POSTER # 235

DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED COMPARED TO VANCOMYCIN/ AZTREONAM (VAN/AZ) IN TREATMENT OF PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) AND HISTORY OF INFECTIOUS HEPATITIS

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A. Tien[1], I. Poromanski[2], L. Lawrence[3], M. Quintas[3] C. Tseng[4], S. Cammarata[3]

[1] Tartu Univ. Hosp. Surgery Clinic, Tartu, Estonia, [2] Univ. Multiprofile Hosp. Active Treatment and Emergency Med., Sofia, Bulgaria, [3] Melinta Therapeutics, Lincolnshire, IL, [4] H2O Clinical, Hunt Valley, MD

Shaina Barnes, PharmD
203-624-5606
Medinfo@melinta.com

ABSTRACT

Background: DLX, an investigational anionic fluoroquinolone antibiotic with Gram-positive and Gram-negative activity, is in development for treatment of ABSSSI. Two global phase 3 ABSSSI trials included patients with history of infectious hepatitis (studies 302 and 303).

Methods: Two multicenter, double-blind, double-dummy trials of adults with ABSSSI randomized patients 1:1 to receive either DLX monotherapy or VAN 15 mg/ kg (actual body weight) with AZ for 5 – 14 days. Study 302 used DLX 300 mg BID IV only; study 303 used DLX 300 mg BID IV for 3 days with a mandatory blinded switch to DLX 450 mg oral BID. Key endpoints were objective response at 48-72 hours with ≥20% reduction in lesion size and investigator assessment of outcome based on resolution of signs and symptoms at Follow-up (FU day 14±1) and Late Follow-up (LFU day 21-28).

Results: In the 2 studies, 438 patients with history of infectious hepatitis were randomized in US, Europe, Latin America and Asia. 73% were male with mean age 48 yrs. Median digital erythema area at baseline was 197 cm^2. 17% had cellulitis, 30% abscesses, 53% wound infections. 92% had a history of substance/drug abuse. *S. aureus* was the most frequent isolate.

Key Endpoints	DLX n/Total (%)	VAN/AZ n/Total (%)	DLX – VAN/AZ (95% CI) stratified by study
Objective response 48 – 72h (ITT)	190/220 (86.4)	189/218 (86.7)	0.3 (-6.2, 6.7)
Investigator-Assessed Success (FU ITT)	183/220 (83.2)	181/218 (83.0%)	1.2 (-5.8, 8.2)
Investigator-Assessed Success (LFU ITT)	176/220 (80.0)	175/218 (80.3)	0.3 (-7.2, 7.8)
Micro Success (FU ME) for MRSA	37/38 (97.4)	38/38 (100.0)	-2.0 (-14.1, 10.0)

The overall % of patients with history of infectious hepatitis with at least one treatment-emergent adverse event (TEAE) was lower for DLX (49.5%) compared to VAN/AZ (60.4%). The most frequent TEAEs were gastrointestinal in nature including nausea seen in 10.2% and 6.0% of DLX and VAN/AZ patients respectively. There were 4 and 6 reports of treatment-related ALT increase for DLX and VAN/AZ respectively. There were no discontinuations on DLX due to treatment related adverse events (AE), but 3 VAN/AZ-treated patients with history of infectious hepatitis discontinued due to treatment related AEs.

Conclusion:

In patients with history of infectious hepatitis and drug abuse, DLX was comparable to VAN/AZ in treatment of ABSSSI based on the prospective endpoints. DLX was also comparable to VAN/AZ in treating patients with MRSA. DLX appears effective and well tolerated in patients with ABSSSI and history of infectious hepatitis and substance abuse.

INTRODUCTION

Delafloxacin (DLX) is an investigational anionic fluoroquinolone antibiotic which is being studied in treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP). DLX has excellent *in vitro* activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) while retaining good activity against Gram-negative organisms.[1]

We conducted two multicenter, double-blind, double-dummy trials (302[2] and 303[3]) 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. Key endpoints included those mandated by both the FDA[4] (objective response at 48-72 hours) and EMA[5] (investigator assessments of response).

Patients with history of hepatitis B or C can have ongoing liver abnormalities. In addition, these patients often have a history of current/past drug use. This evaluation assesses the safety and outcomes of DLX in this patient group.

MATERIALS AND 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 q12h for the full course; in study 303, subjects received DLX 300 mg IV q12h for 3 days followed by a mandatory blinded switch to DLX 450 mg PO q12h;
- Patients were evaluated at screening, daily on therapy, FU (Day 14±1), and LFU (Day 21-28);
- Efficacy was evaluated through assessments of signs and symptoms; digital planimetry measurement of lesion size; and culture and susceptibility testing of bacterial isolates;
- Enrollment was stratified by baseline infection type and prior antibiotic use in study 302 and also by BMI in study 303.
- Patients were limited to 140 kg in study 302 and 200 kg in study 303, due to the limitations of IV blinding and vancomycin volume as well as infusion times.

