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Dalbavancin in the treatment of different gram-positive infections: a real-life experience

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ABSTRACT

Dalbavancin is a lipoglycopeptide with a very prolonged half-life enabling treatment with a single intravenous administration that has been approved to treat complicated skin and soft-tissue infections. Information on the efficacy and safety of dalbavancin in other situations is very scarce. This retrospective study included adult patients who received at least one dose of dalbavancin between 2016 and 2017 in 29 institutions in Spain. The primary objective was to report the use of dalbavancin in clinical practice, including its efficacy and tolerability. The potential impact of dalbavancin on reducing the length of hospital stay and hospital costs was also evaluated. A total of 69 patients received dalbavancin during the study period (58.0% male; median age 63.5 years). Dalbavancin was used to treat prosthetic joint infection (29.0%), acute bacterial skin and skin-structure infection (21.7%), osteomyelitis (17.4%) and catheter-related bacteraemia (11.6%). These infections were mainly caused by *Staphylococcus aureus* (27 isolates), coagulase-negative staphylococci (24 isolates) and *Enterococcus* spp. (11 isolates). All but two patients received previous antibiotics for a median of 18 days. Dalbavancin was administered for a median of 21 days (range 7–168 days), and concomitant antimicrobial therapy was prescribed to 25 patients (36.2%). The overall clinical success rate of dalbavancin was 84.1%. Adverse events, mainly mild in intensity, were reported in nine patients. Overall, dalbavancin was estimated to reduce hospitalisation by 1160 days, with an estimated overall cost reduction of €211 481 (€3064 per patient). Dalbavancin appears to be an effective therapy for many serious Gram-positive infections.

1. Introduction

Gram-positive pathogens are the second leading cause of healthcare-associated infections, accounting for approximately one-third of all episodes [1,2]. These infections are mainly caused by *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) strains, *Enterococcus* spp. and coagulase-negative staphylococci (CoNS) [1–3].

Due to the high proportion of these infections caused by β-lactam-resistant micro-organisms, vancomycin, daptomycin and linezolid are among the most important therapeutic choices [4–6]. However, none of these agents are entirely without drawbacks, including the need for intravenous (i.v.) administration and i.v. lines as well as problems related to compliance and adverse events [7–10]

Dalbavancin is a lipoglycopeptide approved in the USA and Europe for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) [11–13] that has unique pharmacokinetic properties, enabling the treatment of serious infections with once weekly or biweekly administration [14–16], thus decreasing the need to

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maintain i.v. lines, improving compliance and decreasing costly hospital stays.

Pivotal clinical trials of dalbavancin demonstrated its efficacy and safety for the treatment of ABSSSIs [17–19]. However, information regarding its real-life use, efficacy and tolerability in daily clinical practice is limited [20]. Here we report the clinical multicentre experience with dalbavancin to treat or consolidate treatment of serious Gram-positive infections since its recent approval in Spain.

2. Materials and methods

2.1. Study design

This was an observational retrospective study developed in 29 hospitals from 14 urban centres in Spain. Centres taking part were invited to include all cases of infections treated with dalbavancin from January 2016 to January 2017.

Medical records for all patients receiving at least one dose of dalbavancin were retrospectively reviewed. Data collected included patient demographics, underlying conditions, Charlson comorbidity index, McCabe score, infection site, isolation of Gram-positive pathogens, source control of infection when applicable, antimicrobial therapy administered before and concomitant to dalbavancin, reasons for dalbavancin use, dosages of dalbavancin treatment, length of dalbavancin use, adverse events, clinical outcome, relapse and potential hospital days saved.

Culture, identification of micro-organisms and susceptibility testing were performed at each participating centre according to their own practice. As for ABSSSI, bacterial cultures from deep biopsy were considered reliable results for wound microbiological assessment [21].

2.2. Definitions

Infections were classified according to the criteria of the US Centers for Disease Control and Prevention (CDC) [22]. According to the US Food and Drug Administration (FDA), ABSSSI was defined as a bacterial infection of the skin with a lesion size area of ≥75 cm^2. Only patients with cellulitis/erysipelas, wound infection and mayor cutaneous abscess were considered as having ABSSSI [23].

