Eravacycline Associated Hypofibrinogenemia: A Case Series of Transplant Patients With *Mycobacterium Abscessus* Infections and Review of Literature

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Eravacycline is a synthetic fluorocycline within the tetracycline class of antimicrobials. Eravacycline is active in vitro against several clinically important Gram-positive and Gram-negative bacteria [1–2]. In addition, eravacycline has activity against several rapidly growing mycobacteria, including *Mycobacterium abscessus* [3]. In phase 2/3 clinical trials, the most common adverse reactions included infusion reactions, nausea, and vomiting [1]. These side effects are similar to those of tigecycline, a comparable synthetic tetracycline. Tigecycline is also associated with hypofibrinogenemia (<200 mg/dL) and coagulopathies for which the mechanism remains unconfirmed [4–5]. It is unknown whether hypofibrinogenemia is a class effect of the synthetic tetracyclines. In this study, we describe 6 cases of hypofibrinogenemia observed during eravacycline therapy, which has not previously been reported. We discuss the characteristics of eravacycline-induced hypofibrinogenemia, review tigecycline-associated hypofibrinogenemia cases, and assess the impact it may have on laboratory monitoring and patient outcomes.

CASE SERIES

We describe 6 patients seen between July 2021 and July 2022 who developed hypofibrinogenemia during treatment with

eravacycline-containing regimens for *M abscessus* infections. The index patient, Patient 1, was a 73-year-old male with history of bilateral orthotopic lung transplant (BOLT) who presented approximately 2 years posttransplant for treatment of *M abscessus* infection identified from a prior suprapubic catheter site. The patient was admitted for surgical debridement and began empiric treatment of tigecycline 50 mg every 12 hours, together with linezolid and imipenem, in addition to continuing bronchiolitis obliterans syndrome prophylaxis with azithromycin. On hospital day (HD)13, bloody oozing was noted from debridement site. Tigecycline was stopped and eravacycline was started at 1 mg/kg every 12 hours due to a decreased fibrinogen level of 167 mg/dL. Other coagulation parameters were normal with international normalized ratio (INR) of 1.15 and prothrombin time (PT) of 13.6 seconds. The eravacycline was discontinued on HD32 when the fibrinogen level was noted to be 64 mg/dL. The INR had increased to 1.4 and PT was 16.4 seconds. The fibrinogen normalized within 3 days of stopping eravacycline. On HD31, however, the patient developed multidrug-resistant *Pseudomonas* pneumonia leading to septic shock and death on HD36.

Patient 2 was a 72-year-old female with history of deceased donor kidney transplant (DDKT). At 1.5 months after transplant, serosanguinous drainage and a small area of wound dehiscence was noted at the surgical incision site. Cultures revealed 4 + *M abscessus*. She was admitted and initiated treatment with tigecycline 50 mg every 12 hours, azithromycin, imipenem, and surgical debridement of the wound site. On HD8, tigecycline was reduced to 50 mg daily in hopes of minimizing ongoing gastrointestinal side effects. On HD11, it was noted the patient had a fibrinogen of 77 mg/dL, activated partial thromboplastin time (aPTT) of 28.4 seconds, an INR of 1.4, and thrombocytopenia with 95 000 platelets/mL. Given the fibrinogen level <100 mg/dL, 1 unit of cryoprecipitate was given, with an increase to 164 mg/dL. However, the fibrinogen level again decreased, leading to a switch from tigecycline to eravacycline 1 mg/kg every 12 hours on HD20. Despite this change, the fibrinogen persistently trended down, reaching 52 mg/dL after 1 week of eravacycline. Another unit of cryoprecipitate was given with a response to 153 mg/dL, but the fibrinogen level continued to decrease to 79 mg/dL on HD32; thus, eravacycline was stopped. Other coagulation parameters available at that time included a normal INR of 1.33. After cessation of eravacycline, the fibrinogen returned to normal in 5 days without additional cryoprecipitate. A final regimen of azithromycin, tedizolid, and imipenem was used based on resulting antimicrobial susceptibility testing. Unfortunately, the patient died on HD62 secondary to massive upper gastrointestinal bleed from gastric perforation.

