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RESOLUTION OF SIGNS AND SYMPTOMS (S&S) OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) WITH DELAFLOXACIN (DLX) IV/ORAL THERAPY

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INTRODUCTION

Delafloxacin is an anionic fluoroquinolone antibiotic that was recently approved in the US as an intravenous (IV) and oral tablet formulation for the treatment of ABSSSI. Delafloxacin 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 and oral delafloxacin monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSI[2]. Study 303 demonstrated noninferiority of delafloxacin 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.

METHODS

STUDY DESIGN

- Randomized, double-blind, Phase 3, multicenter study of IV/oral delafloxacin 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 (study 303)
- Patients were randomly assigned (1:1) to receive delafloxacin monotherapy or VAN 15 mg/kg (actual body weight) IV q12h with AZ 1-2 g IV q12h. Subjects received delafloxacin 300 mg IV BID for 3 days followed by a mandatory blinded switch to delafloxacin 450 mg PO BID
- Treatment was continued for 5-14 days at the investigators' discretion; aztreonam was discontinued in vancomycin arm once cultures confirmed no Gram-negative pathogens
- Enrollment was stratified by baseline infection type, BMI, and limited to 25% prior antibiotic use.
- Patients were evaluated at screening, daily on therapy, Followup (FU, Day 14±1), and Late Followup (LFU, Day 21-28)

ASSESSMENTS

- Efficacy was evaluated through assessments of the signs and symptoms of infection; measurement of lesion size by digital planimetry[3]; 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[3].
  - Signs and symptoms (S&S) 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 was defined as some S&S persist but the patient no longer needed antibiotic therapy.

METHODS

ASSESSMENTS (continued)

- 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][4] which rates pain from 0 (no pain) to 10 (worst pain imaginable).
- Primary and secondary endpoint data for delafloxacin vs. VAN/AZ have been presented previously (2,5).

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 analysis set. Additionally, Kaplan-Meier plots for the times to 20% reduction, 80% reduction, 100% reduction, and cessation of spread of erythema were presented for the ITT analysis set. 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

- Delafloxacin patients received study drug for an average of 7.3 days. VAN/AZ patients received an average of 7.0 days of treatment and aztreonam for a mean of 3.0 days.

RESULTS

TABLE 1: SUMMARY OF BASELINE DEMOGRAPHICS FOR PATIENTS ANALYSIS SET (ITT)

Baseline Characteristic	DLX N=423	VAN/AZ N=427
Age, years		
Mean (SD)	51.2 (16.0)	50.2 (16.0)
Median (Min, max)	51 (18, 89)	50 (19, 93)
Gender, n (%)		
Male	262 (61.9)	276 (64.6)
Female	161 (38.1)	151 (35.4)
Race, n (%)		
Black or African American	13 (3.1)	18 (4.2)
White	348 (82.3)	355 (83.1)
Other[a]	62 (14.7)	54 (12.6)
Hispanic or Latino, n (%)	132 (31.2)	99 (23.2)
Region, n (%)[b]		
Europe	165 (39.0)	173 (40.5)
North America	202 (47.8)	196 (45.9)
Asia	9 (2.1)	14 (3.3)
Latin America	47 (11.1)	44 (10.3)
BMI (kg/m^2)		
Mean (SD)	30.4 (7.4)	30.7 (7.5)
Median (min, max)	29.7 (15.3, 65.8)	30.0 (17.3, 68.0)
Patients with diabetes, n (%)	53 (12.5)	54 (12.6)

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

[b]Europe includes Latvia, Hungary, Estonia, Moldova, Romania, Bulgaria, Georgia. North America includes United States. Asia includes Taiwan, Korea. Latin America includes Peru, Argentina, Mexico, Chile, Brazil.

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

Baseline Characteristic	DLX N=423	VAN/AZ N=427
Baseline infection type, n (%)		
Cellulitis/erysipelas	202 (47.8)	206 (48.2)
Wound infection	111 (26.2)	112 (26.2)
Major cutaneous abscess	106 (25.1)	106 (24.8)
Burn infection	4 (0.9)	3 (0.7)
Anatomical site of infection, n (%)		
Head/neck/face	15 (3.5)	19 (4.4)
Back	11 (2.6)	12 (2.8)
Thorax	11 (2.6)	5 (1.2)
Upper extremities	106 (25.1)	97 (22.7)
Lower extremities	226 (53.4)	250 (58.5)
Abdomen	22 (5.2)	21 (4.9)
Pubic/perineum/groin	7 (1.7)	8 (1.9)
Buttocks	31 (7.3)	22 (5.2)
Area baseline erythema, digital (cm^2)		
	N= 421[a]	N=426[a]
Mean (SD)	341.5 (312.9)	364.4 (391.7)

[a] 2 patients in delafloxacin group and 1 patient in VAN/AZ group did not have baseline erythema.

