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CANVAS-1: Randomized, Double-blinded, Phase 3 Study (P903-06) of the Efficacy and Safety of Ceftaroline vs. Vancomycin plus Aztreonam in Complicated Skin and Skin Structure Infections (cSSSI)

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Abstract

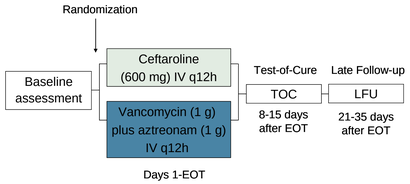
Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a common cause of cSSSI. Increasing antibiotic resistance and significant morbidity in cSSSI have led to a need for new effective and safe therapies. Ceftaroline (CPT) is a novel parenteral cephalosporin with excellent in vitro activity against MRSA, multi-drug resistant *Streptococcus pneumoniae* and many gram-negative pathogens. **Methods:** Adult patients with cSSSI requiring IV therapy received CPT (600 mg) or vancomycin (1 g) plus aztreonam (1 g) (V/A) q12h for 5-14 days (randomized 1:1). Clinical and microbiological response, adverse events (AEs) and laboratory tests were assessed. The primary objective was to determine noninferiority (lower limit of 95% CI -10%) in clinical cure rate of CPT to V/A at 8-15 days post therapy in clinically evaluable (CE) and modified intent-to-treat (MITT) populations. **Results:** Of 702 enrolled patients, 353 received CPT and 349 V/A. Baseline characteristics of treatment groups were comparable. Clinical cure rates were similar for CPT and V/A in CE (91.1%, 288/316 vs. 93.3%, 280/300; 95% CI, -6.6 to 2.1) and MITT (86.6%, 304/351 vs. 85.6%, 297/347; 95% CI, -4.2 to 6.2) populations. Clinical cure rate for MRSA was 94.9% (75/79) for CPT and 95.1% (58/61) for V/A. Microbiological success was similar for CPT and V/A overall (91.8%, 224/244 vs. 92.5%, 210/227) and for MRSA (94.9%, 75/79 vs. 91.8%, 56/61). The rates of AEs, serious AEs, deaths and discontinuations due to AEs were similar for CPT and V/A. Most common AEs for CPT and V/A were nausea (5.7% vs. 4.6%), headache (5.1% vs. 3.7%) and pruritus (3.1% vs. 8.4%). **Conclusions:** CPT had high clinical cure and microbiological success rates, was efficacious against MRSA and other common cSSSI pathogens and was well tolerated. CPT has the potential to provide a monotherapy alternative for treatment of cSSSI.

Introduction

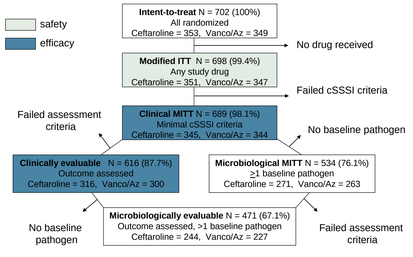
- Complicated skin and skin structure infections (cSSSI) are predominately caused by gram-positive pathogens, but a variety of gram-negative bacteria may also be involved
- The proportion of *S. aureus* isolates resistant to methicillin and *Streptococcus* spp. isolates resistant to macrolides continues to rise
- Ceftaroline has high affinity for *S. aureus* penicillin binding proteins (PBPs) including PBP2A, resulting in effective bactericidal activity against MRSA
- Ceftaroline has demonstrated excellent activity against MRSA (MIC_{90} < 2 µg/ml) and *Streptococcus* spp. (MIC_{90} < 0.2 µg/ml)

