vaccination before enrollment			
History of receiving COVID-19 vaccine	585 (97.5)	552 (92.0)	<0.001
Not received	15 (2.5)	48 (8.0)	-
1 dose	7 (1.2)	16 (2.9)	0.056
2 doses	133 (22.7)	171 (31.2)	0.002
3 doses	278 (47.5)	253 (46.2)	0.677
>3 doses	167 (28.6)	109 (19.8)	0.001
Last dose ≥6 months	545 (97.3)	508 (96.8)	0.596
Last dose ≥12 months	392 (70.0)	414 (78.9)	0.001
History of received LAAB	20 (3.3)	4 (0.7)	0.001
History of received Influenza vaccination	348 (60.4)	362 (62.4)	0.506
Baseline of COVID-19 antibodies			
Anti-S IgG (GMC±GSD) (95% CI)	3516.2 ± 4.7 (3097.5–3991.5)	2200.8 ± 6.8 (1883.1–2572.2)	<0.001
Anti-S IgG positive	572 (98.3)	552 (93.9)	<0.001
Anti-N IgG (mean±SD) (95% CI)	1.7±2.5 (1.5–1.9)	1.8±2.8 (1.6–2.1)	0.433
Anti-N IgG positive	197 (33.9)	188 (32.0)	0.534
History of previous COVID-19 infection	258 (43.0)	259 (43.2)	1.000
Received 1–2 doses	61 (23.6)	73 (28.2)	0.270
Received >2 doses	190 (73.6)	166 (64.1)	0.023
Anti-N IgG positive	123 (49.4)	108 (42.4)	0.129

**Participants aged ≥60 years without CKD, diabetic mellitus, chronic lung diseases, heart diseases, cerebrovascular diseases, and obesity who received LAAB, 4 of them matched with other 4 participants in the same age group with other chronic diseases who did not receive LAAB. †Body mass index ≥ 30 kg/m2. ‡P-value from Mann-Whitney U test. LAAB: long-acting antibody. ESRD: end-stage renal disease. CKD: chronic kidney disease. GMC: geometric mean concentration. GSD: geometric standard deviation. SD: standard deviation. CI: confidence interval.*

Table 2. Effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections and hospitalizations by high-risk categories (n=1,200)

Outcomes	Exposed n=600	Non-exposed n=600	Crude IRR (95% CI)	Adjusted IRR* (95% CI)	Effectiveness† (95% CI)
High-risk groups					
Person-time (weeks)	12,256	12,600	-	-	-
COVID-19 infection	23	24	0.98 (0.53–1.82)	0.88 (0.49–1.60)	12% (NA–51%)
Hospitalized	0	1	-	-	-
High-risk groups with low immunity or inadequate vaccine response					
Person-time (weeks)	1,237	944	-	-	-
COVID-19 infection	1	0	-	-	-
Hospitalized	0	0	-	-	-
All high-risk populations					
Person-time (weeks)	13,493	13,544	-	-	-
COVID-19 infection	24	24	1.00 (0.55–1.85)	0.89 (0.49–1.60)	11% (NA–51%)
Hospitalized	0	1	-	-	-

**IRR was adjusted for age, gender, history of receiving the COVID-19 vaccine, booster ≥2 doses, last COVID-19 vaccine dose ≥12 months, and positive result for anti-S IgG. †Effectiveness = (1−adjusted IRR) × 100. IRR: incidence rate ratio. NA: not available.*

Table 3. Effectiveness of tixagevimab-cilgavimab in preventing COVID-19 infections by number of underlying diseases and COVID-19 vaccination status

Characteristics	Exposed		Non-exposed		Crude IRR (95% CI)	Adjusted IRR* (95% CI)	Effectiveness† (95% CI)
	COVID-19 infection	Person-time (weeks)	COVID-19 infection	Person-time (weeks)			
Underlying diseases							
1	5	3,533	1	4,026	5.70 (0.64–26.96)	16.60 (1.01–27.18)	-
2	6	4,520	8	4,003	0.66 (0.19–2.18)	0.45 (0.13–1.56)	55% (NA–87%)
More than 2	13	5,296	14	5,321	0.93 (0.40–2.14)	0.80 (0.36–1.76)	20% (NA–64%)
COVID-19 vaccination history							
Received ≤2 doses	4	2,890	6	3,842	0.89 (0.18–3.74)	1.30 (0.35–4.90)	-
Received >2 doses	19	10,168	17	8,232	0.90 (0.45–1.85)	0.75 (0.38–1.48)	25% (NA–62%)

