POSTER EV0435

PATIENTS TOLERATE SWITCH FROM IV TO ORAL ANTIBIOTICS IN ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) EARLIER THAN EUROPEAN PHYSICIANS MAY PREDICT

ECCMID 2017
Vienna, Austria
April 22-25th

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INTRODUCTION

A key parameter in antibiotic stewardship is the daily patient assessment for potential switch from IV to oral antibiotics to facilitate earlier hospital discharge.[1] The evaluating physician must recognize the readiness of their patient to make that switch.

Delafloxacin (DLX) is an IV and oral investigational anionic fluoroquinolone antibiotic which is being studied in treatment of acute bacterial skin and skin structure infections (ABSSSIs). Two randomized, double-blind Phase 3 studies have been completed (Study 302 and 303). DLX has excellent *in vitro* activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) while retaining good activity against Gram-negative organisms.[2] The IV and oral dosage forms of DLX provide comparable exposure which allows IV to oral switch. We compared the physician's perception readiness for IV to oral switch versus reality, using European data collected in a double-blind, double dummy phase 3 ABSSSI trial (study 303) of IV and oral DLX vs IV vancomycin/aztreonam (VAN/AZ).

METHODS

STUDY DESIGN

- Two 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 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; AZ was discontinued in VAN arm once cultures confirmed no Gram-negative pathogens;
  - In study 302, DLX treated subjects received DLX 300 mg IV q 12h for the entire study.[3]
  - In study 303, subjects received DLX 300 mg IV q 12h for 3 days followed by a mandatory blinded switch to DLX 450 mg PO q 12h.[4]

REFERENCES

1. NICE guidelines, Antimicrobial stewardship: Systems and processes for effective antimicrobial medicine use; August 2015, https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-1837273110469.
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4. O'Riordan W, et al. A global phase 3 study of delafloxacin (DLX) compared to vancomycin/aztreonam (VAN/AZ) in patients with acute bacterial skin and skin structure infections (ABSSSI). Poster presented at ID Week 2016, New Orleans.
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METHODS

- A double blind/double dummy design dictated patients in study 303 DLX arm received IV throughout (IV placebo was given after the switch to oral in the DLX arm).
- 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.

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) and LFU (Day 21 to 28);
- Time to the investigator perception that the patient could switch to oral was assessed with daily recording of blinded investigator's perception of patient readiness. Investigators were asked: *If an oral formulation was available for this patient, would you feel comfortable switching this patient today?*

ANALYSIS

- The time for switch to oral is defined as the first time point when the investigator was comfortable switching a patient to oral dosing.
- The time point for each assessment is based on the study day relative to the first dose day and the actual dose (first/second) on each study day.
- The proportion of EU patients in DLX arm, who the investigator believed were not ready to be switched to oral DLX in study 303 are displayed by each study day and the dose of each day.
- Analysis sets: ITT: all patients randomized; Clinically evaluable (CE): patients completing protocol activities; Microbiologically evaluable (ME): CE patients with eligible pathogen.

RESULTS

RESULTS IN EUROPEAN PATIENTS IN POOLED PHASE 3 Data

Of the 1510 patients randomized in the two Phase 3 studies 302 and 303, 456 patients were from Europe. 52% of patients were male; the average patient age was ~57 years. The most commonly identified pathogen was *S. aureus* seen in ~43% of patients with eligible pathogens. The median duration of exposure to study drug in both treatment arms was 7 days. Those in the VAN/AZ received AZ for a mean of 3.6 days.

RESULTS

In European patients, as in the overall population, DLX IV/oral was comparable to VAN/AZ in the early Objective Response and in investigator-assessed response of success (Cure or Improved) at both FU and LFU. This was evident in the ITT and CE populations **(Table 1)**. The most common adverse events for DLX treated patients were mild to moderate gastrointestinal complaints and disorders. More detailed patient description and outcomes in European patients are reported in ECCMID POSTER P1352 presented at this meeting.

