Presentation 426
Friday

Evaluation of Patients with Complicated Intra-abdominal Infections (cIAI) and Concomitant Bacteremia (CB) from IGNITE1: A Phase 3 study to Evaluate the Efficacy and Safety of Eravacycline (ERV) versus Ertapenem (ETP) in Complicated Intra-abdominal Infections (cIAI)

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Abstract

Background: Empiric treatment of cIAI represents a clinical challenge because of the polymicrobial infecting flora and the emergence of antibiotic resistance in multiple classes of organisms. The management of bacteremia, occurring in some 10% of cIAI patients, is uncertain. To explore this subject, we examined a subgroup of patients in IGNITE1 with cIAI and CB.

Methods In this randomized, double-blind, non-inferiority phase 3 trial, patients with documented cIAI were randomized (1:1) to either ERV (1.0 mg/kg IV q12h) or ETP (1g IV daily) for up to 14 days. Clinical outcome at the test of cure (TOC) visit, approximately 28 days after randomization, was the primary efficacy endpoint in the microbiological intent-to-treat (micro-ITT) population (≥ 1 pathogen consistent with cIAI in baseline cultures).

	Combined (ERV + ETP)		Eravacycline		Ertapenem	
	CB (n=35)	No CB (n=411)	CB (n=18)	No CB (n=202)	CB (n=17)	No CB (n=209)
Average therapy duration (days) Mean/median (min,max)	8.3/7 (1.5, 14)	7.1/7 (0,14)	8.0/7 (1.5,14)	7.2/7 (1,14)	8.5/7 (2,14)	7.0/7 (0,14)
Diagnosis						
Complicated appendicitis	8 (22.9%)	124 (30.2%)	4 (22.3%)	61 (30.2%)	4 (23.5%)	63 (30.1%)
Other cIAI	27 (77.1%)	287 (69.8%)	14 (77.7%)	141 (69.8%)	13 (76.5%)	146 (69.9%)
Clinical Response						
Cure	29 (82.9%)	360 (87.6%)	17 (94.4%)	174 (86.1%)	12 (70.6%)	186 (89.0%)
Failure	1 (2.8%)	29 (7.1%)	0 (0.0%)	19 (9.4%)	1 (5.9%)	10 (4.8%)
Indeterminant	5 (14.3%)	22 (5.3%)	1 (5.6%)	9 (4.5%)	4 (23.5%)	13 (6.2%)

Results: 541 patients were randomized and 446 were included in the micro-ITT population. The study met criteria for non-inferiority (Δ=-0.8, 95% CI=-7.1 to 5.5). 40 patients had positive blood cultures of which 5 cultures on post-hoc analysis were determined to be contaminants. Among the 35 remaining patients, (ERV 18, ETP 17), there were 43 baseline pathogens identified. The most common pathogens isolated were *Streptococcus* sp. 12 (27.9%), *E. coli* 10 (23.5%), and *Bacteroides* sp. 8 (18.6%). 24/35 (68.6%) patients had at least one organism present in the blood duplicated in the IAI culture. Patients with CB received an average 1.2 days longer duration of antibiotic therapy.

Conclusions: These data suggest that the presence of CB in cIAI does not increase treatment failure or require prolonged antimicrobial therapy duration. Treatment outcomes among patients with cIAI and CB were similar with ERV compared to those without CB. High success rates in this study suggest ERV may be a treatment option for patients with cIAI and CB.

Introduction

Complicated intra-abdominal infection (cIAI) is a common problem, affecting >300,000 patients/year[1]. The management of cIAI involves surgical removal of tissue and/or percutaneous drainage in conjunction with antibiotic therapy. Empiric treatment of cIAI often represents a clinical challenge because of the polymicrobial infecting flora and the emergence of antibiotic resistance in multiple bacterial species. Furthermore, bacteremia can occur in some 10% of cIAI patients and management of this sequela is also uncertain[1]. Major pathogens in community-acquired IAI include *Enterobacteriaceae*, Gram-positive streptococci, enterococci and anaerobes, particularly *Bacteroides fragilis*. More resistant flora, which may include *Pseudomonas aeruginosa* and *Acinetobacter* spp., ESBL producing *Klebsiella* and *E. coli, Enterobacter* spp., *Proteus* spp., MRSA, enterococci, and *Candida* spp., are more commonly the cause of healthcare-associated IAIs[1,2]. While previous studies that have examined secondary bacteremia with Gram-negative organisms have not identified either metastatic abscess or endocarditis as a consequence, concomitant bacteremia can be associated with increased mortality[1,3].

Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. Eravacycline was recently evaluated in a phase 3 trial, IGNITE1 (Investigating Gram-negative Infections Treated with Eravacycline), and compared with ertapenem, in patients with cIAI[4]. As there is no consensus on the best way to treat patients with cIAI and concomitant bacteremia, we explored this subject in a subgroup of patients in the IGNITE1 study with both cIAI and concomitant bacteremia.

