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Review

The role of dalbavancin in the multi-disciplinary management of wound infections in orthopaedic surgery

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Antimicrobial resistance is continuously increasing among bacterial clinical isolates (especially methicillin resistance in *Staphylococcus aureus*, MRSA), negatively impacting on outcomes of patients with Surgical Site Infections (SSIs). A multi-disciplinary team work is essential for SSIs prevention and for the choice of antibiotic therapy of orthopaedic SSIs. In particular, an Antibiotic Stewardship (AS) approach is recommended for preserving the activity of old and new antimicrobials. Dalbavancin is a novel antimicrobial agent, belonging to the lipoglycopeptides family, recently approved by FDA for the treatment of ABSSSIs (Acute Bacterial Skin and Skin Structure Infections) and can be considered as a candidate for the treatment of orthopaedic superficial SSIs. An antimicrobial activity directed against MRSA and other multi-resistant Gram-positive pathogens, a bactericidal effect and an extremely extended half-life are among key features of this drug. Dalbavancin gives to clinicians the option to provide an intravenous antimicrobial agent shown to be as effective as conventional therapies, without requiring prolonged admission into the hospital, drastically reducing the length of hospital stay (without reducing the treatment compliance) and total cost per patient. In this paper, we analyze general, microbiological and pharmacological features of dalbavancin, aiming at supporting clinicians while positioning this drug in the context of orthopaedic SSIs.

Keywords: Long-acting antibiotics, Glycopeptides, MRSA, Surgical Site Infections, Antimicrobial resistance

Surgical Site Infections (SSIs) overview

SSIs, defined as infections that occur after surgery in the part of the body where the surgery took place, are among the most frequent Hospital Acquired Infections (HAI).[1] Superficial incisional (involving only skin or subcutaneous tissue of the incision) SSIs are considered, together with cellulitis and major cutaneous abscesses, a subgroup ABSSSIs (Acute Bacterial Skin and Skin Structure Infections)[2] and belong to the broader chapter of Skin and Soft Tissue Infections.[3,4]

U.S. CDC estimates that patients with SSIs are at 2–11 times higher risk of death and 75% of deaths among these patients are directly attributable to SSI. In addition to the negative impact on patient outcomes, SSIs are associated with substantial economic costs. In fact, patients suffering from a SSI, compared with those who do not, remain in the hospital for longer periods, have a higher probability of intensive care unit (ICU) admission and higher rates of hospital readmissions. Costs are even higher for cases of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) as opposed to other pathogens.[5–8]

The last HAI Prevalence Survey, performed in 2011, estimated that about 150.000 SSIs occurred in U.S. acute care hospitals.[9]

Accordingly, data of the last Point Prevalence Survey for HAI, promoted by the European Centre for Disease Prevention and Control (ECDC), in 2011–2012, showed that SSIs represent the 20% of HAI (16% in Italy) (http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/database/Pages/hai-pps-database-distribution-HAI-types.aspx).

From 2000–2003, in Europe, is active a surveillance programme (the 'ECDC HAISSI protocol for the surveillance

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of SSIs') which gathers data from 16 Countries, including Italy, and generates periodic reports. Last report, referring to years 2013–2014, documented a percentage of SSIs per 100 surgical procedures ranging from 0.6 to 9.5%, depending on the type of procedure.

Infectious complications are particularly relevant in orthopaedic surgery. In Europe, the reported percentages of SSIs were 1.1 and 0.6% for hip prosthesis and knee prosthesis, respectively http://ecdc.europa.eu/en/health-topics/Healthcare-associated_infections/surgical-site-infections/Pages/Annual-epidemiological-report-2016.aspx.

Patients with orthopaedic SSIs have substantially greater physical limitations and significant reduction in their quality of life. In these patients, SSIs clinical manifestations can be subtle and infections are generally difficult to treat. In fact, especially when prosthetic material was implanted, or a multidrug-resistant (MDR) micro-organism is involved, the antibiotic treatment must be continued for long periods and the use of intravenous antibiotics, which can be administered in the hospital setting only, is often required (e.g. glycopeptides or daptomycin).

