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Gastrointestinal risk profile of tigecycline, omadacycline and eravacycline: Evidence from the FDA adverse event reporting system

ZHU WANG[1]
GUOPING GAN[3]
HAIPING YAO[2,3,*]

[1] *Department of Pediatrics, The First College of Clinical Medical Science China Three Gorges University & Yichang Central People's Hospital Yichang, Hubei 443003, P. R. China*

[2] *Department of Pharmacy, The First College of Clinical Medical Science China Three Gorges University & Yichang Central People's Hospital Yichang, Hubei 443003, P. R. China*

[3] *College of Pharmacy, Hubei University of Chinese Medicine Wuhan, Hubei 430065, P. R. China*

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ABSTRACT

This study assessed the gastrointestinal (GI) safety profiles of tigecycline, omadacycline, and eravacycline through a retrospective disproportionality analysis of reports submitted to the FDA Adverse Event Reporting System (FAERS) between the second quarter of 2005 and the first quarter of 2024. Among 3,261 adverse event reports associated with these agents, 809 (24.8 %) involved gastrointestinal disorders, with tigecycline accounting for the largest proportion (588 reports), followed by omadacycline (197) and eravacycline (24). Disproportionality analysis revealed that gastrointestinal disorders ranked among the top three system organ classes for all three drugs, with positive signals observed for tigecycline (ROR = 1.63), omadacycline (ROR = 3.04), and eravacycline (ROR = 1.79), the strongest association being with omadacycline. While most GI events were consistent with known safety information, several unexpected signals were identified, including gastrointestinal haemorrhage, melena, small-intestinal obstruction, tongue discolouration, and intestinal perforation for tigecycline, as well as lip swelling and tongue discolouration for omadacycline. The median onset times of GI events were 4, 0, and 2.5 days for tigecycline, omadacycline, and eravacycline, respectively, with nearly half of the events occurring within three days of treatment initiation. These findings reveal distinct GI safety patterns among newer tetracycline-derived antibiotics and underscore the importance of early and route-specific monitoring in clinical practice.

Keywords: tigecycline, omadacycline, eravacycline, pharmacovigilance, gastrointestinal safety, FAERS

INTRODUCTION

Tetracycline antibiotics have been used for over six decades to treat a broad spectrum of bacterial and atypical infections by reversibly binding to the 30S ribosomal subunit and inhibiting protein synthesis (1). However, widespread use of early-generation agents such as tetracycline and doxycycline has been associated with increased adverse events (AEs)

* Correspondence; e-mail: yaohaiping@ctgu.edu.cn

and rising antimicrobial resistance (2, 3). To overcome these limitations, structurally modified tetracycline derivatives have been developed to expand the antimicrobial spectrum and improve efficacy against resistant pathogens. Among these, tigecycline, omadacycline, and eravacycline represent novel derivatives from distinct chemical subclasses, each exhibiting potent activity against multidrug-resistant (MDR) bacteria. Their broad-spectrum activity and unique pharmacological properties have led to increasing clinical use and make them relevant candidates for evaluating gastrointestinal (GI) AEs. Tigecycline, the first glycylcycline, was approved in 2005 for complicated intra-abdominal infections and community-acquired bacterial pneumonia, whereas omadacycline, an aminomethylcycline, and eravacycline, a fluorocycline featuring fluorine substitution, were both approved in 2018 for treating infections caused by MDR pathogens (4–6).

Although these novel tetracycline-derived agents have expanded antimicrobial spectra, gastrointestinal AEs, including nausea, vomiting, and diarrhoea, remain clinically significant and are frequently reported in drug labelling and early post-marketing observations (7–10). For omadacycline and eravacycline, safety data are still limited due to their recent approval, with current evidence derived primarily from clinical trials and a handful of meta-analyses (11–14). However, real-world studies leveraging large pharmacovigilance databases to evaluate GI risks are scarce. As clinical use continues to rise, robust and comprehensive real-world assessments are urgently needed to detect both common and rare gastrointestinal AEs, thereby supporting safer medication use.

To fill this research gap, real-world data from spontaneous reporting systems (SRSs) can provide additional safety insights. The SRS is essential for pharmacovigilance, enabling early detection of potential AE signals (15). Among these systems, the FDA adverse event reporting system (FAERS) is the largest global database for post-marketing drug safety, compiling millions of AE reports from healthcare professionals, consumers, and manufacturers. FAERS supports ongoing safety monitoring of approved drugs throughout their lifecycle. However, it has several limitations, including under-reporting, reporting bias, lack of control groups, and incomplete clinical information (16).

In this study, we retrospectively analysed gastrointestinal AEs associated with tigecycline, omadacycline, and eravacycline using FAERS data from Q2 2005 to Q1 2024. By applying disproportionality analysis, we aimed to detect potential GI safety signals and provide real-world evidence to support clinical risk assessment and post-marketing surveillance.

DATA COLLECTING AND ANALYSIS

Data source

This study utilised data from the FAERS, the world's largest publicly available data -base for post-marketing drug safety surveillance. The FDA updates and releases FAERS data on a quarterly basis. The database comprises seven core datasets: patient demographic and administrative details (DEMO), drug and biological product information (DRUG), reported adverse events (REAC), patient outcomes (OUTC), sources of reports (RPSR), drug therapy start and end dates (THER), and medical indications or diagnoses (INDI). These datasets are interconnected *via* a relational structure using a unique case identifier

assigned to each report. Data for tigecycline were retrieved for the period from its FDA approval in Q2 2005 through Q1 2024. For omadacycline, records from Q3 2018 to Q1 2024 were included, while eravacycline-related data spanned from Q2 2018 to Q1 2024.

Data cleaning

AEs associated with tigecycline (Tygacil), omadacycline (Nuzyra), and eravacycline (Xerava) were identified using both their generic and brand names within the FAERS data-sets. In the FAERS system, AEs are coded using preferred terms (PTs) from the medical dictionary for regulatory activities (MedDRA), which are further organised into system organ classes (SOCs) (17). Each PT and SOC is assigned a unique numerical code in the MedDRA terminology, such as gastrointestinal disorders (SOC: 10017947) and nausea (PT: 10028813), to ensure standardised data retrieval and analysis across reports. Duplicate entries were eliminated in accordance with the official FAERS de-duplication guidelines. Each reported drug is assigned a role code indicating its relationship to the AE: primary suspect (PS), secondary suspect (SS), concomitant (C), or interacting (I). To ensure the specificity of drug-event association, only reports in which the study drugs were designated as the PS were included in the analysis. A flow diagram summarising the data processing steps is presented in Fig. 1.