Endpoints

- 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 endpoint for EMA: investigator-assessed response based on complete or near resolution of signs and symptoms (Cure + Improved = Success) at FU (Day 14 ±1) and LFU (Day 21 to 28);
- Additional efficacy endpoint: Microbiological response (documented or presumed eradication) for patients in the Microbiologically evaluable (ME) and Microbiological ITT (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).

Statistical Analysis

- For the key endpoints, a 2-sided 95% confidence interval (CI) for noninferiority testing was computed based on difference in responder rates for DLX and VAN/ AZ at 48-72 hours after initiation of treatment as well as the investigator response 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; MITT: 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.[2,3]

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.

TABLE 2: SUMMARY OF PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF ABSSSIs. ITT ANALYSIS SET. PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

Characteristic	DLX (N=220)	VAN/AZ (N=218)
Age, years		
Mean (SD)	47.4 (10.1)	46.1 (10.6)
Median (min, max)	48 (20, 85)	48 (19, 64)
Sex, n (%)		
Male	160 (72.7)	161 (73.9)
Female	60 (27.3)	57 (26.1)
Substance abuse* current or within last 2 years	197 (91.2)	202 (93.1)
Race, n (%)		
American Indian or Native American	9 (4.1)	3 (1.4)
Asian	1 (0.5)	1 (0.5)
Black	11 (5.0)	10 (4.6)
Native Hawaiian or other Pacific Islander	2 (0.9)	0
White	197 (89.5)	204 (93.6)
Region, n (%)		
Europe	3 (1.4)	3 (1.4)
North America	216 (98.2)	215 (98.6)
Asia	1 (0.5)	0
Latin America	0	0
Baseline infection type, n (%)		
Cellulitis/erysipelas	40 (18.2)	35 (16.1)
Wound infection	110 (50.0)	120 (55.0)
Major cutaneous abscess	70 (31.8)	63 (28.9)
BMI, mean (SD)	26.6 (5.0)	27.2 (5.8)
Bacteremia present, n (%)	4 (1.8)	4 (1.8)
Baseline erythema area (digital), cm^2		
Subjects	217	218
Mean (SD)	218.1 (129)	259.7 (193)

*Based on safety analysis set, includes drug dependence/abuse/abuser, substance use/abuse/ abuser, alcoholism, alcohol abuse/alcoholic (N=216 and 217 for DLX and VAN/AZ).

PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS

Of the 1510 patients randomized in the two studies, 438 patients had a history of infectious hepatitis (B or C). 92% of these patients who received study medication had a history of drug abuse or alcoholism. The median duration of exposure to study drug was 5 days in both treatment arms, respectively. Those in the VAN/AZ received AZ for a mean of 1.5 days. Key demographic and clinical characteristics are shown in **Table 2.**

Eligible pathogens identified at baseline, from the site of infection and from blood, are presented in **Table 3.**

TABLE 3: BASELINE ELIGIBLE PATHOGENS. MITT ANALYSIS SET. PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

Organism N (%)	DLX (N=179)	VAN/AZ (N=183)
Staphylococcus aureus	116 (64.8)	123 (67.2)
MSSA	61 (34.1)	65 (35.5)
MRSA	56 (31.3)	58 (31.7)
S. intermedius	21 (11.7)	22 (12.0)
S. anginosus	11 (6.1)	13 (7.1)
K. pneumoniae	12 (6.7)	12 (6.6)
E. cloacae	7 (3.9)	2 (1.1)
P. aeruginosa	3 (1.7)	1 (0.5)

PRIMARY EFFICACY OUTCOMES IN PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS

In patients with history of infectious hepatitis, DLX IV/oral was comparable to VAN/AZ in the primary endpoint. In addition, DLX IV/oral was comparable to VAN/AZ in investigator-assessed response of success (Cure or Improved) at both FU and LFU. This was evident in the ITT and CE populations **(Table 4)**.

