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ORIGINAL RESEARCH

The Spectrum of Tigecycline-Induced Pancreatitis in Clinical Characteristics, Diagnosis, and Management

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Introduction: Tigecycline-induced acute pancreatitis (AP) has been frequently increasingly reported in solid organ transplant patients. This review aimed to summarize the characteristics, possible mechanisms, and management of tigecycline-induced AP.

Methods: Case reports of tigecycline-induced AP published in Chinese or English were collected until February 2023 for retrospective analysis.

Results: Thirty-four patients from 29 articles were included. Fifteen patients (46.9%) had solid organ transplantation, and 4 patients (12.5%) had malignant tumors. Twenty-five patients (89.3%) received a recommended maintenance dose of tigecycline (50 mg q12 h). The median age was 50 years (range 9–87). Compared to the nontransplant patients, the median age of the transplant patients was significantly younger, 44 years (range 12.5–61) versus 57.5 years (range 9–87) (P=0.03). The median time of symptom onset was 7 days (range 2–29), and 91.2% (31/34) were less than 14 days. Typical initial symptoms included abdominal pain (90.6%), nausea (46.9%), vomiting (43.8%), and abdominal distention (21.9%). Most cases were accompanied by elevated levels of pancreatic enzymes. The main radiological features included edematous infiltrate and acute pancreatitis on computed tomography (CT) scan and abdominal ultrasound. Except for one patient who continued tigecycline treatment, all patients discontinued treatment and received symptomatic support such as fasting, acid suppression, and enzyme suppression. The median time to recover pancreatic enzymes to the normal range was 5 days (range 1–43), and the median time to relieve symptoms was 4 days (range 1–12). Four patients died, of whom two died of severe pancreatitis complications and two of cardiogenic shock and septicemia.

Conclusion: Tigecycline-induced AP was a rare and serious complication that occurred mainly within two weeks of the medication. This serious side effect should be kept in mind while treating severe infections especially in transplant recipients.

Keywords: tigecycline, pancreatitis, adverse drug reaction, solid organ transplantation

Tigecycline is the first member of the glycylcycline family, approved by the US Food and Drug Administration (FDA) in 2005. It is a broad-spectrum antibiotic with in vitro activity against most Gram-positive and Gram-negative microbes and anaerobic organisms, including multiresistant bacteria such as extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacilli, carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2] It has high levels of antibacterial activity and tolerability. Tigecycline is indicated for complicated intra-abdominal infections (cIAI), complicated skin and skin structure infections (cSSSI), and community-acquired bacterial pneumonia (CAP) in adults. Recent evidence suggests that tigecycline may effectively treat severe *Clostridioides difficile* infection.[3]

The first case of acute pancreatitis (AP) caused by tigecycline was reported in 2008 by Gilson.[4] Since then, AP has been added to the "Adverse Reactions, Post Marketing Experience" section of the tigecycline label.[5] In 2014, McGovern et al summarized Phase III–IV clinical trial data and concluded that the incidence of tigecycline-associated pancreatitis

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was less than 1%.[6] From 1997 to 2010, the US FDA Adverse Event Reporting System recorded 62 patients with tigecycline-associated pancreatitis.[7] With the increased prescribing of tigecycline, concerns about tigecycline-induced AP have been raised recently, especially in patients with solid organ transplantation. The purpose of this article is to analyse and discuss the clinical characteristics of tigecycline-induced AP and provide a reference for the reasonable clinical application of tigecycline.

Methods

Retrieval Strategy

We searched the databases of PubMed/Medline, Web of Knowledge, Elsevier, Springer Link, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and China Science and Technology Journal Database. The search terms were "tigecycline", "pancreatitis", "lipase", "amylase" and "abdominal pain". Languages were restricted to Chinese and English. The timeframe was January 2005 to February 2023. A case report and case analysis of tigecycline-induced acute pancreatitis were included as a preliminary study. Acute pancreatitis met the Atlanta diagnostic criteria. Duplicates, reviews, observational studies, mechanistic studies, and animal studies were excluded.

According to the Atlanta diagnostic criteria, acute pancreatitis can be diagnosed with two of the following three characteristics: (1) Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, and epigastric pain that often radiates to the back); (2) Serum lipase or amylase activity at least three times higher than the upper limit of normal; and (3) Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasound.[8]

Data Collection

Two researchers independently conducted a preliminary review of the literature according to the inclusion and exclusion criteria. The consensus was reached through group discussion. A self-designed data extraction table extracted the following information: nationality, gender, age, primary disease, accompanying diseases, tigecycline application, concomitant medication, pancreatitis occurrence, treatment, and prognosis.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, Armonk, NY). The count data are expressed as n (%), and the measurement data are expressed as the median value (minimum, maximum).