Study Design

- Multicenter, randomized, double-blind, comparative
- Adults with local and systemic evidence of cSSSI
- Randomized (1:1)
  - IV ceftaroline (600 mg) q12h, 5-14 days
  - IV vancomycin (1 g) plus IV aztreonam (1 g) q12h, 5-14 days. Aztreonam discontinued if gram-negative pathogen not identified or suspected
  - No oral switch therapy allowed
- Primary outcome measure
  - Noninferiority of ceftaroline compared to vancomycin plus aztreonam in clinical cure rate at TOC
  - Noninferiority of ceftaroline concluded if lower limit of 95% confidence interval (CI) difference is -10% or higher
- Other outcome measures
  - Microbiological eradication rate at TOC
  - Population pharmacokinetics
  - Safety



Analysis Populations



Baseline Characteristics

Demographics (MITT)

- Of 689 patients who received study drug, 351 received ceftaroline and 347 received vancomycin plus aztreonam
- Baseline characteristics generally well balanced between treatment groups
- Approximately 1/3 of patients in each treatment group had either diabetes mellitus or PVD
- Disease severity similar between groups

Characteristic	Ceftaroline N=351	Vanco/Az N=347
Age, mean yrs ± SD (range)	47.2 ± 17.0 (18, 90)	49.2 ± 17.2 (18, 87)
Male, % (n)	62.7 (220)	62.8 (218)
Polymicrobial infection, % (n)	20.5 (72)	24.5 (85)
Bacteremia, % (n)	5.7 (20)	2.9 (10)
Recent trauma, % (n)	24.5 (86)	25.6 (89)
Diabetes mellitus, % (n)	17.7 (62)	19.6 (68)
Peripheral vascular disease, % (n)	13.4 (47)	15.3 (53)
Relevant surgical procedure, % (n)	9.1 (32)	6.9 (24)

Infection Types (MITT)

Deep/extensive cellulitis and major abscess were the most common infection types

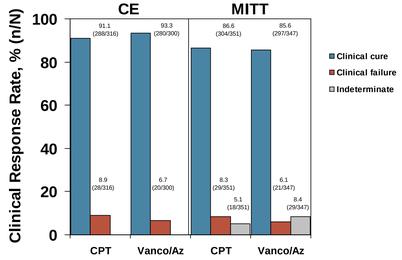
Infection Types[1]	% (n) Ceftaroline N = 351	Vanco/Az N = 347
Deep extensive cellulitis	34.5 (121)	34.6 (120)
Major abscess	28.2 (99)	29.1 (101)
Infected wound	15.4 (54)	12.4 (43)
Infected burn	7.1 (25)	5.8 (20)
Infected ulcer	6.6 (23)	8.9 (31)
Lower extremity (DM or PVD)	6.0 (21)	5.8 (20)
Infected bite	2.0 (7)	2.0 (7)
Other	0.3 (1)	1.4 (5)

1. Not mutually exclusive

Efficacy

Clinical Cure

- Clinical cure rates similar between treatment groups at TOC for CE and MITT populations
- Ceftaroline noninferior to combination of vancomycin/aztreonam for CE and MITT populations

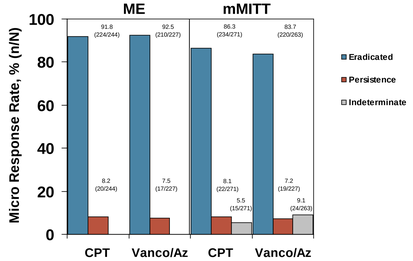


CE Population: 95% CI -2.2 (-6.6, 2.1)

MITT Population: 95% CI 1.0 (-4.2, 6.2)

Microbiological Eradication

Microbiological response exceeded 91% in both treatment groups for ME Population



ME Population: 95% CI -0.7 (-5.7, 4.4)

mMITT Population: 95% CI 2.7 (-3.4, 8.9)

Clinical Cure, Microbiological Eradication, MIC by Most Common Pathogens (ME)

- *S. aureus* most common organism isolated
- Ceftaroline had low MIC_{90} against MRSA (1 µg/mL), MSSA (0.25 µg/mL), and *Streptococcus* spp. (≤ 0.15 µg/mL)
- Treatment groups had similar clinical cure and microbiological eradication rates for MRSA and MSSA