Statistical analysis

Descriptive statistics were used to summarise the demographic and reporting characteristics of AEs associated with tigecycline, omadacycline, and eravacycline. Key variables

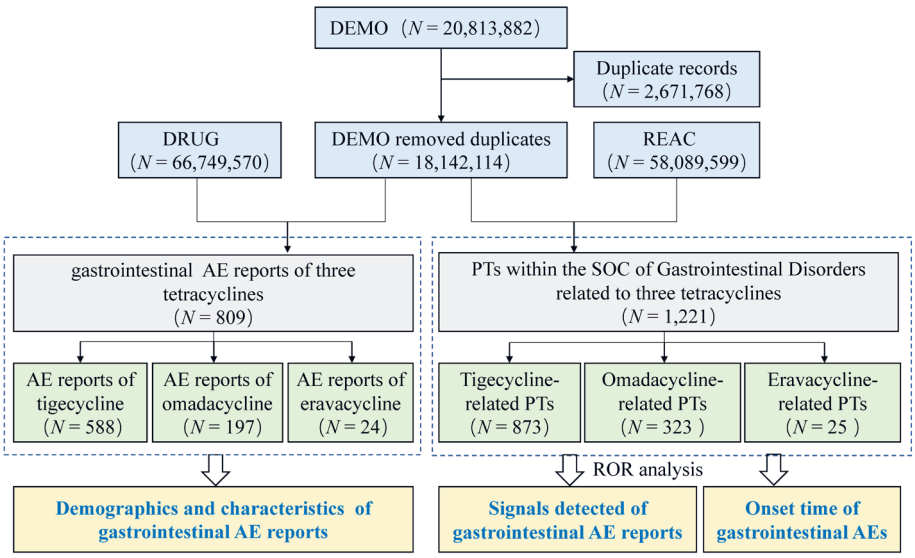

Fig. 1. Flow diagram of the three tetracycline derivatives-related gastrointestinal AEs from the FAERS database.

included patient sex, age, severity of clinical outcomes, and reporter type, which were expressed as the number and percentage of reports. Serious outcomes were defined as death (DE), life-threatening condition (LT), hospitalisation (initial or prolonged, HO), disability (DS), or other medically significant conditions (OT). To evaluate the time to AE onset, the interval between treatment initiation and the onset of each reported AE was calculated.

Potential gastrointestinal safety signals were identified using the reporting odds ratio (ROR), a validated disproportionality metric widely employed in SRS analyses due to its robustness in small samples and the straightforward interpretability of drug-event associations. In the initial phase of analysis, four commonly used disproportionality algorithms, ROR, proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) were examined. However, for the primary multi-drug comparison, only the ROR was retained because it provides an intuitive odds-ratio interpretation, is readily integrated into logistic regression models for covariate adjustment, and is extensively adopted by regulatory agencies such as the European Medicines Agency (18). Prior research has demonstrated that when the number of reports for a given drug-event combination is sufficiently large (*e.g.*, ≥ 3 cases), the concordance among signals detected by different disproportionality algorithms is high (19). Therefore, to ensure analytic consistency and clarity, the present study focuses on ROR-based results; detailed outputs for PRR, BCPNN, and MGPS are provided in the Supplementary Material (Tables S2-S4).

As shown in Table I, the ROR was calculated as ROR = $(a/b)/(c/d)$, where a is the number of reports involving the target drug and target AE, b is the number involving the target drug and non-target AEs, c is the number involving non-target drugs and the target AE, and d is the number involving non-target drugs and non-target AEs. To account for statistical uncertainty, 95 % confidence intervals (CIs) were derived using a natural logarithmic transformation [95 % CI = $e^{\ln(\mathrm{ROR}) \pm 1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$], with a lower CI bound greater than 1 indicating a statistically significant signal.

To minimise false positives, only AE terms reported at least three times were included, consistent with international pharmacovigilance guidelines and previous FAERS-based studies. No multiple-testing correction was applied, as this could obscure rare but clinically meaningful signals, which are critical in post-marketing surveillance (20). All data processing and statistical analyses were conducted using MySQL 8.0 and Microsoft Excel 2019.

Table I. Algorithm used to evaluate potential associations between tetracycline derivatives and AEs

Algorithm	Equation	Criteria
Reporting odds ratio (ROR)	$\mathrm{ROR} = \frac{a/b}{c/d} = \frac{ad}{bc}$ $95\%\,\mathrm{CI} = e^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{1/a+1/b+1/c+1/d}}$	lower limit of 95 % CI > 1, $N \geq 3$

a – number of reports containing both the target drug and the target AE, b – number of reports containing other AEs of the target drug, c – number of reports containing the target AE associated with other drugs, d – number of reports containing other drugs and other AEs, CI – confidence interval, N – number of reports

RESULTS AND DISCUSSION

To explore potential gastrointestinal AEs associated with tigecycline, omadacycline and eravacycline, we analysed FAERS post-marketing reports using disproportionality analysis, allowing signal detection beyond clinical trials. Because FAERS is an SRS, our findings are exploratory and subject to reporting biases such as under-reporting and incomplete clinical information, which limit causal inference (16, 21). Building on this foundation, our analysis adds value by applying a consistent ROR-based approach to characterise and compare the GI safety profiles of the three agents. This method enables the detection of both anticipated and previously unrecognised GI events at the SOC and PT levels, revealing drug-specific patterns that are not fully captured in current labelling or prior studies. By jointly considering signal magnitude and onset timing, the study contributes real-world evidence that may help clinicians anticipate GI risks earlier and implement more tailored monitoring strategies. The following sections outline the demographics and characteristics of GI AE reports, the detected signals, and the onset time distributions.