Patient 3 was a 63-year-old male with history of DDKT more than 10 years prior, who presented to the hospital for acute hypoxic respiratory failure from coronavirus disease 2019, requiring intubation and a prolonged ventilator wean. During his prolonged hospital stay, infectious workup for fever revealed blood cultures and tracheostomy culture positive for *M abscessus*; consistent with disseminated infection. Initial therapy was started with azithromycin, imipenem, tedizolid, and eravacycline 1 mg/kg every 12 hours. On treatment day (TD) 24, the fibrinogen level was 120 mg/dL, which prompted discontinuation of eravacycline. On TD25, bleeding was noted from a sacral wound, with hemoglobin drop requiring 1 unit of packed red blood cells (PRBCs). Other coagulation parameters were normal, with INR 1.29 and PT of 15.1 seconds. The fibrinogen recovered within 5 days and on TD31. Due to toxicities with alternative agents, eravacycline was retrialed on TD31. The fibrinogen trended from 310 to 140 mg/dL over 8 days, leading to discontinuation of eravacycline for the second time. Clofazimine was substituted based on antimicrobial susceptibilities. One day later, bleeding was again noted from the sacral wound with a hemoglobin decrease requiring 1-unit PRBC. The patient developed distributive shock from alternative infectious sources, including *Pseudomonas* bacteremia, and subsequently expired on TD82 upon transition to comfort care.

Patient 4 was a 68-year-old male with history of BOLT 12 months prior, who presented from acute inpatient rehab with concerns for multiple nodules on the left upper extremity that grew *M abscessus* from tissue biopsy. Empirical therapy was started with eravacycline 1 mg/kg every 12 hours together with azithromycin, and imipenem. Baseline coagulation parameters were fibrinogen of 376 mg/dL, INR of 0.85, and PT of 10.0 seconds. On TD17, coagulation parameters showed fibrinogen of 119 mg/dL, INR of 0.95, and PT of 11.4 seconds, leading to discontinuation of the eravacycline. The fibrinogen normalized within 5 days. The patient was eventually transitioned to clofazimine, moxifloxacin, and azithromycin with improvement of soft tissue infection. The patient died on TD62 from unrelated refractory posttransplant lymphoproliferative disorder.

Patient 5 is a 52-year-old male with DDKT who was diagnosed 8 weeks posttransplant surgery with *M abscessus* surgical site infection. Management included extensive surgical debridement and empiric therapy with eravacycline 1 mg/kg every 12 hours together with azithromycin, imipenem, and tedizolid. A decline in fibrinogen levels was noted from 457 mg/dL on TD1 to 165 mg/dL on TD10, with continued drop to 118 mg/dL by TD13. The eravacycline dose was reduced to 1 mg/kg every 24 hours from TD15 to TD18, and the fibrinogen level increased to 144 mg/dL on TD18. The patient was switched to oral omadacycline 300 mg daily on TD19, and the levels increased to 200 mg/dL by TD28. Coagulation parameters available on TD25 were INR 1.37 and PT of 16 seconds. The PT prolongation was near baseline and possibly attributable to the patient's pulmonary hypertension treatment, sildenafil 20 mg 3 times daily [6]. Although sildenafil use may cause increased PT and decreased fibrinogen levels with acute use [6–7], our patient had normal fibrinogen levels for ≥5 years with concurrent sildenafil. The patient is tolerating his treatment regimen, and fibrinogen levels have remained stable on oral omadacycline, most recently at TD51,

Patient 6 is a 67-year-old male who was diagnosed with *M abscessus* sternal osteomyelitis 6 months after BOLT. Management included wide debridement and removal of sternal hardware and empiric therapy with eravacycline 1 mg/kg every 12 hours together with azithromycin, imipenem, and linezolid. Fibrinogen levels trended from 399 to 187 mg/dL on TD11 and to 150 mg/dL on TD21. Other coagulation parameters were normal at this time with INR 1.03 and PT of 12.1 seconds. Eravacycline was stopped and replaced with oral omadacycline 300 mg on TD23; within 72 hours, fibrinogen marginally increased to 166 mg/dL. Complete recovery from hypofibrinogenemia was observed by TD32. The patient has continued on a treatment regimen including oral omadacycline with stable fibrinogen level at TD46.

PATIENT CONSENT STATEMENT

This case series reports clinical outcomes of patients seen within the scope of our collective clinical practice. The data collected were part of routine clinical care. Our local institutional review board (IRB) analysts determined this case series was exempt from requiring IRB approval.

LITERATURE REVIEW AND DISCUSSION

To our knowledge, eravacycline-associated hypofibrinogenemia has not been previously reported. To compare and contrast eravacycline- and tigecycline-associated hypofibrinogenemia, we searched Pubmed for articles related to tigecycline, hypofibrinogenemia, and coagulopathies from database inception to May 31, 2022. The following search terms were used: Pubmed ("tigecycline" AND "hypofibrinogenemia" OR "coagulopathy"). All case reports of tigecycline-associated hypofibrinogenemia that developed during the management of any infection in any host were included in this review.