Correlation Evaluation

The Naranjo Adverse Drug Reaction Probability Scale was used to assess the association between tigecycline and acute pancreatitis.[9]

Results

Patients' Information

A total of 34 patients from 29 case reports[4,10–37] were included in this analysis: 20 men (58.8%) and 13 women (38.2%). The sex of one patient was not reported (Table 1). Fifteen patients (46.9%) had solid organ transplantation. Four (12.5%) had malignant tumors. The median age of the patients was 50 years (range 9–87), and 10 patients (29.4%) were 60 years or older. The median age of the transplant patients was 44 years (range 12.5–61), which was significantly younger than that of the non-transplant patients, 57.5 years (range 9–87), P=0.03. Details are shown in Table 2. Among these patients,18 patients (52.9%) were from Asia,9 patients (26.5%) were from Europe,6 patients (17.6%) were from North America, and 1 patient (2.9%) was from Africa. Tigecycline was prescribed mainly for pulmonary infections (7 patients, 20.6%), prophylaxis after transplantation (6 patients, 17.6%), osteomyelitis (5 patients, 14.7%) and complicated skin and skin-structure infection (5 patients,14.7%). Bloodstream infection (8.8%), donor-derived infection after kidney transplantation (8.8%), complicated intra-abdominal infection (5.9%), and urinary tract infection (5.9%) were also common indications. The most common bacterial species involved were multidrug-resistant *Acinetobacter baumannii* (5 patients,

Table 1 Characteristics of Included Patients with Tigecycline-Induced Pancreatitis

Parameter		Value
Sex[b,34]	Male	20(58.8%)
	Female	13(38.2%)
	No data	1(2.9%)
Age[b,34]	Years	50(9,87)[a]
	≥60 years	10(29.4%)
Region[b,34]	China	18(52.9%)
	The United States	6(17.6%)
	France	4(11.8%)
	Belgium	2(5.9%)
	Turkey	1(2.9%)
	Italy	1(2.9%)
	Spain	1(2.9%)
	Egypt	1(2.9%)
Indication for tigecycline[b,34]	Pulmonary infection	7(20.6%)
	Prophylaxis after transplantation	6(17.6%)
	Osteomyelitis	5(14.7%)
	cSSSI	5(14.7%)
	BSI	3(8.8%)
	Donor-derived infection after kidney transplantation	3(8.8%)
	IAI	2(5.9%)
	Urinary tract infection	2(5.9%)
	Perianal abscess	1(2.9%)
Risk factors for acute pancreatitis[b,34]	Gallstones, alcohol, smoking, hypertriglyceridemia	1(2.9%)
Bacteriumb[,26]	*Acinetobacter baumannii* (MDR)	5(19.2%)
	Mixed bacterial	5(19.2%)
	Escherichia coli (ESBL)	4(15.4%)
	Enterobacter cloacae (ESBL)	2(7.7%)
	Carbapenem-resistant *Klebsiella pneumonia* (CRKP)	2(7.7%)
	Mycoplasma chelonae	2(7.7%)
	G^+ bacteria	2(7.7%)
	Klebsiella pneumoniae (ESBL)	1(3.8%)
	Pseudomonas aeruginosa	1(3.8%)
	MRSA	1(3.8%)
	MSSA	1(3.8%)
Accompanying diseases[b,32]	Kidney transplantation	13(40.6%)
	Malignant tumor	4(12.5%)
	Hypertension	7(21.9%)
	Nephritis or renal insufficiency	4(12.5%)
	Diabetes mellitus	3(9.4%)
	Sickle-cell anemia	2(6.2%)
	Lung transplantation	1(3.1%)
	Liver transplantation	1(3.1%)
Loading dose of tigecycline used[b,28]	YES	18(64.3%)
	NO	10(35.7%)
Maintenance dose of tigecycline[b,28]	50 mg ivgtt q12h	25(89.3%)
	100 mg ivgtt q12h	3(10.7%)
Concomitant medication[b,34]	Antibacterials	25(73.5%)
	Immunosuppression	15(44.1%)
	Corticosteroids	14(41.2%)
	Antifungal drugs	9(26.5%)
	Anti-CD25 monoclonal	5(14.7%)

(*Continued*)

Table 1 (Continued).

