O245
Oral Session
New old antibiotics: safety and efficacy

SAFETY OF DAPTOMYCIN AT DIFFERENT DOSES: RESULTS FROM EU-CORE^SM AND FROM POST-MARKETING SURVEILLANCE

K. Malizos[1], R. Utili[1], P. Gargalianos-Kakolyris[1], G. Dalekos[1], R.A. Seaton[1], P. Dohmen[1], S. Titaevski[1], K. Bouylout[1], A. Trylesinski[1]

[1]on behalf of the EU-CORE^SM Study Group, Basel, Switzerland

Objectives: Daptomycin is approved for treatment of Gram-positive complicated skin and soft tissue infections (cSSTI) and for treatment of right sided endocarditis (RIE) and bacteraemia by *Staphylococcus aureus*. Daptomycin antibacterial activity is dose dependent, and guidelines recommend higher than approved doses for difficult-to-treat infections[1]. Here we evaluate safety of daptomycin at different dose levels based on European Cubicin® Outcomes Registry (EUCORE^{SM}) data and on spontaneous post-marketing surveillance adverse event (AE) reports.

Methods: EU-CORE^{SM} is a multicentre, retrospective, non-interventional registry, describing patients treated with daptomycin in clinical practice. Data were analysed for patients receiving at least 1 dose of daptomycin between January 2006 and April 2012; and safety assessed until 30 days post-treatment. Safety data were evaluated for the following doses: 4-6mg/kg, >6-<=8 mg/kg, >8-<=10 mg/kg and >10 mg/kg. In addition, Novartis safety database was searched for any spontaneous reports of daptomycin use at doses >=6 mg/kg.

Results: 5407 of the 5551 patients (62% male) from the registry had evaluable dosing information. Patient characteristics and demographic data for the different dose groups are shown in the table below. 19% of patients received higher than the approved daptomycin doses (>6 mg/kg). The most common infection for doses <=8 mg/kg was cSSTIs (33%), while foreign body/prosthetic infection (22%) and endocarditis (20%) were most common for doses >8 mg/kg. Most frequent primary pathogen was *S. aureus* for doses <=10 mg/kg and coagulase-negative staphylococci for >10 mg/kg. There were few daptomycin-related AEs (table below), with the highest number (9% AEs and 2% SAEs) observed at doses >8–<=10 mg. CPK increases related to daptomycin were reported in 0.7% patients at doses <=8 mg/kg and in 4% of patients at >8–<=10 mg. Reports on musculoskeletal events and nervous system disorders were rare with no obvious dose-relationship.
Post-marketing surveillance (cut-off 13 September 2013) revealed 268 spontaneous reports (84 for 6–<8 mg/kg, 107 for 8–<10 mg/kg, 47 for 10 mg/kg, and 30 for >10 mg/kg). This includes CPK increases in 4 patients at 6–<8 mg/kg, and in 9 patients each at doses of 8–<10 mg/kg and 10 mg/kg. Rhabdomyolysis was reported in 3 patients at 6–<8 mg/kg daptomycin and peripheral neuropathy in 2 patients at 10 mg/kg. Furthermore there were 2 reports each of eosinophilic pneumonia at the doses 8-<10 mg/kg and at > 10 mg/kg.

Conclusions: Although data from EUCORE^{SM} revealed a trend-wise increase in the number of AEs and SAEs with increasing doses, daptomycin was generally well tolerated at all dose levels and there were no new or unexpected safety findings at doses >6 mg/kg, including data from post-marketing surveillance. 1. Catherine L *et al.* Clin Infect Dis. 2011;52(3):e18–55.

Parameters*	4-6 mg/kg	>6 to <=8 mg/kg	>8 to <=10 mg/kg	>10 mg/ kg
Patients (n)	4391	718	264	34
Age (years), Mean±SD	60±17	60±19	57±20	56±24
>=65 years, n (%)	2000 (46)	331 (46)	112 (42)	13 (38)
Most common infections, n (%)				
cSSTI	1529 (35)	156 (22)	32 (12)	3 (9)
Bacteraemia	885 (20)	129 (18)	48 (18)	2 (6)
Endocarditis	397 (9)	93 (13)	54 (21)	7 (21)
Foreign body/prosthetic	368 (8)	110 (15)	60 (23)	6 (18)
Osteomyelitis	240 (6)	103 (14)	35 (13)	12 (35)
Most common primary pathogens, n (%)				
S. aureus	1198 (43)	199 (42)	88 (44)	6 (27)
CoNS	781 (28)	136 (28)	74 (37)	10 (45)
Enterococci	329 (12)	67 (14)	18 (9)	3 (14)
AEs possibly related to daptomycin, n (%)	116 (3)	41 (6)	23 (9)	0
CPK elevation	28 (0.6)	5 (0.7)	10 (4)	0
Musculoskeletal and connective tissue disorders	8 (0.2)	3 (0.4)	1 (0.4)	0
Nervous system disorders	7 (0.2)	2 (0.3)	0	0
Eosinophilic pneumonia	2 (0.0)	0	0	0
SAEs possibly related to daptomycin, n (%)	24 (0.5)	14 (2)	5 (2)	0

AE, adverse events; cSSTI, complicated skin and soft tissue infection; CoNS, coagulase-negative staphylococci; SAE, serious adverse events; *S. aureus, staphylococcus aureus*
* The table includes data from EU-CORE^{SM}