SSIs causative pathogens and antimicrobial resistance issues

The group of micro-organism most frequently isolated from orthopaedic SSIs is that of Gram-positive cocci (responsible of more than 65% of SSIs occurring after hip or knee surgery), with *S. aureus* being the most frequent micro-organism, followed by Coagulase-negative staphylococci and *Enterococcus* species. http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/surgical-site-infections/Pages/Annual-epidemiological-report-2016.aspx

For *S. aureus* and Enterococci (accounting together for almost one-third of orthopaedic SSIs), although with notable geographical variability, relevant antimicrobial resistance issues have been increasingly reported worldwide, mainly from high-income Countries.[10,11]

In 2015, the EARS-Net surveillance programme reported for Italy a proportion of MRSA, over the total of *S. aureus* isolates from invasive infections, of 34.1% (European population-weighted mean: 16.8%) (data available at http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf).

Data from the last ECDC point prevalence survey of health care-associated infections and antimicrobial use in acute care hospitals, performed in the period 2011–2012, showed that more than 40% of *S. aureus* isolates obtained from HAI, in Italy, were MRSA (therefore considered resistant to all ß-lactams with the exception of fifth generation cephalosporins) (Fig. 1). Similarly, in a surveillance study promoted by AMCLI (Associazione Microbiologi Clinici Italiani), in 2012, that involved 52 Laboratories distributed over the Italian territory, an high prevalence of MRSA (35.5% of *S. aureus*) among isolates obtained from SSIs was reported.[12] For *Enterococcus faecium*, ECDC data relative to year 2015 (invasive infections) reported a percentage of strains resistant to ampicillin greater or equal to 75% in most of European Countries, including Italy (86.7%) (http://ecdc.europa.eu/en/data-tools/atlas/Pages/atlas.aspx).

Robust data on the dissemination, in Italy, of Enterococci resistant to vancomycin (VRE) are lacking. However, recent surveillance data showed a high variability with the presence of VRE endemic areas at a subregional level and in specific hospital settings (https://www.ars.toscana.it/files/pubblicazioni/Volumi/2015/Documento_ARS_84_2015_aggiornamento_16_XII_def.pdf).

Prevention of SSIs in orthopaedic surgery

In recent years, following the implementation of specific prevention guidelines, significant progresses have been done in preventing SSIs in orthopaedic surgery.[1,13]

The most recent CDC's annual National and State Healthcare-Associated Infections Progress Report (2014 data, published 2016) documented a 17% decrease in SSI related to the 10 selected procedures (including knee arthroplasty and hip arthroplasty) tracked in previous reports (www cdc gov/hai/progress report).

In Europe, for knee prosthesis surgery, a significantly decreasing trend for both the yearly percentage of SSIs and the incidence density of SSIs was observed in the period 2011–2014 (p value < 0.001).

As the aetiology of SSIs is multifaceted, existing guidelines recommend strategies based on 'bundling' activities, targeting a variety of risk factors together (Table 1).

Particular attention should be paid to the selection of the agent used for the antimicrobial prophylaxis, that can vary on the basis of surgical procedure, most common pathogens causing SSIs, and published recommendations.[1] The most recent Italian Society of Orthopaedics and Traumatology (SIOT) guidelines recommend the use of a first or second generation cephalosporin or, in selected cases, of a glycopeptide (patients with predisposing factors for MRSA infection).[14] However, due to the observed variability in the prevalence of MRSA and VRE, the selection of the most appropriate prophylactic regimen should be based on facility and ward-stratified antibiograms.

Despite implementation of the above-mentioned strategies, there are multiple non modifiable host- and procedure-related risk factors that make the complete elimination SSIs in orthopaedic surgery of virtually impossible (e.g. diabetes, rheumatoid arthritis, recent weight loss, dependent functional status, estimated blood loss of >1 l, longer procedure time, previous infection at site, low volume of procedures performed at hospital and low volume of procedures performed by surgeon).[13] Furthermore, the increasing number of patients with multiple underlying diseases undergoing surgery and the emergence of MDR pathogens are causes of concerns.

