Figure 1. Cumulative incidence of premature discontinuation of AFP by D+100

Figure 2. Transaminases at baseline, end of treatment (EOT), EOT +7 days and EOT +14 days in ICZ- and VCZ cohorts

Conclusion. There was less premature discontinuation and hepatotoxicity with ICZ AFP, but no increase in IFI or death compared to VCZ AFP in allogeneic HCT pts.

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1292. Safety Profile of the Novel Siderophore Cephalosporin Cefiderocol in Randomized Phase 2 and Phase 3 Clinical Studies of Serious Gram-Negative Infections

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Session: P-58. Novel Agents

Background. Cefiderocol (CFDC), the first siderophore cephalosporin, is approved in the United States (complicated urinary tract infections (cUTI)) and Europe for the treatment of patients with Gram-negative (GN) infections with limited treatment options.
Methods. This analysis investigated the safety profile of CFDC across three prospective, multicenter, randomized clinical studies: APEKS-cUTI (double-blind, non-inferiority Phase 2 study in patients with cUTI) vs imipenem-cilastatin (1 g/1 g, three-times daily); APEKS-NP (double-blind, non-inferiority Phase 3 study in patients with nosocomial pneumonia [NP]) vs meropenem (2 g, q8h); CREDIBLE-CR (open-label, descriptive Phase 3 study in patients with cUTI, NP, bloodstream infections/sepsis [BSI/sepsis]) caused by carbapenem-resistant GN bacteria; patients in the control arm received best available therapy (BAT, up to 3 agents, dosing based on local label). CFDC was given at 2 g, q8h, infused over 1 (APEKS-cUTI) or 3 (APEKS-NP; CREDIBLE-CR) hours. One adjunctive agent with CFDC was only allowed in CREDIBLE-CR.

Results. 549 patients were treated with CFDC, 347 control treated (Table 1). More than 50% of patients were aged ≥65 years, except BAT arm in CREDIBLE-CR. The majority of patients were admitted to the ICU in APEKS-NP and CREDIBLE-CR. The median treatment duration with CFDC was similar (9–11 days) across studies. The rates of TEAEs and serious AEs (SAEs) between CDFC and comparators were similar in each study (Table 2). The rates of adverse drug reactions were lower with CFDC than with comparators in each study, with a greater difference in CREDIBLE-CR than in APEKS-cUTI and APEKS-NP. TEAEs leading to death are shown in Table 2. Eight CFDC-related Clotrimazole infections occurred across studies (APEKS-cUTI: n=1; APEKS-NP: n=4; CREDIBLE-CR: n=3 [ie, C. difficile colitis; pseudomembranous colitis]). In total, eight experienced seizures (APEKS-cUTI: CFDC: n=1; APEKS-NP; CFDC: n=3; meropenem n=2; CREDIBLE-CR: CFDC: n=1; BAT, n=1), none of which were related to study drugs. Parameters of iron homeostasis showed no differences between CDFC and comparators.

Table 1. Baseline characteristics and treatment duration (safety populations)

| Study                | n (N) | Male | Age (years, median) | Median treatment duration (days) |
|---------------------|-------|------|---------------------|---------------------------------|
| APEKS-cUTI          | 159   | 110  | 70 (26-92)          | 10 (7-12)                       |
| APEKS-NP            | 109   | 64   | 69 (26-95)          | 12 (10-15)                      |
| CREDIBLE-CR         | 176   | 111  | 73 (26-96)          | 9 (7-11)                        |

Table 2. Overall safety parameters (safety populations)

| TEAEs, n (%) | APEKS-cUTI (NCT02165188) | APEKS-NP (NCT02718366) | CREDIBLE-CR (NCT02718366) |
|-------------|---------------------------|-------------------------|---------------------------|
| Dose-related | 20 (32)                   | 28 (30)                 | 30 (34)                   |
| Drug-related | 15 (24)                   | 10 (10)                 | 17 (20)                   |

Conclusion. CFDC demonstrated a comparable safety profile to carbapenems or other cephalosporins and was generally well tolerated in critically ill patients.

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1294. A survey on Vancomycin and Beta Lactams usage in critical care settings in Makkah, Kingdom of Saudi Arabia

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Session: S-59. PK/PD studies

Background. Drug pharmacokinetics/pharmacodynamics (pk/PD) play a vital role in the dose optimization of antimicrobials to maintain target effective plasma concentrations. Pharmacokinetics parameters e.g., Volume of distribution, clearance, half-life are highly variable in Critically ill patients, therefore require a patient-specific approach to maximize antimicrobials’ clinical effectiveness.

The percentage of the dosing interval to ensure free plasma concentration more than MIC is an evidence-based approach to achieve pharmacodynamic targets among critically ill patients. Therefore, using Extended and continuous infusions of Vancomycin and Beta lactams will optimize therapy by promising more time for free plasma concentration above MIC in treatment.

Results. The response rate was 95%, as the survey was distributed electronically before the dose optimization workshop conducted at each hospital. The majority (72.5%) of the intensivists were using only extended infusion for Meropenem in practice. Interestingly, none of the hospitals was familiar with the pk/PD target for vancomycin and beta lactams.

Conclusion. This survey concludes the requirement of a dose optimization policy for beta lactam and vancomycin in critical settings by utilizing extended/continuous infusion.

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1295. Activity of SPR206, a Polymyxin B Derivative, Compared to Colistin Alone and in Combination Against Multidrug-Resistant Pseudomonas aeruginosa Strains

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Session: S-59. PK/PD studies

Background. The emergence of multidrug-resistant (MDR) Pseudomonas aeruginosa (PA) has resulted in the use of previously discarded antibiotics, such as the polymyxins (polymyxin B and colistin [COL]). Consequently, the polymyxins are currently being established, quantitative, prevalence-based data are not yet available. Therefore, the potency of SUL-DUR was determined against 190 recent, diverse Ab clinical isolates from this region.

Methods. 190 Ab isolates were collected between 2016 - 2018 from medical centers located in Israel (N = 47), Jordan (N = 36), Qatar (N = 13), Kuwait (N = 42), Lebanon (N = 8), Saudi Arabia (N = 24) and United Arab Emirates (N = 20). Seventy-five percent and 20.5% of these isolates were from respiratory and blood stream infections, respectively. Susceptibility to SUL-DUR and comparator agents was performed according to CLSI guidelines, and data analysis was performed using CLSI and EUCAST breakpoint criteria where available.

Results. This collection of isolates was 86% carbapenem-resistant and 90% sulbactam-resistant (based on a breakpoint of 4 mg/L). The addition of SUL-DUR fixed at 4 mg/L decreased the sulbactam MIC90 from 64 mg/L to 4 mg/L. Only 3 isolates (1.6%) had SUL-DUR MIC values of > 4 mg/L. This potency was consistent across countries, sources of infection and subsets of resistance phenotypes.

Conclusion. SUL-DUR demonstrated potent antibacterial activity against recent clinical isolates of Ab from the Middle East, including MDR isolates. These data support the global development of SUL-DUR for the treatment of MDR Ab infections.

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