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The safety signal detection and analysis of monoclonal antibodies against SARS-CoV-2 based on real-world evidence – the suitable selectivity for different populations

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Abstract. – OBJECTIVE: Bebtelovimab (BEB), Tixagevimab/Cilgavimab (TIX/CIL), and Sotrovimab (SOT) are important agents against the severe acute respiratory syndrome coronavirus 2-Omicron strain. However, due to their short duration of application, little is known about their safety profiles. This research aimed to explore the safety profile of these monoclonal antibodies (mAbs) *via* real-world evidence databases and data mining tools.

MATERIALS AND METHODS: Safety reports were retrieved from the database of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System from April 2022 to March 2023. To detect the safety signal, the disproportionality analysis was performed using the reporting odds ratio method.

RESULTS: SOT had the greatest proportion of "skin and subcutaneous tissue disorders" and "disorders of investigations"; BEB showed significant associations with "gastrointestinal disorders" and "nervous system disorders"; TIX/CIL had the weakest correlation with "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions". Furthermore, there were still other signals related to nervous system disorders, gastrointestinal disorders only caused by BEB. TIX/CIL has been reported solely to be associated with multiple types of cardiovascular disorders. As for SOT alone, signals were strongly related to infusion reactions and hypersensitivity.

CONCLUSIONS: In summary, SOT may be unsuitable for allergic patients and may lead to abnormal test results. BEB showed the highest correlations with gastrointestinal and neuropsychiatric events. In addition, its infusion reactions should also be noted. TIX/CIL can lead to a variety of cardiovascular events.

Key Words:
Monoclonal antibodies, SARS-CoV-2, Omicron, Safety profile, FDA adverse event reporting system.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak-related respiratory injury has been a persistent global public health issue, with more than 770 million confirmed infections and 6.9 million deaths up until now. As it is highly infectious and has a poor prognosis, COVID-19 has brought greater pressure to human society than ever[1]. After being classified as a "Variant of Interest" (VOI) by the World Health Organization (WHO) on August 9th, 2023, COVID-19 mutant EG.5 has once again interfered with people's lives once again. The epidemiological data[2] indicated that EG.5 may possess a higher level of transmissibility, thus rekindling public concern regarding the COVID-19 pandemic. Various biologics have been developed as prophylactic or therapeutic strategies. Of these, monoclonal antibodies (mAbs) have attracted the most attention due to their specificity and sensitivity. The U.S. Food and Drug Administration (FDA) advocated that mAbs therapy can be used with emergency authorization in high-risk groups at an early period to reduce the risk of hospitalization and mortality[3,4]. Bamlanivimab-Etesevimab and Casirivimab-Imdevimab, which were previously used, are not currently employed for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) due to their low sensitivity to the virus mutation[5]. Bebtelovimab (BEB), Sotrovimab (SOT), and Tixagevimab/Cilgavimab (TIX/CIL) are considered anti-omicron agents *in vitro*. However, due to the short time of usage, the evaluation of the safety profile was limited, and the current research mainly uses ran-

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domized controlled trials (RCTs) and systematic reviews concerning the effectiveness data rather than those of the safety profile, which may lack adequate statistical power. The objective of this study was to investigate the safety characteristics of these mAbs using real-world evidence databases and data mining techniques.

Materials and Methods

Data Sources and Procedures

The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a database used by the FDA to collect safety profiles of post-marketing drugs and pharmacological biological agents. Any drug-related safety issue found by doctors, pharmacists, or patients is required to be reported *via* this system. In this study, all safety data of BEB, TIX/CIL, and SOT were retrieved and extracted from the FAERS database from April 2022 to March 2023. The search terms were set as "BEBTELOVIMAB", "LY-CoV1404", "LY-CoV-1404", "LY-3853113", "LY3853113"; "Tixagevimab/cilgavimab", "Evusheld", "AZD7442", "AZD-7442", "AZD1061 and AZD8895", "AZD 7442"; "SOTROVIMAB", "Xevudy", "VIR-7831", "VIR7831", "GSK-4182136", "GSK4182136". Then, we selected adverse drug event (ADE) reports that used BEB, TIX/CIL, and SOT as the primary suspected targets (PSs) and focused the analysis of the reports on the drugs that were most likely to cause ADEs[6]. After that, we excluded the duplicate, incomplete, or incorrect reports according to the FDA recommendation[7]. Finally, the symptoms of ADEs, which were difficult to distinguish, were not included in this study to reduce bias further (Figure 1).

Data Standardization

To ensure the consistency of original data, all ADEs were encoded according to the preferred terms (PTs) in the Standardized Regulatory Activity Medical Dictionary 24.0 (MedDRA 24.0), including five categories: System Organ Category (SOC), high-level group term (HLGT), high-lev-