Therefore, there is increasing evidence that, in order to maximize the impact of preventative strategies and to

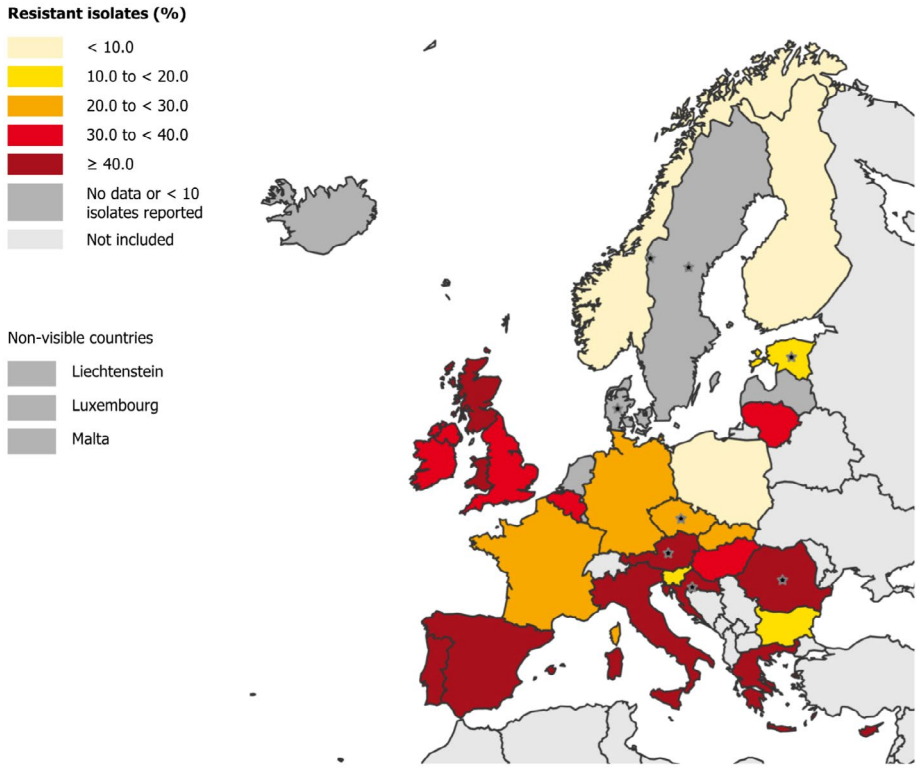

Figure 1 Percentage of Staphylococcus aureus isolates resistant to meticillin (MRSA) in HAIs in acute care hospitals, ECDC PPS 2011–2012

Notes: Data from countries with less than 10 isolates with known antimicrobial susceptibility results excluded. In the Netherlands, antimicrobial resistance data were only collected for non-susceptible isolates in the national PPS protocol. The susceptibility of other isolates could be either 'susceptible' or 'unknown'. The percentage of non-susceptible isolates is therefore not given. NS=non-susceptible. *Country representativeness of the PPS data was optimal or good in 25 (76%) countries, and poor or very poor in 8 (24%) countries. Countries (number of participating hospitals) with poor representativeness were: Austria (*n* = 9), Croatia (*n* = 11), Czech Republic (*n* = 14), Estonia (*n* = 4), Norway (*n* = 7), Romania (*n* = 10) and countries with very poor representativeness were Denmark (*n* = 3) and Sweden (*n* = 4) and are indicated by a '*' in maps and tables.Data from the ECDC point prevalence survey of health care-associated infections and antimicrobial use in acute care hospitals (ECDC PPS) in the period 2011–2012 as reported to TESSy as of 2013–02-06 14:06:48 – See more at: http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/database/Pages/hai-pps-database-microorganisms-antimicrobial-resistance.aspx#sthash.vapF8H1f.dpuf

promptly suspect and confirm SSIs, adopting a multi-disciplinary team approach is essential.[15]

Core members of a SSIs multi-disciplinary team include:

- the orthopaedic surgeon
- an infectious diseases physician
- a clinical microbiologist

The optimum is to obtain the cooperation of other specialists also, including the anesthesiologist, the pharmacologist and the plastic surgeon.

