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OUTCOMES IN PATIENTS WITH HISTORY OF CARDIAC OR VASCULAR DISEASE (CV) DURING TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION (ABSSSI) WITH DELAFLOXACIN (DLX) VS VANCOMYCIN/AZTREONAM (VAN/AZ)

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INTRODUCTION

Delafloxacin (DLX) is an anionic fluoroquinolone antibiotic recently approved for treatment of acute bacterial skin and skin structure infections (ABSSSIs). DLX has excellent in vitro activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) while retaining good activity against Gram-negative organisms.[1] DLX does not have risk for QT prolongation that can be seen with some antibiotics, like levofloxacin, moxifloxacin, or clarithromycin[2,3].

We conducted two multicenter, double-blind, double-dummy trials (302[4] and 303[5]) comparing the efficacy and safety of IV/oral DLX monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSIs caused by both Gram-positive and Gram-negative pathogens. Evaluated endpoints included those mandated by both the FDA[6] (objective response at 48-72 hours) and EMA[7] (investigator assessments of response).

This analysis assesses the efficacy and tolerability of delafloxacin in ABSSSI patients with cardiac or vascular disease.

METHODS

STUDY DESIGN

- Randomized, double-blind, Phase 3, multicenter studies of IV/oral DLX vs IV VAN/AZ in patients with ABSSSI, including wounds, burns, major abscesses, or cellulitis ≥75 cm^2 in size and ≥2 systemic signs of infection;
- Patients were randomly assigned (1:1) to receive DLX monotherapy or VAN 15 mg/kg (actual body weight) IV q12h with AZ 1-2 g IV q12h for 5-14 days at the investigators' discretion; aztreonam was discontinued in VAN arm once cultures confirmed no Gram-negative pathogens
- In study 302, the DLX dose was 300 mg IV BID for the full course; in study 303, subjects received DLX 300 mg IV BID for 3 days followed by a mandatory blinded switch to DLX 450 mg PO BID;
- Patients were evaluated at screening, daily on therapy, FU (Day 14±1), and LFU (Day 21-28);
- Enrollment was stratified by baseline infection type, BMI, and limited to 25% prior antibiotic use.

ENDPOINTS AND ANALYSES

- Primary endpoint for FDA: proportion of patients achieving an objective response at 48-72 hours after start of treatment, defined as ≥20% decrease in lesion size with no further antibiotics, major procedures, or death in the ITT population;
- Key outcome for EMA was the investigator-assessed response based on complete resolution or near resolution of signs and symptoms (Success) at FU (Day 14) and LFU (Day 21 to 28);
- Additional efficacy endpoint: Microbiological response (documented or presumed eradication) for patients in the ME and MITT analysis sets were based on results of baseline and post-baseline cultures (FU) and susceptibility testing, together with the clinical response assigned by investigators;
- Safety: adverse events (AE), vital signs and body temperature measurements, clinical laboratory test abnormalities, physical examination findings, concomitant medications, and ECGs (if clinically indicated).

METHODS

ANALYSIS

- For the key endpoints, a 2-sided 95% CI for noninferiority testing was computed based on difference in responder rates for DLX and VAN/AZ at 48-72 hours (±2) after initiation of treatment as well as for the investigator assessed responses at FU and LFU; DLX was noninferior to VAN/AZ for ABSSSIs if lower limit of 2-sided 95% CI exceeded −0.10;

ANALYSIS POPULATIONS

- ITT: all patients randomized; Microbiological ITT: ITT patients with eligible pathogen; Clinically evaluable (CE): patients completing protocol; Microbiologically evaluable (ME): CE patients with eligible pathogen.

RESULTS

As shown in Table 1, in the two pivotal trials overall, DLX was comparable to VAN/AZ in treatment of ABSSSI patients.[4,5]

TABLE 1: OVERALL OUTCOMES IN STUDIES 302 AND 303

Overall	Study 302			Study 303		
Key Endpoints	DLX n/Total (%)	VAN/AZ n/Total (%)	Delta (95% CI)	DLX n/Total (%)	VAN/AZ n/Total (%)	Delta (95% CI)
Objective response 48-72h (ITT)	259/331 (78.2)	266/329 (80.9)	−2.6 (−8.8, 3.6)	354/423 (83.7)	344/427 (80.6)	3.1 (−2.0, 8.3)
Investigator-Assessed Success (FU ITT)	270/331 (81.6)	274/329 (83.3)	−1.7 (−7.6, 4.1)	369/423 (87.2)	362/427 (84.8)	2.5 (−2.2, 7.2)
Investigator-Assessed Success (LFU ITT)	265/331 (80.1)	267/329 (81.2)	-1.1 (−7.2, 5.0)	353/423 (83.5)	351/427 (82.2)	1.3 (-3.8, 6.3)
Micro Success (FU ME) for MRSA	58/58 (100)	65/66 (98.5)	1.5 (-4.8, 8.1)	48/50 (96.0)	32/33 (97.0)	-1.0 (-11, 11.8)

Difference = Difference in responder rates (Delafloxacin treatment group minus vancomycin + aztreonam treatment group). Confidence intervals are calculated using Miettinen and Nurminen method.

