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Original article

Efficacy, safety, tolerability and population pharmacokinetics of tedizolid, a novel antibiotic, in Latino patients with acute bacterial skin and skin structure infections

Alejandro Ortiz-Covarrubias[a,*], *Edward Fang*[b], *Philippe G. Prokocimer*[b], *Shawn D. Flanagan*[b], *Xu Zhu*[c], *Jose Francisco Cabré-Márquez*[d], *Toshiaki Tanaka*[e], *Julie Passarell*[f], *Jill Fiedler-Kelly*[f], *Esteban C. Nannini*[g]

[a] *Hospital Civil de Guadalajara, Guadalajara, Jalisco, Mexico*
[b] *Merck and Co, Inc., Kenilworth, NJ, USA*
[c] *Bayer HealthCare, Beijing, China*
[d] *Bayer HealthCare, Mexico City, Mexico*
[e] *Bayer Yakuhin, Osaka, Japan*
[f] *Cognigen Corporation, a subsidiary of Simulations Plus, Inc., Buffalo, NY, USA*
[g] *Facultad Ciencias Médicas, Universidad Nacional de Rosario, Sanatorio Británico, Rosario, Argentina*

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ABSTRACT

Acute bacterial skin and skin structure infections are caused mainly by Gram-positive bacteria which are often treated with intravenous vancomycin, daptomycin, or linezolid, with potential step down to oral linezolid for outpatients. Tedizolid phosphate 200 mg once daily treatment for six days demonstrated non-inferior efficacy, with a favourable safety profile, compared with linezolid 600 mg twice daily treatment for 10 days in the Phase 3 ESTABLISH-1 and -2 trials. The objective of the current post-hoc analysis of the integrated dataset of ESTABLISH-1 and -2 was to evaluate the efficacy and safety of tedizolid ($N = 182$) vs linezolid ($N = 171$) in patients of Latino origin enrolled into these trials. The baseline demographic characteristics of Latino patients were similar between the two treatment groups. Tedizolid demonstrated comparable efficacy to linezolid at 48–72 h in the intent-to-treat population (tedizolid: 80.2% vs linezolid: 81.9%). Sustained clinical success rates were comparable between tedizolid- and linezolid-treated Latino patients at end-of-therapy (tedizolid: 86.8% vs linezolid: 88.9%). Tedizolid phosphate treatment was well tolerated by Latino patients in the safety population with lower abnormal platelet counts at end-of-therapy (tedizolid: 3.4% vs linezolid: 11.3%, $p = 0.0120$) and lower incidence of gastrointestinal adverse events (tedizolid: 16.5% vs linezolid: 23.5%). Population pharmacokinetic analysis suggested that

* *Corresponding author at*: Hospital Civil de Guadalajara, Calle Hospital #278 S.H., Guadalajara, 44100 Jalisco, Mexico.
E-mail address: orca0059@prodigy.net.mx (A. Ortiz-Covarrubias).
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estimated tedizolid exposure measures in Latino patients vs non-Latino patients were similar. These findings demonstrate that tedizolid phosphate 200 mg, once daily treatment for six days was efficacious and well tolerated by patients of Latino origin, without warranting dose adjustment.

Introduction

Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), are commonly associated with skin and skin structure infections (SSSIs), bacteraemia and nosocomial pneumonia.[1–3] Infections due to MRSA may be associated with morbidity and mortality, particularly in the elderly.[3] MRSA-related infections are an increasing problem in Latin America,[4–6] both in the healthcare environment and in the community. The epidemiology of MRSA is constantly changing; both hospital-acquired (HA) and community-acquired (CA) MRSA circulating clones and their antibiotic resistance profiles vary considerably throughout regions and countries.[7] In 2003, the first outbreak of infections involving CA-MRSA strains in Latin America was described in Uruguay and was caused by the Southwest Pacific (SWP) clone/sequence type (ST)-30/SCC*mec* IVc.[8] Furthermore, other clones of CA-MRSA have been isolated in Brazil,[9] Argentina,[10] Colombia, Ecuador, Venezuela,[11] Mexico,[12] and Chile.[13] A considerable amount of CA-MRSA has also been found among nosocomial isolates, at least in Colombia and Uruguay.[14,15]