Demographics and characteristics of gastrointestinal AE reports

Between Q2 2005 and Q1 2024, a total of 18,142,114 AE reports were recorded in FAERS. After data cleaning, 3,261 reports identified tigecycline, omadacycline or eravacycline as the PS drug, among which 809 (24.8 %) involved gastrointestinal AEs – 588 for tigecycline, 197 for omadacycline, and 24 for eravacycline. The demographic and clinical characteristics of these cases are summarised in Table II. Excluding reports with unspecified sex, total AE reports slightly favoured males (1,491 *vs.* 1,268), whereas GI AEs were more frequently reported in females (417 *vs.* 303), though reporting bias cannot be excluded. The most frequently reported outcomes were OT (27.8 %), HO (25.8 %) and DE (9.8 %). Mortality was notably higher among tigecycline-related GI AE reports (12.8 %), likely reflecting its use in severe multidrug-resistant infections rather than a direct causal effect (22). Approximately three-quarters of reports originated from healthcare professionals, suggesting good reporting reliability.

Signals detected in gastrointestinal AE reports

At the SOC level, gastrointestinal disorders (SOC: 10017947) consistently ranked among the top three SOC categories for tigecycline, omadacycline and eravacycline, showing gastrointestinal AEs as a major concern, similar to traditional tetracyclines (2). As summarized in Table III, tigecycline accounted for the largest proportion of gastrointestinal PTs (71.5 %; ROR = 1.63), followed by omadacycline (26.5 %; ROR = 3.04) and eravacycline (2.1 %; ROR = 1.79). Notably, although tigecycline involved the greatest number of GI-related PTs, omadacycline showed the highest ROR, suggesting a relatively stronger reporting association with GI AEs (23).

At the PT level, 22 PTs within the SOC of gastrointestinal disorders met the criteria for positive signal detection. The most frequently reported gastrointestinal AEs overall were nausea (PT: 10028813; 25.2 %), vomiting (PT: 10047700; 14.7 %) and pancreatitis (PT: 10033645; 10.1 %), as shown in Table IV. Disproportionate signals were identified for 15 PTs with tigecycline, 12 PTs with omadacycline and 1 PT with eravacycline. Several PTs not listed in package inserts were also detected. Specifically, tigecycline was associated with

Table II. Demographics and characteristics of gastrointestinal AE reports with the three tetracycline derivatives from the FAERS database (April 2005 – March 2024)

Characteristics	Tigecycline		Omadacycline		Eravacycline		Total	
	N	%	N	%	N	%	N	%
Number of cases	588		197		24		809	
Gender								
Female	281	47.8	128	65.0	8	33.3	417	51.5
Male	250	42.5	48	24.4	5	20.8	303	37.5
Unknown	57	9.7	21	10.7	11	45.8	89	11.0
Age (years)								
< 18	22	3.7	3	1.5	1	4.2	26	3.2
18 ≤ and ≤ 65	248	42.2	76	38.6	6	25.0	330	40.8
> 65	135	23.0	43	21.8	5	20.8	183	22.6
Unknown	183	31.1	75	38.1	12	50.0	270	33.4
Serious outcomes								
Death (DE)	75	12.8	3	1.5	1	4.2	79	9.8
Life-threatening (LT)	29	4.9	1	0.5	1	4.2	31	3.8
Hospitalisation-initial or prolonged (HO)	195	33.2	14	7.1	0	0	209	25.8
Disability (DS)	11	1.9	0	0	0	0	11	1.4
Other serious (important medical event) (OT)	203	34.5	17	8.6	5	20.8	225	27.8
Reported persons								
Health profession								
Physician (MD)	197	33.5	30	15.2	10	41.7	237	29.3
Pharmacist (PH)	134	22.8	11	5.6	6	25.0	151	18.7
Other health professional (OT)	183	31.1	24	12.2	7	29.2	214	26.5
Non-healthcare professional								
Consumer (CN)	46	7.8	132	67.0	1	4.2	179	22.1
Unknown	28	4.8	0	0	0	0	28	3.5

N – number of reports

Table III. Signal detection for gastrointestinal toxicities associated with the three tetracycline derivatives

Medications	PT/N	ROR (95 % CI)
Total	1221	1.90 (1.79–2.02)
Tigecycline	873	1.63 (1.52–1.75)
Omadacycline	323	3.04 (2.69–3.43)
Eravacycline	25	1.79 (1.17–2.72)

CI – confidence interval, *N* – number of reports, PT – preferred term, ROR – reporting odds ratio

Table IV. Signal strength of gastrointestinal AE reports of the three tetracycline derivatives at the PT level in the FAERS database

PT	Tigecycline		Omadacycline		Eravacycline		Total	
	N	ROR (95 % CI)	*N*	ROR (95 % CI)	*N*	ROR (95 % CI)	*N*	ROR (95 % CI)
Nausea	191	2.39 (2.07–2.76)	106	6.34 (5.21–7.73)	11	5.40 (2.94–9.93)	308	3.19 (2.84–3.57)
Vomiting	120	2.48 (2.07–2.97)	59	5.95 (4.58–7.71)	0	NA	179	3.04 (2.62–3.53)
Pancreatitis	121	20.20 (16.87–24.18)	0	NA	2	NA	123	16.74 (14.00–20.01)
Diarrhea	78	1.20 (0.96–1.50)	33	2.05 (1.45–2.89)	3	1.54 (0.49–4.81)	114	1.44 (1.20–1.73)
Pancreatitis acute	70	28.98 (22.89–36.69)	0	NA	0	NA	70	23.66 (18.69–29.94)
Abdominal pain upper	11	0.52 (0.29–0.94)	22	4.70 (3.09–7.17)	1	NA	34	1.31 (0.94–1.84)
Abdominal discomfort	17	0.98 (0.61–1.57)	16	3.56 (2.17–5.82)	0	NA	33	1.55 (1.10–2.19)
Gastrointestinal hemorrhage	21	2.11 (1.37–3.24)	0	NA	0	NA	21	1.72 (1.12–2.65)
Pancreatitis necrotizing	17	66.11 (41.00–106.60)	0	NA	0	NA	17	54.04 (33.52–87.13)
Tooth discoloration	1	NA	11	252.01 (138.63–458.13)	1	NA	13	32.95 (19.10–56.84)
Dysbiosis	10	110.98 (59.45–207.16)	0	NA	0	NA	10	90.74 (48.62–169.37)
Lip swelling	3	0.86 (0.28–2.68)	6	8.38 (3.76–18.68)	0	NA	9	2.12 (1.10–4.08)
Melena	6	2.42 (1.08–5.38)	2	NA	0	NA	8	2.63 (1.32–5.27)
Retching	5	2.31 (0.96–5.55)	3	6.75 (2.17–20.95)	0	NA	8	3.02 (1.51–6.05)
Gastroesophageal reflux disease	3	0.32 (0.10–0.99)	5	2.76 (1.15–6.65)	0	NA	8	0.70 (0.35–1.40)
Pancreatitis hemorrhagic	7	124.87 (59.19–263.40)	0	NA	0	NA	7	102.11 (48.41–215.37)
Tongue discoloration	4	7.83 (2.94–20.88)	3	39.13 (12.59–121.62)	0	NA	7	11.22 (5.34–23.55)
Small intestinal obstruction	5	3.51 (1.46–8.44)	0	NA	0	NA	5	2.87 (1.19–6.90)
Ileus	5	3.50 (1.46–8.41)	0	NA	0	NA	5	2.86 (1.19–6.88)
Edematous pancreatitis	5	89.16 (36.94–215.24)	0	NA	0	NA	5	72.92 (30.21–176.01)
Paresthesia oral	1	NA	2	NA	2	NA	5	2.76 (1.15–6.64)
Intestinal perforation	4	3.20 (1.20–8.52)	0	NA	0	NA	4	2.61 (0.98–6.97)
Barrett's oesophagus	4	9.44 (3.54–25.18)	0	NA	0	NA	4	7.72 (2.90–20.59)
Vomiting projectile	0	NA	3	51.03 (16.41–158.67)	0	NA	3	9.24 (2.98–28.68)
Feces soft	0	NA	3	12.76 (4.11–39.63)	0	NA	3	4.04 (1.30–12.52)