Regarding underlying diseases, patients' situations were classified as rapidly fatal, ultimately fatal or non-fatal according to the criteria of McCabe and Jackson. Adequate source control of infection was defined as any documented surgical or radiological procedures to drain abscesses or other fluid collections thought to be the source of infection. Patients were followed-up for ≥1 month after dalbavancin therapy was discontinued. Clinical outcome was considered successful when patients had no clinical (resolution of signs and symptoms related to bacterial infection) or microbiological evidence of infection during the follow-up period. Treatment failure was defined as lack of clinical response, relapse or death.

Adverse events (AEs) were diagnosed according to the definition of the World Health Organization (WHO) [24]. Serious AEs were defined as drug reactions that were life-threatening, led to prolonged hospitalisation or caused disability or resulted in death of the patients. Otherwise, AEs were categorised as mild.

2.3. Dalbavancin administration

Dalbavancin was administered in the same way as approved for ABSSSI, as either a single i.v. dose of 1500 mg over 30 min, or in two doses as an initial i.v. dose of 1000 mg over 30 min followed 1 week later by 500 mg i.v. Dose adjustment was required only for patients with severe renal dysfunction [creatinine clearance (CL_{Cr}) < 30 mL/min].

Dosing as well as length of therapy was chosen by the prescribing physician, who also obtained informed consent from each patient. For off-label prescriptions, each hospital fulfilled pharmacy requirements, including 'compassionate use forms'.

2.4. Cost analysis

The potential cost savings after dalbavancin administration was evaluated by calculating the difference between what would have been spent administering an equal length of therapy with daptomycin in an inpatient setting (standard therapy cost) and what was really spent on the dalbavancin regimen (dalbavancin therapy cost).

Standard therapy cost was calculated as the sum cost associated with line placement (to administer a drug for 14 days, the cost of implantation of a midline catheter was calculated as €460 [25]), antibiotic therapy costs [in Spain, the cost for a daily daptomycin dose of 500 mg (6 mg/kg for 80 kg person) is €100.01] and cost of hospital stay (costs for 1 day of hospitalisation in an internal medicine ward €325.01 [26]).

Dalbavancin therapy cost was calculated as the sum cost of dalbavancin in Spain (€1133.97 for a dose of 1500 mg, which equates to a daily antibiotic cost of €161.91) plus a peripheral catheter inserted each time (€90 for peripheral catheter) plus the costs of nursing visits for each dalbavancin administration (€120 for a 2-h visit).

2.5. Ethics

The study was approved by the Ethics Committee of Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM, Madrid, Spain), which waived the requirement of informed consent owing to the design of the study.

2.6. Statistical analysis

Continuous variables were compared using Student's *t*-test and Mann–Whitney *U*-test for normally and non-normally distributed variables, respectively. The χ^2 test or Fisher's exact test was used to compare categorical variables. All tests of statistical significance were two-tailed. Differences were considered statistically significant for $P < 0.05$. Statistical analysis was performed with the software package PASW Statistics v.18.0 (SPSS Inc., Chicago, IL).

3. Results

In the 12-month period from the date of marketing dalbavancin in Spain, data were collected from 69 patients treated with dalbavancin in the 29 hospitals taking part in the study [mean number of cases per centre, 2.4 (range 1–11)].

3.1. Demographics

Demographic and baseline characteristics of the study population are shown in Table 1. Patient age ranged from 15–90 years [median 63.5 years; interquartile range (IQR) 49.3–72.0 years] and 58.0% were male. The most common underlying condition was diabetes mellitus (33.3%), followed by cardiovascular disease (31.9%). More than one underlying disease was present in 34 patients (49.3%) and the median Charlson comorbidity index was 3 (IQR 1–5). Overall, 17 patients (24.6%) were classified as having an ultimately or rapidly fatal disease according to the McCabe score.