Parameter		Value
	Hydroxyurea	2(5.9%)
	Cyclophosphamide	1(2.9%)
	Propofol	1(2.9%)
Time of symptom onset during the first tigecycline administration[b,34]	Days	7(2,29)[a]
	Symptom onset within 1 week	18(52.9%)
	Symptom onset 1–2 weeks	13(38.2%)
Pancreatitis occurs in two consecutive tigecycline administrations[b,4]	Days	8(3,29)[a]
	The secondary occurred within 1 week	2(50.0%)

Notes: [a]Median (minimum-maximum). [b]Represents the number of patients among a total of 34 on whom information regarding this particular parameter was provided.

Abbreviations: cSSSI, complicated skin and skin-structure infection; BSI, blood stream infection; IAI, intra-abdominal infection; ESBL, extended-spectrum betalactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *Staphylococcus aureus*.

Table 2 Comparison of Clinical Characteristics of Included Patients with or Without Solid Organ Transplantation

Variable	Non-Transplant Patients (n=19)*	Transplant Patients (n=15)	*P* value
Male	10	10	0.63
Female	8	5	0.63
Age (Years)	57.5(9,87)[a]	44(12.5,61)[a]	0.03
AP severity (Moderate/Severe)	17/2	14/1	0.86
Time of symptom onset during the first tigecycline administration (Days)	10(2,29)[a]	7(3,28)[a]	0.68
The peak of Amylase (U/L)	381(180,1250)[a]	632(157,1250.8)[a]	0.17
The peak of Lipase (U/L)	814(134,4089)[a]	682(156,1835)[a]	0.91
Time to symptom relief (Days)	3(1,12)[a]	4.5(1,7)[a]	0.61
Time to recovery of enzymes (Days)	5(1,43)[a]	5(2,14)[a]	0.52

Notes: [a]Median (minimum-maximum). *One patient in this group did not provide gender.

19.2%) and *Escherichia coli*-producing ESBL (4 patients, 15.4%). All patients were taking concomitant drugs, with the other antibacterials in 25 patients (73.5%), immunosuppression (including tacrolimus, mycophenolate mofetil, azathioprine, and cyclosporine) in 15 patients (44.1%), corticosteroids (such as prednisone and meprednisone) in 14 patients (41.2%), antifungal drugs (such as caspofungin, voriconazole and amphotericin B) in 9 patients (26.5%), anti-CD25 monoclonal in 5 patients (14.7%) and hydroxyurea in 2 patients (5.9%). Details are shown in Table 1.

Administration of Tigecycline

The dose of tigecycline was available in 28 patients. Eighteen patients (64.3%) received loading doses of tigecycline, and 25 patients (89.3%) received the recommended maintenance dose (50 mg q12 h). After tigecycline administration, the median time to onset of pancreatitis symptoms was 7 days (range 2–29). The onset time of symptoms was less than 14 days in 31 patients (91.2%). The median onset time for pancreatitis symptoms in patients with or without organ transplantation was 7 days (range 3–28) and 10 days (range 2–29), respectively. Pancreatitis recurred in 4 patients after the tigecycline re-challenge, with 50% of pancreatitis recurring within 7 days.

The Naranjo Adverse Reaction Scale[8] was used to assess tigecycline-induced pancreatitis. The results of the relevance evaluation showed that the correlation between tigecycline and pancreatitis was possible (scores 1–4) in 6 patients (17.6%), probable (scores 5–9) in 24 patients (70.6%), and definite (scores >9) in 4 patients (11.8%).

Clinical Presentation

Table 2 and Table 3 show the clinical manifestations of pancreatitis. Initial symptoms were described in 32 patients. Abdominal pain was the most common clinical symptom (29 patients, 90.6%), followed by nausea (15 patients, 46.9%) and vomiting (14 patients, 43.8%). An analysis of the 34 patients with acute pancreatitis induced by tigecycline showed that 31 patients (91.2%) developed moderate AP, and 3 patients (40.9%) developed severe AP.

Imaging Examination

The computed tomography (CT) scan was reported in 28 patients, and the main findings are summarized in Table 3. CT manifestations of pancreatitis included the following: edematous infiltrate (16 patients, 57.1%), acute pancreatitis (9 patients, 32.1%), and normal (3 patients, 10.7%). Although three cases had normal CT findings, one patient was pathologically confirmed as having extensive hemorrhage and necrosis of pancreatic tissue with inflammatory exudation. Three patients underwent abdominal ultrasound examination and two patient showed pancreatitis with pancreatic edema.

