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Real-World Effectiveness and Safety of Tixagevimab-Cilgavimab: A Target Trial Emulation Study

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Background

Immunocompromised individuals are at high risk of SARS-CoV-2 infection and subsequent severe / fatal COVID-19, yet they have suboptimal response to mRNA & inactivated COVID-19 vaccines.

Objectives

This study aims to evaluate the real-world effectiveness and safety of tixagevimab-cilgavimab for COVID-19 prophylaxis among immunocompromised individuals.

Methods

- **Study design and data source:** target trial emulation using territory-wide electronic health databases in Hong Kong
- **Eligibility:** immunocompromised individuals aged ≥12 years from 1 May to 30 Nov 2022. Those with previous COVID-19 vaccination or infection remains eligible.
- **Treatment strategies:** receipt of a single dose of tixagevimab-cilgavimab, *vs.* not receiving tixagevimab-cilgavimab
- **Outcomes:** COVID-19 infection, COVID-19-related hospitali-sation and mortality, severe COVID, adverse events
- **Matching**: a sequence of trials was emulated for each day during the inclusion period, where each eligible tixagevimab-cilgavimab recipient was matched to 4 eligible controls based on age, sex, COVID-19 vaccination and infection status, baseline comorbidities and chronic medication use.

Table 1. Baseline characteristics

Characteristic	Tixagevimab-cilgavimab (N=746)	Controls (N=2980)	SMD
Age, years - mean (SD)	60.97 (13.45)	61.45 (13.23)	0.036
Sex, male (%)	403 (54.0)	1610 (54.0)	<0.001
Charlson Comorbidity Index - mean (SD)	4.00 (2.01)	3.98 (1.98)	0.010
History of COVID-19 infection (%)	186 (24.9)	742 (24.9)	0.001
Days since last infection - mean (SD)	229.32 (86.28)	237.24 (66.59)	0.103
Days since last COVID-19 vaccine dose - mean (SD)	165.73 (110.44)	157.61 (105.30)	0.075
Immunocompromised condition (%)			
Cancer	586 (78.6)	2336 (78.4)	0.004
Solid organ transplant	24 (3.2)	86 (2.9)	0.019
Hematopoietic stem cell transplant	204 (27.3)	761 (25.5)	0.041
Primary immunodeficiency	6 (0.8)	17 (0.6)	0.028
Immune-mediated inflammatory disorders	71 (9.5)	308 (10.3)	0.027
Splenectomy, asplenia	0 (0.0)	0 (0.0)	<0.001
End-stage renal disease, dialysis	28 (3.8)	96 (3.2)	0.029
COVID-19 vaccination status (%)			0.003
Unvaccinated	61 (8.2)	244 (8.2)	
1 dose	29 (3.9)	114 (3.8)	
2 doses	154 (20.6)	616 (20.7)	
3+ doses	502 (67.3)	2006 (67.3)	
Comorbidities – no. (%)			
Chronic kidney disease	59 (7.9)	210 (7.0)	0.033
Respiratory disease	25 (3.4)	71 (2.4)	0.058
Diabetes	103 (13.8)	359 (12.0)	0.052
Cardiovascular disease	217 (29.1)	859 (28.8)	0.006
Dementia	1 (0.1)	4 (0.1)	<0.001
Immunosuppressive therapy (%)			
Chemotherapy	447 (59.9)	1784 (59.9)	0.001
Radiotherapy	0 (0.0)	0 (0.0)	<0.001
Disease-modifying antirheumatic drugs	88 (11.8)	348 (11.7)	0.004
Immunosuppressants	438 (58.7)	1748 (58.7)	0.001

Results

- 746 tixagevimab-cilgavimab recipients and 2980 controls were included. 67.3% received ≥3 COVID-19 vaccine doses (BNT162b2/CoronaVac) but on average 160 days had passed since their last dose. 24.9% had previous COVID-19 infection.
- During a median follow-up of 60 days, 52 and 286 COVID-19 infections, 21 and 92 COVID-19 hospitalisation, 0 and 8 COVID-19 mortality, 0 and 2 severe COVID were observed among recipients and controls respectively.
- Tixagevimab-cilgavimab was associated with a significantly reduced risk of COVID-19 infection (HR 0.708, 95%CI: 0.527-0.951). No significant difference for COVID-19-related hospitalisation (HR 0.902, 95%CI: 0.562-1.449).
- Risk reduction in COVID-19 infection was consistent in those vaccinated with ≥3 doses or had prior COVID-19 infection.