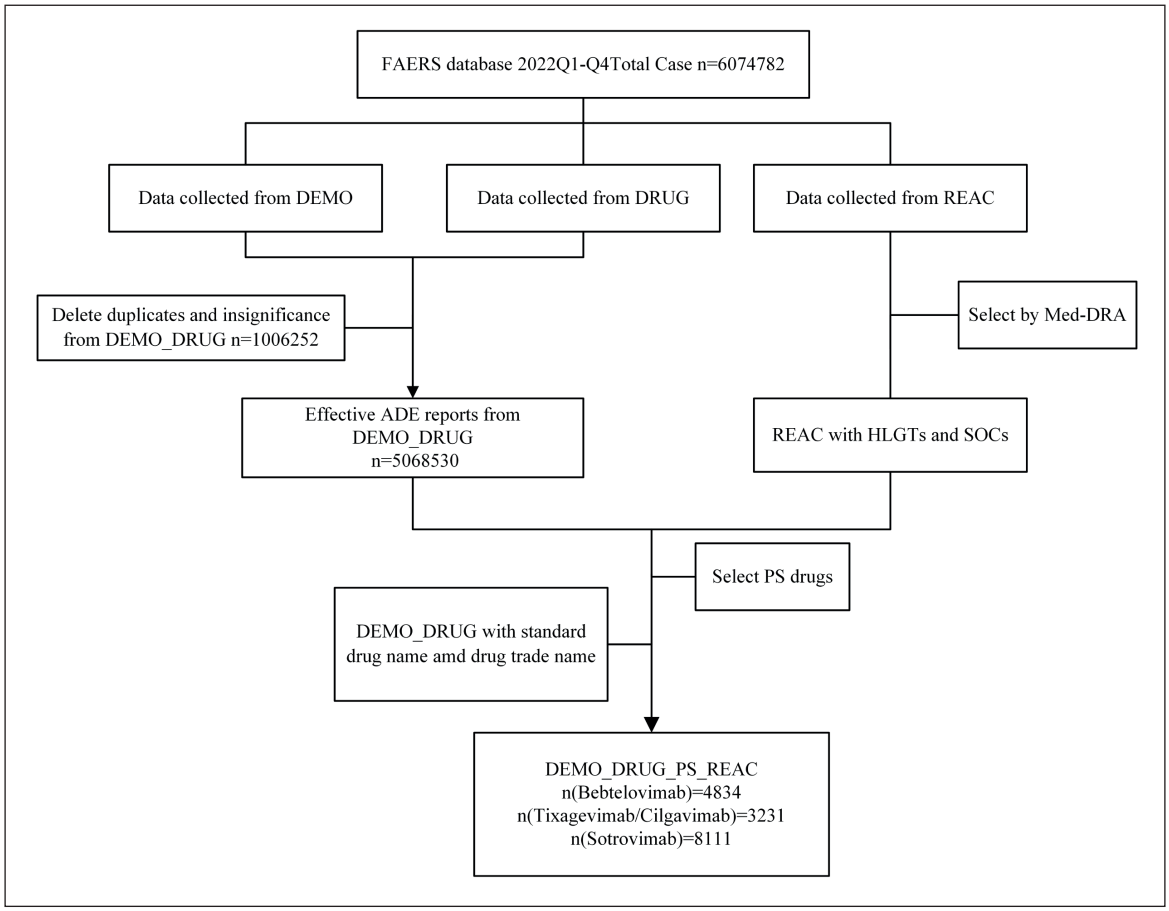

Figure 1. Flowchart of data collection process.

el term (HLT), preferred term (PT), and Lowest Level Term (LLT). Of these, the SOC and PT were used for ADE signal detection. Although a single PT can be grouped into multiple SOCs, a primary SOC exists, which was adopted in this study. Finally, to ensure the accuracy of the results, further exclusion was conducted based on the following criteria: (1) the reports of unclear description or not an ADE; (2) the symptoms of reports cannot be distinguished from the primary disease.

Signal Mining

Disproportionality analysis is the most important method for ADE signal mining, and this can be considered as a case-control study. This study used the reporting odds ratio (ROR) method, which is part of disproportionality analysis. Its advantage lies in the fact that it can easily calculate and estimate the relative risks with high reliability of calculation results and detect spontaneous signals alone[8,9], instead of combining with other methods[10]. In this study, we calculated the ROR values using two-by-two contingency tables of reported event counts for specific drugs and other drugs, respectively, to explore a signal for a potentially increased risk of ADEs (Table I)[11]. If the number of one PT is greater than 3 and the ROR -1.96 SE is greater than 1, a signal is generated suggesting a possible correlation between ADE and drug exposure.

Signal Intensity

ROR sometimes could partially represent the odds of ADEs when individuals are exposed to the agents and is considered a measure of the association between the exposure agents and ADEs. However, it may not be accurate enough. The signal intensity is more effective in depicting the relationship between agents and ADEs, making it a crucial measurement for signal recognition. Meanwhile, it may also reflect the ratios of ADEs to some extent. Based on the calculated response values, the signal intensity can be divided into three categories: $1 < \text{ROR-1.96 SE} < 50$ (weak); $50 \leq \text{ROR-1.96 SE} < 1{,}000$ (medium); $1{,}000 \leq$ ROR-1.96 SE (strong)[12].

Data Control Study

After all mAb signals were detected and analyzed, the total signal intensity of different SOCs was first compared to illustrate the differences in the magnitude of ADE risks caused by different mAbs in specific SOCs and the distribution of ADE signals. Then, the signal strength of the same PT and the signal number detected by only one mAb were also compared to demonstrate the distribution of ADE signals in one SOC.

Table I. Two-by-two contingency table for disproportionality analysis.

	Target event	Other events	Sums
Target drug	a	b	a+b
Other drugs	c	d	c+d
Sums	a+c	b+d	a+b+c+d

ROR = (a*d)/(c*b)
Upper 95% CI = ROR+1.96 SE = $e^{\ln(ROR) + 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}}$
Lower 95% CI = ROR-1.96 SE = $e^{\ln(ROR) - 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}}$

Results

The Signal Intensity Distribution of Three mAbs in Different SOC

SOT correlated with higher skin and subcutaneous tissue disorders [SOT, ROR: 4.85, 95% CI (4.42-5.33); BEB, ROR: 3.92, 95% CI (3.49-4.39); TIX/CIL, ROR: 2.70, 95% CI (2.27-3.21)]. Moreover, SOT had a closer relationship with "abnormal investigation results" than TIX/CIL [SOT, ROR: 5.87, 95% CI (5.12-6.72); TIX/CIL, ROR: 3.62, 95% CI (2.79-4.69)]. The ADE signals of ocular disorders by SOT were stronger [SOT, ROR: 9.79, 95% CI (5.88-16.28); BEB, ROR: 2.49, 95% CI (2.00-3.00)], although the symptoms were not severe.

