Hepatic Safety in Acute Bacterial Skin and Skin Structure Infection Patients Receiving Tedizolid Versus Linezolid

Catherine Hardalo[1], Edward Fang[1], Carisa De Anda[1], Sonia L. Minassian[2], Philippe Prokocimer[1]

[1]Cubist Pharmaceuticals, San Diego, CA; [2]Minassian Biostatistics, San Diego, CA

Philippe Prokocimer, MD
4747 Executive Drive, Suite 1100
San Diego, CA 92121
858 352 2600
philippe.prokocimer@cubist.com

265

ABSTRACT

INTRODUCTION. Tedizolid is a novel oxazolidinone with potent antibacterial activity against a wide range of Gram-positive pathogens. In 2 randomized, double-blind, Phase 3 noninferiority trials, ESTABLISH-1 and ESTABLISH-2, tedizolid 200 mg once daily for 6 days was noninferior to linezolid 600 mg twice daily for 10 days in treating acute bacterial skin and skin structure infections (ABSSSI). This analysis was conducted to identify any evidence of drug-induced serious hepatotoxicity (DISH) in a large tedizolid clinical trial database (Phase 2 and Phase 3) and to assess the effect of tedizolid in Phase 3 ABSSSI patients with normal hepatic function, hepatic impairment (HI), or hepatic disease (HD), as measured by incidence of treatment-emergent adverse events (TEAE), TEAE leading to drug discontinuation, and serious adverse events (SAE).

METHODS. Hy's Law defines DISH as unexplained serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) + total bilirubin (TBL) >2x ULN without alkaline phosphatase elevation; Temple's corollary defines it as ALT elevation >3x ULN without TBL elevation. Patients from Phase 2 and Phase 3 trials who received ≥1 tedizolid or linezolid dose with ≥1 on-treatment ALT/TBL value were included. A scatterplot of maximum ALT/AST divided by ULN (/ULN) versus maximum TBL/ULN was generated on a log10 scale. Safety assessments were performed as described above.

RESULTS. The DISH population comprised 1024 tedizolid- and 621 linezolid-treated patients who had ALT and TBL values. No tedizolid patients but 1 linezolid patient met Hy's Law criteria after the first dose. Thirty-six tedizolid (3.5%) and 26 linezolid (4.1%) patients met Temple's corollary criteria. Tedizolid patients had no evidence of DISH following medical review. The incidence of TEAE, TEAE leading to discontinuation, and SAE was similar in both arms in the Phase 3 trials.

CONCLUSIONS. There was no DISH signal in a safety database from Phase 2 and Phase 3 clinical trials in ABSSSI. TEAE profiles were similar for Phase 3 tedizolid- and linezolid-treated patients with HI/HD, and those with normal hepatic function, suggesting no worsening of hepatic function.

INTRODUCTION

- Tedizolid, the active moiety of tedizolid phosphate, is a novel oxazolidinone antibacterial with potent activity against a wide range of Gram-positive pathogens, including resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.[1-3]
- Tedizolid exerts its antibacterial activity by binding to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis.[4]
- In June 2014, the US Food and Drug Administration (FDA) approved tedizolid for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible Gram-positive pathogens, including MRSA.[5]
- Two phase 3 trials, ESTABLISH-1 and ESTABLISH-2, demonstrated the noninferior efficacy of tedizolid (200 mg once daily for 6 days) to linezolid (600 mg twice daily for 10 days) in patients with ABSSSI.[6,7]
- The purpose of this analysis was to compare the hepatic safety of tedizolid and linezolid by (1) identifying drug-induced serious hepatotoxicity (DISH) in a large, pooled clinical trial safety database and (2) assessing safety and tolerability of tedizolid in patients with ABSSSI according to baseline hepatic function using pooled data from the ESTABLISH-1 and ESTABLISH-2 trials, as measured by the incidence of treatment-emergent adverse events (TEAE), TEAE leading to drug discontinuation, and serious adverse events (SAE).

METHODS

Identification and Analysis of DISH

- The incidence of DISH was analyzed in patients treated with at least 1 dose of tedizolid or linezolid from 2 open-label Phase 2 trials (NCT00761215 and NCT01519778) and from 2 randomized, double-blind, active-controlled Phase 3 trials (NCT01170221 and NCT01421511), for whom at least 1 on-treatment measurement of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and total bilirubin (TBL) was available.

Definition of DISH

- Hy's Law defines DISH as unexplained serum ALT or AST >3x upper limit of normal (ULN) + total bilirubin (TBL) >2x ULN without alkaline phosphatase elevation.
- Temple's corollary defines DISH as ALT elevation >3x ULN without TBL elevation.

Analyses

- Laboratory values were converted to standard reporting units and normalized by reporting values as ratios of ULN. A bivariate analysis (scatterplot) of maximum ALT/AST versus maximum TBL/ULN was generated on a $\log_{10}$ scale.
- The maximum value during treatment was used if a patient had >1 value for ALT and TBL.