Laboratory Tests

The laboratory test results are summarized in Table 2 and Table 3. The median value of serum amylase levels was 570.5 (range 157–1250.8) U/L in 25 patients, and the median value of serum lipase levels was 740.5 (range 134–4089) U/L in

Table 3 Clinical Information on the 34 Included Patients

Parameter	Clinical Features	Value, n (%)
Presenting symptoms[b,32]	Abdominal pain	29(90.6%)
	Nausea	15(46.9%)
	Vomiting	14(43.8%)
	Abdominal distension	7(21.9%)
AP severity[b,34]	Moderate	31(91.2%)
	Severe	3(8.8%)
Imaging examination	CT scan	28
	Oedematous infiltrate	16(57.1%)
	Acute pancreatitis	9(32.1%)
	Normal	3(10.7%)
	Ultrasonogram of the abdomen	3
	Pancreatic oedema	2(66.6%)
	Normal	1(33.3%)
Amylase[b,25]	U//L	570.5(157,1250.8)[a]
Lipase[b,26]	U//L	740.5(134,4089)[a]
Therapy[b,34]	Discontinued tigecycline	33(97.0%)
	Continued tigecycline	1(2.9%)
	Fasting treatment	14(41.2%)
	Inhibition of pancreatic enzyme secretion	12(35.3%)
	Proton pump inhibitor	8(23.5%)
	Drainage tube	2(5.9%)
	Emergency laparotomy	1(2.9%)
Time to symptom relief[b,27]	Days	4(1,12)
	Within 4 days	7(25.9%)
	Within 1 week	25(92.6%)
Time to recovery of enzymes[b,27]	Days	5(1,43)
	Within 4 days	15(55.5%)
	Within 1 week	20(74.1%)
Naranjo score[b,34]	Possible	6(17.6%)
	Probable	24(70.6%)
	Definite	4(11.8%)

Notes: [a]Median (minimum-maximum). [b]Represents the number of patients among a total of 34 on whom information regarding this particular parameter was provided.

26 patients. The peak of amylase in the transplantation group was higher than that in the non-transplantation group, with a median value of 632 (157–1250.8) U/L and 381 (180–1250) U/L, respectively.

Treatment and Prognosis

Table 3 summarizes the treatment and prognosis of 34 patients. All patients, except one, discontinued tigecycline treatment. Fourteen patients (41.2%) received fasting treatment, 12 patients (35.3%) received pancreatic enzyme secretion inhibition treatment, and 8 patients (23.5%) received proton pump inhibitors. Patients' symptoms gradually improved at a median of 4 days (range 1–12): 7 patients (25.9%) within 4 days and 25 patients (92.6%) within one week. The median time to symptom relief in the transplantation group was longer than that in the non-transplantation group, with a median value of 4.5 (range 1–7) days and 3 (range 1–12) days, respectively. The recovery time of pancreatic enzyme levels to normal ranges was within a median of 5 days (range 1–43), and 20 patients (74.1%) whose pancreatic enzyme levels returned to the normal range within 1 week. Four patients (11.8%) died, of whom two died from severe pancreatitis complications,[26,31] and two died of cardiogenic shock and septicemia.[22,30]

Discussion

Pancreatitis is a common digestive tract disease characterized by inflammatory damage caused by self-digestion of pancreatic tissues, including pancreatic edema, hemorrhage, or necrosis. Gallstones (40–70%) and alcohol exposure (25–35%) are the most common causes of pancreatitis.[38] Drug-induced pancreatitis accounts for 0.1–5.3% of the total cases of pancreatitis.[39,40] A systematic review of potential drugs associated with AP suggested a 4-category classification system based on the published evidence weight.[41] Class Ia includes medications with at least one case report, evidence of a positive rechallenge, and the exclusion of other causes of AP, such as cholelithiasis, alcohol, and hypertriglyceridemia. Tetracycline is considered class Ia, with a well-defined risk of pancreatitis. Tigecycline is similar to tetracycline in structure. Based on our findings, tigecycline should also be classified as a class Ia drug.