The results demonstrated a stronger correlation between BEB and gastrointestinal disorders [BEB, ROR: 3.44, 95% CI (3.07-3.85); TIX/CIL, ROR: 2.00, 95% CI (1.63-2.45); SOT, ROR: 2.20, 95% CI (1.96-2.46)] and nervous system disorders [BEB, ROR: 3.95, 95% CI (3.59-4.34); TIX/CIL, ROR: 3.06, 95% CI (2.62-3.57); SOT, ROR: 2.56, 95% CI (2.28-2.87)]; TIX/CIL exhibited a lower ROR value, indicating a smaller likelihood of "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions" occurring with this drug, compared with BEB and SOT [TIX/CIL, ROR: 3.24, 95% CI (2.87-3.65); BEB, ROR: 5.26, 95% CI (4.76-5.81); SOT, ROR: 5.47, 95% CI (4.93-6.06)]. In cardiac disorders, there was no significant difference in signal intensity among the three mAbs (Figure 2).

Signal Intensity Distribution of Three mAbs in the Same PT

BEB had the strongest statistical association with the highest positive signal values of nausea [ROR: 3.75 95% CI (3.23-4.35)], dizziness [ROR:

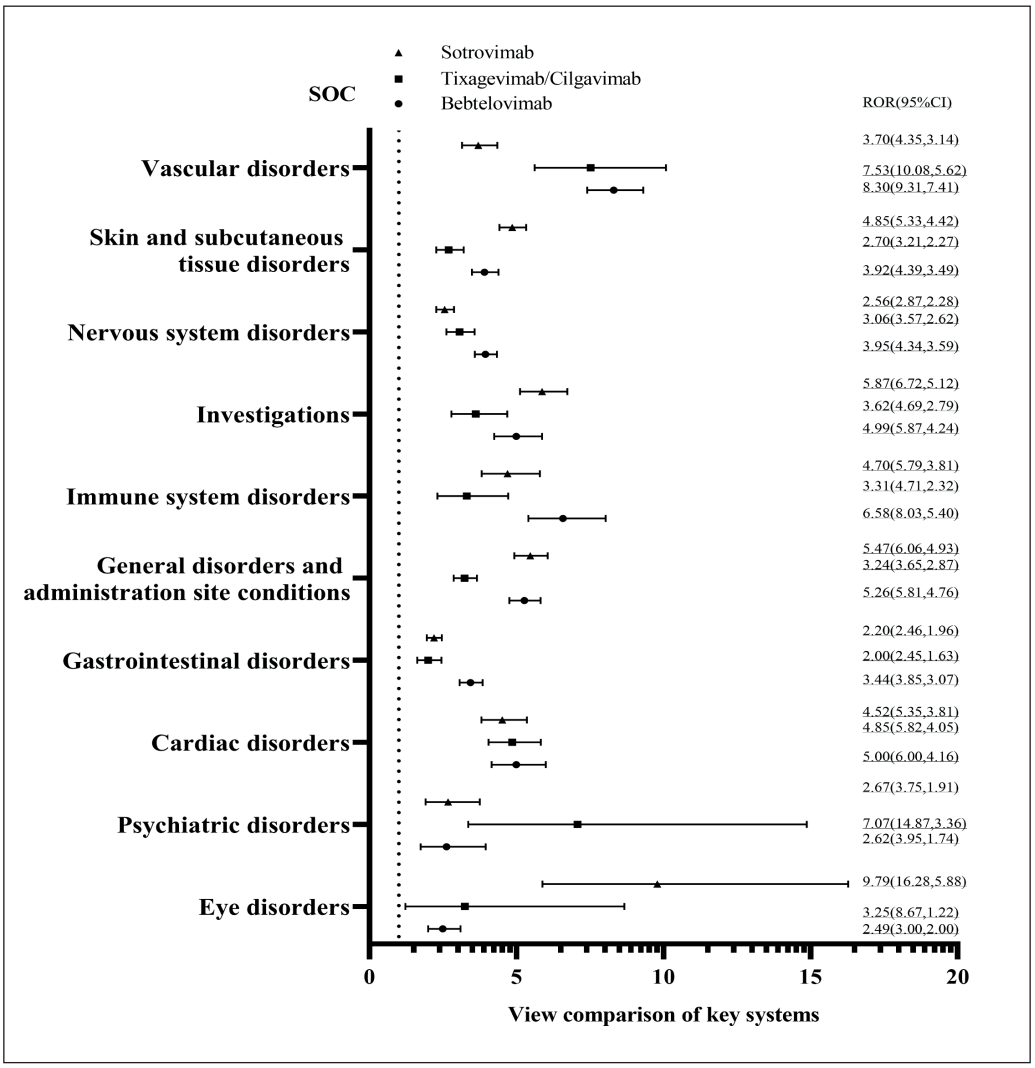

Figure 2. The signal intensity distribution of Sotrovimab, Tixagevimab/Cilgavimab, and Bebtelovimab in different system organ categories (SOC), horizontal coordinate: reporting odds ratio (ROR), vertical coordinate: SOC.

5.94 95% CI (5.11-6.91)], flushing [ROR: 45.41 95% CI (39.34-52.42)] and hyperhidrosis [ROR: 9.71 95% CI (7.74-12.18)] compared with the other two mAbs. SOT was the most reported drug in pruritus [ROR: 4.02 95% CI (3.34-4.83)], rashes [ROR: 3.67 95% CI (3.06-4.4)] and pyrexia cases [ROR: 7.48 95% CI (6.5-8.61)] (Figure 3).

