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Original Article

Efficacy, safety and pharmacokinetics of tedizolid versus linezolid in patients with skin and soft tissue infections in Japan – Results of a randomised, multicentre phase 3 study

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ABSTRACT

The objective of this open-label, randomised (i.e. 2:1 ratio), Phase 3 study was to compare the efficacy and safety of tedizolid phosphate 200 mg, once-daily treatment with that of linezolid 600 mg, twice-daily treatment for 7–14 days in Japanese adult patients (N = 125) with skin and soft tissue infections (SSTIs) and/or for 7–21 days for those with SSTI-related bacteraemia, caused by confirmed or highly suspected methicillin-resistant *Staphylococcus aureus* (MRSA).

Primary outcome was clinical cure rate at test-of-cure (TOC, in SSTI: 7–14 days, in bacteraemia: 4–6 weeks after end-of-therapy [EOT]) time point in the microbiologically evaluable MRSA (ME-MRSA) population (N = 39). Secondary endpoints were clinical and microbiological response rates at EOT. Safety parameters were evaluated in the safety analysis population up to follow up. Data analysis was descriptive in nature.

Baseline characteristics of patients were similar between treatment groups. At TOC in the ME-MRSA population, clinical cure rate was similar in tedizolid phosphate (92.6%) and linezolid (88.9%) groups. At EOT, clinical cure (tedizolid phosphate: 93.1%, linezolid: 90.0%) and microbiological success (tedizolid phosphate: 93.1%, linezolid: 100.0%) rates were similar in the ME-MRSA population.

Both treatments were well tolerated; overall treatment-emergent adverse events (TEAEs) in tedizolid phosphate (79.5%) and linezolid (75.6%) treatment groups were similar. Drug-related TEAEs were numerically lower with tedizolid phosphate versus linezolid (30.1%; 39.0%, respectively), as well as gastrointestinal (21.7%; 26.8%) and myelosuppression-related (2.4%; 22.0%) TEAEs. One death occurred in the linezolid group.

Tedizolid phosphate may be an appropriate antibiotic for the treatment of SSTIs in Japanese adult patients.

International clinical trial registration number: NCT01967225.

Japanese clinical trial registration number: JapicCTI-132308.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a highly concerning multidrug-resistant pathogen causing nosocomial infections globally [1,2]. Despite its declining trend between 2011 and 2015, MRSA remains an important public health problem in Japan [3–5]. Its reported incidence among all *Staphylococcus aureus* infections in patients is approximately 50% [3,4]. For MRSA SSTIs, vancomycin, teicoplanin, arbekacin, linezolid, and daptomycin have been used empirically [6–13]. High susceptibility rates to these antibiotics were demonstrated in MRSA [3–5], however, their associated adverse reactions (e.g. nephrotoxicity, neuropathy, rhabdomyolysis, thrombocytopenia, or anaemia) may limit their

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clinical use [14–22]. Thus, new antibiotics with an improved safety profile are needed in Japan.

Tedizolid phosphate (referred to hereafter as tedizolid), a novel oxazolidinone antibiotic, 200 mg, 6-day, once-daily treatment has recently been approved in the United States, Europe and other countries for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by certain susceptible Gram-positive bacteria, including MRSA [23–28]. Tedizolid treatment versus linezolid, 600 mg, 10-day, twice-daily treatment was non-inferior in efficacy and was associated with lower rates of gastrointestinal adverse events (AEs) and myelotoxicity in ABSSSI patients [25–28]. With its high *in vitro* potency, once-daily dosing, and both intravenous (IV) and oral (PO) formulations, tedizolid is a prospective candidate for the treatment of skin and soft tissue infections (SSTIs) in Japan [24,29–33].

In this study, the clinical and microbiological efficacy and safety profile of tedizolid were compared with those of linezolid in Japanese patients hospitalised with SSTIs (i.e. deep SSTIs, chronic pyoderma, or infection secondary to wound, burn, surgical wound or ulcer) and/or SSTI-related bacteraemia, caused by suspected or confirmed MRSA.

2. Patients and methods

2.1. Study design and treatments

This study was a prospective, randomised (i.e. 2:1 ratio), open-label, active-controlled, multicentre Phase 3 study comparing the efficacy and safety of tedizolid (200 mg, once daily) versus linezolid (600 mg, twice daily) in intravenous-to-oral (IV/PO) switch therapy for the treatment of SSTIs for 7–14 days and of SSTI-related bacteraemia for 7–21 days [34]. Tedizolid phosphate intravenous infusion is administered over 60 min, in a 250 mL solution, once daily, while linezolid intravenous infusion is administered over 60 min, in a 300 mL solution, twice daily. Switch from IV to PO route of either treatment was allowed at the discretion of the investigator after 3–4 days. The study was designed in accordance with the draft Guidelines for Clinical Evaluation of Antibiotics produced by the Ministry of Health, Labour and Welfare in Japan.