**IRR adjusted for age, gender, COVID-19 vaccination, booster ≥2 doses, last COVID-19 vaccination ≥12 months, positive anti-S IgG result. †Effectiveness = (1−adjusted IRR) × 100. IRR: incidence rate ratio. NA: not available.*

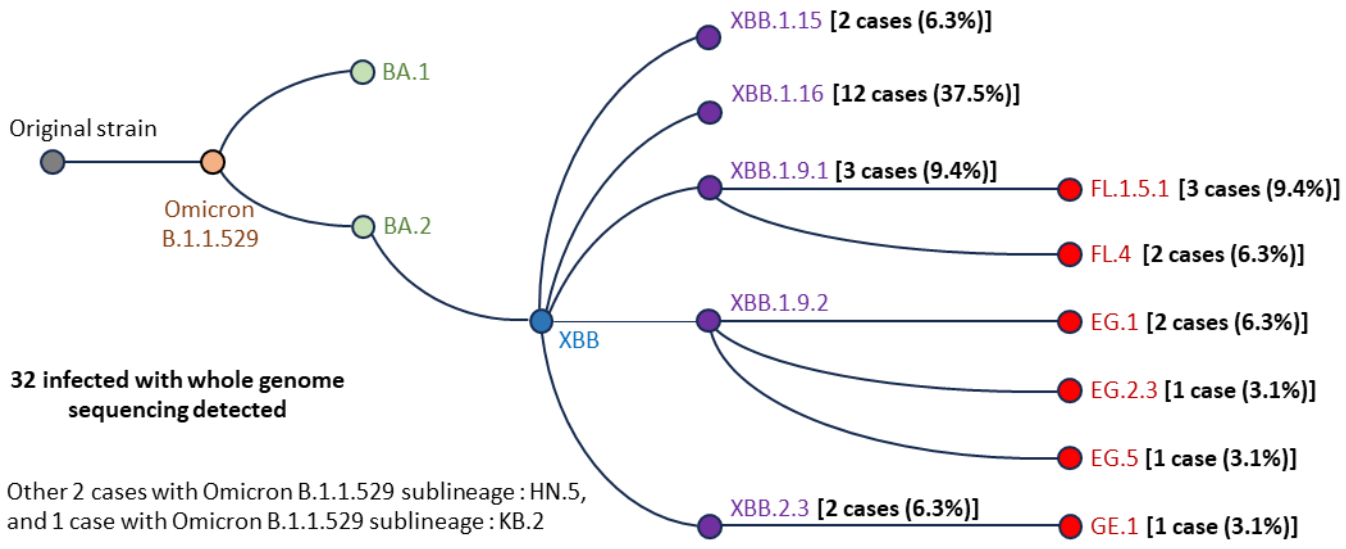

Figure 2. Diagram of SARS-CoV-2 variant strain with sublineages by whole genome sequencing among 32 infected cases

Safety Profile of Tixagevimab-cilgavimab

Among the 647 enrolled with exposed, 42 (6.5%) experienced adverse events; 17 (2.6%) within one hour and 19 (2.9%) 24 hours after receiving the drug. All recovered and there were no hospitalizations. No adverse events were recorded at the four-week follow-up time point, as shown at Figure 3.

