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OUTCOMES WITH IV/ORAL DELAFLOXACIN (DLX) COMPARED TO VANCOMYCIN/AZTREONAM (VAN/AZ) IN TREATMENT OF PATIENTS (PTS) WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) AND GRAM-POSITIVE (GP) PATHOGENS

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ABSTRACT

Background: Delafloxacin (DLX) is a broad-spectrum fluoroquinolone antibiotic which has been approved by FDA for the treatment in adults with ABSSSI caused by designated susceptible bacteria. Two global phase 3 ABSSSI trials included patients with both Gram-positive and -negative pathogens including MRSA.

Material/methods: Two double-blind trials of adults with ABSSSI randomized patients 1:1 to receive either q12h DLX IV/oral monotherapy or VAN 15 mg/kg with AZ for 5 – 14 days. Key endpoints were objective response at 48-72 hours; and investigator assessment of outcome based on resolution of signs and symptoms at Follow-up (FU day 14) and Late Follow-up (LFU day 21-28).

Results: 1042/1510 patients enrolled had a pathogen at baseline. 987 patients (95%) had a GP pathogen isolated at baseline; 14% were part of a mixed infection. Median erythema area at baseline was ~195 cm^2. 30% had cellulitis, 31% abscesses, and 38% wounds. *S. aureus* was the most frequent isolate. The MIC_{50}, MIC_{90} and MIC range for key pathogens were 0.008 ,0.015, 0.002-0.5 µg/mL for MSSA; 0.12, 0.25, 0.002-4 µg/mL for MRSA; 0.015, 0.06, 0.015-0.06 µg/mL for *S. pyogenes*. Key endpoints are shown below:

Key Endpoints Phase 3 Patients with GP pathogens	DLX n/Total (%)	VAN/AZ n/Total (%)
Objective response 48-72h (ME)	405/461 (87.9)	388/446 (87.0)
Investigator-Assessed Success (FU ME)	381/389 (97.9)	361/368 (98.1)
Investigator-Assessed Success (LFU ME)	377/388 (97.2)	358/367 (97.5)
Micro Success (FU ME) for key GP organisms:		
S. aureus	244/248 (98.4)	233/239 (97.5)
MSSA	140/142 (98.6)	136/140 (97.1)
MRSA	106/108 (98.1)	97/99 (98.0)
S. pyogenes	18/19 (94.7)	15/15 (100)

In the overall population, DLX was well tolerated. The most frequent treatment-related adverse events were gastrointestinal in nature including nausea seen in 6.1% and 4.3% and diarrhea seen in 6.1% and 2% of DLX and VAN/AZ patients, respectively. There were 0.8% of DLX patients and 2.4% VAN/AZ patients who discontinued treatment due to treatment related AEs.

Conclusions: GP pathogens, particularly MRSA, are the most frequent pathogens in ABSSSI. Fixed dose DLX IV/oral monotherapy was effective in patients with GP pathogens based on the early objective response as well as investigator-assessed response and microbiologic response. DLX appears effective and well tolerated in patients with GP pathogens in ABSSSI.

INTRODUCTION

DLX is an anionic fluoroquinolone antibiotic, approved for the treatment of ABSSSI, with a number of unique properties that may make it useful in treatment of severe infections. 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] Two Phase 3 studies were conducted to compare the efficacy and safety of IV or IV/oral DLX monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSIs. The endpoints reflect those mandated by the FDA[2] and EMA[3]. Baseline pathogens were also evaluated and analyzed for an endpoint of microbial response and tested for susceptibility.

