POSTER # 68

OBESE PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) HAVE DOUBLE THE RATE OF KEY COMORBIDITIES COMPARED TO NON-OBESE PATIENTS WHICH IMPACTS ANTIBIOTIC SELECTION

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ABSTRACT

Background: The successful management of ABSSSI requires prompt assessment and appropriate antibiotic therapy. Antibiotic selection requires consideration of patient comorbidities to ensure appropriate pathogen coverage and to avoid contraindications related to comorbidities and concomitant medications. Two global phase 3 ABSSSI trials (study 302 and 303), comparing delafloxacin (DLX), an anionic fluoroquinolone, to vancomycin/aztreonam (VAN/AZ), provide data to assess comorbidities that may impact antibiotic choice particularly in obese patients.

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 300mg q12h IV only; study 303 used IV DLX for 3 days with a mandatory blinded switch to DLX 450 mg oral q12h. 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 later timepoints.

Results: In the 2 studies, 1510 patients were randomized between the 2 groups (DLX or VAN/AZ) including 63% who were male. Mean age ~48 years. 69% of patients had pathogens identified at baseline; *S. aureus* (62%) was the most frequent isolate with MRSA seen in ~27%. Enterobacteriaceae were identified in ~10% of patients.

Overall, the pooled phase 3 population included subjects with vascular disease (29.0%), diabetes (11%), and cardiac disease (9.7%). Thirteen percent of subjects were >65 years of age, including 5.5% who were >75 years of age, and 16.2% of subjects had renal impairment (CrCl < 90ml/min). 42% of subjects were obese (BMI ≥ 30 kg/m^2). By medical history, the obese subjects had at least twice the rates of vascular disease, metabolism and nutrition disorders, and cardiac disease when compared to the non-obese subjects. Approximately 19% of the obese subjects were diabetic.

Conclusion: Subjects enrolled in the DLX phase 3 ABSSSI clinical program reflect the challenging ABSSSI patient population commonly seen in clinical practice today. Key patient populations included obese patients, diabetics, and the elderly due to their general risk of infection, including mixed infections. Patients with renal impairment provide challenges in antibiotic selection and dosing, especially when considering the monitoring requirements for vancomycin therapy, as well as the potential for adverse events (AEs) such as nephrotoxicity and infusion site and skin reactions. The obese population acts as natural aggregators of comorbidities and show twice the rate of comorbidities when compared to non-obese patients. These factors are important considerations in antibiotic selection.

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The successful management of ABSSSI requires prompt assessment and appropriate antibiotic therapy. Antibiotic selection requires consideration of patient comorbidities to ensure appropriate pathogen coverage and to avoid contraindications related to comorbidities and concomitant medications.

Delafloxacin (DLX) is an IV and oral investigational anionic fluoroquinolone antibiotic which is being studied in 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] The IV and oral dosage forms of DLX provide comparable exposure which allows IV to oral switch. Two global phase 3 ABSSSI trials (study RX-3341-302 and -303) comparing DLX to vancomycin/aztreonam (VAN/AZ), provide data to assess comorbidities that may impact antibiotic choice particularly in obese 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 IV 300mg/450mg oral q12h 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, DLX treated subjects received DLX 300 mg IV q12h for the entire study.[2]
  - 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.[3]
- Patients were evaluated at screening, daily on therapy, FU (Day 14±1), and LFU (Day 21-28).
- Medical and surgical history was recorded at screening and included clinically significant medical or surgical history ongoing at baseline or with onset in the previous 2 years. Patients with end-stage renal disease were excluded from the study.
- Efficacy was evaluated through assessments of signs and symptoms; digital planimetry measurement of lesion size; and culture and susceptibility testing of bacterial isolates.

ENDPOINTS

- Analysis sets: Intent to Treat (ITT): all patients randomized; clinically evaluable (CE): patients completing as per protocol; Microbiologically evaluable (ME): CE patients with eligible pathogens.
- 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).