Distribution of Signals Caused by Only One mAbs

The more PTs of ADE signals caused by only one mAb in a SOC, the more concern was given to the safety profile of this agent. Notably, when there were more signal PTs related to ocular disorders only caused by BEB, some events were severe, such as acute macular neuroretinopathy [ROR: 70.4 95% CI (22.06-224.66)]. Furthermore, there were still other PTs related to nervous system disorders and gastrointestinal disorders by BEB. It suggests that there were indeed potential safety risks in these SOCs (Table II).

In our research, TIX/CIL has been found solely to cause multiple types of cardiovascular disorder signals with higher ROR values, mainly thrombotic disease. Meanwhile, it is notable that in non-cardiovascular PTs, a significant number of signals may be related to embolisms. Also, numerous signal PTs associated with infections by TIX/CIL alone have not been reported previously and warrant further confirmation (Table III).

For SOT alone, signals were mainly related to the infusion and hypersensitivity, including pap-

ule, pruritic, rash macular, anaphylactoid reaction, infusion site rash, etc. Besides, SOT has been found to cause signals of anaphylactic shock, which have not been reported in other drugs in our research (Table IV).

The Emerging ADE Signals

The ADE signals detected in this study were all new reports except for infusion-related reactions, pruritus, rash, headache, fatigue, cough, rash, diarrhea, and hypersensitivity adverse reactions.

Discussion

BEB, TIX/CIL, and SOT are the three mAbs effective against omicron strains of SARS-CoV-2. They were considered useful and safe agents in RCTs. Although the effectiveness evaluation may be sufficient, their safety cannot be elaborated fully in RCTs. It is necessary to comprehensively evaluate the safety profile, depending on the big data platforms used for post-listing.

BEB is the latest embodiment of science and

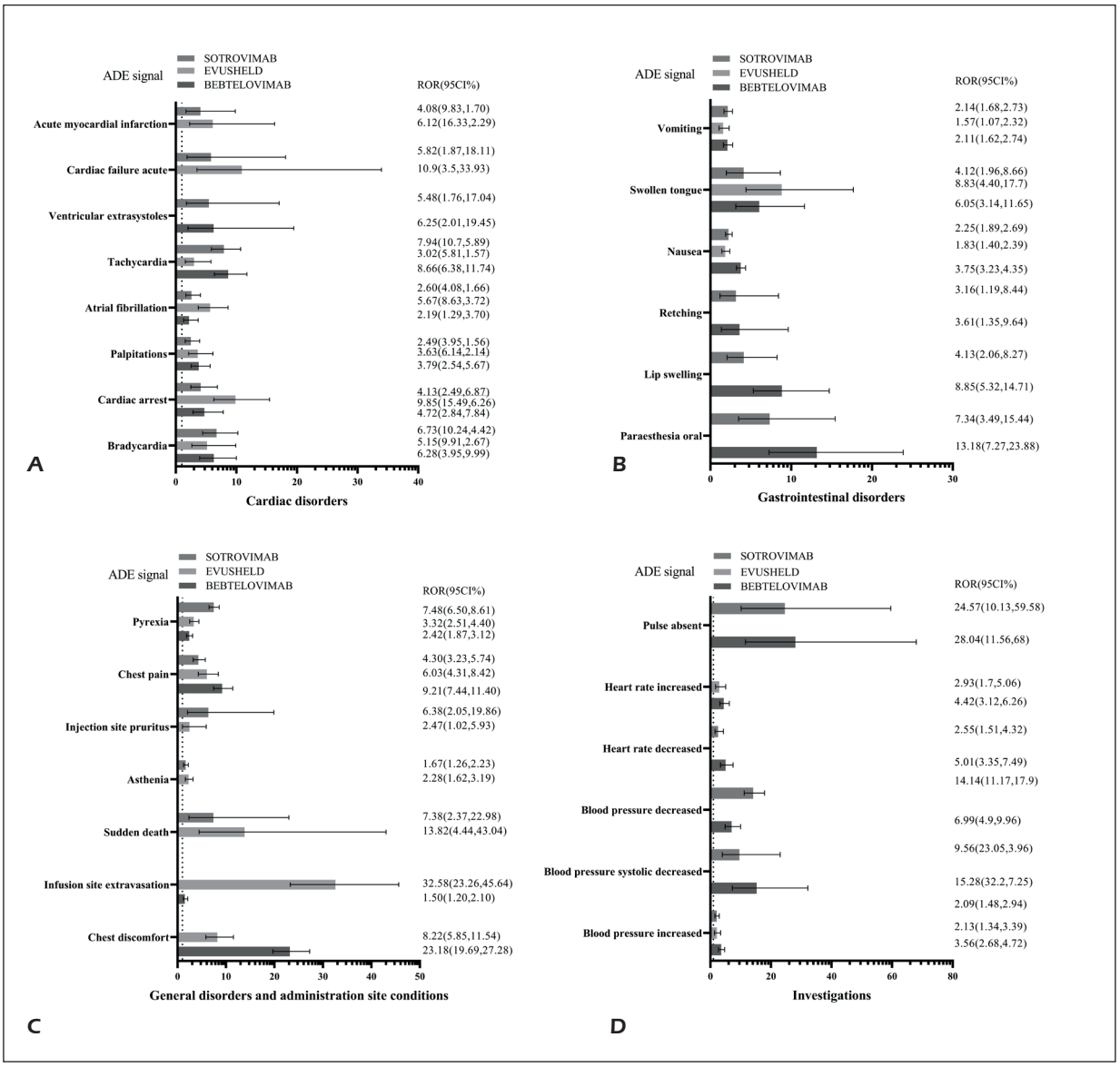

Figure 3. The signal intensity distribution of Sotrovimab, Tixagevimab/Cilgavimab, and Bebtelovimab in the same preferred term (PT). **A**, Cardiac disorders, (**B**) Gastrointestinal disorder, (**C**) General disorders and administration site conditions, (**D**) Investigations, (**E**) Nervous system disorders, (**F**) Skin and subcutaneous tissue disorders, (**G**) Vascular disorders, (**H**) Immune system disorders. Horizontal coordinate: reporting odds ratio (ROR), vertical coordinate: PT.