METHODS (CONT'D)

Evaluation of Tolerability According to Baseline Liver Function

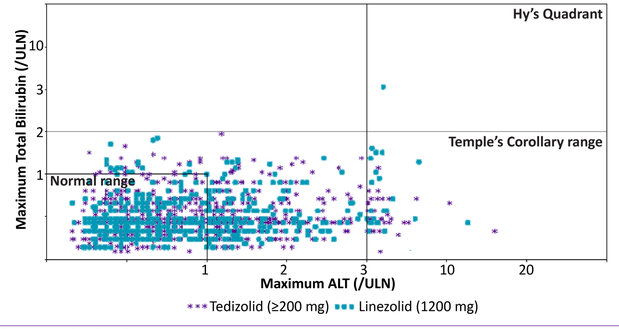
- Pooled safety data from the Phase 3 ESTABLISH-1 and ESTABLISH-2 clinical trials were used to compare the tolerability of tedizolid and linezolid.
- In the Phase 3 trials, patients were randomly assigned 1:1 to receive tedizolid 200 mg once daily for 6 days (N = 664) or linezolid 600 mg twice daily for 10 days (N = 669).
- ESTABLISH-1 patients received oral therapy exclusively, whereas ESTABLISH-2 patients first received intravenous therapy for 24 hours and then could be switched to oral study drug when prespecified clinical improvement criteria were met.
- The safety population for the integrated database included all patients treated with at least 1 dose of study drug in Phase 2 and Phase 3 studies: tedizolid (n = 662 in Phase 3; n= 388 in Phase 2) and linezolid (n = 662).
- Patients with hepatic impairment were defined as those with Child-Pugh classification B or C (total score ≥7) at baseline.
- Patients with hepatic disease were defined as those with ALT or AST >2x ULN or who were positive for hepatitis C at baseline.
- Safety assessments included TEAE, TEAE leading to treatment discontinuation, and SAE.

RESULTS

Evaluation of DISH

- In the 2 open-label Phase 2 trials and 2 randomized, double-blind, active-controlled Phase 3 trials, a total of 1050 patients were treated with tedizolid and 662 patients were treated with linezolid (pooled safety population, of whom 1024 and 621 in the tedizolid and linezolid treatment arms, respectively, had ALT and TBL values and were included in this analysis).
- The scatterplot (**Figure 1**) shows that no patient treated with tedizolid met the DISH criteria according to Hy's Law; 1 patient treated with linezolid met criteria after the first dose.
- A total of 36 tedizolid-treated patients (3.5%) and 26 linezolid-treated patients (4.1%) met criteria for DISH according to Temple's corollary.

Figure 1. Scatterplot of DISH Among Patients in Phase 2 and Phase 3 Clinical Trials



ALT, alanine aminotransferase; ULN, upper limit of normal.

RESULTS (CONT'D)

Evaluation of Tolerability According to Baseline Liver Function in Pooled Phase 3 Studies

- Hepatic impairment was present in 14 (2.1%) and 12 (1.8%) patients in the tedizolid and linezolid groups, respectively (**Table 1**).
- Hepatic disease was present in 175 (26.4%) and 209 (31.6%) patients in the tedizolid and linezolid groups, respectively.
- The incidence of TEAE, TEAE leading to discontinuation, and SAE was similar between tedizolid and linezolid in patients with or without hepatic disease or hepatic impairment.
- The AE profile of tedizolid in patients with hepatic disease or impairment was similar to that in the normal adult population.

Table 1. Adverse Event Profile of Patients in the Pooled Phase 3 Safety Population According to Baseline Hepatic Function

Adverse Event	Tedizolid 200 mg once daily for 6 days (n = 662) n (%)	Linezolid 600 mg twice daily for 10 days (n = 662) n (%)
Normal hepatic function	474 (71.6)	443 (66.9)
≥1 TEAE	202 (42.6)	183 (41.3)
TEAE leading to discontinuation	1 (0.2)	3 (0.7)
≥1 SAE[a]	9 (1.9)	7 (1.6)
Hepatic impairment	14 (2.1)	12 (1.8)
≥1 TEAE	3 (21.4)	5 (41.7)
TEAE leading to discontinuation	0 (0)	0 (0)
≥1 SAE[a]	1 (7.1)	2 (16.7)
Hepatic disease	175 (26.4)	209 (31.6)
≥1 TEAE	78 (44.6)	98 (46.9)
TEAE leading to discontinuation	2 (1.1)	3 (1.4)
≥1 SAE[a]	2 (1.1)	4 (1.9)

SAE, serious adverse events; TEAE, treatment-emergent adverse events.
[a]Includes deaths.

CONCLUSIONS

- There was no DISH signal in a safety database from Phase 2 and Phase 3 clinical trials in ABSSSI.
- TEAE profiles were similar for Phase 3 tedizolid- and linezolid-treated patients with hepatic impairment/hepatic disease and those with normal hepatic function, suggesting no worsening of hepatic function with treatment.
- The findings suggest that tedizolid is not hepatotoxic and can be safely used at recommended doses in patients with hepatic impairment or hepatic disease.

ACKNOWLEDGMENTS

Editorial support for this poster was provided by ApotheCom ScopeMedical, Yardley, PA, and funded by Cubist Pharmaceuticals, Lexington, MA. The authors would like to thank Howard Dreskin (Cubist Pharmaceuticals) for on-site support at IDWeek 2014.

REFERENCES

1. Brown SD et al. *Antimicrob Agents Chemother.* 2010;54:2063-2069.
2. Schaadt R, et al. *Antimicrob Agents Chemother.* 2009;53:3236-3239.
3. Thomson KS et al. *Antimicrob Agents Chemother.* 2013;57:2892-2895.
4. Locke JB et al. *Antimicrob Agents Chemother.* 2010;54:5337-5343.
5. SIVEXTRO® (tedizolid phosphate) [prescribing information]. Lexington, MA: Cubist Pharmaceuticals US; 2014.
6. Prokocimer P et al. *JAMA.* 2013;309:559-569.
7. Moran GJ et al. *Lancet Infect Dis.* 2014;14:696-705.