IN PATIENTS WITH CARDIAC OR VASCULAR DISEASE

- Of the 1510 patients randomized in the two studies, 488 patients had CV (32.3%). The mean duration of exposure to study drug was 7.5 and 7.6 days in the DLX and VAN/AZ arms, respectively. Those in the VAN/AZ arm received AZ for a mean of 3.2 days. Key demographic and clinical characteristics **(Table 2)**.

PRIMARY EFFICACY OUTCOME IN PATIENTS WITH CARDIAC OR VASCULAR DISEASE

- In patients with cardiac or vascular disease, DLX IV/oral was comparable to VAN/AZ in the early objective response. DLX IV/oral was also comparable to VAN/AZ in the investigator-assessed response of success (Cure + Improved) at both FU and LFU **(Table 3)**.

MICROBIOLOGIC OUTCOMES IN PATIENTS WITH CARDIAC OR VASCULAR DISEASE

- DLX was as effective as VAN/AZ against key ABSSSI pathogens like *S. aureus*, including MRSA, and against Gram-negative organisms **(Table 4)**.

RESULTS

TABLE 2: SUMMARY OF PATIENTS WITH CV DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF ABSSSI (ITT) - POOLED PHASE 3

Characteristic	DLX (N = 260)	VAN/AZ (N = 228)
Age, years		
Mean (SD)	58.6 (13.4)	58.8 (14.7)
Median (min, max)	58.0 (26, 94)	59.0 (20,93)
Sex, n (%)		
Male	145 (55.8)	132 (57.9)
Female	115 (44.2)	96 (42.1)
Race, n (%)		
American Indian or Alaska Native	4 (1.5)	2 (0.9)
Asian	8 (3.1)	11 (4.8)
Black or African American	12 (4.6)	11 (4.8)
Native Hawaiian or other Pacific Islander	3 (1.2)	1 (0.4)
White	223 (85.8)	196 (86.0)
Other	10 (3.8)	7(3.1)
Region		
Europe	118 (45.4)	107 (46.9)
North America	118 (45.4)	101 (44.3)
Asia	8 (3.1)	9 (3.9)
Latin American	16 (6.2)	11 (4.8)
Received antibiotics in the 14 days prior to enrollment	70 (26.9)	65 (28.5)
Baseline infection type, n (%)		
Cellulitis/erysipelas	148 (56.9)	136 (59.6)
Wound infection	56 (21.5)	49 (21.5)
Major cutaneous abscess	53 (20.4)	42 (18.4)
Burn infection	3 (1.2)	1 (0.4)
BMI, mean (SD)	32.3 (7.5)	33 (8.3)
Bacteremia present, n (%)	7 (2.7)	8 (3.5)
Baseline erythema area (digital), cm^2		
Subjects	256	228
Mean (SD)	426 (406)	475 (475)

TABLE 3: CLINICAL EFFICACY OF PATIENTS WITH CV - POOLED PHASE 3

ENDPOINT	POPULATION	DLX	VAN/AZ	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	208/260 (80.0)	183/228 (80.3)	0.2 (-6.9, 7.4)
	CE	205/243 (84.4)	174/212 (82.1)	2.4 (-4.6, 9.4)
Investigator-Assessed Response of Success at FU	ITT	220/260 (84.6)	202/228 (88.6)	-3.0 (-9.0, 3.1)
	CE	204/217 (94.0)	176/185 (95.1)	-0.9 (-5.9, 4.0)
Investigator-Assessed Response of Success at LFU	ITT	212/260 (81.5)	199/228 (87.3)	-5.0 (-11.5, 1.4)
	CE	194/207 (93.7)	173/182 (95.1)	-1.3 (-6.4, 3.8)

TABLE 4: PER PATHOGEN MICROBIOLOGICAL ERADICATION OF PATIENTS WITH CV[1] (ME AT FU ANALYSIS SET) - POOLED PHASE 3

Organism[2]	DLX	VAN/AZ
Staphylococcus aureus	72/74 (97.3)	57/61 (93.4)
MSSA	46/48 (95.8)	40/42 (95.2)
MRSA	26/26 (100)	17/19 (89.5)
S. haemolyticus	8/8 (100)	3/3 (100)
P. aeruginosa	6/6 (100)	8/8 (100)
S. agalactiae	6/6 (100)	6/7 (85.7)
S. pyogenes	5/5 (100)	5/5 (100)
E. coli	4/4 (100)	8/9 (88.9)
K. pneumoniae	4/4 (100)	2/2 (100)
E. faecalis	3/3 (100)	7/8 (87.5)
P. mirabilis	3/3 (100)	5/5 (100)