Diagnosis of SSIs after orthopaedic surgery

In countries like Italy where a high prevalence of MDR pathogens has been observed, proceeding with an aetiologic diagnosis, based on microscopic and cultural exams of pathologic material obtained from SSIs, is recommended. In addition to conventional cultural methods, significant advancements, in terms of reduction of the time to personalized therapy for in-patients and out-patients with SSIs, can be achieved with the implementation of rapid, molecular test for bacterial identification and detection of selected antibiotic resistance markers (e.g. *mecA* and *mecC*) directly from clinical sample (including swabs and pus).[16]

The choice of the sample type to be collected for laboratory diagnosis is of paramount importance.[17] Samples should be collected carefully to avoid touching non-involved surfaces of mucosae, colonized by contaminating bacteria.

For superficial SSIs, aspirations of pus or local irrigation fluid are preferable. The use of swabs should be avoided, however, swabs of purulence originating from beneath the dermis can be considered appropriate in selected cases. Swabs with transport system must be used. Storage at room temperature for less than 24 h is acceptable. In any case, transport and storage time should be kept to the minimum. For deep wounds, purulence, necrosis, or tissue from deep subcutaneous site is considered appropriate. The purulent fluid material should be aspirated with needle and syringe and aseptically transferred into an anaerobic transport system. The quantity of the aspirate must be greater than or equal to 1 mL. In deep infections, when implanted material is involved immediate inoculation of aspirated purulent material in blood culture vials is recommend to increase culture sensitivity.[18] Therefore, the

Table 1 Summary of CDC bundles strategy to prevent SSIs, from: www.cdc.gov/hai/pdfs/toolkits/SSI_toolkit021710SIBT_revised.pdf

Preoperative measures (high levels of scientific evidence and demonstrated feasibility)	
Administer antimicrobial prophylaxis in accordance with evidence-based standards and guidelines	• Administer within 1 h prior to incision (2 h for vancomycin and fluoroquinolones)
Remove infections whenever possible	• Select appropriate agents on basis of surgical procedure and most common SSI pathogens for the procedure
Do not remove hair at the operative site unless it will interfere with the operation; do not use razors	• Identify and treat before elective operation
Skin Prep	• Postpone operation until infection has resolved
	• If necessary, remove by clipping or by use of a depilatory agent
	• Use appropriate antiseptic agent and technique for skin preparation (chlorhexidine solutions)
Maintain intraoperative and immediate postoperative normothermia	
Intraoperative measures	
Operating Room (OR) Traffic	• Keep OR doors closed during surgery except as needed for passage of equipment, personnel and the patient
Postoperative measures	
Surgical Wound Dressing	• Protect primary closure incisions with sterile dressing for 24–48 h post-op.
Control blood glucose level during the immediate post-operative period	• Maintain post-op blood glucose level at <200 mg/dL
Discontinue antibiotics within 24 h after surgery end time	
Supplemental strategies (some scientific evidence and variable levels of feasibility)	
• Nasal screen and decolonize only *Staphylococcus aureus* carriers undergoing elective cardiac and other procedures (i.e. orthopaedic, neurosurgery procedures with implants) with preoperative mupirocin therapy	
• Screen preoperative blood glucose levels and maintain tight glucose control in patients undergoing select elective procedures (e.g. arthroplasties, spinal fusions)	
• During surgery, re-dose antimicrobials at intervals of 2 half-lives	
• Adjust antimicrobial prophylaxis dose for obese patients (body mass index > 30)	

selection of the more appropriate clinical sample should be done case by case depending also on the results of imaging studies used for differential diagnosis between SSIs and bone and joint infections (plain radiography, ultrasonography, CT scan or Magnetic Resonance).[19]