MATERIALS AND METHODS

- Additional efficacy endpoint: Microbiological response (documented or presumed eradication) for patients in the ME analysis sets were based on results of baseline and post-baseline cultures (FU) and susceptibility testing, together with the clinical response assigned by investigators.
- Medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Medical and surgical history was summarized by system organ class (SOC) and preferred terms (PT) and characterized for the overall, obese and non-obese populations.

STATSTICAL 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 for the investigator assessed responses at FU and LFU; DLX was noninferior to VAN/AZ for ABSSSIs if lower limit of 2-sided 95% CI exceeded −0.10;

ANALYSIS POPULATION

- Pooled Phase 3 Intent-to-treat (ITT) population.

RESULTS

RESULTS IN POOLED PHASE 3 DATA

In the 2 studies, 1510 patients were randomized between the 2 groups (DLX or VAN/AZ) including 63% who were male. Mean age ~49 years **(Table 1)**. 69% of patients had pathogens identified at baseline. In the 1042 patients with pathogens identified, *S. aureus* (62%) was the most frequent isolate with MRSA seen in ~27%. Enterobacteriaceae were identified in ~10% of patients.

Overall, the pooled phase 3 population included subjects with vascular disease (29.0%), diabetes (11%), and cardiac disease (9.7%) **(Table 2)**.

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN DELAFLOXACIN PHASE 3 STUDIES

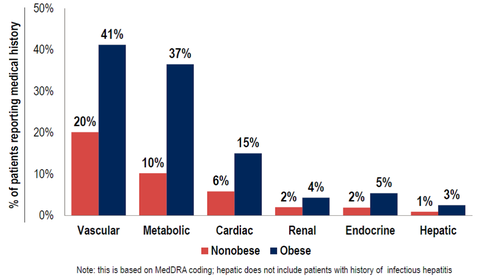
Characteristic	DLX (N=754)	VAN/AZ (N=756)
BMI ≥ 30 kg/m^2	331 (43.9)	308 (40.7)
Age, years		
Mean (SD)	49.0 (15.3)	48.1 (15.5)
Median (min, max)	49.0 (18, 94)	48.0 (19, 93)
Sex, n (%)		
Male	468 (62.1)	485 (64.2)
Female	286 (37.9)	271 (35.8)
Baseline infection type, n (%)		
Cellulitis/erysipelas	330 (43.8)	334 (44.2)
Wound infection	227 (30.1)	228 (30.2)
Major cutaneous abscess	190 (25.2)	189 (25.0)
Burn infection	7 (0.9)	5 (0.7)
History of diabetes, n (%)	83 (11.0)	81 (10.7)

RESULTS

Thirteen percent of subjects were >65 years of age, including 5.5% who were >75 years of age, and 16.2% of subjects had renal impairment (CrCl < 90ml/min). 42% of subjects were obese (BMI ≥ 30 kg/m^2) **(Table 1)**. By medical history, the obese subjects had at least twice the rates of vascular disease, metabolism and nutrition disorders, cardiac disease, endocrine disorders and renal disorders when compared to the non-obese subjects Approximately 19% of the obese subjects were diabetic **(Figure 1 and Table 2)**.

DLX IV/oral monotherapy provided outcomes comparable to the IV combination of VAN/AZ in the various patient subgroups **(Table 3)**. The most common adverse events for DLX-treated patients were mild to moderate gastrointestinal complaints and disorders which did not routinely lead to discontinuations. There was no increase in glucose or liver function test (LFT) abnormalities on DLX compared to VAN/AZ.[2,3]

FIGURE 1: CONTRAST IN BASELINE MEDICAL HISTORY IN OBESE COMPARED TO NON-OBESE PATIENTS FROM POOLED PHASE 3 ABSSSI TRIALS



Note: this is based on MedDRA coding; hepatic does not include patients with history of infectious hepatitis

