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Pooled analysis of single-dose oritavancin in the treatment of acute bacterial skin and skin-structure infections caused by Gram-positive pathogens, including a large patient subset with methicillin-resistant *Staphylococcus aureus*

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ABSTRACT

Oritavancin is a lipoglycopeptide antibiotic with bactericidal activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). The phase 3 studies SOLO I and SOLO II demonstrated comparable efficacy and safety of a single dose of oritavancin compared with 7–10 days of twice-daily vancomycin in adults with acute bacterial skin and skin-structure infections (ABSSSIs). The present analysis assessed clinical responses by pathogen at 48–72 h and at study days 14–24 in SOLO patients within the pooled data set. Of the 1959 patients in the pooled SOLO studies, 1067 had at least one baseline Gram-positive pathogen and 405 had MRSA. Clinical response rates were similar for oritavancin- and vancomycin-treated patients by pathogen, including *Staphylococcus aureus* with or without the Panton–Valentine leukocidin (*pvl*) gene and from different clonal complexes, and were similar for pathogens within each treatment group. Oritavancin exhibited potent in vitro activity against all baseline pathogens, with MIC_{90} values (minimum inhibitory concentration required to inhibit 90% of the isolates) of 0.12 μg/mL for *Staphylococcus aureus*, 0.25 μg/mL for *Streptococcus pyogenes* and 0.06 μg/mL for *Enterococcus faecalis*. Whereas both oritavancin and vancomycin achieved similarly high rates of clinical response by pathogen, including methicillin-susceptible and -resistant *Staphylococcus aureus*, oritavancin provides a single-dose alternative to 7–10 days of twice-daily vancomycin to treat ABSSSIs.

1. Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs) are common and frequently require hospitalisation, posing a substantial economic burden on healthcare systems [1,2]. Extrapolations from the Premier Hospital Database estimated that more than 750,000 ABSSSI hospitalisations occur in the USA each year, with a projected economic burden of more than US$6 billion annually [3]. Antibiotic treatments that can be administered in ambulatory or observational settings to avoid or shorten hospital stay due to ABSSSI may therefore reduce costs to healthcare systems.

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains an important pathogen both in community and hospital settings. Approximately one-half of all cases of community-onset ABSSSI in the US Military Health System in 2010 were due to MRSA [4]; similarly high rates of community-associated (CA) MRSA were determined in a recent clonal typing study of patients with skin and soft-tissue infections [5]. Whilst CA-MRSA remains uncommon in Europe,

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empirical treatment of ABSSSI in many geographic locations may require antibiotics with MRSA coverage [2,6]. However, many antibiotics with reliable activity against MRSA require dosage adjustments in special populations or have warnings and precautions that limit their use. Furthermore, therapeutic drug concentration monitoring to optimise efficacy or avoid toxicities is commonly performed for vancomycin, a widely used agent for the treatment of ABSSSI.

Oritavancin is a lipoglycopeptide antibiotic with activity against Gram-positive pathogens, including MRSA, β-haemolytic and anginosus group streptococci, and enterococci [7–9]. It exerts its antibacterial activity via three mechanisms of action [10–12]: (i) inhibition of the transglycosylation (polymerisation) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and (iii) disruption of bacterial membrane integrity, leading to depolarisation, permeabilisation and cell death. In addition, oritavancin exhibits concentration-dependent bactericidal activity [13] and an extended plasma elimination half-life [14]. Based on pharmacokinetic/pharmacodynamic data [15], single-dose oritavancin was evaluated as a treatment for Gram-positive infections [16,17]. The attributes of oritavancin, including its once-only dosing and long-lived antibacterial activity, may reduce healthcare resource utilisation [18,19], increase flexibility for infection management [19], assure treatment compliance, and improve quality of life and patient satisfaction [20]. The phase 3 studies SOLO I [21] and SOLO II [22] demonstrated that a single 1200 mg intravenous (i.v.) dose of oritavancin was non-inferior to twice-daily vancomycin for 7–10 days, with a similar safety profile, for the treatment of ABSSSI. This analysis describes the pooled clinical efficacy results by pathogen from the SOLO studies, including a pre-specified analysis of a large subset of patients with documented MRSA infection.