N – number of reports, PT – preferred term, ROR – reporting odds ratio, CI – confidence interval, NA – not applicable

gastrointestinal hemorrhage (PT: 10017955), melena (PT: 10027141), small intestinal obstruction (PT: 10041101), ileus (PT: 10021328), tongue discoloration (PT: 10043949), and intestinal perforation (PT: 10022694), whereas omadacycline showed novel signals for lip swelling (PT: 10024570) and tongue discoloration (PT: 10043949). These findings underscore both known and potentially novel GI safety concerns for these newer tetracycline derivatives, warranting further clinical evaluation.

Due to limited reports, eravacycline was linked only to nausea, the most frequent PT across all three drugs. Nausea and vomiting were positive signals for tigecycline and omadacycline, consistent with class effects of tetracyclines and their derivatives. Clinical evidence suggests these AEs may be dose-related, implying that dose reduction could alleviate symptoms without compromising efficacy (24, 25). Tongue discolouration showed positive signals for both tigecycline and omadacycline. Although this specific AE has not been previously reported, a related tongue abnormality (black hairy tongue) has been described in the literature and is generally considered benign and self-limiting, resulting from microbial dysbiosis (26). Positive signals for Barrett's oesophagus (PT: 10004137) for tigecycline and gastroesophageal reflux disease (PT: 10017885) for omadacycline, both oesophagal lesions, were also noted. Barrett's oesophagus is often a sequela of reflux disease and may progress to cancer (27). Omadacycline-associated reflux disease is thought to stem from oral administration, causing local mucosal injury, similar to traditional tetracycline-class agents (28). However, the detection of Barrett's oesophagus with intravenous tigecycline suggests that additional mechanisms may contribute to oesophagal AEs.

Tigecycline exhibited several PTs that were negative for omadacycline, including pancreatitis, pancreatitis acute (PT: 10033647), gastrointestinal hemorrhage, pancreatitis necrotizing (PT: 10033654), dysbiosis (PT: 10082129), melena, pancreatitis hemorrhagic (PT: 10033650), small intestinal obstruction, ileus, edematous pancreatitis (PT: 10052400), intestinal perforation, and Barrett's esophagus. Five pancreatitis-related signals were detected for tigecycline, with pancreatitis being the second-most frequent gastrointestinal PT after nausea (29, 30). Although eravacycline showed no pancreatitis-related PTs, a signal for elevated pancreatic enzymes was identified (three cases; ROR = 954.37), consistent with its low (< 1 %) incidence reported in the label. Omadacycline demonstrated no evidence of pancreatitis in our analysis or in prior reports (31, 32). Nonetheless, continued vigilance is necessary due to shorter post-marketing exposure for omadacycline and eravacycline. Monitoring abdominal symptoms and pancreatic enzymes is crucial for early detection of acute pancreatitis (33). Several positive PTs related to GI bleeding (*e.g.*, gastrointestinal haemorrhage, melena) and digestive tract obstruction (*e.g.*, small intestinal obstruction, ileus, intestinal perforation) were also not mentioned in tigecycline package inserts. Proposed mechanisms in the literature suggest that tigecycline-related GI haemorrhage may result from coagulation abnormalities secondary to reduced vitamin K absorption caused by disruption of intestinal microbiota (34–36). The mechanisms underlying bowel obstruction associated with tetracycline-derived antibiotics are unclear but may involve alterations in gut microbiota and intestinal motility (37, 38). These findings underscore the importance of monitoring coagulation parameters and gastrointestinal function during treatment with these agents.

Conversely, omadacycline exhibited unique positive PTs absent for tigecycline, including diarrhea (PT: 10012735), abdominal pain upper (PT: 10000087), abdominal discomfort (PT: 10000059), tooth discoloration, lip swelling, retching (PT: 10038776), gastro-

esophageal reflux disease, vomiting projectile (PT: 10047708), and feces soft (PT: 10074859). Most of these appear in the omadacycline insert except lip swelling. Tooth discolouration is a class effect of tetracyclines; however, only omadacycline showed a positive signal in our study (31, 39). Among five evaluable cases (after excluding six with missing age), three involved adults and two adolescents (aged 14 and 15 years). These findings underscore the importance of avoiding tetracycline derivatives during tooth development (from late pregnancy through early childhood) to prevent permanent discolouration and enamel defects. Lip swelling lacks specificity and could reflect allergy, infection or inflammation; omadacycline also showed a positive signal for hypersensitivity (16 cases; ROR = 3.33), but a direct causal link remains uncertain (31).

