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DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED IN TREATMENT OF OBESE PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) VERSUS VANCOMYCIN/AZTREONAM (VAN/AZ)

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ABSTRACT

Background: DLX, an investigational anionic fluoroquinolone antibiotic with activity against Gram-positive and Gram-negative pathogens, including MRSA, is in development for treatment of ABSSSI. Two global phase 3 ABSSSI trials (studies 302 and 303) included obese patients (BMI ≥30kg/m^2).

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, 639 obese patients were randomized in US, Europe, Latin America and Asia. 56% were male with mean age 51 yrs. Average erythema area at baseline was 408 cm^2. 55% had cellulitis, 22% abscesses, 23% wound and 1% burn infections. 53% of patients had *S. aureus*, with over 1/3 being MRSA. Patients were treated for a median of 6 days. Key endpoints are shown below:

Key Endpoints	DLX n/Total (%)	VAN/AZ n/Total (%)	DLX – VAN/AZ (95% CI) stratified by study
Objective response 48 – 72h (ITT)	266/331 (80.4)	244/308 (79.2)	1.7 (-4.5, 7.9)
Investigator-Assessed Success (FU ITT)	285/331 (86.1)	262/308 (85.1)	1.3 (-4.2, 6.8)
Investigator-Assessed Success (LFU ITT)	278/331 (84.0)	250/308 (81.2)	3.1 (-2.9, 9.0)
Micro Success (FU ME) for *S. aureus*	99/101 (98.0)	64/69 (92.8)	8.4 (0.6, 16.2)
Micro Success (FU ME) for MRSA	40/40 (100.00)	19/21 (90.5)	15.4 (-1.2, 32.0)

The overall % of patients with at least one treatment-emergent adverse event (TEAE) was comparable for DLX (44.3%) compared to VAN/AZ (42.8%). The most frequent TEAEs were gastrointestinal in nature including diarrhea seen in 6.1% of DLX and nausea seen in 4.6% of VAN/AZ patients, which were primarily mild to moderate in severity. There was one case of *C. difficile* diarrhea. Discontinuations due to treatment-related AEs were lower with DLX (0.6%) compared to VAN/AZ (2%).

Conclusion: Fixed dose DLX monotherapy was comparable to VAN/AZ combination therapy in treatment of ABSSSI in obese patients based on the early objective response as well as investigator-assessed response at FU and LFU. DLX was also comparable to VAN/AZ in treating patients with *S. aureus*. DLX appears effective and well tolerated in obese patients with ABSSSI.

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INTRODUCTION

Delafloxacin (DLX) is an investigational anionic fluoroquinolone antibiotic which is being studied in treatment of acute bacterial skin and skin structure infections (ABSSSIs). 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 VAN/AZ combination therapy in patients with ABSSSIs caused by both Gram-positive and Gram-negative pathogens. Key endpoints included both those mandated by both the FDA[4] (objective response at 48-72 hours) and EMA[5] (investigator assessments of response).

Obesity is an established risk factor for antibiotic treatment failure[6]; however, there are limited data on correct dosing recommendations in obese patients[7]. The correct dosing of vancomycin in obese patients is still not clear [8]. Simpler treatment options are needed for these patients.

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 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);
- 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 140kg in study 302 and 200kg 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 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).

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 (±2) 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; 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.[2,3]

TABLE 1: OVERALL OUTCOMES IN STUDIES 302 AND 303.

Overall Key Endpoints	STUDY 302 DLX n/Total (%)	STUDY 302 VAN/AZ n/Total (%)	STUDY 302 Delta (95% CI)	STUDY 303 DLX n/Total (%)	STUDY 303 VAN/AZ n/Total (%)	STUDY 303 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. OBESE PATIENTS, POOLED PHASE 3.

Characteristic	DLX (N=331)	VAN/AZ (N=308)
BMI, mean (SD)	35.7 (5.75)	36.1 (6.26)
Age, years		
Mean (SD)	51.8 (14.80)	51.2 (14.43)
Median (min, max)	52.0 (18, 89)	51.0 (22, 90)
Sex, n (%)		
Male	180 (54.4)	180 (58.4)
Female	151 (45.6)	128 (41.6)
Race, n (%)		
American Indian or Native American	7 (2.1)	5 (1.6)
Asian	3 (0.9)	1 (0.3)
Black	17 (5.1)	14 (4.5)
Native Hawaiian or other Pacific Islander	--	1 (0.3)
White	287 (86.7)	274 (89.0)
Other	17 (5.1)	13 (4.2)
Region		
Europe	148 (44.7)	142 (46.1)
North America	159 (48.0)	142 (46.1)
Asia	1 (0.3)	1 (0.3)
Latin America	23 (6.9)	23 (7.5)
Received antibiotics in the 14 days prior to enrollment	77 (23.3)	79 (25.6)
Baseline infection type, n (%)		
Cellulitis/erysipelas	150 (35.5)	161 (35.9)
Wound infection	149 (35.2)	162 (36.2)
Major cutaneous abscess	120 (28.4)	121 (27.0)
Burn infection	4 (0.9)	4 (0.9)
Patients with diabetes, n (%)	62 (18.7)	59 (19.2)
Bacteremia present, n (%)	8 (2.4)	7 (2.3)
Baseline erythema area (digital), cm^2		
Subjects	328	306
Mean (SD)	393.7 (369.29)	422.4 (445.99)

PATIENTS

Of the 1510 patients randomized in the two studies, 639 were obese (BMI ≥30 kg/m^2) (42.3%). The median duration of exposure to study drug was 7 and 6.5 days in the DLX and VAN/AZ treatment arms, respectively. Those in the VAN/AZ received AZ for a mean of 3.2 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. OBESE PATIENTS, POOLED PHASE 3.