Vancomycin, teicoplanin, daptomycin, tigecycline, linezolid, clindamycin, and ceftaroline are commercially available as parenteral intravenous agents for MRSA infections in many countries in Latin America.[16] Despite the broad range of anti-MRSA antibiotics, initial empirical therapy is inappropriate in a large number of patients leading to treatment failures,[17] increased healthcare costs,[18] and potentially increasing resistance levels.[19]

Tedizolid phosphate is a novel oxazolidinone antibiotic[20] with at least 4-times higher potency than linezolid against Gram-positive bacteria including MRSA, vancomycin-resistant enterococci (VRE), linezolid-resistant *cfr*+ *S. aureus*, and *Streptococcus pyogenes*.[21,22] Tedizolid phosphate is converted in vivo by non-specific phosphatases to its active moiety tedizolid (TZD).[23] Two pivotal randomised, double-blind, double-dummy, multicentre, controlled, Phase 3 clinical trials (ESTABLISH-1 and ESTABLISH-2) conducted in patients with acute bacterial skin and skin structure infections (ABSSSI; i.e. cellulitis/erysipelas, wound infection and major cutaneous abscess)[24,25] demonstrated that tedizolid phosphate, 200 mg, once daily (QD) treatment for six days was non-inferior to linezolid (LZD), 600 mg, twice daily (BID) treatment for 10 days.[26–28] In addition, TZD had an improved tolerability and safety profile compared with LZD, particularly in terms of gastrointestinal (GI) adverse events (AEs) and haematological parameters.[26–28]

Interethnic pharmacokinetic (PK) differences exist for certain antibacterial agents potentially influencing the efficacy and safety of the antibiotic drug in patients.[29] For example, ciprofloxacin metabolism in Brazilian subjects differs from that in other ethnic populations, while tigecycline clearance in young healthy Afro-American subjects is higher than in Caucasian subjects.[29] Furthermore, both intrinsic (e.g. genetics, body size and fat distribution) and extrinsic ethnic factors may influence the effects of an investigational drug via altered PK and pharmacodynamics.[30–32]

The objectives of the current post-hoc analysis were to evaluate the efficacy and safety of TZD vs LZD for the treatment of ABSSSI in patients of Latino origin enrolled into the Phase 3 ESTABLISH studies. Furthermore, the TZD PK profile of these patients was evaluated based on population PK analysis.

Methods

Study design and treatments

Both ESTABLISH-1 (NCT01170221) and ESTABLISH-2 (NCT01421511) were randomised, multicentre, double-blind, double-dummy, active-controlled Phase 3 studies comparing tedizolid phosphate 200 mg QD (6-day course followed by 4-day placebo treatment) vs LZD 600 mg BID (10-day treatment) for the treatment of patients with ABSSSIs. Patients enrolled into ESTABLISH-1 received exclusively oral (PO) therapy,[26] while patients in ESTABLISH-2 received intravenous (IV) therapy with an optional switch to PO therapy when certain criteria were met.[27] The integrated dataset of ESTABLISH-1 and ESTABLISH-2 trials was analysed and reported by Shorr et al.[28]

Ethical approval

No ethical approval of this post-hoc analysis was required. The ESTABLISH-1 and ESTABLISH-2 studies were conducted in accordance with the 2008 Declaration of Helsinki and all relevant international, European Union, national, and local rules and legislation. Institutional review board or ethics committee approval was obtained at each participating centre and all participants provided written informed consent. A data and safety monitoring board reviewed safety data during the conduct of the study.[26,27]

Enrolment criteria

Patients (aged ≥18 years old in ESTABLISH-1 and ≥12 years old in ESTABLISH-2) were enrolled in both trials if they had an ABSSSI (cellulitis/erysipelas, wound infection, or major cutaneous abscess) with a minimum lesion surface area of 75 cm^2;