Finally, omadacycline's distinct oral and intravenous formulations allowed route-specific comparison. As shown in Table S1, reports included 1,253 PTs for oral use and 172 PTs for intravenous use. Positive GI signals predominantly originated from oral reports, while no such signals were detected for intravenous administration. Although report numbers varied markedly between routes, this suggests a lower incidence of gastrointestinal AEs with intravenous administration, consistent with data from other antibiotics, showing higher GI toxicity with oral formulations (40, 41). Thus, switching to intravenous omadacycline may be advisable when patients experience intolerable gastrointestinal AEs with oral therapy (42).

Onset time of gastrointestinal AEs

As shown in Fig. 2, most gastrointestinal AEs associated with tigecycline, omadacycline, and eravacycline occurred shortly after treatment initiation, with an overall median onset of 3 days (4 days for tigecycline, 0 days for omadacycline, and 2.5 days for eravacycline). Nearly half of all events appeared within the first three days, and 81 % of omadacycline-related AEs occurred on the day of administration. Although only a few eravacycline cases reported onset time, these also indicated early onset. A small proportion (6.7 %)

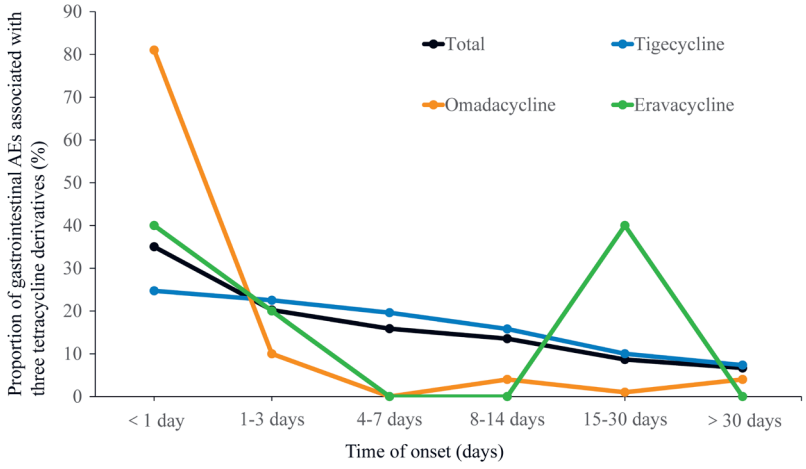

Fig. 2. Time to onset of gastrointestinal AEs related to the three tetracycline derivatives.

occurred beyond 30 days, suggesting that delayed gastrointestinal AEs can occur and warrant continued follow-up (43).

Fig. S1 presents the onset times of AEs for cases involving significant PTs, excluding those with missing timing information. For the eight PTs unrecorded in package inserts, all three cases of lip swelling occurred on the day of drug administration, tongue discoloration (five cases) appeared within the first six days, gastrointestinal hemorrhage (ten cases) and melena (six cases) occurred between days 0 and 18, small intestinal obstruction (four cases), ileus (three cases), and intestinal perforation (two cases) generally emerged between days 3 and 19, except for one ileus case on day 31. For PTs shared across multiple drugs, such as vomiting and tongue discolouration, the onset timing differed between agents. Omadacycline-related events predominantly appeared on the day of dosing, whereas tigecycline-related events showed a broader distribution across the treatment period. These discrepancies may reflect differences in pharmacokinetic properties or mechanisms of action (44).

Limitations of the study

Although this study outlines GI safety signals for these agents, several methodological caveats should be noted. Because FAERS relies on voluntary submissions, the detail and consistency of case information vary, which may affect the stability of the findings. The database also lacks information on the size of the exposed population, preventing estimation of event rates or absolute risk levels. Interpretation is further constrained by clinical factors, such as concomitant medications and underlying conditions, that cannot be systematically assessed.

During the initial phase of analysis, four commonly used disproportionality algorithms were examined: the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS). However, the comparative design involving multiple agents, including all four measures, would complicate interpretation and reduce clarity. For this reason, we chose ROR to ensure methodological consistency.

Although PRR, BCPNN, and MGPS results are provided in the Supplementary Material, the primary analysis is focused on ROR, limiting methodological breadth. Importantly, disproportionality signals represent statistical associations rather than confirmed causality, and thus require prospective studies for verification. Even so, FAERS remains a widely used post-marketing resource, and the patterns identified here may still inform clinical monitoring of these agents.

Future studies

Future research could expand the comparative scope to include other tetracycline--derived agents, beyond tigecycline, omadacycline, and eravacycline, enabling a broader evaluation of GI safety patterns across this drug class. Employing multiple signal-detection methods along with additional sensitivity analyses may strengthen the assessment of signal consistency and robustness. Prospective studies using electronic health records, active surveillance systems, or population-based cohorts are warranted to confirm temporal associations suggested by spontaneous reports and to quantify absolute and compara-

tive risks. Such investigations could also clarify dose-response relationships, identify patient-specific risk factors, and validate signals of severe or unexpected GI events. Together, these efforts would provide a more comprehensive understanding of GI safety profiles among tetracycline-derived antibiotics and support evidence-informed clinical decision-making.

CONCLUSIONS

Based on AE reports for tigecycline, omadacycline and eravacycline in the FAERS database, this study conducted a GI safety signal spectrum analysis using the ROR method and quantitatively assessed the potential risks associated with drug treatment. The findings indicate that most identified gastrointestinal AEs are consistent with those described in the approved drug labelling and previous literature. However, several severe or previously unreported signals emerged. For tigecycline, marked disproportionality was observed for gastrointestinal haemorrhage (ROR = 2.11), melena (ROR = 2.42), small intestinal obstruction (ROR = 3.51), ileus (ROR = 3.50), tongue discolouration (ROR = 7.83) and intestinal perforation (ROR = 3.20). Omadacycline showed novel signals for lip swelling (ROR = 8.38) and tongue discolouration (ROR = 39.13), while eravacycline exhibited no significant GI disproportionality except for nausea. The temporal analysis revealed that most AEs occurred within the first few days of therapy, emphasising the need for early monitoring. These findings provide crucial safety insights for clinical research and practice. Nonetheless, due to the intrinsic limitations of SRSs, such as under-reporting, duplicate entries, and a lack of clinical detail, these findings should be interpreted with caution. Further confirmation through well-designed cohort studies and long-term surveillance data is warranted to fully elucidate the GI risk profiles of these agents.

