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Clinical outcomes with daptomycin: a post-marketing, real-world evaluation

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Abstract

The Cubicin Outcomes Registry and Experience (CORE) is an ongoing, retrospective, post-marketing database of daptomycin use in the USA. Although non-comparative, CORE offers insight into real-life clinical experience with daptomycin in various Gram-positive infections and specific patient types. Analyses of daptomycin treatment outcomes using the CORE database revealed that treatment with daptomycin has resulted in high rates of clinical success for a variety of Gram-positive infections, including indicated infections such as complicated skin and soft tissue infections, *Staphylococcus aureus* bacteraemia and right-sided infective endocarditis, and non-indicated infections such as osteomyelitis. Treatment outcomes did not differ significantly according to the causative pathogen for any of the analyses performed and were not influenced by the vancomycin MIC. Patients frequently received therapy with alternative antibiotics prior to treatment with daptomycin, particularly those patients with more serious infections. However, similar treatment outcomes were observed when daptomycin was used as first-line therapy or as salvage therapy, demonstrating the effectiveness of daptomycin in the treatment of these patients.

Keywords: Bacteraemia, daptomycin, Gram-positive infections, infective endocarditis, osteomyelitis, skin and soft tissue infection

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Introduction

Over the past decade, several new antibiotics have been approved for the treatment of resistant Gram-positive infections, including quinupristin–dalfopristin, approved in the USA and the EU in 1999 [1,2]; linezolid, approved in the USA in 2000 and in the EU in 2001 [3,4]; tigecycline, approved in the USA in 2005 and in the EU in 2006 [5,6]; and daptomycin, approved in the USA in 2003 and in the EU in 2006 [7,8]. Although the availability of more antibiotics can provide clinicians with various treatment options, they can also potentially complicate medical decision-making, particularly in cases where published clinical data are sparse.

When selecting the most appropriate antimicrobial therapy, clinicians are frequently forced to extrapolate antibiotic properties displayed *in vitro* or in animal models to the individual patient's circumstances and specific pathogen-related factors. For example, clinicians may favour the use of antibiotics with bactericidal activity *in vitro* when dealing with bacteraemia, endocarditis and meningitis, because this property has been demonstrated to be important in the treatment of these serious infections [9], even when clinical experience with these agents is limited. The adverse event profile of certain antibiotics may steer clinicians away from using them in some patient populations. For example, clinicians may avoid aminoglycosides and high-dose vancomycin therapy in non-dialysis patients with renal failure, because these agents are associated with a high incidence of nephrotoxicity [10]. Host factors that influence antimicrobial selection include the presence of comorbidities, such as immunosuppression, neutropenia, renal failure and prior antibiotic exposure, the severity of illness, and the epidemiological setting of infection onset. The site of infection will have an impact, because of the varying abilities of individual antibiotics to penetrate or retain activity in certain *in vivo* compartments.

Microbiological considerations are becoming increasingly important in the current climate of increasing antimicrobial

resistance. A recent concern is the upwards shift in vancomycin MIC for *Staphylococcus aureus* strains over time, the 'MIC creep', which has been demonstrated in a number of single-centre studies [11–13] and was reported recently in a study of three hospitals in the Detroit area of the USA over a 22-year period [14]. The adverse impacts of these increases in vancomycin MIC on various clinical parameters, such as efficacy [15–17], mortality [18], duration of hospital stay and overall cost of therapy [19], have been demonstrated. The phenomenon of MIC creep is not limited to vancomycin, and has been demonstrated in one study for both linezolid and oxacillin [11]; however, the clinical significance of this is less well documented. One study showed that a linezolid MIC of 4 mg/L, the upper limit of susceptibility, was associated with inferior microbiological eradication of methicillin-resistant *S. aureus* infections when compared with those where the organism had a linezolid MIC of ≤2 mg/L [20]. Although rare, glycopeptide-intermediate *S. aureus* strains with vancomycin MICs of 4–8 mg/L may be of particular concern, as these strains show raised MICs *in vitro* (as compared with vancomycin-susceptible strains) for many of the newer classes of Gram-positive agents, such as the lipoglycopeptides [21–23] and daptomycin [24], although the clinical relevance of this is unknown.

The Cubicin Outcome Registry and Experience (CORE) is an ongoing, retrospective, post-marketing database of infection outcomes with daptomycin therapy in the USA. Daptomycin was approved initially for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2003, with subsequent approval being given in 2006 for *S. aureus* bacteraemia (SAB) and right-sided infective endocarditis (RIE) in the USA [7], and in 2007 for RIE caused by *S. aureus* and SAB associated with RIE or cSSTIs in the EU [8]. Analyses of the data from CORE have been, and continue to be, performed for numerous types of Gram-positive infections and in various patient groups, by calendar year. By reviewing the published clinical outcomes with daptomycin, as reported to the CORE database during 2004 (n = 1160) and 2005 (n = 1172) [25], this article offers insights into the real-life experience of daptomycin therapy in various infections and specific patient types.

An Introduction to CORE

The primary objective of CORE is to evaluate retrospectively the clinical outcomes of patients treated with daptomycin, with additional objectives that include the characterization and description of the patient populations being treated with daptomycin, as well as the types of infections and pathogens [26]. Patients were eligible for inclusion if they have received at least one dose of daptomycin, but not as part of a controlled clinical trial, and have initiated and completed daptomycin treatment within the calendar year [26]. Data on patient demographics, microbiological characteristics, antibiotic therapy and efficacy and safety outcomes are extracted from standardized case report forms that have been completed by trained investigators.

Standard definitions are used to classify clinical outcomes at the end of therapy as success (the sum of cure plus improvement) or failure. Cure is defined as resolution of clinical signs and symptoms and/or no additional antibiotic therapy being considered necessary, or as infection being cleared with a negative culture reported at the end of daptomycin therapy. Patients are deemed to have improved if there is partial resolution of clinical signs and symptoms and/or additional antibiotic therapy is considered necessary at the end of daptomycin therapy (e.g. a patient who is switched to oral antibiotic therapy at the time of hospital discharge). Patients with an inadequate response to daptomycin therapy, the development of resistance, worsening or new/recurrent signs and symptoms, the need for a change in antibiotic therapy or with a positive culture reported at the end of therapy [26] are classified as failures. A non-evaluable outcome is assigned when investigators are unable to determine response at the end of daptomycin therapy because the records do not contain adequate information [26].

A Summary of the Results of CORE

Clinical experience with daptomycin by infection type

The types of infections treated with daptomycin in 2004 and 2005 are shown in Fig. 1 [25]; the microbiological characteristics and antibiotic therapy for these infections in 2004 are summarized in Table 1. Outcomes for 750 patients (522 patients with skin infections, 126 patients with bacteraemia, 35 patients with infective endocarditis (IE) and 67 patients with osteomyelitis) treated with daptomycin in 2004 and 565 patients (478 patients with skin infections, 61 patients with non-catheter-related bacteraemia and 26 patients with IE) treated in 2005 are reviewed [27–34].

Skin infections. Surgical site infections constituted the most common type of cSSTI treated in both 2004 [27] and 2005 [31], followed by infected wounds and major abscesses. The median daptomycin dose and treatment duration for these infections were in line with the treatment recommendation for cSSTIs (4 mg/kg/day for 7–14 days) [8]. In 2004, the overall rate of treatment success was 97% (Table 2), ranging