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Safety of treatment with high-dose daptomycin in 102 patients with infective endocarditis

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ABSTRACT

Daptomycin is commonly used at doses >6 mg/kg/day for various indications, including infective endocarditis (IE). A systematic assessment of skeletal muscle, renal, haematological, hepatic and pulmonary toxicity of high-dose daptomycin (HDD) in IE is lacking. A total of 102 IE patients treated with HDD were included in this non-comparative, observational, single-centre cohort study conducted from 2007 to 2014. The incidence, timing, severity and evolution of adverse events (AEs) were assessed. Patients had a median age of 61.5 years and a high prevalence of co-morbidities. Staphylococci were cultured in 87.2% of cases (62.2% meticillin-resistant). The median daptomycin dose was 8.2 mg/kg/day for a median of 20 days (range, 1–60 days). HDD was withdrawn due to AEs in 12 patients (11.8%). On-treatment death occurred in 4 cases (3.9%, none HDD-related). Muscle toxicity occurred in 15 patients in a median of 15 days after HDD starts, which was largely mild and reversible with ongoing HDD use. Mild renal toxicity was observed in 9 patients (8.8%) after a median of 12 days of HDD (RIFLE—Risk in 8, Injury in 1). A rise of peripheral blood eosinophils occurred in 16 patients (15.7%). There were three cases of eosinophilic interstitial pneumonia. Four patients (3.9%) had mild allergic or idiosyncratic reactions. No other hepatic or haematological AEs were observed. Our current experience with 102 patients suggests that HDD is safe in significantly ill IE patients with multiple co-morbidities. Muscle toxicity was clinically negligible. Most importantly, there was no significant renal toxicity. Eosinophils should be carefully monitored.

1. Introduction

Infective endocarditis (IE) is a life-threatening systemic disorder showing significant morbidity and constant high rates of mortality [1–4]. In the vast majority of cases, IE is due to Gram-positive cocci, including staphylococci, streptococci and enterococci [4,5]. Improved therapeutic regimens covering these pathogens are therefore essential.

Daptomycin is a lipopeptide antibiotic showing rapid, concentration-dependent bactericidal activity both against meticillin-sensitive and meticillin-resistant staphylococcal species, as well as activity in vitro against most enterococci and some streptococci [6]. It has a low volume of distribution, a high penetration coefficient within bacterial biofilms, and an efficient concentration in IE vegetations [7–11]. All these features make daptomycin a theoretically optimal choice for IE therapy [6,12]. However, at the currently approved dose of 6 mg/kg intravenously once daily, daptomycin was not shown to be more effective than the standard of care in the only randomised trial published to date [13].

Subsequent studies have therefore evaluated the results of therapy with higher doses of daptomycin, investigating outcomes, rates of bacteraemia clearance and adverse events (AEs) [14–19]. In the absence of a randomised controlled design, however, superior efficacy could not be demonstrated [20]. Also, the actual number of IE patients included in these studies was limited, ranging from 15 to 70 [14–19]. Regarding safety, experience has been substantial but mostly involved settings lacking severity, co-morbidities, cardiac surgery sequelae and the effect of heart failure [8,20–25], which are all features of IE. Moreover, safety assessments were largely limited to skeletal muscle toxicity. Indeed, although standard-dose daptomycin (SDD) proved to portend lower renal toxicity compared with gentamicin- and vancomycin-containing regimens [26], a systematic assessment of renal as well as haematological, hepatic and pulmonary toxicity of high-dose daptomycin (HDD) is lacking [20]. Accordingly, in this study, the abovementioned safety outcomes of HDD were analysed in detail in a large cohort of IE patients.

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2. Patients and methods

2.1. Study design and setting

This was a non-comparative, prospective, observational, single-centre cohort study performed from October 2007 to June 2014 in a tertiary-care regional referral centre for IE, operating in a 450-bed, partly academic facility with a large cardiac surgery programme (Monaldi Hospital, Naples, Italy). Enrolled patients were assessed daily throughout hospitalisation and were followed-up at biweekly and then monthly intervals after discharge. Data collection was performed prospectively by means of a pre-defined case report form. Patients or their legal representatives gave their informed consent to clinical data collection and storage. Moreover, an informed consent to receive 'off label' a higher than approved dose of daptomycin was obtained. The Institutional Review Board of Monaldi Hospital approved the study protocol and observational procedures.

2.2. Participants

All subjects admitted to our unit as inpatients who fulfilled Duke's diagnostic criteria for definite IE were screened for inclusion in this study [27] and were treated with HDD. Patients with a diagnosis of possible IE were excluded. Evidence of muscle damage, defined as a creatine phosphokinase (CPK) level above the upper normal limit (UNL) at baseline, was not an exclusion criterion. The current study included 25 device-related IE patients treated with daptomycin who have been the subject of a prior study from our group [16].