Acronyms, abbreviations, symbols. – AE – adverse event, BCPNN – Bayesian confidence propagation neural network, C – concomitant, CI – confidence interval, DE – death, DEMO – patient demographic and administrative details dataset in FAERS, DRUG – drug and biological product information dataset in FAERS, DS – disability, FAERS – FDA Adverse Event Reporting System, FDA – Food and Drug Administration, GI – gastrointestinal, HO – hospitalization (initial or prolonged), I – interacting, INDI – medical indications or diagnoses dataset in FAERS, LT – life-threatening condition, MDR – multidrug–resistant, MedDRA – Medical Dictionary for Regulatory Activities, MGPS – multi–item gamma Poisson shrinker, MySQL – MySQL database management system, Nuzyra – omadacycline brand name, OT – other medically significant condition, OUTC – patient outcomes dataset in FAERS, PRR – proportional reporting ratio, PS – primary suspect, PT – preferred term, Q – quarter (of year), REAC – adverse event dataset in FAERS, ROR – reporting odds ratio, RPSR – report source dataset in FAERS, SOC – system organ class, SRS – spontaneous reporting system, SS – secondary suspect, THER – drug therapy start and end dates dataset in FAERS, Tygacil – tigecycline brand name, Xerava – eravacycline brand name.

Availability of data and materials. – The datasets analysed in this study are publicly accessible *via* the FAERS database and can be retrieved from: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. All authors had full access to the data used in this study and accept responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest. – The authors declare no conflicts of interest related to this work, including employment, consultancies, stock ownership, honoraria, research funding, patents, or royalties. The study used publicly available, anonymised FAERS data.

Authors contributions. – Conceptualisation, Z.W. and H.Y.; study design, Z.W.; data curation, Z.W. and G.G.; methodology, Z.W.; analysis, H.Y.; investigation, Z.W.; writing, original draft preparation, Z.W.; writing, review and editing, G.G. and H.Y.; project administration, H.Y.; supervision, H.Y.; funding acquisition, Z.W. All authors meet ICMJE authorship criteria, approved the final manuscript, and are accountable for all aspects of the work.

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Supplementary Material

Table S1. Signal strength of gastrointestinal adverse event reports for oral and intravenous omadacycline at the PT level in the FAERS database

PT	Oral		Intravenous		Total	
	N	ROR(95% CI)	N	ROR(95% CI)	N	ROR(95% CI)
Nausea	94	7.06 (5.72-8.72)	0	NA	106	6.34 (5.21-7.73)
Vomiting	54	6.82 (5.19-8.96)	0	NA	59	5.95 (4.58-7.71)
Diarrhea	29	2.25 (1.55-3.25)	1	0.55 (0.08-3.96)	33	2.05 (1.45-2.89)
Abdominal pain upper	22	5.88 (3.86-8.96)	0	NA	22	4.70 (3.09-7.17)
Abdominal discomfort	15	4.16 (2.50-6.93)	0	NA	16	3.56 (2.17-5.82)
Tooth discoloration	6	169.64 (75.81-379.63)	0	NA	11	252.01 (138.63-458.13)
Lip swelling	6	10.45 (4.68-23.30)	0	NA	6	8.38 (3.76-18.68)
Retching	3	8.41 (2.71-26.12)	0	NA	3	6.75 (2.17-20.95)
Gastroesophageal reflux disease	5	3.45 (1.43-8.30)	0	NA	5	2.76 (1.15-6.65)
Tongue discoloration	3	48.77 (15.69-151.63)	0	NA	3	39.13 (12.59-121.62)
Vomiting projectile	3	63.60 (20.45-197.82)	0	NA	3	51.03 (16.41-158.67)
Feces soft	3	15.91 (5.12-49.41)	0	NA	3	12.76 (4.11-39.63)

Table S2. Four primary algorithms used to evaluate potential associations between the three tetracycline derivatives and adverse events during the initial phase of analysis

Algorithms	Equation	Criteria
Reporting odds ratio (ROR)	$ROR=\frac{a/b}{c/d}=\frac{ad}{bc}$ $95\ \%\ CI=e^{\ln(ROR)\pm1.96\sqrt{1/a+1/b+1/c+1/d}}$	lower limit of 95 % CI > 1, $N \geq 3$
Proportional reporting ratio (PRR)	$PRR=\frac{a/(a+b)}{c/(c+d)}=\frac{a(c+d)}{c(a+b)}$ $\chi^2=\frac{(ad-bc)^2(a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}$	PRR ≥ 2, $\chi^2 \geq 4$, $N \geq 3$
Bayesian confidence propagation neural network (BCPNN)	$IC=\log_2\left(\frac{a(a+b+c+d)}{(a+c)(a+b)}\right)$ $95\ \%\ CI=E(IC)\pm2\sqrt{V(IC)}$	IC025 > 0
Multi-item gamma Poisson shrinker (MGPS)	$EBGM=\frac{a(a+b+c+d)}{(a+c)(a+b)}$ $95\ \%\ CI=e^{\ln(EBGM)\pm1.96\sqrt{1/a+1/b+1/c+1/d}}$	EBGM05 > 2

a - Number of reports containing both the target drug and the target AE

b - Number of reports containing other AEs of the target drug

c - Number of reports containing the target AE associated with other drugs

d - Number of reports containing other drugs and other AEs

CI - confidence interval, *N* - number of reports, χ^2 - chi-squared, IC - information component, IC025 - lower limit of the 95 % CI of the IC, E(IC) - expected value of the IC, V(IC) - variance of the IC, EBGM - empirical Bayesian geometric mean, EBGM05 - lower limit of the 95 % CI of the EBGM

Table S3. Signal detection of gastrointestinal toxicities associated with the three tetracycline derivatives using four primary algorithms

Medications	PT/*N*	ROR (95 % CI)	PRR (95% CI)	χ2	IC (IC025)	EBGM (EBGM05)
Total	1221	1.90 (1.79-2.02)	NA	444.63	0.82 (0.73)	NA
Tigecycline	873	1.63 (1.52-1.75)	NA	183.36	0.63 (0.52)	NA
Omadacycline	323	3.04 (2.69-3.43)	2.61 (2.37-2.88)	349.63	1.39 (1.19)	2.61 (2.31)
Eravacycline	25	1.79 (1.17-2.72)	NA	7.49	0.75 (0.08)	NA