Transport and storage conditions are identical to those indicated above for swabs. Swabs are not appropriate for sampling deep lesions. Tissue obtained during surgery or cutaneous biopsy can be used in case of insufficient fluid material. Tissue must be placed in an anaerobic transport system or sterile screw cap container. Several drops of sterile saline can be added to keep small pieces of tissue moist.[20]

The selection of the SSIs antibiotic treatment; an antimicrobial stewardship approach

The choice of antibiotic therapy for orthopaedic SSIs, as well as in other bacterial infections, should respect the principles of a good Antibiotic Stewardship (AS).

In recent years, AS programmes have emerged as a powerful tool for fighting antimicrobial resistance. The AS concept is synonymous of a prescriptive approach that takes into account the conventional criteria of efficacy and tolerability and is also aimed at: (i) reducing the selective pressure on bacterial populations and; (ii) rationalizing health-care facilities resources.[21]

Literature data suggest that a substantial percentage of the patients, ranging from 25 to 50%, receive antibiotics inappropriately, also in settings with a traditionally low use of antimicrobials.[22]

The inappropriateness of antibiotics prescriptions is generally linked to the wrong choice of drug (typically quinolones), use of antibacterials with an excessively broad spectrum or to unnecessary continuation of the treatment.[23]

The primary objective of AS programmes is to optimize clinical outcomes, minimizing the undesired consequences of antibiotics use, preventing the selection of other pathogens and the emergence of antibiotic-resistant strains. In a broader context, the AS can be considered an essential part of a patient safety approach and should be combined with surveillance and infection control programmes.

There is growing evidence that the implementation of AS programmes is effective in reducing the unnecessary prescription of antibiotic therapies and the incidence *Clostridium difficile* infections, while reducing the dissemination of MDR pathogens and realizing significant costs savings.[24,25]

A multi-disciplinary team including an infectious disease physician, a clinical microbiologist, a clinical pharmacist, an information system specialist, an infection control professional and hospital epidemiologist is required to maximize the impact of an AS programme.[26]

The empiric therapy for orthopaedic SSIs should include an agent that is effective against MRSA, especially in settings with a high prevalence of MRSA and in patients presenting known risk factors for MRSA infection (e.g. recent hospital admission, recent antibiotic therapy, history of MRSA infection or colonization). In fact MRSA infection is a risk factor for inappropriate initial antimicrobial treatment (IIAT).[27] Clinicians should be aware that IIAT of complicated skin and soft tissue infections is associated with significantly worse clinical and economic outcomes.[28]

The most recent Infectious Diseases Society of America (IDSA) guidelines for diagnosis and management of skin and soft tissue infections, in the SSIs section, primarily underscore the importance of suture removal plus incision and drainage. Adjunctive systemic antimicrobial therapy is recommended for infections associated with a significant systemic response, such as erythema and induration extending >5 cm from the wound edge, temperature >38.5 °C, heart rate >110 beats/minute or white blood cell (WBC) count >12.000/μL. A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high are recommended.[29] Depending on the surgical site, it can be necessary to include an antibiotic active against Gram-negative bacteria and anaerobes.

Modification of empirical therapy and discontinuation of unnecessary antimicrobials (generally within 48–72 h), when warranted by preliminary culture results or clinical signs, is recommended to control antimicrobials overuse and resistance.

Once organism definitive identification and susceptibility testing are available, the possibility of a switch to a narrower-spectrum drug, to oral therapy or to a long-acting antibiotic can be considered

In particular, in the context of orthopaedic SSIs the use of antibiotics combining a long half-life with an anti-MRSA activity could be strategic.

The long-acting antibiotic dalbavancin

Dalbavancin is a novel antimicrobial agent, belonging to the lipoglycopeptides family (a subclass of glycopeptides), recently approved by FDA for the treatment of ABSSSI. The recommended dose is 1500 mg, given either as a single infusion or as 1000 mg in the first week followed by 500 mg one week later http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002840/human_med_001848.jsp.