TABLE 3: ASSESSMENT OF INFECTIOUS SITE AT BASELINE (ITT)

Presence of Local Sign, n (%)	DLX (N = 423)	VAN /AZ (N = 427)
Drainage/Discharge	270 (63.8)	264 (61.8)
Erythema/Extension of Redness	422 (99.8)	426 (99.8)
Fluctuance	184 (43.5)	206 (48.2)
Heat/Localized Warmth	421 (99.5)	423 (99.1)
Swelling/Induration	398 (94.1)	395 (92.5)
Pain/Tenderness	422 (99.8)	423 (99.1)
Lymphangitis	95 (22.5)	109 (25.5)
Lymphadenopathy	273 (64.5)	280 (65.6)

TABLE 4: REDUCTION IN PAIN REPORTED BY PATIENT USING NRS AT STUDY VISITS (ITT)

Visit	DLX N = 423	VAN/AZ N = 427	Change from Baseline for DLX	Change from Baseline for VAN/AZ
Baseline, n	422	426		
Mean (SD)	7.4 (2.3)	7.2 (2.4)	NA	NA
Median (Min, Max)	8.0 (0, 10)	8.0 (0, 10)		
End of Treatment, n	401	403	400	403
Mean (SD)	1.2 (1.9)	1.2 (2.0)	--6.2 (2.7)	--5.9 (2.8)
Median (Min, Max)	0 (0, 10)	0 (0, 10)	-6.0 (-10, 1)	-6.0 (-10, 2)
Follow Up, n	385	378	384	378
Mean (SD)	0.5 (1.3)	0.6 (1.5)	-6.8 (2.4)	-6.6 (2.7)
Median (Min, Max)	0.0 (0, 7)	0.0 (0, 10)	-7.0 (-10, 1)	-7.0 (-10, 0)
Late Follow up, n	376	373	375	373
Mean (SD)	0.3 (1.0)	0.3 (1.1)	-7.0 (2.4)	-6.8 (2.6)
Median (Min, Max)	0.0 (0, 7)	0.0 (0, 9)	-8.0 (-10, 0)	-7.0 (-10, 1)

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

FIGURE 1: DIGITAL PLANIMETRY OF ERYTHEMA AT STUDY VISIT (A) AND PERCENT CHANGE IN BASELINE ERYTHEMA AT STUDY VISIT (B) (ITT)

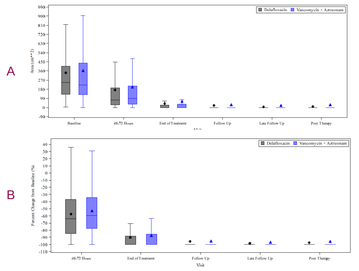
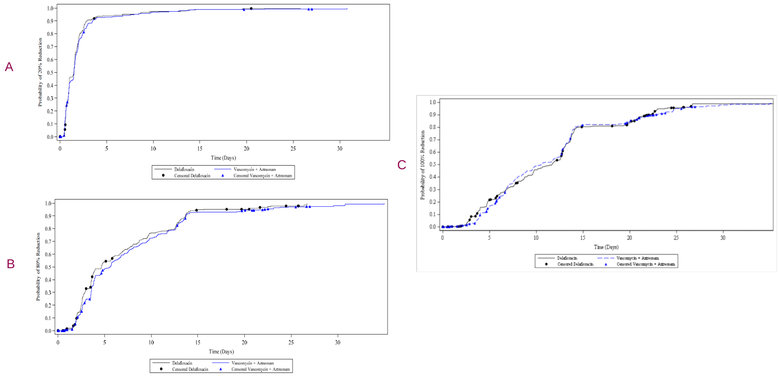


FIGURE 2: KAPLAN-MEIER PLOT OF TIME TO 20% (A), 80% (B) and 100% (C) REDUCTION OF ERYTHEMA (ITT)



CONCLUSION

- Baseline demographics of age, gender, race, and ethnicity were similar between treatment arms. Patients were primarily North American or European, 30 kg/m^2 mean BMI, and 12% of patients were diabetic.
- Study 303 patient 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 2 or more systemic signs at baseline.
- 43.6% of those administered DLX and 39.3% of the VAN/AZ group reported at least 1 adverse event. The most common adverse events for delafloxacin were nausea, diarrhea, headache[2].
- Delafloxacin was comparable to VAN/AZ in resolution of all baseline symptoms at EOT, FU and LFU visits.
- Median baseline pain rated by patients using a Patient Reported Outcome was ~7 for both delafloxacin and VAN/AZ, and decreased similarly to 0 by FU and LFU visits.
- Area of ABSSSI erythema, measured with digital planimetry, decreased similarly between delafloxacin and VAN/AZ resolving by FU and LFU visits.
- The time in days for delafloxacin and VAN/AZ to achieve 20%, 80% and 100% reduction in erythema were nearly superimposable.
- Delafloxacin is comparable to vancomycin/aztreonam in the reduction of the S&S of ABSSSI.

REFERENCES

1. Van Bambeke F. Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics, and clinical efficacy. *Future Microbiol.* 2015; 10:1111–1123.
2. O'Riordan W, McManus A, et al. A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin With Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Multinational, Double-Blind, Randomized Study. Clinical Infectious Diseases 2018; 67 (5): 657–666
3. Jaharis M, et. al. Evaluation of Digital vs. Manual Measures of Lesion Size in a Phase 3 Trial of Delafloxacin in Patients with Acute Bacterial Skin and Soft Tissue Infections (ABSSSI). IDWeek, New Orleans, LA; October, 2016.
4. 0–10 Numeric Pain Rating Scale: From McCaffery M, Pasero C. Pain: Clinical Manual, St. Louis, 1999, P. 16. Copyrighted by Mosby, Inc.
5. Pullman J, Gardovskis J, et al. Efficacy and Safety of Delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. Journal of Antimicrobial Chemotherapy 2017; 72 (12): 3471–3480