In total, 10 cases representing 11 treatment courses of tigecycline-associated hypofibrinogenemia were identified spanning 2010–2021 (Table 1). Tigecycline was used for various infections, most commonly pneumonia ($n = 4$) followed by intra-abdominal infection ($n = 3$). Dosing of tigecycline was split between standard ($n = 5$) and high dose ($n = 4$) (200 mg load followed by 100 mg every 12 hours). Time to hypofibrinogenemia varied drastically from 2 to 35 days, with a median of 10 days. Most cases noted a triad of coagulopathy marker changes with elevated aPTT and INR with low fibrinogen. Time to resolution of hypofibrinogenemia was rapid after discontinuing tigecycline, generally ranging from 3 to 5 days

Table 1. Review of Tigecycline-Associated Hypofibrinogenemia Cases

Case No. [Refs.]	Indication	TGC Dose	Comorbidity	TGC Duration (d)	Fibrinogen (mg/dL) [Start]	Fibrinogen (mg/dL)	Time to HF (d)	Time to Resolution(d)	aPTT (s) [Start-End]	INR (Start-End)	Bleeding	Thrombosis
1[8]	Peritonitis	NR	ESRD	39	855	30	35	4	30.5->160	NR-3.08	None	None
2[9]	Bacteremia	LD: 100 mg MD: 25 mg q12h	CKD Cirrhosis	6	~1000	UD	6	3	NR	1.5-5.5	GI bleed	None
3[10]	Prosthetic Joint Infection	LD: 100 mg MD: 50 mg q12h	ESRD	19	499	42	19	4	25.6-57	1.21-1.71	None	None
4[11]	Cholangitis	LD: 100 mg MD: 100 mg q12h	DM Pancreatitis	3	284	69	2	5	35.1-94.5	1.18-2.09	None	None
5[12]	Intra-abdominal abscess	LD: 100 mg MD: 50 mg q12h	CKD DDKT	16	NR	59	8	4	NR-48.6	NR-1.73	None	UE DVT
6[13]	Ventilator-associated pneumonia	LD: 100 mg MD: 50 mg q12h	CKD	14	400	141	7	5	NR	0.98-0.98	Patchy Ecchymosis	None
7[14]	Complicated Pneumonia	NR	CKD Asthma	10	400	115	10	5	31.1-62	1.28-1.92	None	None
8[15]	Prosthetic Joint Infection	LD: 200 mg MD: 100 mg q12h	MDS	18	393	158	18	3	40.0-54.3	1.15-1.78	Hemarthrosis	None
9[16]	Ventilator-associated pneumonia	LD: 200 mg MD: 100 mg q12h	CKD HTN	14	380	118	7	5	37-45	~1.1-1.4	None	None
10[16]	Ventilator-associated pneumonia	LD: 200 mg MD: 100 mg q12h	CKD HTN	18	490	66	18	3	27-47	~1.1-1.4	None	None
11[17]	Skin and soft tissue infection	LD: 100 mg MD: 50 mg q12h	DDKT	31	NR	UD	31	5	NR->180	NR	None	None