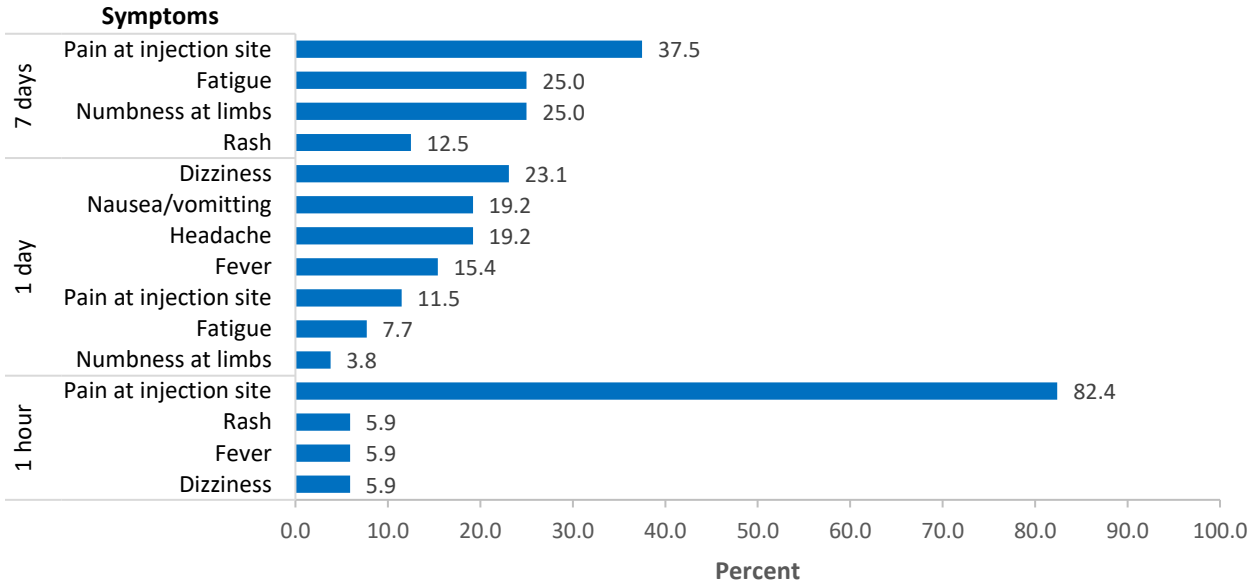

Figure 3. Distribution of adverse events among 42 participants who developed symptoms after receiving tixagevimab-cilgavimab by follow-up time

Discussion

Although there is evidence that the use of LAAB is effective in preventing COVID-19 in high-risk groups, our study found that the effectiveness of tixagevimab-cilgavimab in preventing COVID-19 hospitalizations among high-risk groups was low in both hospital and community settings.[17–19] However, one infected individual from the non-exposed group was hospitalized. Those who did not receive the study drug might have a higher tendency to avoid engaging in several hihg-risk activities since they may perceive themselves as being unprotected. Therefore, they might have a lower "baseline risk" of getting an infection.

Assessing the neutralizing activity of LAAB against variant strains of the virus remains challenging to be timely due to the rapidly changing nature of the virus. In Thailand, the B.1.1.529 omicron variant was subsequently detected in 2022 and lower neutralizing activity of tixagevimab-cilgavimab against the emergence of this omicron sub-variant, including BA.2, BA.5 and XBB, was observed in 2023.[20–24] This observation was similar to SARS-CoV-2 variants circulating in the United States.[25]

A key finding from this study was that nearly 90% of participants, regardless of whether they received the study drug, had immunity from a previous COVID-19 infection or vaccination, as confirmed by positive serostatus for anti-S IgG and anti-N IgG, indicating a history of vaccination or prior infection. Consequently, the observed cases of infection were not severe. Additionally, symptom and ATK screening, along with rapid access to treatment, may have further reduced the risk of severe illness. However, the level of immunity against COVID-19 in preventing severe illness among high-risk groups varies depending on the virus variants, with antibody levels after SARS-CoV-2 omicron infections being lower than those following delta infections.[26]

We found that tixagevimab-cilgavimab is safe for use among high-risk groups. We did not find any serious adverse events in individuals who received the drug, with most individuals experiencing only mild symptoms, such as pain at the injection site, rash, or occasional fever. Although there was one report of an adverse reaction involving difficulty breathing and a skin rash within 40 minutes of drug administration, the majority of adverse events reported were mild.[27,28]

Limitations

In our study, less than four percent of high-risk groups were infected with COVID-19 compared to the expected value of 8%.[2] Since most COVID-19 infections were among the elderly, some with underlying diseases, they tended to avoid engaging in high-risk activities. Therefore, the incidence of COVID-19 reported in our study was lower than expected. Recall bias may be attributable to undetected mild symptoms or asymptomatic cases, which were difficult to identify through weekly phone interviews over six months.

Recommendations

The country's COVID-19 preparedness strategy aims to develop a broad range of prevention and treatment options using both existing and innovative technologies. Early in the pandemic, it could still be crucial to offer pre-exposure prophylaxis or treatments with monoclonal antibodies (including LAAB) to protect high-risk groups, especially those with compromised immune systems who may not respond well to vaccinations, but timely development and administration of the antiboodies is essential in pandemic preparedness.[29–32]

Conclusion

Although tixagevimab-cilgavimab was associated with only mild adverse reactions, there was no statistically significant evidence of its effectiveness in preventing COVID-19 infections or severe outcomes among high-risk groups in Thailand. The year 2023 was during the recovery phase of the pandemic. Most of the population, including immunocompromised and other high-risk individuals, had been vaccinated and had previous natural infections. Tixagevimab-cilgavimab may still have some potential benefit in future pandemics if it is developed rapidly and provided to target populations at appropriate time points.

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Conflicts of Interests

The authors declare no conflicts of interest related to the work presented in this manuscript.

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