MATERIALS AND METHODS

STUDY DESIGN

- Adults with ABSSSI randomized 1:1 received either DLX monotherapy or vancomycin (VAN) 15 mg/kg (actual body weight) with aztreonam (AZ) in two stratified, randomized, double-blind Phase 3 global studies (302 and 303).
- Patients had wounds, burns, major abscesses, or cellulitis of ≥75 cm^2 in size; at least 2 systemic signs of infections; and met other entry criteria.
- Patients received DLX 300 mg IV q12 (302), or DLX 300 mg IV q12h for 3 days with a mandatory blinded switch to DLX 450 mg oral q12h (303), or VAN 15 mg/kg IV (actual body weight) with AZ. Total treatment duration was 5 – 14 days at the investigator's discretion.
- Enrollment was stratified by baseline infection type, prior antibiotic use, and BMI (303 only), and patients were evaluated at screening, daily on therapy, at the Follow-up (FU, Day 14 ± 1) and Late Follow-up Visits (LFU, Day 21 to 28).
- Efficacy was evaluated through assessments of the signs and symptoms of infection; measurement of lesion size by digital planimetry; and culture and susceptibility testing of bacterial isolates.
- Isolates were submitted to the central laboratory (JMI Laboratories, North Liberty, IA) for identification and susceptibility testing per CLSI guidelines.[4]

Endpoints and Analysis

Primary endpoint: Proportion of patients who achieved an objective response at 48-72 hours following initiation of treatment, based on at least a 20% decrease in lesion size with no further antibiotics, major procedures or death, in the intent-to-treat (ITT) population.

Secondary efficacy endpoint for FDA and Primary endpoint for EMA: Investigator-assessed response based on complete resolution of signs and symptoms (cure) at FU and LFU visits.

- In the primary analysis of the investigator response, it was required that patients were completely cured (ie, no signs or symptoms), not merely improved (ie, some symptoms remain, but the patient has improved to an extent that no additional antibiotic treatment is necessary), for the positive investigator response. Improved responses were considered failures for purposes of the primary analysis.
- An additional analysis was completed to assess the proportion of patients who were a clinical success (cure + improved).
- Microbiological response to treatment was an additional efficacy endpoint.
- Safety was assessed through adverse event reporting, vital sign and body temperature measurements, clinical laboratory test abnormalities, physical examination findings, concomitant medications, and ECGs (if clinically indicated).

Key analysis populations included:

- Intent-to-treat (ITT; all patients randomized)
- Microbiological intent-to-treat (MITT; ITT patients with eligible pathogen)
- Clinically evaluable (CE; patients who completed activities as defined in the protocol)
- Microbiologically evaluable (ME; CE patients with eligible pathogen)

RESULTS

DEMOGRAPHICS

Patients (n=1510) were randomized in North America, Asia, Europe, and Latin America (ITT population). 69% (n=1042) of patients had pathogens identified at baseline (MITT). DLX patients received study drug for an average of 6.8 days. Vancomycin patients received an average of 6.6 days of treatment and aztreonam for a mean of 2.8 days.

TABLE 1. SUMMARY OF SUBJECT DEMOGRAPHICS & BASELINE CHARACTERISTICS OF ABSSSI IN IN PATIENTS WITH GRAM-POSITIVE VERSUS GRAM-NEGATIVE PATHOGENS (MITT)[a]

Baseline Characteristic	Gram-positive Patients[a] N=845	Gram-negative Patients[a] N=197
Age, years		
Mean (SD)	46.7 (14.79)	52.5 (15.24)
Median (Min, max)	47.0 (18, 94)	53.0 (18, 87)
Sex, n/N (%)		
Male	530 (62.7)	130 (66.0)
Female	315 (37.3)	67 (34.0)
Race, n/N (%)		
Black or African American	52 (6.2)	5 (2.5)
White	745 (88.2)	182 (92.4)
Other[b]	48 (5.7)	10 (5.1)
Region, n/N (%)[c]		
Europe	210 (24.9)	73 (37.1)
North America	601 (71.1)	116 (58.9)
Asia	2 (0.2)	1 (0.5)
Latin America	32 (3.8)	7 (3.6)
Baseline infection type, n /N(%)		
Cellulitis/erysipelas	261 (30.9)	49 (24.9)
Wound infection	310 (36.7)	93 (47.2)
Major cutaneous abscess	267 (31.6)	53 (26.9)
Burn infection	7 (0.8)	2 (1.0)
BMI (kg/m^2) Mean (SD)	28.6 (6.51)	29.8 (7.71)
Patients with diabetes, n (%)	88 (10.4)	16 (8.1)
Anatomical site of infection n (%)		
Head/neck/face	37 (4.4)	4 (2.0)
Back	28 (3.3)	6 (3.0)
Thorax	19 (2.2)	5 (2.5)
Upper extremities	279 (33.0)	48 (24.4)
Lower extremities	349 (41.3)	98 (49.7)
Abdomen	42 (5.0)	14 (7.1)
Pubic/perineum/groin	17 (2.0)	4 (2.0)
Buttocks	86 (10.2)	21 (10.7)
Area baseline erythema (digital), cm^2	273.3 (N=845)	284.2 (N=195[d])