2.3. Outcomes and definitions

The primary outcome of the study was the development of major HDD-related AEs, including death, prolongation of hospital stay (permanence in hospital solely due to monitoring or treatment of an AE), muscle toxicity (increase of CPK levels above the UNL or its doubling when higher than at baseline), renal impairment (according to the RIFLE criteria) [28], hepatic toxicity (rise to 2.5-fold the UNL of aminotransferases and/or γ-glutamyl transferase and direct bilirubin), peripheral blood eosinophilia (>450 cells/μL) with or without evidence of interstitial pneumonia [29] or bleeding events. Injection-related and infusion-related reactions (rash, pruritus) were also noted. Gastrointestinal and other miscellaneous AEs (e.g. hypertension, hypotension, headache, anxiety, insomnia, dizziness, asthenia, arthralgia) were not recorded. Secondary outcomes were microbiological response and clinical success. These efficacy outcomes were assessed during treatment and at the end of follow-up, i.e. at the last patient visit after antimicrobial therapy discontinuation. Microbiological response was defined as clearance of bacteraemia and complete resolution of fever and acute-phase response during daptomycin treatment, irrespective of the final disease outcome. Clinical success was defined as complete cure of the disease with resolution of clinical signs and symptoms and no recurrence during follow-up. Treatment failure was defined as an inadequate response to daptomycin with persistence of fever and/or bacteraemia by the causative pathogen after 6 days of therapy, requiring a change in antibiotic course.

Subjects were stratified by type of heart structure infected, i.e. native valve, prosthetic valve or implantable electronic device. A daptomycin daily dose >6 mg/kg/day was defined as a 'high dose'.

2.4. Interventions and data measurement

All patients enrolled in the study were managed according to a pre-defined clinical protocol employed in our unit. On admission, at least two sets of blood cultures were obtained from all patients, irrespective of prior treatment or the presence of fever, in order to attain the microbiological diagnosis or to prove clearance of a previous bacteraemia in transferred patients. Moreover, all included patients underwent transthoracic echocardiography; where indicated, transoesophageal echocardiography was performed. After the treatment starts, surveillance blood cultures were drawn every 48 h until they become sterile. The presence of synchronous or metastatic foci of infection was investigated by means of clinical and imaging examinations and, whenever present, fluid collections or abscesses were drained and were sent for culture. Excised valves and cardiovascular implantable electronic device (CIED) leads were also subjected to standard microbiological cultures. No molecular microbiology methods were routinely used.

In the case of coagulase-negative staphylococci (CoNS), at least three positive blood cultures for the same species or at least two blood cultures drawn more than 12 h apart plus the same microorganism (at species level) in surgical specimens were required to confirm the aetiological diagnosis of IE. The minimum inhibitory concentration (MIC) of daptomycin was assessed by Etest (bioMérieux, Marcy-l'Étoile, France), whilst MICs of the other major anti-Gram-positive antibiotics were determined using a VITEK®2 automated system (bioMérieux). European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for staphylococci were used to assess antimicrobial susceptibility of isolates [30].

Daptomycin was started as first-line empirical antibiotic treatment in patients who were febrile on presentation with suspected IE, or as second-line treatment after diagnosis of definite IE with failure of a prior antibiotic regimen.

Where appropriate, patients underwent on-site cardiac surgical consultation.

2.5. Variables analysed

Clinical, echocardiographic and microbiological data were collected by means of a dedicated case report form and were entered in a database for subsequent analysis.

The estimated glomerular filtration rate was assessed by the Cockcroft–Gault formula, and baseline renal dysfunction was classified according to current guidelines [31]. Among the echocardiographic data, size and location of vegetations were recorded.

The following microbiological data were obtained and were included in the analysis: isolated pathogen species; susceptibility to penicillin, oxacillin and gentamicin (also at high levels for enterococci); and strain MICs for penicillin, oxacillin, vancomycin and daptomycin.

Safety analysis included systematic recording of the abovementioned AEs during hospitalisation and during the initial month of follow-up after discharge. It was also recorded whether an AE required daptomycin dose adjustment or discontinuation.

2.6. Statistical analyses

Statistical analyses were carried out using SPSS 11.5 software (SPSS Inc., Chicago, IL). Numerical data are presented as mean ± standard deviation or median and range. Categorical data are presented as number and percent. Comparisons between groups were carried out with Mann–Whitney *U*-test and Fisher's exact test for continuous and categorical data, respectively. The significance level was set at 5%.

3. Results

3.1. Patient clinical features

During the study period, HDD was prescribed to 114 patients with suspected or proven IE admitted to the hospital, of whom 102

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