An antimicrobial activity directed against Gram-positive pathogens, a bactericidal effect and an extremely extended half-life are among peculiar features of this drug.[30]

Dalbavancin has an antimicrobial profile comparable to that of older glycopeptides (vancomycin and teicoplanin) with a spectrum targeting *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Enterococcus faecalis* e *Enterococcus faecium* (including ampicillin-resistant isolates). Furthermore, dalbavancin is active *in vitro* against

S. aureus isolates with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus*, VISA) and *Enterococcus* spp. isolates resistant to vancomycin due to *vanB* gene acquisition. VanA producing enterococci and *S. aureus* isolates resistant to vancomycin according to Clinical Laboratory Standard Institute (CLSI) criteria are resistant to dalbavancin. Retrospective data, obtained testing large collections of bacterial pathogens, showed that resistance to dalbavancin is very rare among staphylococci and streptococci.[31–34] The EUCAST committee states that in case of isolation of *Staphylococcus* spp. isolate resistant to dalbavancin the identification and antimicrobial susceptibility test must be confirmed and the isolate sent to a reference laboratory for further characterization. However, although infrequently, there is the possibility to find dalbavancin-resistant isolates in SSIs clinical samples (mainly VRE). For this reason, and also for epidemiological purpose, it is important to perform dalbavancin antimicrobial susceptibility testing (AST) for all clinically significant Gram-positive pathogens obtained from patients with SSIs.

Both the EUCAST committee and the FDA provide interpretative criteria for dalbavancin susceptibility testing. However, automated AST systems commonly used in the Clinical Microbiology Laboratory (Vitek2, Phoenix and MicroScan systems) are not yet updated for dalbavancin test and the updating process will require a relatively long period. For this reason, at least in the near future, alternative, less practicable techniques (e.g. agar gradient diffusion) will be adopted by most of Laboratories. Disc diffusion test is not recommended for this molecule (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.0_Breakpoint_Tables.pdf).

If the Laboratory is unable to report dalbavancin AST, susceptibility to this drug can be deduced with sufficient accuracy from vancomycin test. In fact, a recent study, reported that for *S. aureus*, *S. pyogenes*, *S. agalactiae* and *S. anginosus*, a vancomycin Minimum Inhibitory Concentrations (MICs) below or equal to 1 μg/mL is highly predictive of susceptibility to dalbavancin.[35]

Dalbavancin pharmacokinetics

Dalbavancin peculiar pharmacokinetics (PK) was evaluated in both animal models and clinical studies. Indeed, molecule PK, was assessed in healthy volunteers (either in single-dose or in multiple-dose studies), adolescent subjects, special populations (renal or hepatic dysfunction)

Table 2 Main pharmacokinetic parameters of dalbavancin

	Healthy volunteers* Dose: [mg]	Healthy Japanese subjects** Dose: [mg]		Patients with renal impairment*** Dose: [mg]	Patients with hepatic impairment*** Dose: [mg]
C_{max} (mg/l)	[140]: 40.1 [500]: 133 [840]: 239 [1120]: 312	[500]: 158.2	[1000]: 301.2	[1000]: 266.8[b] [1000]: 330.7[c] [1000]: 315.3[d] [500]: 145.8[e]	[1500][i]: 331.7[f] [1500][i]: 227.2[g] [1500][i]: 199.0[h]
$T_{1/2}$ (h)	[140]: 188 [500]: 162 [840]: 149 [1120]: 149	[500]: 204	[1000]: 193.1	[1000]: 389[b] [1000]: 432[c] [1000]: 469[d] [500]: 347[e]	[1500][i]: 323[f] [1500][i]: 320[g] [1500][i]: 322[h]
AUC (mg h/l)	[140]: 3234 [500]: 11,393 [840]: 21,949 [1120]: 27,103	[500]: 12,242[a]	[1000]: 24,824[a]	[1000]: 27,047[a, b] [1000]: 37,665[a, c] [1000]: 44,497[a, d] [500]: 15,587[a, e]	[1500][i]: 33,117[a, f] [1500][i]: 23,628[a, g] [1500][i]: 21,639[a, h]
V_{ss} (l)	[140]: 10.9 [500]: 9.01 [840]: 7.85 [1120]: 7.93	[500]: 12.182	[1000]: 11.301	[1000]: 16.5[b] [1000]: 14.7[c] [1000]: 14.2[d] [500]: 14.6[e]	[1500][i]: 18.1[f] [1500][i]: 24.4[g] [1500][i]: 25.2[h]
CL (l/h)	[140]: 0.0433 [500]: 0.0439 [840]: 0.0383 [1120]: 0.0413	[500]: 0.0422	[1000]: 0.0405	[1000]: 0.038[b] [1000]: 0.027[c] [1000]: 0.024[d] [500]: 0.035[e]	[1500][i]: 0.047[f] [1500][i]: 0.065[g] [1500][i]: 0.074[h]

