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IMPACT OF DELAFLOXACIN (DLX) AND VANCOMYCIN/AZTREONAM (VAN/AZ) ON RESOLUTION OF SIGNS AND SYMPTOMS OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI)

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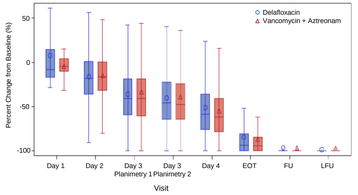
ABSTRACT

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. A global phase 3 ABSSSI trial included patients with both Gram-positive and -negative pathogens (study 302). DLX was non-inferior to VAN/AZ in both objective and clinical response endpoints. Clinical signs and symptoms and lesion size measurements also were evaluated in this trial.

Material/methods: A multicenter, double-blind trial of adults with ABSSSI randomized patients 1:1 to receive either DLX monotherapy 300mg q12h IV or VAN 15 mg/kg (actual body weight) with AZ for 5 – 14 days. Aztreonam was discontinued once Gram-negative infection was excluded. The presence or absence of signs and symptoms (S&S) were collected at each evaluation point. Patients with complete resolution of clinical S&S were classified as complete cures. Lesions were measured by digital planimetry. Patient-reported pain was recorded by numerical rating scale (NRS; 0=no pain, 10=worst pain). Assessment were completed at baseline, during treatment, at Follow-up (FU day 14), and Late Follow-up (LFU day 21-28).

Results: 660 patients were randomized in US, Europe, and Israel. 63% were male with mean age 46 yrs. 39% had cellulitis, 25% abscesses, 35% wound and 1% burn infections. Baseline erythema and induration were seen in 100% and 98% of patients, respectively. Mean area of erythema and induration at baseline was 307 cm^2 and 107 cm^2 respectively. The most common locations for lesions were the lower extremities (40%) and upper extremities (35%). *S. aureus* was the most common isolate. Mean days of treatment was 6 days. DLX and VAN/AZ patients had comparable impact on S&S with complete resolution seen in 22% vs 19% at EOT, and 52% vs 51% at FU, and 70% vs 67% at LFU for DLX vs VAN/AZ, respectively. DLX was comparable to VAN/AZ in percent reduction in erythema over time with median reduction at 48-72 h, EOT, and FU with DLX of 58%, 94%, and 100% compared to VAN/AZ with 59%, 94%, 100%, respectively. Percent change from baseline erythema size is shown in figure. Baseline mean pain scores were 8 with scores of ~2.5 at EOT and 1 at FU for both treatment groups.



Conclusions: Treatment with either DLX and VAN/AZ provided rapid improvement in clinical signs and symptoms in ABSSSI with comparable reductions in S&S, lesion size, and pain score.

INTRODUCTION

Delafloxacin (RX-3341) is an anionic fluoroquinolone antibiotic with a number of unique properties that was recently approved in the US as both an intravenous (IV) and oral tablet formulation for the treatment of ABSSSI. 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] A Phase 3 study was conducted to compare the efficacy and safety of IV DLX monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSIs. Study 302 demonstrated noninferiority of DLX to VAN/AZ for US and EMA endpoints of objective measurement and test of cure (TOC) clinical response. The various signs and symptoms of clinical response measurement for all patients are presented.

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 a stratified, randomized, double-blind Phase 3 global study (302).
- Patients had wounds, burns, major abscesses, or cellulitis of ≥75 cm^2 size; and at least 2 systemic signs of infections.
- DLX 300 mg IV q12 or VAN 15 mg/kg IV (actual body weight) with AZ was administered to patients for a total treatment duration of 5 – 14 days at the investigator's discretion.
- Enrollment was stratified by baseline infection type and prior antibiotic use 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).

ASSESSMENTS

- 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.
  - Erythema was measured by digital planimetry via photographs of the infection site using a digital camera at Screening, Day 1, Day 2, twice on Day 3 (prior to each dose), Day 4, Day 5, End of Treatment, Follow-up, and Late Follow-up.[2]
  - Signs and symptoms of ABSSSI, vital signs, and body temperature were assessed by the investigator at each visit and included drainage/discharge, erythema/extension of redness, fluctuance, heat/located warmth, swelling/induration, pain/tenderness, lymphangitis and lymphadenopathy. Cure was defined as complete resolution of all S&S, while Improved = some S&S persist but the patient no longer needed antibiotic therapy.
- For the Patient Reported Outcome (PRO) of pain, patients answered questions at each visit to assess their current level of pain related to the infection using the 11-point Numerical Rating Scale [NRS][3] which rates pain from 0 (no pain) to 10 (worst pain imaginable).
- Primary and secondary endpoint data for DLX vs. VAN/AZ have been presented previously.[4,5]

STATISTICAL METHODS

The Intent to Treat (ITT) analysis set included all patients who were randomly assigned to treatment and patients were analyzed according to the treatment they were assigned at randomization.

