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Brazilian experience in EU-CORE: daptomycin registry and treatment of serious Gram-positive infections

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ABSTRACT

Objectives: To collect data about non-controlled prescribing use of daptomycin and its impact among Brazilian patients with serious Gram positive bacterial infection, as well as the efficacy and safety outcomes.

Materials and methods: This is a multi-center, retrospective, non-interventional registry (August 01, 2009 to June 30, 2011) to collect data on 120 patients (44 patients in the first year and 76 patients in the second year) who had received at least one dose of commercial daptomycin in Brazil for the treatment of serious Gram-positive bacterial infection.

Results: Right-sided endocarditis (15.8%), complicated skin and soft tissue infections (cSSTI)-wound (15.0%) and bacteremia-catheter-related (14.2%) were the most frequent primary infections; lung (21.7%) was the most common site for infection. Daptomycin was used empirically in 76 (63.3%) patients, and methicillin-resistant *Staphylococcus aureus* (MRSA) was the most common suspected pathogen (86.1%). 82.5% of the cultures were obtained prior to or shortly after initiation of daptomycin therapy. *Staphylococcus* spp. – coagulase negative, MRSA, and methicillin-susceptible *S. aureus* were the most frequently identified pathogens (23.8%, 23.8% and 12.5%, respectively). The most common daptomycin dose administered for bacteremia and cSSTI was 6 mg/kg (30.6%) and 4 mg/kg (51.7%), respectively. The median duration of inpatient daptomycin therapy was 14 days. Most patients (57.1%) did not receive daptomycin while in intensive care unit. Carbapenem (22.5%) was the most commonly used antibiotic concomitantly. The patients showed clinical improvement after two days (median) following the start of daptomycin therapy. The clinical success rate was 80.8% and the overall rate of treatment failure was 10.8%. The main reasons for daptomycin discontinuation were successful end of therapy (75.8%), switched therapy (11.7%), and treatment failure (4.2%). Daptomycin demonstrated a favorable safety and tolerability profile regardless of treatment duration.

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Conclusions: Daptomycin had a relevant role in the treatment of Gram-positive infections in the clinical practice setting in Brazil.

Introduction

Gram-positive bacteria are a major cause of complicated skin and soft tissue infections (cSSTI) as well as etiologic agent of bacteremia with or without infective endocarditis, with *Staphylococcus aureus* (including methicillin-resistant [oxacillin-resistant] *S. aureus*), *Streptococcus* species, and *Enterococcus* species being the most common pathogens. cSSTI are considered those in deep soft tissue, or requiring surgical intervention (infected ulcers, burns, major abscesses), or associated with comorbidities (diabetes mellitus, obesity, immune deficiency, underlying venous or arterial insufficiency).[1] Methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant coagulase-negative *Staphylococcus* (MR-CoNS) are well-recognized causes of both community-acquired and healthcare-associated infections.[2] MRSA infections have risen in the last few years. In Europe, the reported rate of MRSA is as low as 5% in Denmark, Finland, Netherlands, and Sweden and as high as above 40% in Greece, Ireland, Italy, Malta and the UK.[3] In USA,[4] MRSA caused 53% of all *S. aureus* healthcare-associated infections reported to NHSN in 2006–2007, ranging from 49.2% of *S. aureus* SSIs to 65.2% of *S. aureus* catheter-associated urinary tract infections (CAUTI). In Brazil, the overall MRSA rate was 31%.[5] Coagulase-negative staphylococci (CoNS) are important etiologic agents of bacteremia among immunocompromised patients, mainly when they are using catheters. They are increasingly involved in infective endocarditis,[6] greatly associated with the use of intravenous catheters.

Although vancomycin has been considered the first-line drug of choice for treating MRSA and MRCoNS, evidence of clinical failures are increasing, suggesting that vancomycin is losing its clinical and microbiological potency, resulting in increased use of novel antibiotics such as daptomycin.[7] These poor vancomycin results have been more evident when staphylococcal infections are associated to bacteremia.

The objective of the daptomycin registry in Brazil was to collect data about non-controlled prescribing use of daptomycin and its the impact in Brazilian patients with serious Gram positive bacterial infection, as well as the efficacy and safety outcomes.

Materials and methods

EU-CORE was a multi-center, retrospective, non-interventional registry over a five-year (2007–2012) period to annually collect outcome data on patients who have received at least one commercial dose of daptomycin for the treatment of serious Gram-positive bacterial infection. Collected data concerned patient population, infections, pathogens, adverse events (AEs) and clinical outcomes. Brazil participated during three years, from 2009 to 2012 and this is the report of the first two years of participation, from August 01, 2009 to July 31, 2010 and from August 01, 2010 to July 31, 2011. During these two years, Brazil included 120 patients in the study, being 44 patients in the first year and 76 patients in the second year.

The sample size of this patient registry is not based on statistical considerations. The primary study objectives were to characterize and describe the population of patients receiving daptomycin and the infections and pathogens treated with daptomycin; to evaluate the clinical outcomes of daptomycin therapy; to characterize, describe and evaluate AEs in patients receiving daptomycin. Data for efficacy assessment were collected for clinical outcome assessment, duration of treatment, time to clinical improvement, and safety issues (AE/serious AE [SAE]). The outcome of clinical improvement was considered in the case of partial resolution of clinical signs and symptoms and/or when there was a need for additional antibiotic therapy at the end of daptomycin therapy; failure was defined as inadequate response to daptomycin therapy or development of resistance, worsening or new/recurrent signs and symptoms, or the need to change antibiotic therapy, or a positive culture reported at the end of therapy.

The inclusion criteria for a patient record to be eligible for retrospective data collection and inclusion in the registry database were treatment with at least one dose of daptomycin, having initiated and completed daptomycin therapy within the trial timelines, follow-up of at least 30 days after end of treatment, all mandatory information available in hospital files. Written informed consent was waived due to the nature of study design – registry (retrospective, observational). Patients who had received daptomycin as part of a controlled clinical trial were not eligible for this study.

Although seventeen institutions were initially evaluated for participation, only some of them had sufficient time and adequate number of patients who met eligibility criteria (daptomycin had been recently launched in the Brazilian market, on April, 2009). From seven Brazilian institutions that were considered for participation in the study, six collected retrospective clinical data from medical records using a standardized clinical research form (CRF) and protocol (approved by the health authority and Institutional Review Boards). All information collected reflected standard practice in each site and there was no intervention or restriction in clinical practice. Patient data could be recorded into this registry after a minimum of 30 days after the end of daptomycin therapy in order to capture AEs/SAEs. The reasons for premature study drug discontinuation, reason for completion of daptomycin treatment, and antibiotic use after daptomycin treatment were recorded. In cases of multiple infections, investigators entered the type of infection in order of clinical significance (in order of most to least severe): endocarditis, osteomyelitis, bacteremia, other [CNS infection, foreign body/prosthetic infection, metastatic abscess, necrotizing fasciitis, necrotizing infection, surgical/non-surgical antibiotic prophylaxis, septic arthritis and urinary tract infection/pyelonephritis], cSSTI, and uncomplicated skin and soft tissue infection. Safety