Figure continued

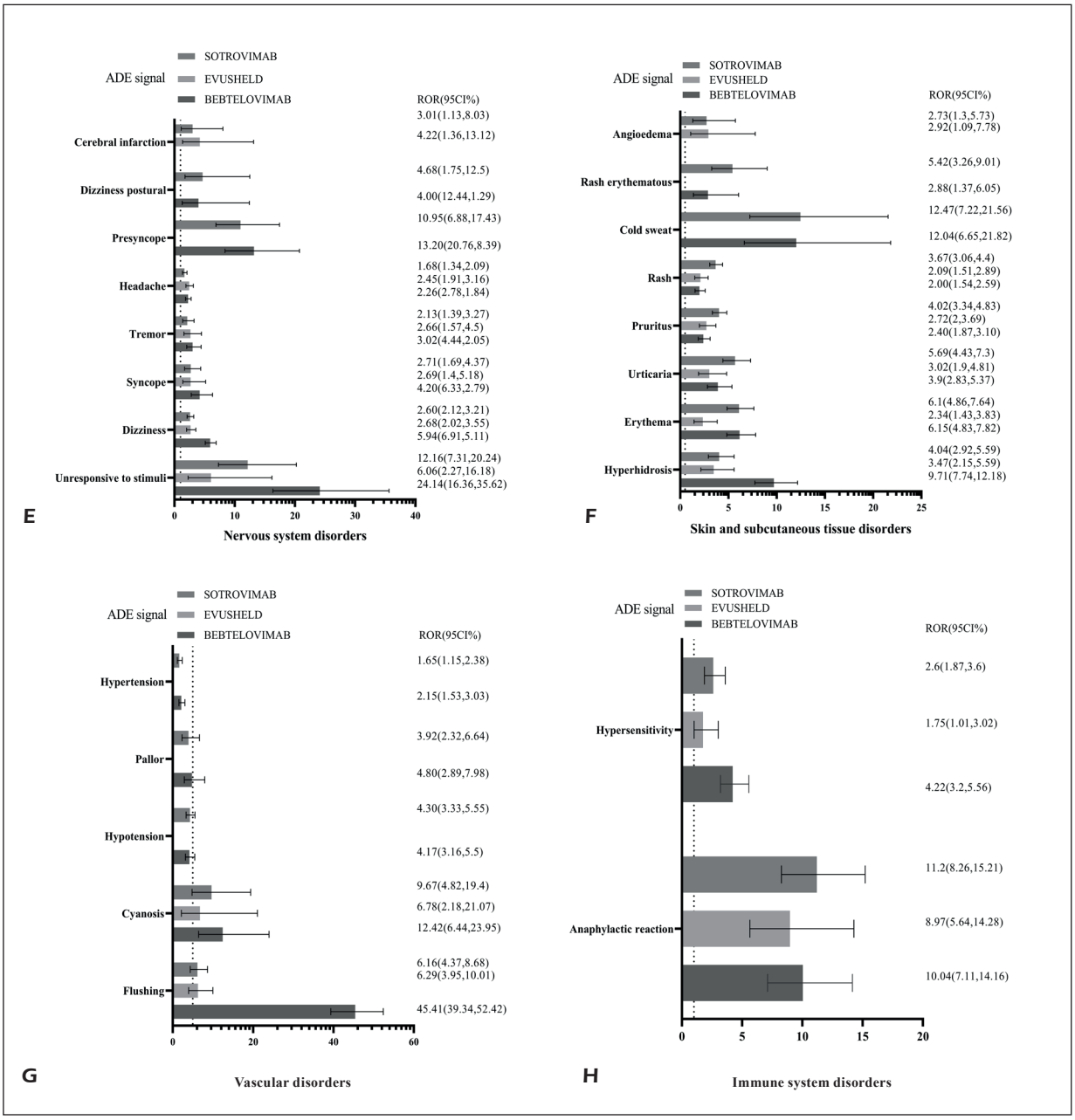

Figure 3 ***(Continued).*** The signal intensity distribution of Sotrovimab, Tixagevimab/Cilgavimab, and Bebtelovimab in the same preferred term (PT). **A**, Cardiac disorders, (**B**) Gastrointestinal disorder, (**C**) General disorders and administration site conditions, (**D**) Investigations, (**E**) Nervous system disorders, (**F**) Skin and subcutaneous tissue disorders, (**G**) Vascular disorders, (**H**) Immune system disorders. Horizontal coordinate: reporting odds ratio (ROR), vertical coordinate: PT.

technology in facing health emergencies, a hybrid of genetic engineering and artificial intelligence in medicine. It was isolated *via* high-throughput B cell screening from a COVID-19 convalescent donor and screened among thousands of antibodies to ensure maximum neutralization and safety[13]. In this study, it was found that BEB may be more likely to be associated with ADEs of gastrointestinal and nervous system disorders. Nausea and dizziness may contribute to this effect significantly. Additionally, ADE signals caused by BEB only in these two SOCs are more than those by the other two mAbs. This evidence tends to reveal the high correlation between BEB and gastrointestinal or neurological disorders. Nevertheless, these ADEs are generally mild and usually do not cause discontinuation. The correlation between BEB and hyperhidrosis or flushing, which are mainly infusion reactions, was higher than SOT and TIX/CIL. This mechanism needs more investigation. While

Table II. The distribution of signals caused by Bebtelovimab alone.

