Daptomycin (Cubicin) in patients with complicated skin or soft-tissue infections

BRIEF DRUG PROFILE

Edited by AdRes Health Economics & Outcomes Research

Last revision June 2008

INTRODUCTION

Skin and soft-tissue infections (SSTIs) are commonly observed and differ in terms of site and localization, clinical characteristics, and the aetiological agent; these infections are usually caused by *Staphylococcus aureus* or beta-haemolytic streptococci, and are the most frequent forms of methicillin-resistant *S. aureus* (MRSA) infections. SSTIs are considered complicated if they involve deeper skin structures (fascia or muscle layers), require significant surgical intervention or arise in the presence of significant co-morbidity. The progressive increase of bacterial resistance, in particular for Gram-positive bacteria infections, to currently used agents is a serious and growing problem, and in particular MRSA, GISA (glycopeptides-insusceptible *S. aureus*), VRE and GRE (glycopeptides-resistant enterococci) are of concern. There is, therefore, a need for additional agents active against these difficult-to-treat pathogens.

INDICATIONS AND DOSING

Daptomycin (DPT) is a novel macrocyclic lipopeptide antibiotic for the treatment of complicated skin and soft-tissues infections caused by multi-resistant gram-positive bacteria. The drug is derived from a natural product of *Streptomyces roseosporus*, and is active against methicillin-resistant staphylococci and vancomycin-resistant enterococci. Recently, DPT obtained the indication for *Staphylococcus aureus* bacteraemia (SAB) when associated with right-sided infective endocarditis (RIE) or with SSTIs, and for RIE due to *Staphylococcus aureus*. DPT is approved at the recommended dose of 4 mg/kg for SSTIs and at a higher dose for bacteraemia or endocarditis (6 mg/kg), and must be administered as a single daily dose for 7-14 days or until the infection is resolved. The drug is active against Gram-positive bacteria only; if mixed infection (Gram-negative or anaherobic bacteria) is suspected, it should be co-administred with appropriate antibacterial agents. This drug is currently included by AIFA (Agenzia Italiana del Farmaco) in a drug efficacy and safety monitoring program.

PHARMACOKINETICS

DPT is prevalently excreted by the kidneys: therapeutic response and renal function should be closely monitored in patients with renal insufficiency, and dosage adjustment is needed if Ccr is less than 30 ml/min. There is no evidence of hepatic metabolism with involvement of CYP450 enzymes, or of biological activity for metabolites.

PHARMACODYNAMICS

DPT exerts its antibiotic action by inserting into the cytoplasmic membrane of Gram-positive bacterial cells and causing the dissipation of membrane electrical potential, which results in

Absorption and distribution			
Cmax	**Tmax**	**Binding to plasma proteins**	**Volume of distribution**
54.6 mg/l (10.0)	0.5 (0.5) h	90-95%	0.093 (12.1) l/kg
Elimination			
Systemic clearance	**Plasma terminal half-life**	**Elimination**	**Interactions**
9.6 (13.5) ml/h/kg	7.4 (12.3) h	78% urine, 5.7% faeces	HMG-CoA reductase inhibitors, tobramycin

Table I
Mean (%CV) value for absorption, distribution, metabolism and elimination of DPT after administration of a single dose

Address for correspondence
sdp@advancedresearch.it

Study	Design	Comparator	Efficacy (% clinical success)	Safety
DAP-SST-9801	547 patients with diagnosis of SSTIs. Multicenter (USA + South Africa), randomized 1:1, single-blind study	DPT 4 mg/kg once daily (265 pt) vs SSP* (4-12 g iv once daily) or VNC (1 g iv every 12 h)	**MITT**: 67% DPT (N = 209), 67% COMP (N = 212) **CE**: 75% DPT (N = 140), 75% COMP (N = 142)	20% pt in DPT group and 19% in the comparative group had drug-related adverse effects (in both groups: 7% gastrointestinal disorders, 2% nausea or diarrhea, 1% vomit or constipation)
DAP-SST-9901	571 patients with diagnosis of SSTIs. Multicenter (39 European sites), randomized 1:1, single-blind study	DPT 4mg/kg once daily (269 pt) vs SSP* (4-12 g iv once daily) or VNC (1g iv every 12 h)	**MITT**: 84.5% DPT (N = 140), 83.9% COMP (N = 142) **CE**: 88.6% DPT (N = 209), 89.7% COMP (N = 212)	

Table II

Summary of main studies investigating efficacy and safety of daptomycin in patients with skin or soft-tissues infections

* nafcillin, cloxacillin, fluxloxacillin or oxacillin

CE = clinically evaluable population; COMP = comparator; DPT = daptomycin; MITT = Modified Intent-To-Treat population; SSP = penicillase-resistant penicillins; VNC = vancomycin

bacterial cell death. Bactericidal activity is concentration-dependent against *S. aureus* and vancomycin-resistant enterococci; there is also a concentration-dependent post-antibiotic affect against *E. faecalis* and *S. aureus.*

EFFICACY AND SAFETY

Efficacy and safety of DPT in SSTIs were compared with those of conventional antibiotics in two pivotal studies having similar but not identical design, including patients with SSTIs suspected to be due to Gram+ bacteria. One of them was conducted in USA and South Africa, and the other prevalently in European countries.

