Pancreatitis in tigecycline Phase 3 and 4 clinical studies

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Objectives: To examine the incidence of pancreatitis among subjects enrolled in the tigecycline clinical trial programme, summarize cases and examine concomitant use of other pancreatitis-causing medications.

Methods: Subject data from Phase 3 and 4 comparative tigecycline studies were included in the analysis; investigator-reported adverse events of ‘pancreatitis’, ‘necrotizing pancreatitis’ or ‘pancreas disorder’ were reviewed. Data were summarized and cases were reported. No statistical comparisons were made. The incidence of overall pancreatitis with 95% CIs was calculated. The Wilson score method was used to calculate CIs.

Results: Nineteen subjects with investigator-determined pancreatitis were identified from the programme database, which included 3788 subjects treated with tigecycline and 3646 subjects treated with a comparator. There were 9 cases identified among the tigecycline-treated subjects [9 of 3788 (0.24%; 95% CI, 0.11–0.45)] and 10 cases among the comparator-treated subjects [10 of 3646 (0.27%; 95% CI, 0.13–0.50)]. The demographic characteristics of the subjects with pancreatitis were similar between treatment groups. The median duration of tigecycline therapy was 8.0 days compared with 11.0 days of comparator treatment. Concomitant or prior exposure to a Badalov class I medication was evident in the majority of subjects who developed pancreatitis. A numerically higher number of tigecycline-treated subjects were exposed to furosemide prior to the onset of pancreatitis than comparator-treated subjects.

Conclusions: Pancreatitis was uncommon in subjects treated with tigecycline, with an occurrence of <1%. Concomitant medications known to cause pancreatitis should be considered when prescribing tigecycline, but may not identify those at risk of developing pancreatitis.

Keywords: adverse events, glycylcycline, furosemide

Introduction

Pancreatitis is a serious and potentially fatal disease with diverse aetiology, including medications. Pancreatitis is a recognized, but uncommon, side effect of orally administered tetracycline.1 The exact mechanism of tetracycline-induced pancreatitis is not known. Tigecycline is a glycylcycline antibiotic and an analogue of the semi-synthetic tetracycline, minocycline. Cases of pancreatitis in patients receiving tigecycline have been reported.2–9 In several of these cases, concomitant or prior exposure to another drug (e.g. acetaminophen,3,6 omeprazole8 and propofol4) with a known association with drug-induced pancreatitis was evident from the case report descriptions. We conducted this study to examine the incidence of pancreatitis among subjects enrolled in the tigecycline clinical trial programme, in the context of predisposing conditions and use of other medications associated with pancreatitis.

Methods

Subject data from 13 Phase 3 and 4 comparative tigecycline studies were included in the analysis. The tigecycline dose was a 100 mg loading dose followed by 50 mg every 12 h, administered by intravenous infusion over 30–60 min except for the diabetic foot infection trial that tested a dose of 150 mg every 24 h. The population for the analysis included subjects in the modified intent-to-treat population who received at least one dose of tigecycline or comparator (vancomycin, imipenem/cilastatin, ceftriaxone and metronidazole, levofloxacin, etoposene, lineozid, aztreonam, ampicillin/subactam and amoxicillin/clavulanate). Three of the comparator drugs were included in the original Badalov class designation: metronidazole (class Ia), ceftriaxone (class III) and ampicillin (class IV).10 Investigator-reported adverse events of ‘pancreatitis’, ‘necrotizing pancreatitis’ or ‘pancreas disorder’ were reviewed and subject cases were summarized. Demography was described and risk factors, including medical history, procedures and concomitant medications known to cause pancreatitis using the Badalov classification,10 were
Table 1. Summary of pancreatitis cases