N - number of reports, PT - preferred term, ROR - reporting odds ratio, CI - confidence interval, NA - not applicable, PRR - Proportional reporting ratio, χ^2 - chi-squared, IC - information component, IC025 - lower limit of the 95% CI of the IC, EBGM - empirical Bayesian geometric mean, EBGM05 - lower limit of the 95 % CI of the EBGM

Table S4. Signal strength of gastrointestinal adverse event reports for the three tetracycline derivatives at the PT level in the FAERS database using four algorithms

PT	Tigecycline						Omadacycline						Eravacycline						Total					
	N	ROR (95% CI)	PRR (95% CI)	χ2	IC (IC025)	EBGM (EBGM05)	*N*	ROR (95% CI)	PRR (95% CI)	χ2	IC (IC025)	EBGM (EBGM05)	*N*	ROR (95% CI)	PRR (95% CI)	χ2	IC (IC025)	EBGM (EBGM05)	*N*	ROR (95% CI)	PRR (95% CI)	χ2	IC (IC025)	EBGM (EBGM05)
Nausea	191	2.39 (2.07-2.76)	2.35 (2.05-2.71)	150.46	1.23 (1.01)	2.35 (2.04)	106	6.34 (5.21-7.73)	5.98 (4.98-7.19)	444.68	2.58 (2.22)	5.98 (4.91)	11	5.40 (2.94-9.93)	5.14 (2.90-9.12)	37.12	2.36 (1.06)	5.14 (2.80)	308	3.19 (2.84-3.57)	3.10 (2.78-3.46)	444.63	1.63 (1.46)	3.10 (2.77)
Vomiting	120	2.48 (2.07-2.97)	2.46 (2.06-2.93)	104.34	1.30 (1.02)	2.46 (2.05)	59	5.95 (4.58-7.71)	5.76 (4.48-7.40)	233.56	2.53 (2.04)	5.76 (4.44)	NA	NA	NA	NA	NA	NA	179	3.04 (2.62-3.53)	3.00 (2.59-3.46)	239.86	1.58 (1.35)	3.00 (2.58)
Pancreatitis	121	20.20 (16.87-24.18)	19.84 (16.63-23.68)	2162.17	4.31 (3.84)	19.80 (16.54)	NA	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	NA	123	16.74 (14.00-20.01)	16.50 (13.84-19.66)	1788.25	4.04 (3.61)	16.46 (13.77)
Diarrhea	78	NA	NA	NA	NA	NA	33	2.05 (1.45-2.89)	2.03 (1.45-2.84)	17.33	1.02 (0.48)	NA	3	NA	NA	NA	NA	NA	114	1.44 (1.20-1.73)	NA	15.06	0.52 (0.25)	NA
Pancreatitis acute	70	28.98 (22.89-36.69)	28.68 (22.71-36.22)	1864.81	4.84 (4.02)	28.59 (22.58)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	70	23.66 (18.69-29.94)	23.46 (18.57-29.63)	1500.77	4.55 (3.81)	23.39 (18.48)
Abdominal pain upper	11	NA	NA	4.93	NA	NA	22	4.70 (3.09-7.17)	4.65 (3.07-7.04)	63.24	2.22 (1.41)	4.65 (3.05)	1	NA	NA	NA	NA	NA	34	NA	NA	NA	NA	NA
Abdominal discomfort	17	NA	NA	NA	NA	NA	16	3.56 (2.17-5.82)	3.53 (2.17-5.75)	29.12	1.82 (0.93)	3.53 (2.16)	NA	NA	NA	NA	NA	NA	33	1.55 (1.10-2.19)	NA	6.46	0.63 (0.12)	NA
Gastrointestinal hemorrhage	21	2.11 (1.37-3.24)	2.11 (1.37-3.23)	12.22	1.07 (0.40)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	21	1.72 (1.12-2.65)	NA	6.38	0.78 (0.13)	NA
Pancreatitis necrotizing	17	66.11 (41.00-106.60)	65.94 (40.94-106.20)	1079.22	6.03 (3.17)	65.46 (40.60)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	17	54.04 (33.52-87.13)	53.93 (33.48-86.87)	876.64	5.74 (3.10)	53.54 (33.21)
Tooth discoloration	1	NA	NA	NA	NA	NA	11	252.01 (138.63-458.13)	250.24 (138.22-453.03)	2688.33	7.94 (2.70)	246.37 (135.52)	1	NA	NA	NA	NA	NA	13	32.95 (19.10-56.84)	32.90 (19.09-56.70)	400.23	5.03 (2.57)	32.75 (18.98)