TABLE 3: CLINICAL SUCCESS AT FU IN PATIENT SUBGROUPS IN POOLED PHASE 3 POPULATION (ITT)

Population	DLX (300 mg IV and 450 mg Oral)	VAN/AZ 15 mg/kg + Aztreonam IV
	n/N (%)	n/N (%)
Overall success at FU	639/754 (84.7)	636/756 (84.1)[2,3]
Diabetes mellitus	71/83 (85.5)	68/81 (84.0)[4]
No diabetes mellitus	568/671 (84.6)	568/675 (84.1)
≤ 65 years of age	550/653 (84.2)	551/661 (83.4)[5]
> 65 years of age	89/101 (88.1)	85/95 (89.5)
BMI ≥ 30 kg/m^2	285/331 (86.1)	262/308 (85.1)[6]
BMI < 30 kg/m^2	354/423 (83.7)	374/448 (83.5)
Renal impairment*	107/122 (87.7)	108/122 (88.5)[7]
No renal impairment	525/618 (85.0)	522/627 (83.3)

* Calculated CrCl <90mL/min

TABLE 2: BASELINE MEDICAL HISTORY FROM POOLED PHASE 3 STUDIES*

All Patients Regardless of Treatment, Pooled Phase 3 Safety Analysis Set			
Characteristic	OVERALL (N = 1510) n (%)	NON-OBESE (N = 871) n (%)	OBESE (N=633) n (%)
Vascular Disorders	438 (29.0)	175(20.1)	263 (41.2)
Metabolism and Nutrition Disorders	320 (21.2)	88 (10.1)	232 (36.3)
Nervous System Disorders	259 (17.2)	166 (19.1)	93 (14.6)
Musculoskeletal and Connective Tissue Disorders	225 (14.9)	123 (14.1)	102 (16.0)
Immune System Disorders	194 (12.8)	138 (15.8)	56 (8.8)
Gastrointestinal Disorders	187 (12.4)	100 (11.5)	87 (13.6)
Cardiac Disorders	146 (9.7)	51 (5.9)	95 (14.9)
Respiratory, Thoracic and Mediastinal Disorders	135 (8.9)	71 (8.2)	64 (10.0)
Skin and Subcutaneous Tissue Disorders	86 (5.7)	48 (5.5)	38 (5.9)
Blood & Lymphatic System Disorders	60 (4.0)	36 (4.1)	24 (3.8)
Endocrine Disorders	52 (3.4)	18 (2.1)	34 (5.3)
Renal and Urinary Disorders	45 (3.0)	17 (2.0)	28 (4.4)
Neoplasms (Benign or Malignant)	40 (2.6)	25 (2.9)	15 (2.3)
Hepatobiliary Disorders	24 (1.6)	8 (0.9)	16 (2.5)

* Based on MedDRA coding 16.1, listed in descending order in the overall population

CONCLUSION

DISCUSSION/CONCLUSIONS

Subjects enrolled in the DLX phase 3 ABSSSI clinical program reflect the challenging ABSSSI patient population commonly seen in clinical practice today. When selecting an appropriate antibiotic for patients with ABSSSI, the prescribing physician has to consider a number of issues including potential pathogens, the patient's comorbid conditions, concomitant medications, and challenges for drug administration. While most ABSSSIs are associated with Gram-positive pathogens, some patient profiles require consideration of Gram-negative pathogens when selecting initial empiric therapy. Key patient populations include obese patients, diabetics, and the elderly due to their general risk of infection, including mixed infections. Patients with renal impairment provide challenges in antibiotic selection and dosing, especially when considering vancomycin with its requirement for therapeutic monitoring, as well as the potential for AEs such as nephrotoxicity and infusion site and skin reactions.

The obese population acts as a natural aggregator of comorbidities and shows twice the rate of comorbidities compared to non-obese patients. These factors are important considerations in antibiotic selection. IV/oral DLX may offer a treatment option for these patients.