a. Gram-negative includes polymicrobial gram negative, monomicrobial Gram-negative or polymicrobial gram mixed. Gram-positive includes monomicrobial Gram-positive or polymicrobial Gram-positive.
b. American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Other
c. Europe includes Latvia, Hungary, Estonia, Moldova, Romania, Bulgaria, Georgia, Spain, Croatia, Israel, Ukraine. North America includes United States. Asia includes Taiwan, Korea. Latin America includes Peru, Argentina, Mexico, Chile, Brazil.
d. Two patients in this group did not have baseline erythema measurements

TABLE 2. GRAM-POSITIVE BASELINE PATHOGENS (≥1%) IN POOLED PHASE 3 PATIENTS (MITT) AND DLX SUSCEPTIBILITY RESULTS

Organism	DLX N = 518	DLX + VAN N = 1042	DLX $MIC_{50}/_{90}$ (Range) ALL PATIENTS
Gram-positive organisms[a], n			
S. aureus	339	685	0.008/0.25 (0.002 – 4)
MRSA	149	294	0.12/0.25 (0.002 – 4)
MSSA	194	395	0.008/0.03 (0.002 – 0.5)
S. pyogenes	25	46	0.015/0.06 (0.008 – 0.06)
S. anginosus	20	44	0.015/0.03 (≤0.004 – 0.06)
S. haemolyticus	16	24	0.008/0.5 (0.008 – 8)
S. agalactiae	14	27	0.03/0.06 (0.015 – 0.06)
E. faecalis	11	27	0.12/1 (≤0.004 – 2)
S. dysgalactiae	11	23	0.015/0.03 (0.008 – 0.03)
S. intermedius	11	34	0.008/0.015 (≤0.004 – 0.03)
S. lugdunensis	10	19	0.015/0.03 (0.008 – 0.03)
S. constellatus	6	12	≤0.004/0.008 (≤0.004 – 0.015)

a. Eligible pathogens are organisms identified as potential pathogens from blood or skin specimens by the investigator and submitted for culture and susceptibility testing at the central laboratory. The n in the table is the number of all available MIC values in the specified pathogen within each treatment group.

TABLE 3. RESULTS FOR KEY ENDPOINTS IN POOLED PHASE 3 PATIENTS WITH GRAM-POSITIVE PATHOGENS

Endpoint	DLX n/Total (%)	VAN/AZ n/Total (%)
Objective response 48-72h (ME)	405/461 (87.9)	388/446 (87.0)
Investigator-Assessed Success (FU ME)	381/389 (97.9)	361/368 (98.1)
Investigator-Assessed Success (LFU ME)	377/388 (97.2)	358/367 (97.5)

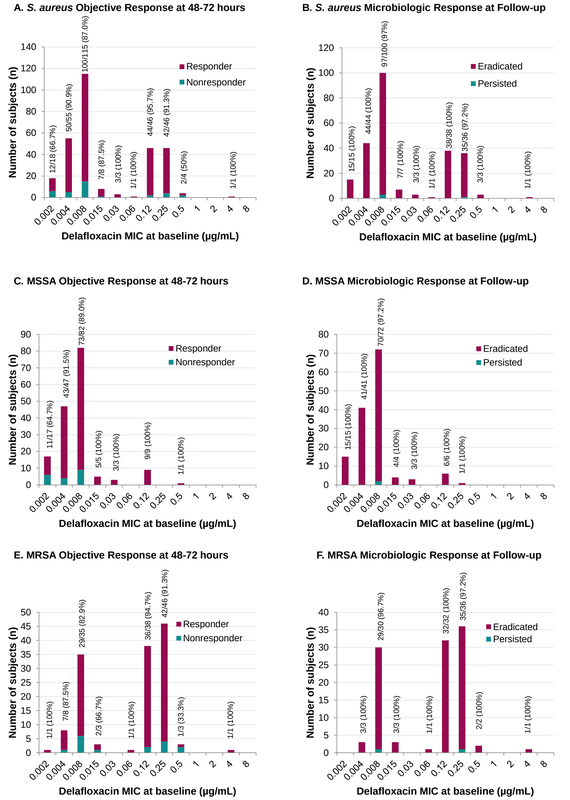
TABLE 4. BY PATHOGEN MICROBIOLOGICAL RESPONSE AT FOLLOW-UP (ME)[a,b]