Descriptive statistics were presented for the screening measurements of the infection site using digital planimetry and manual measurements. The assessment of the actual infection site at baseline was summarized by treatment group and by type of ABSSSI infection for local signs.

In the analyses of erythema, if more than 1 measurement was taken between 48 to 72 hours (± 2 hours) after the first dose of study drug, the latest one was used for the time point of 48 to 72 hours (± 2 hours) after initiation of study drug. The areas of erythema as well as their reductions and percentage reductions from baseline, were summarized for each time point. Box-plots of the actual result and percentage reduction from baseline at each assessment were provided for erythema for the ITT. Additionally, Kaplan-Meier plots for the times to 20% reduction, 80% reduction, 100% reduction, and cessation of spread of erythema were presented for ITT. Each time to reduction was defined in days (or fractions thereof) as the date/time of the first digital planimetry meeting the reduction criterion, minus the date/time of the first dose of study drug. The date/time of cessation of spread of erythema was defined as the first time point after which there was no increase in area of erythema. Patients no longer at risk of an event were censored at the last time the patient was known to be at risk.

For the reduction in pain endpoint, the numeric rating scale was used. Mixed models repeated measures model for reduction in pain had baseline pain level as the covariate with visit, treatment, and treatment by visit as categorical factors and assumed an unstructured covariance matrix. The analysis included all treatment visit measurements, as well as EOT visit measurements, but the mean treatment difference was assessed and tested at EOT.

RESULTS

DEMOGRAPHICS

DLX patients received study drug for an average of 6.2 days. VAN/AZ patients received an average of 6.2 days of treatment and aztreonam for a mean of 2.5 days.

TABLE 1. SUMMARY OF BASELINE DEMOGRAPHICS FOR PATIENTS (ITT)

Baseline Characteristic	DLX N=331	VAN/AZ N=329
Age, years		
Mean (SD)	46.3 (13.91)	45.3 (14.44)
Median (Min, max)	47 (18, 94)	46 (19, 90)
Gender, n (%)		
Male	206 (62.2)	209 (63.5)
Female	125 (37.8)	120 (36.5)
Race, n (%)		
Black or African American	27 (8.2)	19 (5.8)
White	297 (89.7)	304 (92.4)
Other[a]	7 (2.1)	6 (1.8)
Hispanic or Latino, n (%)	101 (30.5)	103 (31.3)
Region, n (%)[b]		
Europe	63 (19.0)	55 (16.7)
North America	268 (81.0)	274 (83.3)
BMI (kg/m^2)		
Mean (SD)	28.4 (6.42)	27.9 (6.36)
Median (min, max)	27.2 (16.5, 52.0)	26.7 (17.3, 52.8)
Patients with diabetes, n (%)	30 (9.1)	27 (8.2)

a. American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, or other

b. Europe includes Croatia, Hungary, Israel, Latvia, Spain, and Ukraine. North America = United States.

TABLE 2. SUMMARY OF BASELINE LESION CHARACTERISTICS OF ABSSSI IN PATIENTS (ITT)

Baseline Characteristic	DLX N=331	VAN/AZ N=329
Baseline infection type, n (%)		
Cellulitis/erysipelas	128 (38.7)	128 (38.9)
Wound infection	116 (35.0)	116 (35.3)
Major cutaneous abscess	84 (25.4)	83 (25.2)
Burn infection	3 (0.9)	2 (0.6)
Anatomical site of infection n (%)		
Head/neck/face	12 (3.6)	12 (3.6)
Back	9 (2.7)	8 (2.4)
Thorax	9 (2.7)	8 (2.4)
Upper extremities	108 (32.6)	119 (36.2)
Lower extremities	135 (40.8)	131 (39.8)
Abdomen	21 (6.3)	13 (4.0)
Pubic/perineum/groin	6 (1.8)	6 (1.8)
Buttocks	34 (10.3)	38 (11.6)
Area baseline erythema (digital), cm^2	N= 326[a]	N=328[a]
Mean (SD)	294.8 (308.3)	319.1 (314.0)

a. 5 patients in DLX group and 1 patient in VAN/AZ group did not have baseline erythema measurements

TABLE 3. ASSESSMENT OF ACTUAL INFECTIOUS SITE AT BASELINE (ITT)

Presence of Local Sign, n (%)	DLX (N = 331)	VAN /AZ (N = 329)
Drainage/Discharge	209 (63.1)	207 (62.9)
Erythema/Extension of Redness	329 (99.4)	328 (99.7)
Fluctuance	175 (52.9)	179 (54.4)
Heat/Localized Warmth	328 (99.1)	326 (99.1)
Swelling/Induration	323 (97.6)	324 (98.5)
Pain/Tenderness	328 (99.1)	327 (99.4)
Lymphangitis	72 (21.8)	60 (18.2)
Lymphadenopathy	282 (85.2)	285 (86.6)