Figure. 60-day cumulative incidence of outcomes

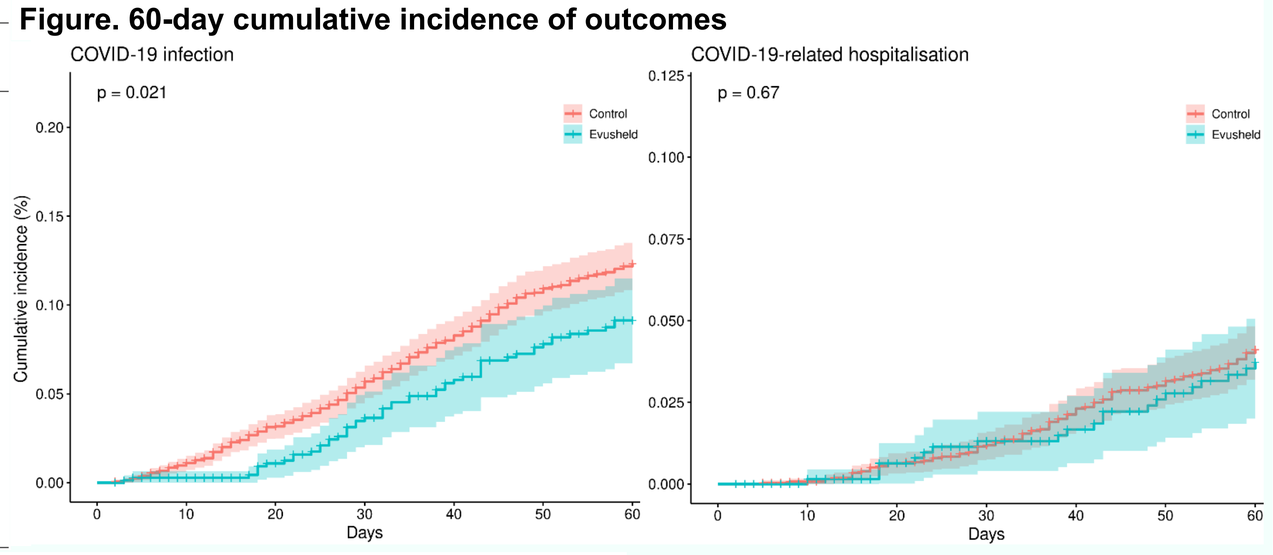

Table 2. Incidence rates of adverse events (per 10000 person-years)