EUROPEAN PATIENTS IN STUDY 303

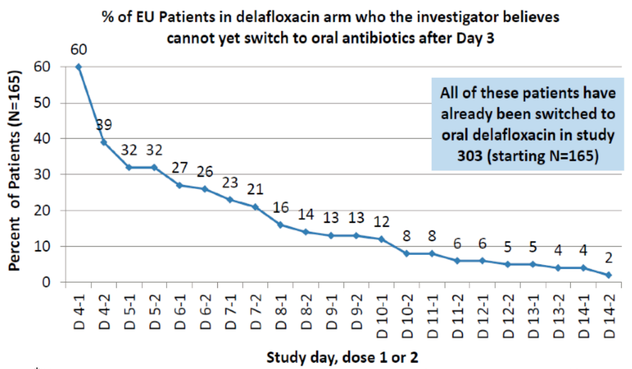
Investigator perception of patient readiness for switch to oral therapy was assessed in study 303. Average days of therapy overall was 8 days. Those in the VAN/AZ received AZ for a mean of 3.5 days.

TABLE 1: OUTCOMES IN EUROPEAN PATIENTS IN STUDIES 302 AND 303.

European Patients*		STUDY 302 (IV DLX only)		STUDY 303 (IV DLX with mandatory switch at day 3 to oral DLX)	
Key Endpoints		**DLX n/Total (%)**	**VAN/AZ n/Total (%)**	**DLX n/Total (%)**	**VAN/AZ n/Total (%)**
Objective Response 48-72h	ITT	46/63 (73.0%)	40/55 (72.7%)	132/165 (80.0%)	134/173 (77.5%)
	CE	46/61 (75.4%)	40/53 (75.5%)	131/161 (81.4%)	129/165 (78.2%)
Investigator-Assessed Success (FU)	ITT	58/63 (92.1%)	48/55 (87.3%)	152/165 (92.1%)	158/173 (91.3%)
	CE	52/53 (98.1%)	40/41 (97.6%)	143/146 (97.9%)	142/149 (95.3%)
Investigator-Assessed Success (LFU)	ITT	58/63 (92.1%)	49/55 (89.1%)	147/165 (89.1%)	153/173 (88.4%)
	CE	55/56 (98.2%)	44/44 (100%)	133/137 (97.1%)	141/149 (94.6%)

*Latvia, Hungary, Estonia Moldova, Ukraine, Romania, Bulgaria, Georgia, Spain, Croatia, and Israel

FIGURE 1: INVESTIGATOR ASSESSMENT OF PATIENT READINESS FOR IV TO ORAL SWITCH. STUDY 303.*



*165 patients who were randomized to DLX group were from Europe, 47% male, average age was 60 years. 61%, 18%, 19% in DLX group had cellulitis, major abscess or wounds respectively, most commonly on the lower extremities (67%). Most commonly identified pathogen was *S. aureus* seen in 41% of patients with eligible pathogens.

Since all DLX patients were switched to oral after day 3 (after 6 IV doses) in a blinded fashion, physicians were not aware which patients switched. When asked daily if they would be comfortable switching the patient to oral therapy, some physicians felt that some patients should remain on IV therapy through day 14 (**Figure 1**). However, all of these patients had been switched to oral on day 4.

CONCLUSION

DISCUSSION/CONCLUSIONS

- Antibiotic stewardship has a goal of appropriate use of antibiotics that can be realized in part by facilitating changes in prescribing practice which may help slow the emergence of antimicrobial resistance, result in the safer use of antibiotics and improve patient outcomes.[1]
- Switching to oral therapy as soon as possible may facilitate discharge, and decrease complications from continued IV access
- In Study 303, all patients were switched to oral DLX on study day 4. However physicians were blinded to this since all patients also continued to receive IV placebo in the DLX arm.
- Physicians believed that ~20% of patients needed longer IV therapy beyond 7 days, whereas the patients appeared to do well on the oral switch.
- Based on clinical outcomes, it appears that the patients in study 303 with the mandated oral switch had similar outcomes to patients that were on IV DLX for the entire treatment course in study 302.
- These data support an earlier switch from IV to oral.
- The reasons for physician's reluctance to switch to oral can be manifold. Further investigation and subsequent training may lead to earlier IV to oral switch in the hospital setting.