Organisms	Clinical Cure % (n/N) Ceftaroline N = 244	Clinical Cure % (n/N) Vanco/Az N = 227	Microbiological Eradication % (n/N) Ceftaroline N = 244	Microbiological Eradication % (n/N) Vanco/Az N = 227	MIC_{90} µg/mL Ceftaroline N = 244	MIC_{90} µg/mL Vancomycin N = 227	MIC_{90} µg/mL Aztreonam N = 227
Gram-positive							
S. aureus	92.9 (169/182)	94.7 (162/171)	94.0 (171/182)	92.4 (158/171)	0.5	1	
MRSA	94.9 (75/79)	95.1 (58/61)	94.9 (75/79)	91.8 (56/61)	1	1	
MSSA	91.3 (94/103)	94.5 (104/110)	93.2 (96/103)	92.7 (102/110)	0.25	1	
S. pyogenes	100 (23/23)	100 (32/32)	100 (23/23)	100 (32/32)	≤ 0.004	0.5	
S. agalactiae	92.9 (13/14)	100 (13/13)	85.7 (12/14)	100 (13/13)	0.015	0.5	
E. faecalis	92.9 (13/14)	91.7 (11/12)	92.9 (13/14)	91.7 (11/12)	8	2	
Gram-negative							
E. coli	90.0 (9/10)	86.7 (13/15)	90.0 (9/10)	86.7 (13/15)	1		0.12
K. pneumoniae	90.9 (10/11)	100 (10/10)	90.9 (10/11)	100 (10/10)	> 16		> 32
P. mirabilis	70.0 (7/10)	90.0 (9/10)	80.0 (8/10)	90.0 (9/10)	> 16		0.25
P. aeruginosa	100 (9/9)	90.0 (9/10)	88.9 (8/9)	90.0 (9/10)	> 16		> 32

Safety

AE Summary (MITT)

- Most AEs mild and judged not related to treatment
- Percentage of patients who experienced an AE was similar in both treatment groups
- Most common AE was nausea (5.7%) in ceftaroline group and pruritus (8.4%) in vancomycin/aztreonam group

Adverse Event	% (n/N) Ceftaroline	Vanco/Az
Subjects with a TEAE	47.0 (165/351)	48.1 (167/347)
Subjects with an SAE	4.6 (16/351)	3.5 (12/347)
Subjects discontinued from study drug due to AE	3.7 (13/351)	4.6 (16/347)
AEs judged related[1]	43.2 (216/500)	47.0 (253/538)
Severity of AEs		
Mild	72.0 (360/500)	71.6 (385/538)
Moderate	23.6 (118/500)	24.0 (129/538)
Severe or life-threatening	4.4 (22/500)	4.5 (24/538)
Most common AEs		
Nausea	5.7 (20/351)	4.6 (16/347)
Headache	5.1 (18/351)	3.7 (13/347)
Pruritus generalized	3.7 (13/351)	4.6 (16/347)
Pruritus	3.1 (11/351)	8.4 (29/347)
Subjects who died during study	0.9 (3/351)	0

1. Related = possibly and probably related

Conclusions

- Ceftaroline monotherapy was as effective and well tolerated as vancomycin plus aztreonam combination therapy in treating patients with cSSSI due to both gram-positive and gram-negative pathogens
- Ceftaroline had high clinical cure and microbiological success rates against a variety of gram-positive and gram-negative pathogens, most commonly *Staphylococcus* spp. including MRSA
- Ceftaroline was well tolerated, consistent with the good safety and tolerability profile of the cephalosporin class
- Due to ceftaroline's activity against a broad range of gram-positive and gram-negative pathogens as demonstrated in this study, ceftaroline has the potential to provide a monotherapy option for the treatment of cSSSI

Acknowledgement

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