Adverse events of special interest (AESIs)	Tixagevimab-cilgavimab Events	Tixagevimab-cilgavimab Incidence rate	Controls Events	Controls Incidence rate
Anaphylaxis and autoimmune				
Anaphylaxis	0	0	3	0.217 (0.045-0.635)
Acute aseptic arthritis	0	0	1	0.072 (0.002-0.401)
Acute disseminated encephalomyelitis	0	0	0	0
Guillain-Barré Syndrome	0	0	0	0
Idiopathic thrombocytopenia	0	0	3	0.227 (0.047-0.664)
Narcolepsy	0	0	1	0.073 (0.002-0.407)
Subacute thyroiditis	0	0	0	0
Type 1 Diabetes	0	0	0	0
Cardiovascular system				
Major CVD (heart failure, stroke, coronary artery disease)	1	0.312 (0.008-1.74)	4	0.316 (0.086-0.81)
Heart failure	0	0	2	0.144 (0.017-0.52)
Myocardial Infarction	0	0	1	0.075 (0.002-0.418)
Arrhythmia	0	0	2	0.148 (0.018-0.536)
Microangiopathy	0	0	0	0
Myocarditis	0	0	0	0
Pericarditis	0	0	0	0
Hepato-renal system				0
Acute kidney injury	0	0	0	0
Acute liver injury	0	0	0	0
Acute pancreatitis	0	0	0	0
Circulatory system				
Thromboembolism	1	0.299 (0.008-1.667)	5	0.378 (0.123-0.883)
Ischemic stroke	0	0	2	0.143 (0.017-0.518)
Transient ischemic attack	1	0.282 (0.007-1.573)	0	0
Intracranial hemorrhage	0	0	0	0
Gastrointestinal bleeding	0	0	4	0.292 (0.079-0.747)
Other bleeding	0	0	0	0
Hemorrhagic disease	0	0	3	0.231 (0.048-0.675)
Single Organ Cutaneous Vasculitis	0	0	0	0
Nervous system				0
Bell's Palsy	0	0	0	0
Herpes zoster	2	0.609 (0.074-2.199)	5	0.388 (0.126-0.905)
Meningoencephalitis	0	0	0	0
Seizure	0	0	1	0.072 (0.002-0.399)
Transverse myelitis	0	0	0	0
Skin and musculoskeletal				0
Chilblain-like lesions	0	0	0	0
Erythema multiforme	0	0	0	0
Rhabdomyolysis	0	0	0	0

Table 3. Subgroup analyses

Outcome	Hazard ratio (95% CI)
COVID-19 infection	
Age <60 years	0.621 (0.371-1.040)
Age ≥60 years	0.762 (0.531-1.093)
Male	0.723 (0.479-1.090)
Female	0.692 (0.452-1.059)
CCI 0-3	0.560 (0.336-0.934)
CCI ≥4	0.816 (0.568-1.173)
Previous vaccination: 3+ doses	0.636 (0.449-0.901)
Previous vaccination: none, 1 or 2 doses	0.970 (0.551-1.707)
History of COVID-19 infection	0.576 (0.245-1.357)
No previous COVID-19 infection	0.728 (0.532-0.998)
COVID-19-related hospitalization	
Age <60 years	0.864 (0.354-2.105)
Age ≥60 years	0.936 (0.535-1.638)
Male	0.817 (0.427-1.565)
Female	1.018 (0.508-2.039)
CCI 0-3	0.542 (0.190-1.550)
CCI ≥4	1.092 (0.640-1.863)
Previous vaccination: 3+ doses	0.879 (0.492-1.568)
Previous vaccination: none, 1 or 2 doses	0.952 (0.417-2.174)
History of COVID-19 infection	0.462 (0.107-1.998)
No previous COVID-19 infection	1.004 (0.607-1.661)

- **Index date** for recipients is the date of first tixagevimab-cilgavimab prescription. Index date for controls were assigned as per their matched tixagevimab-cilgavimab recipients.
- **Follow-up:** from index date till outcome occurrence, death, 60 days after index, or end of the study (January 31, 2023)
- **Causal estimand:** observational analogue of the average treatment effect of tixagevimab-cilgavimab
- **Statistical analysis:** Kaplan Meier and Cox regression

Discussion and Limitations

- Even though tixagevimab-cilgavimab have reduced neutralizing activity against newer XBB variants, this study shows that it still has a protective role among the immunocompromised who may have poor vaccine response after 4 or even 5 booster doses, especially in regions where BA.2 and BA.5 are still predominant.
- Absolute incidence for all adverse events were low (<1 / 10000-person-days). Only 1 transient ischemic attack and 2 herpes zoster cases occurred in tixagevimab-cilgavimab group.

Discussion and Limitations (cont'd)

- >60% of subjects in this study were vaccinated with three doses, in contrast to PROVENT and TACKLE RCT studies which recruited subjects without COVID-19 vaccination.
- Limited statistical power to evaluate the risk of rare adverse events. Some asymptomatic COVID-19 infection may not be captured.

Conclusions

Tixagevimab-cilgavimab was effective in reducing COVID-19 infection among immunocompromised individuals during an Omicron outbreak, including those with prior COVID-19 vaccination or infection. Further studies are warranted to confirm its safety in a larger real-world population.