2.2. Patients

Japanese adults (≥18 years) were enrolled between October 2013 and September 2016 if they had a suspected or confirmed MRSA 1) SSTI or 2) SSTI-related bacteraemia.

1) Patients required hospitalisation and IV systemic antibiotics, were diagnosed with a deep SSTI (e.g. cellulitis, erysipelas, lymphangitis), or chronic pyoderma (hidradenitis suppurativa, dermatitis papillaris capillitii), or infection secondary to wound, burn, surgical wound or ulcer; and had erythema with a diameter of ≥5 cm and induration; at least one of the following: fever (axillary temperature of >37.5 °C), leukocyte count >10,000/mm^3 or <4000/mm^3 (or a band cell count >10%), elevated C-reactive protein level, lymph node tenderness and volume increase or palpable proximal to the primary SSTI; and MRSA was suspected or confirmed from culture or Gram-stain <72 h before first study drug administration.
2) Bacteraemia patients had a suspected or confirmed SSTI-derived MRSA in their blood and at least two of the following: fever (axillary temperature of >38.0 °C or <36.0 °C), heart rate >90 beats/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg, leukocyte count >12,000/mm^3 or <4000/mm^3 (or a band cell count >10%).

Patients were ineligible if they had received any systemic antibacterial drugs potentially effective against MRSA for ≥24 h within 3 days prior to the first infusion of either study drug, or expected to receive medication <24 h prior to the first infusion, unless antibacterial therapy for ≥72 h proved to be ineffective on, or lack appropriate potency to MRSA (see supplementary materials for full list of exclusion criteria).

The study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and Independent Ethics Committee/Institutional Review Board approval for each centre was obtained. All patients or their legal representative/guardian provided written informed consent.

2.3. Outcome assessments

The primary efficacy endpoints were exploratory in nature and included clinical cure and microbiological eradication rates at test-of-cure (TOC) and were assessed in the microbiologically evaluable MRSA (ME-MRSA) population of all randomised patients. The TOC was assessed 7–14 days and 4–6 weeks after end-of-treatment (EOT) for SSTIs and bacteraemia, respectively. Patients were followed up for 30 ± 5 days after EOT for SSTIs and until the TOC visit for bacteraemia.

Secondary efficacy endpoints included clinical and microbiological response rates at EOT (SSTIs and bacteraemia), and percentage reduction of lesion size from screening to Day 3 or 4 (only SSTIs) in ME-MRSA. Exploratory subgroup analyses for patients with/without renal impairment were carried out for secondary efficacy endpoints. Full definitions of clinical and microbiological outcome parameters, and susceptibility testing description are given in the supplementary material.

2.4. Safety assessments

AEs, including those of special interest (myelosuppression, *Clostridium difficile*-associated diarrhoea [CDAD], and optical and peripheral neuropathy), and vital signs were monitored until the follow-up period for SSTI and TOC for bacteraemia. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 18 or later). Safety analyses were performed on the safety population.

2.5. Statistical analyses

The statistical evaluation was performed using SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). The statistical design of this study was to confirm the superiority of tedizolid in TOC cure rate to the threshold of 30%, predefined on the clinical perspective of cure rates previously achieved with linezolid (i.e. 52.9%) [7,35] and daptomycin (i.e. 40.0%) [36] in Japanese SSTI patients. This study was not designed to demonstrate the superiority or non-inferiority of tedizolid versus linezolid in clinical cure rate at any time point. It was postulated that if a tedizolid cure rate of 50% was achieved, then 60 patients in the ME-MRSA population would result in a statistical power of >85% to show that the lower limit of the two-sided 95% confidence interval (CI) is greater than the threshold value (30%), thus confirming superiority. A sample size of 150 enrolled patients was proposed to confirm superiority to the threshold. Patients with an SSTI lesion size of ≥75 cm^2 were to comprise 20% of the total population.

To compare primary efficacy variables between tedizolid and linezolid in an exploratory way, descriptive frequency tables were summarised, and point estimates of the incidence rates and the corresponding 2-sided "Clopper-Pearson exact" 95% CI were calculated by treatment group and infection [37]. Treatment groups

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