Notes: C_{max} = maximum plasma concentration; $T_{1/2}$ = half-life; AUC = area under the plasma concentration-time curve; V_{ss} = volume of distribution at steady state; CL = total body clearance.

a = $AUC_{0-\infty}$; b = mild renal impairment; c = moderate renal impairment; d = severe renal impairment; e = ESRD; f = mild hepatic impairment; g = moderate hepatic impairment; h = severe hepatic impairment; i = 1000 mg on day 1 and 500 mg on day.

*Ref. [37].

**Ref. [39].

***Ref. [45].

and patients. Main pharmacokinetic parameters are shown in Table 2.

A three-compartment open model was used to describe the pharmacokinetic behaviour of this drug.[36]

Pharmacokinetic parameters showed no significant inter-individual variability. In healthy subjects, dalbavancin exhibited linear dose-correlated pharmacokinetics: mean peak (or area under the plasma concentration-time curve, AUC) values increase proportionally with dose-escalation, whereas mean half-life, clearance and volume of distribution values do not change.[37]

As shown in the table, the main pharmacokinetic property of this new lipoglycopeptide is represented by the long half-life, which reached an average value of about 7–8 days, thereby allowing mono-weekly administration.[36–39]

The 1500 mg dose of dalbavancin recommended for Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) may be administered either as a single or double infusion (1000 mg followed by 500 mg a week apart): a single intravenous (IV) administration demonstrated to be not inferior to the double regimen, both in terms of safety and clinical outcomes.[40]

Dalbavancin demonstrated is highly bound to serum proteins (93%), in particular albumin.[41] Nevertheless, molecule penetration into animal tissues was thoroughly proved.[36]

From a clinical point of view, drug concentrations in soft tissue interstitial fluid were investigated in healthy volunteers, showing values similar to those of plasma: tissue/plasma ratio reached a mean value of 0.60 (cantharidin-induced blister technique).[37,42]

Dalbavancin distribution into bone and joint tissues was also studied: pharmacokinetic profile was analyzed in patients undergoing joint surgery, collecting bone and joint tissue samples at 0.5, 24, 72, 168, 240 and 336 h after the end of a single 1000 mg infusion. Mean drug concentrations in cortical bone and synovia at the end of infusion (12 h) and at 14 days (336 h) were 6.3, 25 μg/g and 4.1, 15.9 μg/g, respectively.[43] Furthermore, concerning bone drug penetration, dalbavancin effectiveness in the treatment of MRSA osteomyelitis was demonstrated in rats, showing a reduction in bone CFUs superior to placebo and similar to vancomycin.[44]

No tissue accumulation after a multiple-dose regimen (1000 mg IV loading-dose on day 1 followed by 500 mg/week for 7 weeks) was observed.[43]

Dalbavancin elimination follows two routes (renal/non-renal): after a 1000 mg single dose, in healthy volunteers, unchanged drug excretion into urine was 42% after 42 days, thus underlining the importance of non-renal elimination pathway.[41] Dose adjustment is required only in patients with severe renal impairment (<30 creatinine clearance <30 ml/min) not undergoing dialysis. Indeed, following a 1000 mg single dose, the AUC0-∞ of patients with mild and moderate renal dysfunction increased by about 10 and 50%, respectively, whereas, after a 500 mg single dose, patients with severe renal dysfunction showed a 100% increase in AUC0-∞.