Preferred Term	System Organ Category	ROR	95% CI upper-bound	95% CI lower-bound
Fear	Psychiatric disorders	6.37	13.40	3.03
Nervousness	Psychiatric disorders	3.73	6.94	2.00
Hallucination, auditory	Psychiatric disorders	3.28	10.19	1.06
Anxiety	Psychiatric disorders	2.18	2.98	1.60
Pulse abnormal	Investigations	17.38	54.29	5.56
Pyelonephritis	Infections and infestations	4.87	15.15	1.57
Acute macular neuroretinopathy	Eye disorders	70.40	224.66	22.06
Eye movement disorder	Eye disorders	11.12	29.77	4.16
Visual impairment	Eye disorders	1.91	3.12	1.17
Atrioventricular block first degree	Cardiac disorders	13.10	40.86	4.20
Hot flush	Vascular disorders	2.19	3.77	1.27
Head discomfort	Nervous system disorders	4.94	10.39	2.35
Ageusia	Nervous system disorders	3.95	8.31	1.88
Burning sensation	Nervous system disorders	3.01	5.19	1.74
Hypoesthesia	Nervous system disorders	1.66	2.72	1.02
Somnolence	Nervous system disorders	1.62	2.57	1.02
Immediate post-injection reaction	General disorders and administration site conditions	54.65	173.32	17.23
Swelling face	General disorders and administration site conditions	4.39	7.29	2.64
Sensation of foreign body	General disorders and administration site conditions	8.03	21.46	3.00
Feeling abnormal	General disorders and administration site conditions	3.79	4.90	2.94
Feeling jittery	General disorders and administration site conditions	6.55	15.78	2.72
Malaise	General disorders and administration site conditions	1.48	2.01	1.09
Abdominal pain lower	Gastrointestinal disorders	4.95	10.41	2.36
Abdominal pain	Gastrointestinal disorders	2.22	3.08	1.60
Toothache	Gastrointestinal disorders	3.36	8.97	1.26
Tongue discoloration	Gastrointestinal disorders	13.66	42.62	4.38
Feces discolored	Gastrointestinal disorders	3.28	8.76	1.23
Tinnitus	Ear and labyrinth disorders	3.30	6.61	1.65

there have been reports[14] of severe allergic-like reactions during administration, this study did not show a significant correlation between hypersensitivity and BEB compared with SOT and TIX/CIL. If the high allergenicity of SOT and warning of hypersensitivity by Polysorbate 80 excipient in TIX/CIL are taken into account[15], BEB may be a suitable alternative agent for patients with the risk of hypersensitivity when the small molecule antiviral drugs are unavailable.

In addition, BEB may be correlated with more acute macular neuroretinopathy, eye movement disorders, and visual impairment cases, while SOT is correlated with more eyelid edema and swelling cases. SOT had a significantly greater reported association with ocular adverse events than BEB, but given the severity of BEB's symptoms, it may raise security concerns. Thus, taking the above considerations into account, TIX/CIL appears to be more suitable for patients with pre-existing ocular diseases.

TIX/CIL was derived from B lymphocytes of two convalescent patients with SARS-CoV-2 infection. A subset of these antibodies bound to the recombinant receptor-binding domain (RBD) and exhibited neutralizing properties in a quantitative focus reduction neutralization test (qFRNT)[16,17].

We observed that TIX/CIL was associated with more cardiovascular ADEs, although it is still controversial[18,19]. This study found that TIX/CIL had the greatest proportion of the overall cardiovascular ADEs compared with SOT and BEB. It should be noted that there were more cardiovascular signal PTs by TIX/CIL alone than the others, including embolisms, arrhythmias, and heart failure. Therefore, the cardiovascular ADEs of TIX/CIL should not be ignored.

In this study, TIX/CIL was found to increase the risk of infections such as aseptic meningitis, septic shock, and endocarditis. However, due to the absence of other reports, this conclusion needs to be further confirmed by prospective studies.

To our knowledge, SOT was obtained from memory B lymphocytes immortalized with the Epstein-Barr virus from an individual infected with SARS-CoV in 2003. It is a human IgG1k mAbs against pan-arbovirus, capable of neutralizing SARS-CoV-2, SARS-CoV-1, and several

Table III. The distribution of signals caused by Tixagevimab/Cilgavimab alone.