Objective

The objective of this current study is to report the characteristics, details of treatment and outcomes of patients with cIAI and concomitant bacteremia from IGNITE1.

Methods

- This was a post-hoc analysis describing the patients with cIAI infections with concomitant bacteremia from IGNITE1, a non-inferiority cIAI study that compared eravacycline to ertapenem.
- The microbiological intent-to-treat (micro-ITT) population, all randomized subjects who had baseline bacterial pathogens that cause cIAI and against at least one of which the investigational drug has *in vitro* antibacterial activity, was used to evaluate outcomes of therapy at the primary test of cure visit.

IGNITE1 Study Design:

- Randomization system/blinding
  - Centralized, computer-generated randomization
  - Stratification based upon site of infection (complicated appendicitis versus other) – Restricted appendicitis to 30% or less per site
  - Double-blind, double-dummy study design
- Key Inclusion Criteria
  - Age > 18 years
  - Hospitalized for confirmed cIAI with one of following diagnoses:
    - Intra-abdominal abscess
    - Gastric or intestinal perforation associated with diffuse peritonitis
    - Peritonitis due to perforated viscus or other focus of infection
    - Appendicitis with perforation, peritonitis, or abscess
    - Cholecystitis with perforation or abscess
    - Peritonitis (local or diffuse)
  - Evidence of a systemic inflammatory response with ≥ 1 of the following
    - Fever or hypothermia
    - Elevated white blood cell (WBC) count or proportion of band forms of the WBC differential beyond the ULN laboratory range
    - Increased pulse (heart rate [HR] > 90 beats per minute)
    - Increased respiratory rate (> 20 breaths per minute)
  - Specified abdominal pain or flank pain (with or without rebound tenderness)
  - Not pregnant and committed to use of contraception
- Key Exclusion Criteria
  - Renal failure or possible signs of hepatic disease
  - Immunocompromised condition
  - Antibiotic-related exclusions
    - Receipt of effective antibacterial drug therapy for cIAI for > 24 hrs during the 72 hrs preceding enrollment
    - Receipt of carbapenem or tigecycline for current infection
    - Need for concomitant antibiotic other than study drug
    - Need for a systemic antibiotic for > 14 days
  - Known or suspected CNS disorder that may predispose to seizures
  - Known resistant pathogen at study entry
- Length of antibiotic therapy was at the discretion of the investigator up to 14 days

Results

Table 1. Baseline Concomitant Bacteremia Patient Demographics in the micro-ITT Population

	Eravacycline		Ertapenem	
	CB n=18	No CB n=202	CB n=17	No CB n=209
Average Age	55.1	54.8	61.0	54.9
Gender				
Male	10 (55.6%)	116 (57.4%)	13 (76.5%)	119 (56.9%)
Female	8 (44.4%)	86 (42.6%)	4 (23.5%)	90 (43.1%)
Baseline APACHE II				
<10	16 (88.9%)	157 (77.7%)	12 (70.6%)	162 (77.5%)
≥10	2 (11.1%)	45 (22.3%)	5 (29.4%)	47 (22.5%)
Median	7.3	6.5	6.3	6.8
Diagnosis				
Complicated Appendicitis	4 (22.3%)	61 (30.2%)	4 (23.5%)	63 (30.1%)
Other cIAI*	14 (77.7%)	141 (69.8%)	13 (76.5%)	146 (69.9%)
IAI abscess(es)	8 (44.4%)	84 (41.6%)	9 (52.9%)	90 (43.1%)
Perforation of intestine	2 (2/11.1%)	29 (14.4)	2 (11.8%)	34 16.3%)
Gastric Duodenal perforation	0	20 (9.9%)	2 (11.8%)	24 (11.5%)
Peritonitis	6 (33.3%)	65 (32.2%)	8 (47.1%)	73 (34.9%)
Complicated cholecystitis	1 (5.5%)	41 (20.3%)	1 (5.9%)	2 (1.6%)
Other	3 (16.7%)	8 (4.0%)	0	5 (2.4%)
Type of Surgery				
Open	9 (50.0%)	125 (61.9%)	13 (76.5%)	132 (63.1%)
Laparoscopic	4	64	5	66
Percutaneous	5	20	0	19
Other	0	1	0	2

*May have more than one other cIAI

Table 2. Patient Outcomes in the micro-ITT Population at the TOC Visit

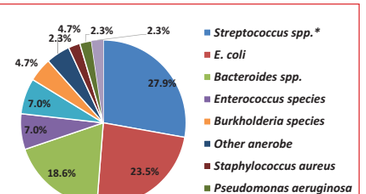
	Combined (ERV + ETP)		Eravacycline		Ertapenem	
	CB (n=35)	No CB (n=411)	CB (n=18)	No CB (n=202)	CB (n=17)	No CB (n=209)
Average therapy duration (days)	8.3	7.1	8.0	7.2	8.5	7.0
Clinical Response						
Cure	29 (82.9%)	360 (87.6%)	17 (94.4%)	174 (86.1%)	12 (70.6%)	186 (89.0%)
Failure	1 (2.8%)	29 (7.1%)	0 (0.0%)	19 (9.4%)	1 (5.9%)	10 (4.8%)
Indeterminate	5 (14.3%)	22 (5.3%)	1 (5.6%)	9 (4.5%)	4 (23.5%)	13 (6.2%)