TABLE 4: CLINICAL EFFICACY. PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	190/220 (86.4)	189/218 (86.7)	0.3 (-6.2, 6.7)
	CE	186/197 (94.4)	177/191 (92.7)	1.3 (-4.0, 6.5)
Investigator-Assessed Response of Success at FU	ITT	183/220 (83.2)	181/218 (83.0)	1.2 (-5.8, 8.2)
	CE	160/161 (99.4)	157/158 (99.4)	0.2 (-3.4, 3.8)
Investigator-Assessed Response of Success at LFU	ITT	176/220 (80.0)	175/218 (80.3)	0.3 (-7.2, 7.8)
	CE	160/162 (98.8)	156/157 (99.4)	-0.8 (-4.6, 3.1)

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

MICROBIOLOGIC EFFICACY OUTCOMES IN PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS

DLX was as effective as VAN/AZ against key ABSSSI pathogens like *S. aureus*, including MRSA, and against Gram-negative organisms as well **(Table 5)**.

TABLE 5: PER PATHOGEN MICROBIOLOGICAL RESPONSE[1] RATE. ME AT FU ANALYSIS SET, PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

Organism[2]	DLX n/N (%)	VAN/AZ n/N (%)
Staphylococcus aureus	80/81 (99)	85/85 (100)
MSSA	44/44 (100)	47/47 (100)
MRSA	37/38 (97)	38/38 (100)
S. intermedius	14/14 (100)	16/16 (100)
K. pneumoniae	8/8 (100)	10/10 (100)
S. mitis/oralis	6/6 (100)	1/1 (100)
E. cloacae	5/5 (100)	2/2 (100)
P. aeruginosa	3/3 (100)	1/1 (100)

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

SAFETY IN PATIENTS WITH RENAL IMPAIRMENT

- The incidence of TEAEs was comparable in the two treatment arms, as was the incidence of drug-related TEAEs **(Table 6)**.
- The incidence of serious adverse events (SAEs) was comparable in the two arms, and the majority of these events were considered unrelated to study therapy.
- GI events were the most common TEAE in both treatment arms **(Table 7)**, generally mild to moderate in nature. There were no cases of *C. difficile* diarrhea in the DLX arm in this subgroup.
- Reports of skin reactions were more common in the VAN/AZ group.
- There were no significant differences in laboratory values between the two treatment groups overall during the study including liver or glucose measures.
- There were no reports of cases meeting the Hy's law definition in DLX-treated patients.

TABLE 6: OVERALL SUMMARY OF ADVERSE EVENTS. SAFETY ANALYSIS SET, PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

	DLX (N=216)	VAN/AZ (N=217)
Any TEAE	107 (49.5%)	131 (60.4%)
TEAE related to study drug	58 (26.9%)	64 (29.5%)
TEAE with moderate or severe intensity	43 (19.9%)	46 (21.2%)
Any TEAE leading to premature study drug DC	2 (0.9%)	8 (3.7%)
Any related TEAE leading to premature study drug DC	0	3 (1.4%)
Any SAE	8 (3.7%)	4 (1.8%)
Any SAE related to study drug	0	0
Death	0	0

TABLE 7: ALL RELATED TREATMENT-EMERGENT ADVERSE EVENTS, OCCURRING IN ≥ 1% OF PATIENTS. SAFETY ANALYSIS SET, PATIENTS WITH HISTORY OF INFECTIOUS HEPATITIS, POOLED PHASE 3.

	DLX (N=216)	VAN/AZ (N=217)
Patients with ≥1 TEAE	58 (26.9)	64 (29.5)
Nausea	22 (10.2)	13 (6.0)
Diarrhea	18 (8.3)	3 (1.4)
Increased ALT	4 (1.9)	6 (2.8)
Headache	3 (1.4)	5 (2.3)
Infusion Site Extravasation	2 (0.9)	4(1.8)
Increased AST	3 (1.4)	7 (3.2)
Dyspepsia	3 (1.4)	1 (0.5)
Vomiting	2 (0.9)	5 (2.3)
Pruritis generalized	2 (0.9)	4 (1.8)
Increased CPK	2 (0.9)	3 (1.4)
Pruritis	0	4 (1.8)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase.

CONCLUSION

DISCUSSION/CONCLUSIONS

- Patients with history of infectious hepatitis can have complicating medical history such as active substance abuse. In this study, almost all of the patients with history of infectious hepatitis also had recent or current history of substance abuse.
- *S. aureus* was the most common pathogen in these patients with ~50% being MRSA.
- In a population of patients with history of infectious hepatitis, IV/oral monotherapy with DLX was as effective as the combination of IV VAN/AZ when used to treat ABSSSIs caused by both Gram-negative and Gram-positive organisms including MRSA.
  - 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 (Cure + Improved) at FU and LFU.
  - 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) and Gram-negative bacteria.
- DLX was well tolerated in this study; the most common TEAEs among DLX-treated patients were mild-to-moderate gastrointestinal events.
- There was no signal for significant abnormalities in laboratory values, with no significant difference between treatment groups.

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