Abbreviations: aPTT, activated partial thromboplastin time; CKD, chronic kidney disease; d, days; DDKT, diseased donor kidney transplant; DM, diabetes mellitus; DVT, deep vein thrombosis; ESRD, end-stage renal disease; GI, gastrointestinal; HF, hypofibrinogenemia; HTN, hypertension; INR, international normalized ratio; LD, loading dose; MD, maintenance dose; MDS, myelodysplastic syndrome; NR, not reported; TGC, tigecycline; UD, undetectable; UE, upper extremity.
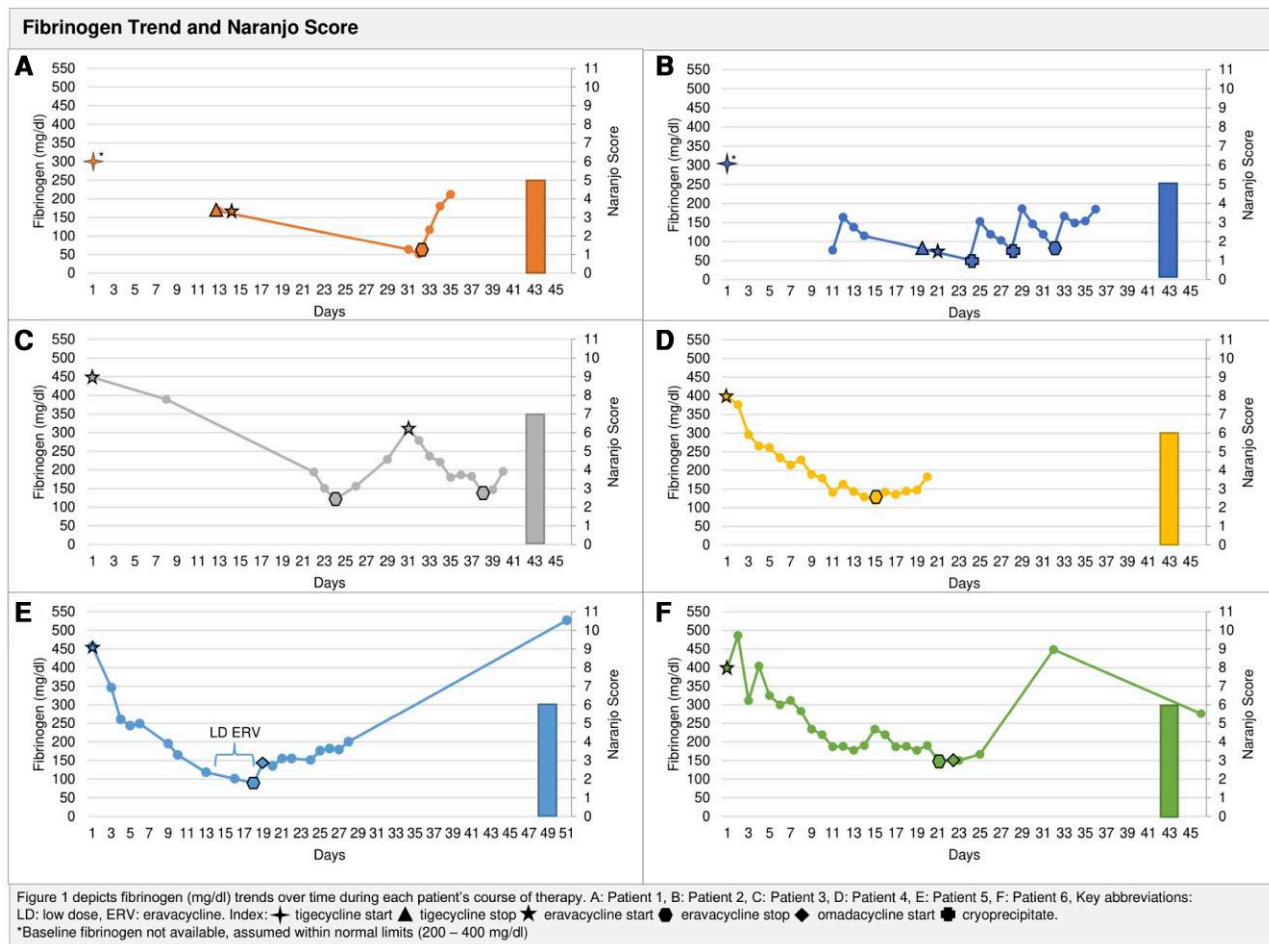
Figure 1 depicts fibrinogen (mg/dl) trends over time during each patient's course of therapy. A: Patient 1, B: Patient 2, C: Patient 3, D: Patient 4, E: Patient 5, F: Patient 6, Key abbreviations: LD: low dose, ERV: eravacycline. Index: + tigecycline start ▲ tigecycline stop ★ eravacycline start ● eravacycline stop ◆ omadacycline start ⬢ cryoprecipitate.
*Baseline fibrinogen not available, assumed within normal limits (200 – 400 mg/dl)

Figure 1. Trend of fibringoen over time of treatment along with asssociated Naranjo Score for each case.

[8–17]. Of the 11 courses described, 3 developed a bleeding event including a gastrointestinal bleed, patchy ecchymosis, and spontaneous hemarthrosis [9, 13, 15].