No dose adjustment is necessary in hepatic dysfunction.[45]

Dalbavancin PK was also described in hospitalized adolescents aged 12–17 years: average half-life and volume of distribution values were similar to those observed in adult patients affected by skin and skin structure infections, whereas mean AUC values appeared to be reduced by 30%.[46]

As regards safety and tolerability, in healthy volunteers, dalbavancin was overall well tolerated, causing mild AEs such as pyrexia, headache and nausea.[37]

A recent pooled analysis collected safety data from seven phase II and III studies: regarding this pre-marketing phase, this new antibiotic revealed a similar adverse effect profile to comparator molecules, such as cephalosporins, vancomycin, oxacillin, nafcillin and linezolid.[47]

Additionally, dalbavancin did not affect cardiac electrophysiology, not prolonging the QTc interval.[48]

Concerning PK-PD behaviour, this antibiotic is characterized by a concentration-dependent killing pattern. Indeed, Andes and Craig, demonstrated *in vivo* dose-dependent bactericidal activity: high doses and long intervals of administration guaranteed a faster bacterial killing, preventing pathogen regrowth. Peak/MIC and AUC/MIC ratios were the best PK/PD indices able to predict antimicrobial efficacy. Considering free-drug 24 h AUC to MIC ratio as the PK/PD index that most correlates with the efficacy in the animal model, target values between 100 and 300 should be reached *in vivo*.[49]

In patients affected by Acute Bacterial Skin and Skin Structure Infections (ABSSSI), in comparison to conventional therapy (twice daily vancomycin infusion eventually switched with twice daily oral linezolid), dalbavancin showed similar results in terms of both early and late clinical outcomes.[50]

Concluding remarks

Dalbavancin presents a promising alternative to conventional antibacterials for the treatment of ABSSSIs in adult patients.[51,52] The favourable pharmacokinetic profile, the broad antimicrobial spectrum (covering most frequently isolated Gram-positive MDR pathogens, e.g. MRSA and ampicillin-resistant Enterococci) and the safety features of dalbavancin make this drug suitable for the treatment of patients with orthopaedic superficial SSIs. In fact, dalbavancin gives to clinicians the option to provide an intravenous antimicrobial agent shown to be as effective as conventional therapies, without requiring prolonged admission into the hospital.[53] These features are expected to cause benefits for both the patient and the overall health care system.[54] Since dalbavancin has been introduced in the clinical practice only recently, robust evaluations of the economic impact of its use are not yet available. However, a recent HTA evaluation, conducted by a panel of Italian experts, concluded for a sustainable

and potentially positive economic impact of dalbavancin use for the treatment of ABSSSIs, mainly related to the opportunity of earlier discharge of patients treated with dalbavancin in comparison with patients treated with other therapeutic regimens.[54]

A setting where dalbavancin use could be significantly advantageous (for its safety profile and need of a single-shot intravenous administration) is that of outpatients with risk of low compliance to long-term antibiotic treatment such as drug addicted and old patients admitted to long-term care facilities.

Regarding future perspectives we should mention that dalbavancin has demonstrated, an *in vitro* anti-biofilm activity. In fact, a recent study showed that dalbavancin is able to successfully reduce MRSA and MRSE in biofilms, and therefore provides a promising option for the treatment of biofilm-associated infections, including those related to implant of prosthetic material.[55]

Contributors

FA wrote the article in whole, and revised the article. ER wrote the article in part, and revised the article. CS wrote the article in part, and revised the article. GT wrote the article in part, and revised the article. CP wrote the article in part, and revised the article. MF wrote the article in part, and revised the article.

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