Organism[2]	DLX (N = 91)	VAN/AZ (N = 78)
Staphylococcus aureus	120 (56.9%)	93 (48.7%)
MSSA	72 (34.1%)	60 (31.4%)
MRSA	49 (23.2%)	33 (17.3%)
S. epidermidis	17 (8.1%)	25 (13.1%)
S. pyogenes	6 (2.8%)	12 (6.3%)
E. coli	7 (3.3%)	9 (4.7%)
E. faecalis	4 (1.9%)	9 (4.7%)
S. agalactiae	8 (3.8%)	10 (5.2%)
K. pneumoniae	7 (3.3%)	9 (4.7%)
E. cloacae	6 (2.8%)	4 (2.1%)
P. aeruginosa	5 (2.4%)	9 (4.7%)

PRIMARY EFFICACY OUTCOME IN OBESE PATIENTS

In obese patients, DLX IV/oral was comparable to VAN/AZ in the primary endpoint. In addition, DLX IV/oral was comparable to VAN/AZ in the secondary endpoints of investigator-assessed response of success (Cure + Improved) at both FU and LFU **(Table 4)**.

TABLE 4: CLINICAL EFFICACY OBESE PATIENTS, POOLED PHASE 3.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	266/331 (80.4)	244/308 (79.2)	1.7 (-4.5, 7.9)
	CE	259/309 (83.8)	231/281 (82.2)	2.2 (-3.9, 8.3)
Investigator-Assessed Response of Success at FU	ITT	285/331 (86.1)	262/308 (85.1)	1.3 (-4.2, 6.8)
	CE	305/312 (97.8)	330/337 (97.9)	-0.3 (-3.0, 2.5)
Investigator-Assessed Response of Success at LFU	ITT	278/331 (84.0)	250/308 (81.2)	3.1 (-2.9, 9.0)
	CE	308/315 (97.8)	335/341 (98.2)	-0.9 (-3.5, 1.7)

MICROBIOLOGIC EFFICACY OUTCOMES

- 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)**.

SAFETY IN OBESE PATIENTS

- 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)**. There was one case of *C. difficile* diarrhea in the DLX arm, which was considered mild in severity. This occurred in a patient who had entered the trial as a prior treatment failure with prior antibiotics (Bactrim™/clindamycin).
- There were 3 AEs of renal failure in the VAN/AZ group, none in the DLX group.
- There were no significant differences in laboratory values between the two treatment groups 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 5: PER PATHOGEN MICROBIOLOGICAL RESPONSE[1] RATE. ME AT FU ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

Organism[2]	DLX (N=180)	VAN/AZ (N=145)
Staphylococcus aureus	99/101 (98.0%)	64/69 (92.8%)
MSSA	60/62 (96.8%)	45/48 (93.8%)
MRSA	40/40 (100.0%)	19/21 (90.5%)
S. epidermidis	12/14 (85.7%)	20/20 (100.0%)
S. pyogenes	6/6 (100.0%)	10/10 (100.0%)
E. coli	6/6 (100.0%)	7/8 (87.5%)
E. faecalis	4/4 (100.0%)	6/7 (85.7%)
S. agalactiae	7/7 (100.0%)	9/10 (90.0%)
K. pneumoniae	6/6 (100.0%)	5/5 (100.0%)
E. cloacae	4/5 (80.0%)	3/4 (75.0%)
P. aeruginosa	5/5 (100.0%)	8/8 (100.0%)

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

TABLE 6: OVERALL SUMMARY OF ADVERSE EVENTS. SAFETY ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

	DLX (N=327)	VAN/AZ (N=306)
Any TEAE	145 (44.3%)	131 (42.8%)
TEAE related to study drug	74 (22.6%)	73 (23.9%)
TEAE with moderate or severe intensity	64 (19.6%)	60 (19.6%)
Any TEAE leading to premature study drug DC	6 (1.8%)	9 (2.9%)
Any related TEAE leading to premature study drug DC	2 (0.6%)	6 (2.0%)
Any SAE	12 (3.7%)	13 (4.2%)
Any SAE related to study drug	2 (0.6%)	3 (1.0%)
Death	--	2 (0.7%)

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

	DLX (N=121)	VAN/AZ (N=121)
Patients with ≥1 TEAE	74 (22.6%)	73 (23.9%)
Diarrhea	20 (6.1%)	7 (2.3%)
Nausea	16 (4.9%)	14 (4.6%)
Headache	5 (1.5%)	6 (2.0%)
Vaginal yeast infection	5 (1.5%)	2 (0.7%)
Increased ALT	5 (1.5%)	4 (1.3%)
Infusion site phlebitis	4 (1.2%)	1 (0.3%)
Increased AST	3 (0.9%)	4 (1.3%)
Pruritus	2 (0.6%)	5 (1.6%)
Pruritus generalized	2 (0.6%)	5 (1.6%)
Urticaria	2 (0.6%)	3 (1.0%)
Vomiting	--	5 (1.6%)
Chills	--	4 (1.3%)
Rash	--	3 (1.0%)
Renal failure	--	3 (1.0%)
Upper abdominal pain	--	3 (1.0%)

CONCLUSION

DISCUSSION/CONCLUSIONS

- Obese patients are at risk for serious skin infections. However, the correct antibiotic dosing in these patients is often not clear. Patients are often inadequately dosed.
- In a population of obese patients, 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. DLX does not require weight-based dosing or therapeutic monitoring.
- 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.