Tigecycline-induced AP was more common in transplant patients in our analysis. The incidence of acute pancreatitis in these patients ranges from 1% to 8% after solid organ transplantation.[42,43] Virus or drug-induced pancreatitis is more prevalent in transplant recipients.[44] Immunosuppressive drugs can induce pancreatitis in renal transplant patients, such as tacrolimus, mycophenolate mofetil, and glucocorticoid.[45–47] When these drugs are combined with tigecycline, it can increase the risk of developing pancreatitis. Drug interactions between tacrolimus and tigecycline are suspected of playing a role in developing AP.[23] According to two separate studies conducted by Pavan et al[48] and Chow et al,[49] serum tacrolimus levels increased when tigecycline was administered but decreased after discontinuation of tigecycline. It was hypothesized that there was a possible inhibition of CYP_3A_4 related to tigecycline.[48] Furthermore, tigecycline and tacrolimus are substrates for the membrane transport protein p-glycoprotein (P-gp). Both drugs can alter their serum levels by sharing a similar excretion mechanism. This interaction might also contribute to elevated levels of tigecycline that might lead to AP.[23] Caution should be taken when tigecycline is taken with immunosuppressants.

We found that most patients who developed tigecycline-induced pancreatitis were either men or less than 60 years old. However, female or older patients were observed in other studies of drug-induced pancreatitis.[7,50,51] In addition to the male sex predominance, the median age of patients in the transplant group was lower than that of the nontransplant group, which may be related to the survival age of transplantation. The fact that younger and middle-aged patients have more transplant opportunities than older patients may also contribute to this result.[52–54]

We observed that most patients had multiple comorbid conditions, supporting the hypothesis postulated by Balani and Grendell[51] They found that drug-induced pancreatitis was more common in patients with multiple comorbid conditions on various medications or polypharmacy. More attention should be paid to these special populations in clinical treatment.

In our study, 91.2% of the patients had symptoms that occurred within two weeks, and the median time was 7 days. This finding is similar to a previous study in which the duration of tigecycline use before the onset of pancreatitis symptoms was 12.5 days.[7] Therefore, monitoring should be strengthened within two weeks after tigecycline administration. We found that the time of symptom onset in patients with solid organ transplantation was shorter than in patients without transplantation. An apparent explanation is that tigecycline is partially excreted through the kidneys. In renal

transplant patients, kidney function is not fully recovered, leading to a higher serum tigecycline concentration and increased risk of pancreatitis.

The mechanism of tigecycline-induced pancreatitis is still unclear. The mechanism may be similar to that caused by tetracycline. Steinberg[55] hypothesized that accumulating an unidentified toxic metabolite could cause tetracycline-induced pancreatitis. Elmore and Rogger[56] hypothesized that tetracycline precipitated an episode of pancreatitis by reacting with 30S ribosomal units and blocking protein synthesis that caused the accumulation of triglycerides in the pancreas. Gilson et al[4] suggested that a high biliary concentration of tetracycline could be associated with tetracycline-induced pancreatitis. A single 100 mg dose of intravenous tigecycline produced considerably higher tissue/fluid concentrations in bile than simultaneous serum concentrations. The respective site-to-serum ratios based on the area under the mean concentration-time curve from 0 to 24 h ($AUC_{0–24}$) for mean and median bile concentrations are 537 and 368, respectively.[57]

Tigecycline-induced pancreatitis can be resolved by discontinuing the drug, fasting, inhibiting pancreatic enzyme secretion, a short course of proton pump inhibitors, and symptomatic support. Symptom relief and pancreatic enzymes returned to normal within one week, accounting for 92.6% and 74.1% of the cases. The prognosis of pancreatitis related to tigecycline is generally excellent, with prompt and complete clinical recovery.

Conclusion

Pancreatitis is a relatively rare adverse reaction to tigecycline. Clinicians should strictly follow the indications for the use of tigecycline, particularly in patients with solid organ transplantation. If tigecycline treatment is necessary, pancreatic enzymes and clinical symptoms should be monitored regularly, especially about 14 days after starting the medication. Once patients develop severe nausea, vomiting, and abdominal pain, an abdominal CT or ultrasound should be performed for early diagnosis and treatment.

Data Sharing Statement

The data that support the findings of this study were sourced directly from the published studies included in this study.

Ethics Approval and Consent to Participate

The data and information used in this study is publicly available, and the researchers recorded the information in a way that does not directly identify the subjects. Therefore, this study was exempt from ethical review by the ethics committee. For this type of study, formal consent is not required.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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