FIGURE 1. PROPORTION OF PATIENTS WITH COMPLETE RESOLUTION OF ALL LOCAL SIGNS AND SYMPTOMS PRESENT AT BASELINE (INVESTIGATOR-ASSESSED RESPONSE OF CURE FOR ITT)

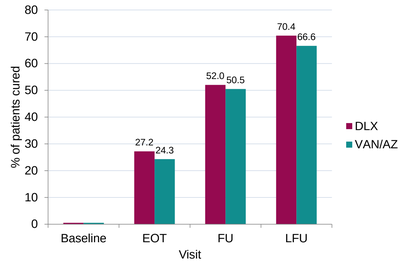


TABLE 4. REDUCTION IN PAIN REPORTED BY PATIENT USING NUMERIC RATING SCALE AT STUDY VISITS (ITT)

Visit	DLX N = 331	VAN/AZ N = 329	Change from Baseline for DLX	Change from Baseline for VAN/AZ
Baseline, n	309	309		
Mean (SD)	7.9 (2.02)	7.8 (2.16)	NA	NA
Median (Min, Max)	8.0 (0, 10)	8.0 (0, 10)		
End of Treatment, n	308	308	288	289
Mean (SD)	2.4 (2.77)	2.6 (2.83)	-5.4 (3.14)	-5.1 (3.18)
Median (Min, Max)	1.0 (0, 10)	2.0 (0, 10)	-6.0 (-10, 4)	-5.0 (-10, 5)
Follow-up, n	255	258	242	240
Mean (SD)	0.9 (1.93)	1.1 (2.12)	-6.9 (2.73)	-6.7 (2.60)
Median (Min, Max)	0.0 (0, 10)	0.0 (0, 10)	-7.0 (-10, 4)	-7.0 (-10, 1)
Late Follow-up, n	265	257	250	240
Mean (SD)	0.7 (1.93)	0.7 (1.68)	-7.1 (2.71)	-6.9 (2.75)
Median (Min, Max)	0.0 (0, 10)	0.0 (0, 10)	-8.0 (-10, 4)	-8.0 (-10, 6)

Note: SD = Standard Deviation, Scale 0 = no pain and 10 = worst pain imaginable

FIGURE 2. DIGITAL PLANIMETRY OF ERYTHEMA AT STUDY VISIT (ITT)

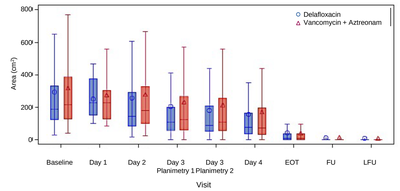


FIGURE 3. PERCENTAGE CHANGE FROM BASELINE IN DIGITAL PLANIMETRY OF ERYTHEMA AT STUDY VISIT (ITT)

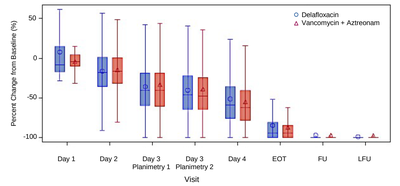


FIGURE 4A. TIME TO 20% REDUCTION OF ERYTHEMA

Note: All digital planimetry results are used, including unscheduled measurements.

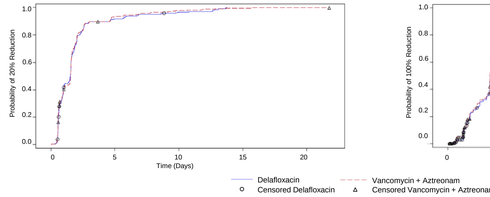
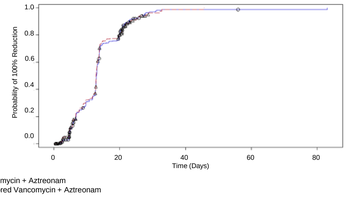


FIGURE 4B. TIME TO 100% REDUCTION OF ERYTHEMA



CONCLUSION

- Baseline demographics of age, gender, race, and ethnicity were similar between treatment arms. Patients were primarily North American, 28 kg/m^2 mean BMI, and 8-9% of patients were diabetic.
- Study 302 patients' infections were comprised of cellulitis, wound, and major abscesses of at least 75 cm^2 of erythema, and primarily were infections of the upper and lower extremities. The majority of patients had at least 3 systemic signs at baseline.
- DLX was comparable to VAN/AZ in resolution of all baseline symptoms at EOT, FU and LFU visits.
- Median baseline pain rated by patients using PRO was 8.0 for DLX and VAN/AZ, and decreased similarly to 0 at FU and LFU visits.
- Area of ABSSSI erythema measured with digital planimetry decreased similarly between DLX and VAN/AZ, resolving by FU and LFU visits.
- The time in days for DLX and VAN/AZ to achieve 20% and 100% reduction in erythema were nearly superimposable between treatment groups.
- Delafloxacin appears comparable to vancomycin/aztreonam in the reduction of the S&S of ABSSSI.

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