Preferred Term	System Organ Category	ROR	95% CI upper-bound	95% CI lower-bound
Aortic thrombosis	Vascular disorders	109.53	299.00	40.13
Hypertensive urgency	Vascular disorders	95.99	304.99	30.21
Deep vein thrombosis	Vascular disorders	10.39	17.60	6.14
Dermatitis bullous	Skin and subcutaneous tissue disorders	14.95	46.55	4.80
Cerebral thrombosis	Nervous system disorders	42.09	113.26	15.64
Bell's palsy	Nervous system disorders	16.87	52.56	5.41
Hemorrhage intracranial	Nervous system disorders	10.05	31.27	3.23
Myasthenia gravis	Nervous system disorders	8.69	27.03	2.80
Guillain-Barre syndrome	Nervous system disorders	34.18	72.19	16.19
Bedridden	Nervous system disorders	5.91	18.37	1.90
Generalized tonic-clonic seizure	Nervous system disorders	5.19	16.14	1.67
Blood lactic acid increased	Investigations	13.31	41.44	4.28
White blood cell count increased	Investigations	4.64	10.34	2.08
Heart rate irregular	Investigations	3.66	9.77	1.37
Meningitis aseptic	Infections and infestations	19.58	61.06	6.28
Endocarditis	Infections and infestations	17.39	54.18	5.58
Septic shock	Infections and infestations	8.17	14.41	4.63
Sepsis	Infections and infestations	2.30	4.43	1.20
Eye swelling	Eye disorders	3.25	8.67	1.22
Acute cardiac event	Cardiac disorders	252.43	832.69	76.52
Ventricular fibrillation	Cardiac disorders	17.90	43.20	7.42
Acute coronary syndrome	Cardiac disorders	15.67	48.80	5.03
Ventricular tachycardia	Cardiac disorders	3.02	5.81	1.57
Myocardial infarction	Cardiac disorders	3.60	6.35	2.04
Myocarditis	Cardiac disorders	5.53	17.17	1.78
Cardiac failure	Cardiac disorders	2.31	4.84	1.10
Cardiac disorder	Cardiac disorders	2.13	4.48	1.02
Splenic necrosis	Blood and lymphatic system disorders	378.64	1,286.36	111.45
Hemolytic anemia	Blood and lymphatic system disorders	33.19	70.07	15.72
Agranulocytosis	Blood and lymphatic system disorders	12.45	26.21	5.92
Lymphadenopathy	Blood and lymphatic system disorders	4.42	9.85	1.98
Shock	Vascular disorders	2.71	7.24	1.02
End stage renal disease	Renal and urinary disorders	5.10	13.62	1.91
Acute kidney injury	Renal and urinary disorders	2.09	3.53	1.23
Insomnia	Psychiatric disorders	11.35	30.34	4.25
Chills	General disorders and administration site conditions	7.23	9.97	5.25
Multiple organ dysfunction syndrome	General disorders and administration site conditions	5.18	10.88	2.46
Generalized edema	General disorders and administration site conditions	6.76	21.01	2.17
Feeling abnormal	General disorders and administration site conditions	2.06	3.20	1.32
Fatigue	General disorders and administration site conditions	1.65	2.12	1.29
General physical health deterioration	General disorders and administration site conditions	2.20	3.88	1.25
Mouth swelling	Gastrointestinal disorders	15.54	41.58	5.81
Gastrointestinal hemorrhage	Gastrointestinal disorders	2.68	7.14	1.00
Ear discomfort	Ear and labyrinth disorders	7.00	21.77	2.25
Vertigo	Ear and labyrinth disorders	2.86	6.38	1.28
Chronic lymphocytic leukemia	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19.76	52.93	7.38
Lymphoma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9.40	19.76	4.47
Acute myeloid leukemia	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5.71	17.75	1.84
Plasma cell myeloma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3.58	7.99	1.61
Malignant neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2.04	3.93	1.06

Table IV. The distribution of signals caused by Sotrovimab alone.

Preferred Term	System Organ Category	ROR	95% CI upper-bound	95% CI lower-bound
Phlebitis	Vascular disorders	20.18	45.23	9.00
Circulatory collapse	Vascular disorders	4.06	12.61	1.31
Basal ganglia hemorrhage	Nervous system disorders	58.70	187.07	18.42
Sensory disturbance	Nervous system disorders	5.33	12.84	2.21
Anosmia	Nervous system disorders	3.13	9.72	1.01
Depressed level of consciousness	Nervous system disorders	4.55	8.22	2.51
Altered state of consciousness	Nervous system disorders	4.18	9.32	1.87
Lethargy	Nervous system disorders	2.26	4.75	1.08
Hypoglycemia	Metabolism and nutrition disorders	3.27	6.87	1.56
Malnutrition	Metabolism and nutrition disorders	5.69	15.20	2.13
Dehydration	Metabolism and nutrition disorders	1.83	3.04	1.10
Blood creatine phosphokinase abnormal	Investigations	121.31	397.66	37.01
Procalcitonin increased	Investigations	33.70	106.17	10.70
Fibrin D dimer increased	Investigations	19.77	41.74	9.36
Blood lactate dehydrogenase increased	Investigations	13.78	24.99	7.60
Aspartate aminotransferase increased	Investigations	8.31	12.23	5.64
Alanine aminotransferase increased	Investigations	5.64	8.67	3.67
Brain natriuretic peptide increased	Investigations	10.77	33.57	3.45
Blood urea increased	Investigations	7.81	18.82	3.24
Heart rate abnormal	Investigations	5.53	17.20	1.78
Gamma-glutamyltransferase increased	Investigations	3.32	8.86	1.24
Liver function test abnormal	Investigations	5.01	12.06	2.08
Pupillary reflex impaired	Eye disorders	53.52	170.16	16.83
Photopsia	Eye disorders	11.18	29.94	4.18
Eyelid oedema	Eye disorders	9.99	26.73	3.73
Swelling of eyelid	Eye disorders	5.08	13.57	1.90
Systemic inflammatory response syndrome	General disorders and administration site conditions	30.60	68.85	13.60
Hypothermia	General disorders and administration site conditions	8.37	22.38	3.13
Administration site extravasation	General disorders and administration site conditions	46.68	114.10	19.10
Infusion site rash	General disorders and administration site conditions	23.68	63.72	8.80
Infusion site reaction	General disorders and administration site conditions	13.43	41.92	4.30
Infusion site erythema	General disorders and administration site conditions	8.51	17.06	4.24
Infusion site pain	General disorders and administration site conditions	6.57	11.90	3.63
Infusion site swelling	General disorders and administration site conditions	5.18	12.48	2.15
Swelling face	General disorders and administration site conditions	2.81	5.09	1.56
Face oedema	General disorders and administration site conditions	3.51	10.91	1.13
Leukocytosis	Blood and lymphatic system disorders	3.82	10.20	1.43
Cytopenia	Blood and lymphatic system disorders	3.21	7.73	1.34
Lymphadenopathy	Blood and lymphatic system disorders	2.36	5.25	1.06
Leukocytosis	Blood and lymphatic system disorders	3.82	10.20	1.43
Cytopenia	Blood and lymphatic system disorders	3.21	7.73	1.34
Lymphadenopathy	Blood and lymphatic system disorders	2.36	5.25	1.06
Hepatitis fulminant	Hepatobiliary disorders	16.77	52.43	5.36
Jaundice	Hepatobiliary disorders	3.70	9.87	1.39
Hepatic function abnormal	Hepatobiliary disorders	2.76	5.53	1.38
Papule	Skin and subcutaneous tissue disorders	7.50	20.06	2.81
Rash pruritic	Skin and subcutaneous tissue disorders	3.14	5.55	1.78
Rash macular	Skin and subcutaneous tissue disorders	3.12	6.25	1.56
Rash papular	Skin and subcutaneous tissue disorders	3.73	9.95	1.40
Urine abnormality	Renal and urinary disorders	7.66	23.85	2.46
Delirium	Psychiatric disorders	3.27	6.87	1.56
Sepsis	Infections and infestations	2.05	3.41	1.23
Anaphylactoid reaction	Immune system disorders	38.29	81.30	18.03
Anaphylactic shock	Immune system disorders	3.18	7.64	1.32
Infusion related reaction	Immune system disorders	38.77	43.63	34.46
Feces soft	Gastrointestinal disorders	5.63	12.56	2.52
Glossoptosis	Gastrointestinal disorders	362.67	1,102.29	119.32
Diarrhea	Gastrointestinal disorders	1.57	1.95	1.27
Hypoesthesia oral	Gastrointestinal disorders	3.11	9.66	1.00
Ear discomfort	Ear and labyrinth disorders	3.74	11.62	1.20
Pulseless electrical activity	Cardiac disorders	11.44	35.69	3.67
Cardio-respiratory arrest	Cardiac disorders	3.49	7.79	1.57
Chronic lymphocytic leukemia	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7.91	24.63	2.54