The increased reporting of tigecycline-associated hypofibrinogenemia led to several retrospective reviews assessing tigecycline and coagulopathies/hypofibrinogenemia. These studies predominantly included critically ill patients; although it is difficult to compare them given varying designs, the absolute and relative magnitude of fibrinogen decrease from baseline were similar (150–276 mg/dL and ~35%–50%, respectively) [18–21]. Most recently, Guo et al [4] conducted a review of the Food and Drug Administration adverse event reporting system (FAERS) database from January 2005 to December 2020 identifying 223 reports of coagulation dysfunction with a median time to event of 10 days. Tigecycline was associated with an increased coagulation dysfunction risk compared with alternative antibacterials with a reporting odds ratio (ROR) of 3.55 (95% confidence interval, 3.08–4.09). Hypofibrinogenemia had the strongest association with tigecycline (ROR, 705.41) [4]. It is notable that other drugs commonly used in multidrug

therapy for *M abscessus* infection (such as amikacin, cefoxitin, imipenem, macrolides, linezolid/tedizolid, and clofazimine) do not associate with hypofibrinogenemia in the FAERS database. These data, although limited by reporting bias and confounders, support continued concern for coagulopathies with tigecycline.

Given low mean inhibitory concentrations to tigecycline, we initiated these 6 posttransplant patients with standard dose eravacycline in conjunction with other antimicrobials and surgical debridement of skin and soft tissue sites when possible. Eravacycline was selected as a "fibrinogen sparing option" in 2 cases who had already experienced tigecycline-associated hypofibrinogenemia and as initial therapy in 4 cases. The time to onset (4–22 days, median 10 days), resolution (3–5 days), and magnitude of decrease were consistent with tigecycline-associated hypofibrinogenemia (Figure 1). A similar triad of prolongation of PT and INR was also observed; however, the extent of change appeared smaller. Two patients had documented bleeding events within close proximity to eravacycline use. For patient 5, fibrinogen levels were stable and

slightly increased by day 5 of reduced dose eravacycline, and the patient continued to recover after switching to omadacycline. A similar trend of fibrinogen recovery after switching to omadacycline was seen in patient 6. According to the Naranjo algorithm, an adverse drug reaction probability scale, the range across patients was 5–7 (Figure 1), consistent with eravacycline as a probable cause of hypofibrinogenemia [22].

Risk factors for tigecycline-associated hypofibrinogenemia include duration of therapy more than 14 days, renal failure, and low baseline fibrinogen [5, 21, 23–25]. Among our 6 patients treated with eravacycline, 4 had chronic kidney disease and most were treated longer than 14 days. In all cases, fibrinogen levels recovered within days after discontinuation of eravacycline, similar to reports of tigecycline-induced hypofibrinogenemia.

These data on eravacycline and hypofibrinogenemia add to growing evidence of synthetic tetracycline-associated hypofibrinogenemia. Structurally, these compounds all differ from tetracycline, which has no associated reports of hypofibrinogenemia. Tigecycline, eravacycline, and omadacycline all contain a C9 substitution on the D ring (*t*-butylglycylamido group, pyrrolidinoacetamido group, and alkylaminomethyl group, respectively), and eravacycline differs with a fluorine at C7 [2, 26]. It is unknown whether hypofibrinogenemia is a class effect, although it is encouraging that patients 5 and 6 have maintained normal fibrinogen levels while on oral omadacycline therapy beyond 30 days. In addition, long-term omadacycline use appears well tolerated. In a separate case series of 12 patients treated with omadacycline as part of an *M abscessus* regimen, bleeding complications did not occur, although fibrinogen levels were not reported [27]. If omadacycline is not associated with hypofibrinogenemia, it is possible that the formulation or structural differences in the drug itself accounts for the varying impact on fibrinogen.

Our data are not without limitations, because our case series included only immunocompromised, critically ill patients who had other risk factors for coagulopathies for which we did not control. Given the repeatable nature and consistency with which we saw this effect, however, eravacycline has an association with hypofibrinogenemia. Future studies with appropriately matched control groups are needed to determine the relative risk of eravacycline-induced hypofibrinogenemia and patient-specific risk factors for its development. Fortunately, omadacycline appears to be well tolerated based on our limited experience, but this stands to be corroborated.

CONCLUSIONS

This report and literature review support the continued analysis of synthetic tetracycline-associated hypofibrinogenemia to better understand its clinical impact on coagulopathies and patient outcomes. Our current institutional practice is to monitor

fibrinogen levels 1–2 times a week and replace it with cryoprecipitate as needed. Although no current minimum fibrinogen level has been defined for when synthetic tetracyclines should be discontinued, monitoring of fibrinogen, other coagulation parameters, and bleeding complications should be considered for patients on eravacycline for more than 7 days until further data are available. Furthermore, given that there remains no consensus a first-line regimen for treating *M abscessus*, our findings support the need for further investigations to more precisely estimates the risk, risk factors, mechanisms, and consequences of coagulation-related toxicities in patients receiving extended-spectrum tetracyclines [28].

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