Table 3. Description of Bacteremic Patients That Were Classified as Failure or Indeterminate

Patient Number	Study drug	Therapy Duration (days)	Age Gender	APACHE II	Diagnosis	Procedure Type	Baseline Blood Organism (s)	Other Notes
Failure								
008-119-0001	ETP	14	82F	11	IAI abscess	Open	*Enterococcus faecalis* and *Escherichia coli*	Unplanned surgical procedure or percutaneous drainage procedures
Indeterminate								
008-073-0005	ERV	1.5	45M	15	Perforation of intestine and peritonitis	Open	*Escherichia coli*	Adverse Event (Patient died on Day 3, prior to assessment of outcome)
008-021-0013	ETP	2	49F	4	Complicated Appendicitis & peritonitis	Laparoscopic	*Bacteroides stercoris*	Lost to Follow-Up
008-097-0001	ETP	7	75M	10	IAI abscess	Open	*Escherichia coli*	Adverse Event (Patient died 13 days after EOT, prior to assessment of outcome)
008-111-0003	ETP	8	63F	11	Perforation of intestines	Open	*Escherichia coli*	Adverse Event (Patient died 4 days after EOT, prior to assessment of outcome)
008-158-0001	ETP	7	30M	0	Complicated Appendicitis & peritonitis	Laparoscopic	*Escherichia coli* and *Eggerthella lenta*	Non-compliance with study drug

- Non-bacteremic patients (no CB) were classified as Failure (N=29) for one or more of the following reasons
  - Persistence of clinical symptoms of cIAI (n=6)
  - Unplanned surgical procedure or percutaneous drainage procedures (n=15)
  - Post-surgical wound infections requiring systemic antibiotics (n=6)
  - Initiation of rescue antibacterial therapy for cIAI (n=8)
  - (n=7) (pneumonia in right lung, additional antibiotics administered at discretion of local antibiotic expert, removed by medical team due to positive culture resistant to study drug ertapenem, clinical failure carried forward, AE/took non-study antibiotics)
- Non-bacteremic patients (no CB) were classified as Indeterminate (N=22) for one or more of the following reasons
  - Persistence of clinical symptoms of cIAI (n=3)
  - Unplanned surgical procedure or percutaneous drainage procedures (n=3)
  - Inappropriate source control (Surgical Adjudication Committee decision) (n=3)
  - Post-surgical wound infections requiring systemic antibiotics (n=1)
  - Did not have TOC visit due to the following reasons (n=13)
    - Adverse event (n=4)
    - Withdrawal by subject (n=3)
    - Non-compliance with study drug (n=3)
    - Lost to follow-up (n=3)
    - Other (n=1)

Figure 1. Overall Baseline Pathogens in the Blood as Percentage of Patients with Specific Organisms (n=43 organisms)



Streptococcus* spp. Includes *Streptococcus mitis group, Streptococcus anginosus group, Streptococcus parasanguinis

Result Summary

- Forty (40) subjects in IGNITE1 were coded with bacteremia in the micro-ITT population. Five bacteremia patients were removed from the post-hoc analysis as the blood culture isolates in these subjects were determined to be contaminants.
- Baseline demographics of the 35 patients with cIAI infections and concomitant bacteremia are listed in Table 1. Demographics were balanced across treatment arms for the patients with concomitant bacteremia and were reflective of the overall demographics for all patients in this trial. Patients with concomitant bacteremia did not appear to have more comorbidities.
- Furthermore, patients with concomitant bacteremia received only an average 1.2 days longer duration of antibiotic therapy and had similar outcomes compared to those patients without bacteremia (Table 2).
- Five patients in the two treatment arms (1 in ERV and 5 in ETP groups) were considered a treatment failure or were indeterminate at the test of cure visit in the micro-ITT population. More information is presented in Table 3 describing those patients.
- There were 43 baseline blood organisms identified in the 35 patients with concomitant bacteremia (Figure 1). Over half of the organisms were *Streptococcus* species and *E. coli*.

Conclusions

- These data suggest that the presence of concomitant bacteremia in cIAI does not increase treatment failure nor require prolonged antimicrobial therapy. Treatment outcomes among patients with cIAI and concomitant bacteremia were similar with eravacycline and ertapenem compared to those without concomitant bacteremia.
- The current treatment guidelines, which do not recommend a routine collection of blood cultures in IAI patients, is further supported by the outcomes of the subset of these patients in IGNITE1 with cIAI and concomitant bacteremia.
- High success rates in this study suggest eravacycline or ertapenem may be potential treatment options for patients with cIAI and concomitant bacteremia.

References

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Acknowledgments

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