2. Materials and methods

2.1. Study design and treatments

The SOLO I and II clinical studies were identically designed phase 3, global, multicentre, randomised, double-blind, non-inferiority, comparative efficacy and safety studies evaluating a single 1200 mg i.v. dose of oritavancin followed by placebo compared with i.v. vancomycin (1 g or 15 mg/kg twice daily) for 7–10 days in adults with ABSSSI [21,22]. At least 175 patients with confirmed MRSA were to be enrolled in each study and an enrolment cap of 30% for major cutaneous abscesses was to be observed [23]. The studies were conducted from January 2011 to June 2013.

2.2. Key eligibility criteria

Eligible patients were ≥18 years of age with a diagnosis of cellulitis/erysipelas, major cutaneous abscess or wound infection suspected or proven to be caused by a Gram-positive pathogen and which, in the judgement of the investigator, would require ≥7 days of i.v. therapy; further eligibility criteria may be found in the protocol [21,22].

2.3. Microbiology

ABSSSI site and blood specimens for culture were obtained at screening; additional ABSSSI site specimens were obtained only if clinically indicated [21,22]. Specimens were obtained surgically or by aspiration, biopsy or deep swab and were cultured locally using standard procedures. Unique organisms were sent to a central laboratory (Eurofins Medinet Inc., Chantilly, VA) for confirmation of identification and for susceptibility testing by broth microdilution [24,25]. All quality control results were within published acceptable ranges [25]. The minimum inhibitory concentrations (MICs) of oritavancin and vancomycin were determined for post-therapy pathogens and were compared with those of the corresponding baseline isolate to identify any susceptibility changes that may have occurred upon treatment. Methicillin resistance in *Staphylococcus aureus* was confirmed by PCR targeting the *mecA* gene and/or by oxacillin susceptibility phenotype [25]. The presence of the Panton–Valentine leukocidin (*pvl*) gene in *Staphylococcus aureus* was determined by PCR [26]. The *spa* types of *Staphylococcus aureus* isolates were characterised by PCR and sequencing and were grouped into multilocus sequence typing (MLST) clonal complexes [27].

2.4. Analysis populations

Whereas the modified intent-to-treat (mITT) population included all randomised patients who received any study drug and was used to determine the primary efficacy endpoint in each study [21,22], the main patient population for these analyses was the microbiologically intent-to-treat (MicroITT) population, which consisted of the subset of patients within the mITT population with baseline Gram-positive pathogen(s) known to cause ABSSSI. The microbiologically evaluable (MicroE) population, which consisted of the clinically evaluable subset of patients within the MicroITT population, was used for confirmatory analysis.

2.5. Efficacy endpoints

The primary efficacy endpoint was a composite outcome at early clinical evaluation (ECE) (48–72 h), which comprised: (i) cessation of spreading or reduction in size of the baseline lesion; (ii) absence of fever; and (iii) no rescue antibiotics [23]. The key secondary endpoint was investigator-assessed clinical cure at post-therapy evaluation (PTE) (days 14–24) [23]. An additional secondary efficacy endpoint was ≥20% lesion area decrease from baseline at ECE [28].

2.6. Clinical responses by pvl gene status and spa type

Clinical outcomes for patients with *Staphylococcus aureus* were determined for subgroups based on (i) presence or absence of the *pvl* gene and (ii) MLST clonal complex assignment (determined on the basis of *spa* type) for clonal complexes with a minimum of 20 patients in each treatment group.

2.7. Data analysis

Clinical responses by pathogen for the present analyses were based on pooled data across both SOLO studies since the protocols were identical in patient selection criteria, design, conduct, monitoring and planned analyses. Pooled analyses also provided a larger patient sample with which to improve the precision in the estimate of treatment differences in the subpopulations of patients with specific pathogens. Whereas subgroup analyses of clinical response by pathogen including MRSA were pre-specified in the statistical analysis plans for each study, efficacy analyses by pathogen in the pooled data set were conducted post-hoc and hence statistical analyses in this data set are descriptive.

Efficacy data were analysed using a meta-analytical approach. Success rates were calculated as simple pooled percentages of success (i.e. the proportion of patients with success in the pooled data set). Missing data for efficacy evaluations were categorised as failures for the primary and secondary endpoints. The estimate of event rate differences between oritavancin and vancomycin in the pooled data was based on a weighted average of event rate differences in the