The appropriate comparator (penicillase-resistant penicillins or vancomycin) was choosed prior to randomization; both protocols provided for a switch to oral medication when certain criteria were met, and the duration of iv therapy was 7 to 14 days, extensible on demand. Population for analysis was distinguished in ITT (Intent-To-Treat, all the treated population with SSTIs), MITT (Modified Intent-To-Treat, patients infected with a Gram+ pathogen), and

	Ex-factory price (€)	Daily price (€)	
		min	max
Ampicillin + Sulbactam	2.62	2.62	10.46
Cefazolin (1 vial)	1.13	1.13	3.40#
Cloxacillin	0.82	6.53	19.58
Daptomycin	101.55	56.87	56.87
Flucloxacillin (100 vial)	180.61	7.22	21.67
Levofloxacin	24.62	12.31	49.25
Linezolid (10 vial)	548.41	109.68	109.68#
Meropenem (10 vial)	256.22	38.43	76.87
Oxacillin	1.80	7.20	21.59
Piperacillin/tazobactam	17.11	17.11	68.43
Quinupristin/dalfopristin	47.20	141.61	141.61#
Teicoplanin	24.96	24.96	49.92
Tigecycline (10 vial)	486.45	97.29	145.94*#
Vancomycin (1 vial)	5.15	20.59	20.59

Table III

Daily pharmaceutical costs for different available therapies for SSTIs treatment [Informatore Farmaceutico 2008]

* only for 1st day of therapy

price neglects further negotiated discount on supplies for NHS

CE (Clinically Evaluable, all treated patients for whom the clinical outcome reflected the effect of the study compound): CE patients can be judged as clinical successes if they resulted as cured (return to the pre-infection baseline, with resolution of clinical signs and symptoms) or improved (partial resolution of the infection and no need of further antibacterial therapy) after receiving the study medication for at least 4 days, and having not received other antibiotics. The primary objective was to demonstrate non-inferiority of DPT, reached if the difference in success rates between treatment groups was less than 10%.
Results showed that success rates were numerically similar between the two treatments, and also comparable in sub-groups (severe infection, surgical intervention, bacteraemia), but lower for DPT-treated patients in the subgroup with over 65 years. Duration of therapy resulted lower in DPT-treated patients (63% versus 33% required only 4-7 days of therapy, $p<0,0001$). Safety also appeared comparable between DPT and conventional therapy, whereas a rapid elevation in CPK levels was seen in 2.1% of DPT and only in 1.4% of comparator-treated patients. Skeletal muscle toxicity (seen in early studies), renal risk and the use of this drug in aged population (where an higher incidence of adverse effects has been seen) will be monitored in further studies.

ECONOMIC EVALUATIONS

We found only one analysis assessing cost outcomes associated with the use of DPT in SSTIs; this study, performed by Fossaceca and colleagues in 2007, analyzed the first 50 inpatients treated with DPT in USA, and found an average cost of $ 727 for DPT course, reduced to only $ 287 in patients who did not respond to prior antibiotic treatment for a Gram-positive bacterial infection. In patients with renal insufficiency the mean cost is $ 390, and for patient transitioned to outpatient therapy hospital charges were reduced by an estimated $ 102,340. Infection was resolved with DPT therapy in 96% of patients; cost savings were determined essentially by early identification of antibiotic failure, first-line use of DPT in patients with SSTIs and outpatient therapy.
In Table III we calculated daily pharmaceutical costs of available therapies for SSTIs treatment. For each formulation we valorized minimum and maximum dosing (from the SPCs or from reference trials), using retail price deduced from Informatore Farmaceutico 2008: we considered always an ex-factory price. For packages with identical price, we considered the less costly one. This is not to be intended as a cost-minimization analysis, but as a simple overlook of currently available treatments.

Name of the Medicinal Product	Cubicin
Marketing Authorisation Holder	Novartis Europharm Ltd
Active Substance	Daptomycin
Pharmaco-therapeutic Group	Antibacterials for systemic use, Other antibacterials
ATC Code	J01XX09
Date of issue of Marketing Authorisation valid throughout the European Union	19 January 2006

REFERENCES

- AIFA – Agenzia Italiana del Farmaco – Elenco dei farmaci sottoposti a monitoraggio intensivo http://www.agenziafarmaco.it/REGISTRAZIONE_FARMACO/sectionb998.html?target=&area_tematica=REGISTRAZIONE_FARMACO§ion_code=AIFA_FARMACOV_MONIT_INT&cache_session=false
- Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI; DPT 98-01 and 99-01 Investigators The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004; 38: 1673-81
- Cubicin – EPAR summary for the public
- Cubicin official FDA information, side effects and uses – Professional information. Available on http://www.drugs.com/ppa/daptomycin.html
- Cubicin Scientific Discussion – European Medicines Agency (EMEA), 2006 available on http://www.emea.europa.eu/humandocs/PDFs/EPAR/cubicin/2907006en6.pdf
- Fossaceca C. Outcomes analysis of daptomycin use in a community hospital. *Adv Ther*

2007; 24: 517-28

- Gazzetta Ufficiale della Repubblica Italiana – GU n. 43 del 21-2-2001
- Gazzetta Ufficiale della Repubblica Italiana – GU n. 86 del 11-4-2008
- Gazzetta Ufficiale della Repubblica Italiana – GU n. 124 del 29-5-2002
- Gazzetta Ufficiale della Repubblica Italiana – GU n. 298 del 23-12-2006
- HDA drugs file – Cubicin, available on http://www.uvef.it/web/?pag=schede-informative-sui-farmaci
- Hernández MV, Romá SE, Salavert LM, Bosó RV, Poveda AJL. Daptomycin: revitalizing a former drug due to the need of new active agents against grampositive multiresistant bacterias. *Rev Esp Quimioter* 2007; 20: 261-76
- Informatore Farmaceutico 2008, Ed. Elsevier Masson, updated to July, 2008
- Prescrivere News – Nuove entità terapeutiche in ospedale. DAPTOMICINA: ruolo incerto. Dialogo sui farmaci 2007: 4