[1] Documented or presumed eradicated; [2] Baseline pathogens isolated from skin or blood

TABLE 5: OVERALL SUMMARY OF ADVERSE EVENTS IN ALL PATIENTS WITH CV (SAFETY ANALYSIS SET) - POOLED PHASE 3

n (%)	DLX (N = 255)	VAN/AZ (N = 228)
Any TEAE	130 (51.0)	105 (46.1)
TEAE related to study drug	58 (22.7)	51 (22.4)
TEAE with moderate or severe intensity	54 (21.2)	51 (22.4)
Any TEAE leading to premature study drug D/C	3 (1.2)	7 (3.1)
Any related TEAE leading to premature study drug D/C	2 (0.8)	5 (2.2)
Any SAE	6 (2.4)	15 (6.6)
Any SAE related to study drug	-	2 (0.9)
Death	1 (0.4)	3 (1.3)

TABLE 6: RELATED TREATMENT-EMERGENT ADVERSE EVENTS OCCURING in ≥1% OF PATIENTS WITH CV (SAFETY ANALYSIS SET) - POOLED PHASE 3

n (%)	DLX (N = 255)	VAN/AZ (N = 228)
Patients with ≥1 Treatment-Related TEAE	58 (22.7)	51 (22.4)
Diarrhea	21 (8.2)	7 (3.1)
Nausea	10 (3.9)	8 (3.5)
Headache	7 (2.7)	2 (0.9)
ALT increased	3 (1.2)	2 (0.9)
Vulvovaginal mycotic infection	3 (1.2)	1 (0.4)
Generalized Pruritis	0	5 (2.2)
Pruritus	0	3 (1.3)
Rash	0	3 (1.3)
Renal Failure	0	3 (1.3)

SAFETY IN PATIENTS WITH CV

- The incidence of treatment-emergent adverse events was comparable in the 2 groups as was the incidence of drug-related **TEAEs (Table 5).**
- There were more premature discontinuations of treatment in the VAN/AZ arm. Most were not considered related to treatment.
- The incidence of SAEs was slightly higher in the VAN/AZ group and the majority of these were considered unrelated to study therapy.
- Gastrointestinal events were the most common treatment-related AEs with diarrhea seen in 8.2% and 3.1% of DLX and VAN/AZ patients respectively **(Table 6)**. Adverse events were generally mild to moderate severity with no cases of *C. difficile* diarrhea.
- There were no reports of cases meeting the Hy's law definition in DLX-treated patients.
- There were no treatment-related cardiac adverse events in either group. There were no reported EKGs performed for cause.
- None of the deaths were considered treatment-related. There were no study drug discontinuations due to cardiac events. The only serious cardiac event was in a vancomycin/aztreonam patient who died from a myocardial infarction after the end of therapy.

CONCLUSION

- In preclinical and clinical testing, delafloxacin does not have risk of QT prolongation or major drug-drug interactions[2].
- Treatment of ABSSSI in patients with cardiac or vascular disease can be complicated by concomitant medications or significant comorbidities. Some antibiotics like moxifloxacin, levofloxacin or clarithromycin have risk for QT prolongation[3].
- In a Scientific Statement from the American Heart Association and the American College of Cardiology Foundation, administration of a QT-prolonging drug to a hospitalized population should be avoided since these patients often have other risk factors such as concomitant medications or complicating comorbidities which can contribute to a proarrhythmic response such as torsade de pointes[8].
- In a population of patients with cardiac or vascular disease, IV/oral monotherapy with DLX was as effective as the combination of IV VAN/AZ when used to treat ABSSSIs caused by both Gram-positive and Gram-negative organisms.
- IV/oral DLX monotherapy was comparable to IV VAN/AZ combination therapy for both the objective response (decrease in lesion size ≥20%) at 48-72 hours after initiation of study drug, and the investigator-assessed response rates of success at FU.
- DLX patients had comparable per-pathogen microbiological response rates vs VAN/AZ patients against important pathogens that cause ABSSSIs, including *S. aureus* (both MSSA and MRSA), streptococci and Gram-negative bacteria.
- DLX was well tolerated in this study; the most common TEAEs among DLX-treated patients were gastrointestinal events like diarrhea and nausea.
- There was no signal for significant cardiac adverse events in DLX-treated patients.

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