| Test drug | Subject characteristics (clinically relevant history/procedures) | Day of onset | Outcome/complications | Severity | Non-study class I–II medications prior to pancreatitis (class); time period of exposure relative to test drug | Investigator-determined relationship |
|-----------|---------------------------------------------------------------|--------------|-----------------------|----------|------------------------------------------------------------------------------------------------|-----------------------------------|
| Tigecycline<sup>a</sup> | 76 yo, F: intra-abdominal abscess (ERCP day 1) | 7 | resolved | severe | oestrogen (Ib); P acetaminophen (II); P, C, A furosemide (Ia); C, A | possibly related |
| | 69 yo, M: complicated cholecystitis | 2 | (necrotizing pancreatitis) | death day 3 from MODS | life-threatening | furosemide (Ia); A acetaminophen (II); C, A metronidazole (Ia); P | probably not related |
| | 31 yo, M: peritonitis/large bowel perforation | 13 | resolved | moderate | furosemide (Ia); P acetaminophen (II); C, A metronidazole (Ia); P | probably not related |
| | 48 yo, F: complicated appendicitis | 3 | NR | moderate | furosemide (Ia); P, C probably not related |
| | 73 yo, M: MRSA primary bacteremia | 13 | persisted; candidaemia/sepsis day 30; death day 35 | moderate | furosemide (Ia); P, C acetaminophen (II); C, P | probably not related |
| | 69 yo, M: CABP | 9 | resolved | moderate | furosemide (Ia); P, C acetaminophen (II); C, A | probably not related |
| | 50 yo, M: HAP | 20 | resolved; necrotizing pancreatitis at enrolment; surgical drainage of the post-necrotic cyst on day 26; drainage of abdominal cavity and sequestrectomy on day 47 | moderate | furosemide (Ia); C | definitely not related |
| | | | | | | |
| | 63 yo, M: HAP | 5 | resolved | mild | furosemide (Ia); P, C | probably related |
| | 70 yo, F: HAP (gastric ventricular resection, Billroth II and splenectomy on day 2) | 6 | persisted; Pseudomonas/Serratia pneumonia with Pseudomonas bacteremia day 8; septic shock/death day 9 | life-threatening | furosemide (Ia); P, C amiodarone (Ib); P, C propofol (II); P, C | probably not related |
| | Imipenem | 42 yo, M: peritonitis; small bowel perforation (Roux-en-Y anastomosis on day 1) | 5 | resolved | moderate | omeprazole (Ib); P | probably not related |
| | | 35 yo, M: post-traumatic peritonitis | 5 | (post-traumatic pancreatitis) | resolved | moderate | none | probably not related |
| | | 78 yo, M: HAP | 8 | resolved; necrotic bowel and surgery day 13; pneumonia and bacteremia day 14; septic shock/death day 15 | life-threatening | enalapril (Ia); P, C furosemide (Ia); P, C, A metronidazole (Ia); P propofol (II); P, C acetaminophen (II); P, C, A | definitely not related |
| | | 40 yo, M: HAP | 13 | persisted | mild | acetaminophen (II); P, C, A propofol (II); P metronidazole (Ia); P | probably not related |
| | | 44 yo, M: HAP (necrotizing pancreatitis at enrolment) | 26 (chronic pancreatitis) | persisted | mild | furosemide (Ia); P omeprazole (Ib); P enalapril (Ia); P, C, A furosemide (Ia); C, A metronidazole (Ia); P | definitely not related |
| | | 57 yo, F: HAP | 18 (chronic pancreatitis) | persisted | mild | furosemide (Ia); C, A | probably not related |
## Results

Nineteen subjects with investigator-determined pancreatitis were identified from the programme database of comparative studies, which included 3788 (0.24%; 95% CI, 0.11–0.45) and 10 cases were identified among the tigecycline-treated subjects [9 of 3788 (0.24%; 95% CI, 0.11–0.45)] and 10 cases were identified from the programme database of comparative studies, which included 3788 (0.24%; 95% CI, 0.11–0.45) and 10 cases were identified among the tigecycline-treated subjects [9 of 3788 (0.24%; 95% CI, 0.11–0.45)].

### Table 1. More tigecycline-treated subjects (77.8%) were exposed and the specific class I–II medication exposures are provided in Table 1. Two cases of necrotizing pancreatitis in patients where the pancreatitis was considered ‘probably not related’ or ‘possibly related’. No time pattern

| Medication                  | Age (years) | Sex | Race | Weight (kg) | Height (cm) | Death | Cause of Death |
|-----------------------------|-------------|-----|------|-------------|-------------|-------|----------------|
| Ceftriaxone/metrodinazole   | 91          | F   | W    | 65          | 170         | No    | None           |
| 34                          | M           |      | W    | 70          | 175         | No    | None           |
| Vancomycin                  | 44          | F   | W    | 70          | 170         | Yes   | Sepsis          |
| 66                          | M           |      | W    | 80          | 180         | No    | None           |

### Table 2. More tigecycline-treated subjects (77.8%) were exposed and the specific class I–II medication exposures are provided in Table 1. Two cases of necrotizing pancreatitis in patients where the pancreatitis was considered ‘probably not related’ or ‘possibly related’. No time pattern

Exposure to specific medications known to cause pancreatitis and exposure to specific medications known to cause pancreatitis and the specific class I–II medication exposures are provided in Table 1. Two cases of necrotizing pancreatitis in patients where the pancreatitis was considered ‘probably not related’ or ‘possibly related’. No time pattern

*Artefactual, ARF, acute renal failure; C, concomitant; ChF, congestive heart failure; CSTEMI, complicated skin and tissue infection; CABP, community-acquired bacterial pneumonia; ERCP, endoscopic retrograde cholangiopancreatography; F, female; HAP, hospital-acquired pneumonia; M, male; MI, myocardial infarction; MODS, multiple organ dysfunction syndrome; MRSA, methicillin-resistant Staphylococcus aureus; NR, not reported; P, prior to; yo, years old.

\*Relevant clinical information at the time of enrolment, including medical conditions (e.g. cholithiasis) or procedures (e.g. endoscopic retrograde cholangiopancreatography) known to cause or elevate the risk of pancreatitis.

\*Study day relative to start of therapy.

\*Excludes medications given after test regimen that were started after pancreatitis diagnosis.

\*All tigecycline subjects who developed pancreatitis received a 100 mg loading dose then 50 mg every 12 h.