Organism	Follow Up Visit	
	DLX N=410	VAN/AZ N=396
S. aureus, (%)	244/248 (98.4)	233/239 (97.5)
MRSA, (%)	106/108 (98.1)	97/99 (98.0)
MSSA, (%)	140/142 (98.6)	136/140 (97.1)
S. intermedius (%)	21/21 (100)	19/19 (100)
S. pyogenes (%)	18/19 (94.7)	15/15 (100)
S. anginosus (%)	16/16 (100)	13/14 (92.9)
E. faecalis (%)	14/14 (100)	12/13 (92.3)
S. agalactiae (%)	11/11 (100)	11/12 (91.7)
S. constellatus (%)	10/10 (100)	12/12 (100)
S. haemolyticus (%)	12/12 (100)	7/7 (100)
S. lugdunensis (%)	10/10 (100)	7/7 (100)

a. Documented or Presumed Eradicated
b. Baseline pathogens from blood or skin

FIGURE 1. MICROBIOLOGICAL RESPONSE BY MIC DISTRIBUTION OF DLX AGAINST PHASE 3 STAPHYLOCOCCI (EVALUABLE PATIENTS FROM POOLED PHASE 3 STUDIES)[a]

Correlation of Delafloxacin MIC Against Target:



a. Documented or presumed eradicated/persisted

SAFETY FOR ALL POOLED PHASE 3 PATIENTS

TABLE 5. TREATMENT EMERGENT ADVERSE EVENTS (TEAE)

TEAEs, Regardless of Causality, ≥2% (Safety Analysis Set)	DLX N=741 (%)	VAN/AZ N=751 (%)
Patients with any TEAE, n (%)	334 (45.1)	358 (47.7)
Patients with any related TEAE, n (%)	164 (22.1)	196 (26.1)
Patients with any TEAE leading to premature study drug discontinuation, n (%)	13 (1.8)	26 (3.5)
Patients with any related TEAE leading to premature study drug discontinuation, n (%)	6 (0.8)	18 (2.4)
Patients with any serious adverse event (SAE), n (%)	27 (3.6)	26 (3.5)
Patients with any related SAE, n (%)	2 (0.3)	4 (0.5)
Patient Deaths*, n (%)	1 (0.1)	3 (0.4)
Subjects with any TEAE presented by maximum severity		
Mild	198 (26.7)	206 (27.4)
Moderate	110 (14.8)	131 (17.4)
Severe	26 (3.5)	21 (2.8)

* All deaths were considered unrelated to treatment

CONCLUSION

- IV and oral monotherapy DLX had outcomes comparable to IV VAN/AZ combination therapy for ABSSSI patients with Gram-positive infections with both objective response (decrease in lesion size ≥ 20%) at 48 to 72 hours after initiation of study drug, and investigator-assessed response rates of success at the Follow-up visit by Gram-positive pathogens (MITT and ME populations).
- DLX patients had comparable per-pathogen microbiological response rates vs. VAN/AZ patients against important Gram-positive pathogens that cause ABSSSI.
- DLX is comparable to VAN/AZ in terms of incidence of AEs, and 96% of TEAEs were mild or moderate for both groups.
- The most common TEAEs in DLX-treated patients were mild to moderate gastrointestinal events, but these did not lead to treatment discontinuation.

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