Dysbiosis	10	110.98 (59.45-207.16)	110.81 (59.42 - 206.65)	1074.71	6.77 (2.48)	109.45 (58.63)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	90.74 (48.62 - 169.37)	90.63 (48.59 - 169.03)	875.43	6.48 (2.45)	89.52 (47.96)
Lip swelling	3	NA	NA	NA	NA	NA	6	8.38 (3.76-18.68)	8.35 (3.76-18.56)	38.81	3.06 (0.95)	8.35 (3.74)	NA	NA	NA	NA	NA	NA	NA	9	2.12 (1.10-4.08)	2.12 (1.10-4.07)	5.32	1.08 (0.03)	NA
Constipation	4	NA	NA	14.54	NA	NA	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	9	NA	NA	11.68	NA	NA
Melena	6	2.42 (1.08-5.38)	2.41 (1.08-5.37)	4.97	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8	2.63 (1.32-5.27)	2.63 (1.32-5.26)	8.10	1.40 (0.21)	NA
Retching	5	NA	2.31 (0.96-5.54)	NA	NA	NA	3	6.75 (2.17-20.95)	6.74 (2.17-20.87)	14.66	2.75 (0.05)	6.74 (2.17)	NA	NA	NA	NA	NA	NA	NA	8	3.02 (1.51-6.05)	3.02 (1.51-6.04)	10.81	1.59 (0.36)	NA
Gastroesophageal reflux disease	3	NA	NA	4.32	NA	NA	5	2.76 (1.15-6.65)	2.76 (1.15-6.62)	5.61	NA	NA	NA	NA	NA	NA	NA	NA	NA	8	NA	NA	NA	NA	NA
Pancreatitis hemorrhagic	7	124.87 (59.19-263.40)	124.73 (59.18 - 262.91)	847.22	6.94 (1.92)	123.01 (58.31)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	102.11 (48.41 - 215.37)	102.02 (48.40 - 215.05)	690.44	6.65 (1.90)	100.61 (47.70)
Tongue discoloration	4	7.83 (2.94-20.88)	7.82 (2.94-20.85)	23.79	2.97 (0.46)	7.82 (2.93)	3	39.13 (12.59 - 121.62)	39.05 (12.59 - 121.13)	110.97	5.28 (0.48)	38.96 (12.53)	NA	NA	NA	NA	NA	NA	NA	7	11.22 (5.34-23.55)	11.21 (5.34-23.51)	64.98	3.48 (1.30)	11.19 (5.33)
Small intestinal obstruction	5	3.51 (1.46-8.44)	3.51 (1.46-8.43)	8.97	1.81 (0.15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5	2.87 (1.19-6.90)	2.87 (1.19-6.89)	6.09	NA	NA
Ileus	5	3.50 (1.46-8.41)	3.50 (1.46-8.40)	8.92	1.81 (0.15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5	2.86 (1.19-6.88)	2.86 (1.19-6.87)	6.05	NA	NA
Edematous pancreatitis	5	89.16 (36.94-215.24)	89.10 (36.93 - 214.94)	431.18	6.46 (1.35)	88.22 (36.54)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5	72.92 (30.21 - 176.01)	72.87 (30.20 - 175.80)	350.88	6.17 (1.33)	72.15 (29.89)
Paresthesia oral	1	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	NA	NA	5	2.76 (1.15-6.64)	2.76 (1.15-6.63)	5.61	NA	NA
Intestinal perforation	4	3.20 (1.20-8.52)	3.20 (1.20-8.51)	6.03	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	NA	2.61 (0.98-6.96)	NA	NA	NA

Barrett's esophagus	4	9.44 (3.54-25.18)	9.44 (3.54-25.15)	30.14	3.24 (0.55)	9.43 (3.54)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	7.72 (2.90-20.59)	7.72 (2.90-20.57)	23.37	2.95 (0.45)	7.71 (2.89)
Dysphagia	3	NA	NA	5.72	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3	NA	NA	8.00	NA	NA
Vomiting projectile	NA	NA	NA	NA	NA	NA	3	51.03 (16.41 - 158.67)	50.93 (16.41 - 158.03)	146.38	5.67 (0.50)	50.77 (16.33)	NA	NA	NA	NA	NA	NA	NA	3	9.24 (2.98-28.68)	9.24 (2.98-28.66)	22.01	3.21 (0.18)	9.23 (2.97)
Dyspepsia	NA	NA	NA	NA	NA	NA	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3	NA	NA	7.22	NA	NA
Feces soft	NA	NA	NA	NA	NA	NA	3	12.76 (4.11-39.63)	12.74 (4.11-39.47)	32.43	3.67 (0.28)	12.73 (4.10)	NA	NA	NA	NA	NA	NA	NA	3	4.04 (1.30-12.52)	4.03 (1.30-12.51)	6.84	NA	NA

N - number of reports, PT - preferred term, ROR - reporting odds ratio, CI - confidence interval, NA - not applicable, PRR - Proportional reporting ratio, χ^2 - chi-squared, IC - information component, IC025 - lower limit of the 95% CI of the IC, EBGM - empirical Bayesian geometric mean, EBGM05 - lower limit of the 95% CI of the EBGM

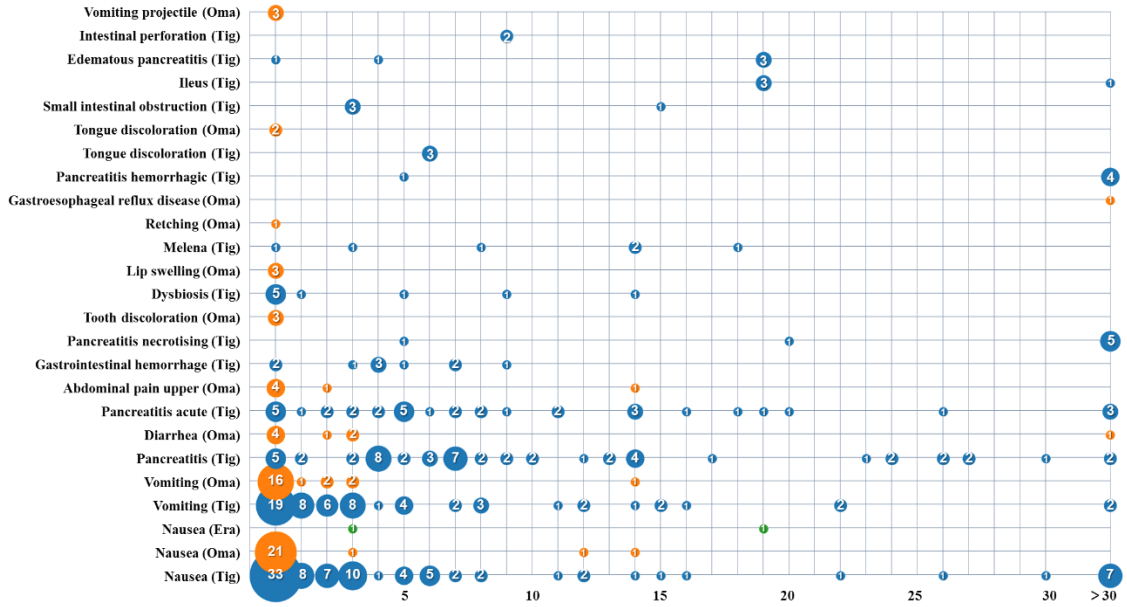

Fig. S1. Time to onset of gastrointestinal AEs related to the three novel tetracyclines. The vertical axis represents PTs, while the horizontal axis indicates the time to onset of AEs. The size of the bubbles and the numbers within them represent the number of cases for a specific PT, and the color coding indicates different drugs (blue for tigecycline, orange for omadacycline, and green for eravacycline).