\*Resistant pathogen study.
2593 (0.27%) comparator subjects developed pancreatitis. For those with furosemide exposure, 1.03% of tigecycline and 0.58% of comparator subjects developed pancreatitis. Propofol-exposed subjects developed pancreatitis in 0.49% and 1.00% of tigecycline- and comparator-treated subjects, respectively.

**Discussion**

Based on clinical trial data, the incidence of pancreatitis associated with tigecycline exposure is uncommon at an incidence rate of 0.24%. Of the nine cases of pancreatitis in subjects treated with tigecycline, however, only one-third were probably or possibly related based on investigator-determined relationship to tigecycline use. Pancreatitis has been identified in pharmacovigilance databases during post-approval use of tigecycline.9,11,12 Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

Pancreatic drug injury is often idiosyncratic and mechanistically may represent hypersensitivity or toxic metabolite formation rather than direct toxicity.10 The mechanism of tigecycline-induced pancreatitis is unknown, but is likely to be similar to that of other tetracyclines. Hypertriglyceridaemia13 and toxic metabolite formation14 have been proposed as possible mechanisms that contribute to tetracycline-induced pancreatitis; however, lipid levels were not captured in our subjects and, therefore, correlations with the onset of pancreatitis cannot be made. Alternatively, Gilson et al. have hypothesized that high biliary concentrations of tigecycline might play a role in the development of pancreatitis.

Formation of atoxic metabolite seems unlikely in the case of tigecycline. First-pass metabolism does not occur, because tigecycline is administered only intravenously. After administration, it distributes widely in the body, but undergoes limited metabolism. Unchanged drug was the predominant drug-related compound in serum, urine and faeces in a metabolic study of [14C]tigecycline administration to healthy volunteers.15 The major metabolic pathways identified...
were glucuronidation of tigecycline and amide hydrolysis followed by N-acetylation to form N-acetyl-9-aminomycincycline. The glucuronide metabolites were 5%–20% of serum radioactivity and ~90% of the dose was excreted as glucuronide conjugates within 48 h. Unchanged drug is eliminated in the urine as well as by biliary excretion.

Subjects treated with tigecycline or a comparator had a relatively high rate of exposure to Badalov class I–II medications. Despite extensive exposure to these medications, relatively few individuals developed pancreatitis. Our data identified a possible relationship between pancreatitis and furosemide. Pancreatitis due to furosemide is rarely reported in the literature, but has a strong class Ia designation by Badalov. However, the difference in the development of pancreatitis between tigecycline- and comparator-treated subjects exposed to furosemide is small (Table 2), the mechanism of such a relationship is unclear and the limited number of subjects precludes further analysis.

As it has been previously hypothesized in the case of propofol and tigecycline, either agent could sensitize the pancreas to a possible adverse reaction upon subsequent exposure to the other. In this analysis, exposure to propofol resulted in a small difference in pancreatitis incidence between tigecycline- and comparator-treated subjects (Table 2). Drug interactions that resulted in increased exposure or formation of toxic metabolites of either compound do not appear to be likely in the case of either concomitant tigecycline and furosemide administration or concomitant tigecycline and propofol administration. Neither tigecycline nor furosemide are substrates of cytochrome P450 (CYP450) drug-metabolizing enzymes and neither is shown to alter the activity of CYP450 enzymes. Propofol undergoes metabolism, but, because it is not administered chronically, is unlikely to alter the exposure to tigecycline.

Tigecycline had just become commercially available at the time the Badalov classification was published. Tetracycine is considered class Ia and minocycline is considered class III. Based on the available published reports of pancreatitis associated with tigecycline, we suggest that tigecycline would have a class Ib designation as the one paediatric patient with a positive rechallenge had sickle cell anaemia, which can be associated with the development of pancreatitis. In addition, pancreatitis has been described in patients with sickle cell anaemia and should be considered as a differential diagnosis of abdominal pain cause in such patients.

From a clinical perspective, one must also consider whether a past history or baseline pancreatitis (unrelated to tigecycline) should preclude further tigecycline exposure. We suggest that caution should be exercised with close monitoring of the patient when tigecycline is the most appropriate therapy. There are documented instances of the safe use of tigecycline in patients with a history of chronic pancreatitis or an episode of acute pancreatitis; including one subject reported here who was enrolled for the treatment of hospital-acquired pneumonia with necrotizing pancreatitis at baseline.

There are limitations that should be acknowledged. Pancreatitis was identified by the investigators as an adverse event among patients included in individual clinical studies and therefore diagnostic criteria were not standardized a priori. The data do not permit a determination of cause and effect, and rechallenge was not possible in a clinical trial setting. Finally, the results may not be broadly generalizable to clinical practice, where patients may differ from populations and infections studied in the clinical studies.

In our review of clinical trial data, pancreatitis was uncommon in subjects treated with tigecycline, with an occurrence of <1%.

Clinician awareness of this potential adverse effect is necessary. Prior or concurrent history of pancreatitis as well as the use of concomitant medications known to cause pancreatitis should be taken into consideration when prescribing tigecycline, but may not identify those at risk of developing pancreatitis.

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