other coronaviruses. Due to its earlier emergence and broader cross-coronavirus neutralization capacity, it might exert more effects on the human immune system, although SOT's strong immunogenicity has not been found in RCTs[20]. However, another study[21] provided an interesting result. 24 hours after SOT infusion, COVID-19 patients with pre-infusion oxygen saturation below 96.5% and/or temperature exceeding 36.7°C may experience temperature elevation or dyspnea, which suggests the enhanced immunoreactivity of SOT as there are no similar reports for other mAbs. It remains difficult to explain this difference currently, especially when the antigenic determinant is unknown.

In this study, SOT also showed stronger immunoreactivity compared with the other mAbs. Rashes and fever are the prominent symptoms that are both associated with hypersensitivity. Simultaneously, no signals of severe allergic reactions, such as anaphylactic shock, were observed in reports of the other two mAbs. Thus, although mAbs are known to increase the risk of immunogenicity or hypersensitivity[22], however, more attention to SOT should be given[21]. Also, it is controversial that SOT may lead to bad investigation results instead of the other mAbs, including cardiac, liver, and kidney. This still cannot be explained.

Limitations

This study has certain limitations. Firstly, the data was obtained from the FDA, which means that the majority of reports were from the United States, potentially introducing geographic bias. Secondly, FAERS is a spontaneous report system; some cases lack confirmation by healthcare professionals, and even the patients can submit the reports and determine the primary suspect drug by themselves, which may lead to misleading results. Additionally, due to insufficient information, it was difficult to establish a definite causal relationship between ADEs and drugs in the reports, especially when symptoms of primary disease and the agents are similar. Moreover, the impact of the "Weber effect or non-Weber effect" on signal appearance should not be ignored. Therefore, the conclusions of this study need more confirmation. Signals of ADEs may change over time, so continuous monitoring is necessary. At last, almost all SARS-CoV-2-infected individuals can manifest respiratory symptoms, which can confuse the correlation between symptoms and drugs or diseases. Thus, this study did not investigate respiratory ADE signals.

Conclusions

This study found that the safety profiles of the three mAbs targeting omicron exhibited distinct characteristics: SOT and BEB may not be suitable for patients with pre-existing eye disease; SOT exhibits a higher correlation with immune reactions and may be unsuitable for patients with allergies and it might lead to abnormal test results which require close monitoring during administration; BEB had a higher correlation with gastrointestinal and neuro-psychiatric ADEs, although the majority were not severe and its infusion reactions should also be noted specifically. The use of TIX/CIL should be cautious in patients with pre-existing cardiovascular diseases as it can lead to a variety of cardiovascular ADEs.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed Consent

All the data in this study were sourced from The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), an open-access database. Therefore, informed consent is not applicable.

Ethics Approval

All the data in this study was sourced from The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), which is an open-access database. Therefore, ethics approval is not applicable.

Data Availability

The data that support the findings of this study are openly available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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Authors' Contributions

Conceptualization, Y. Wang. Methodology, Y. Wang, J.-N. Li. Software, J.-N. Li, X.-W. Xu. Validation, Y. Wang, S. Zhou. Investigation, Y. Wang J.-N. Li, X.-W. Xu. Resources, Y. Wang. Data Curation, J.-N. Li, X.-W. Xu, S. Zhou. Writing-original draft preparation, Y. Wang, X.-W. Xu.

Writing-review and editing, S. Zhou, J.-N. Li. Visualization, J.-N. Li, X.-W. Xu. Supervision, J.-N. Li. Project administration, J.-N. Li, Y. Wang. All authors contributed to the article and approved the submitted version.

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