Clinical Response of Tedizolid Versus Linezolid in Acute Bacterial Skin and Skin Structure Infections by Severity Measure: Pooled Analysis of Two Phase 3 Double-Blind Trials

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ABSTRACT

INTRODUCTION. There is no consensus on defining disease severity in acute bacterial skin and skin structure infection (ABSSSI) trials. In 2 ABSSSI, noninferiority Phase 3 trials (ESTABLISH-1 and ESTABLISH-2), 6 days of tedizolid, a novel oxazolidinone antibacterial, demonstrated noninferior efficacy to 10 days of linezolid. In this prespecified subgroup analysis, the effect of different measures of disease severity at baseline (lesion size, fever, increased white blood cell count, Systemic Inflammatory Response Syndrome [SIRS], lymphadenopathy, and presence of immature neutrophils [bands]) on clinical response was investigated.

METHODS. Eligible patients were randomized 1:1 to receive 200 mg tedizolid once daily for 6 days or 600 mg linezolid twice daily for 10 days. ESTABLISH-1 patients received oral therapy, whereas ESTABLISH-2 patients received IV therapy with an optional switch to oral. The primary end point was early clinical response (≥20% reduction in lesion area compared to baseline at 48 to72 hours after start of study drug). Investigator-assessed clinical response at the posttherapy evaluation (PTE; 7-14 days posttherapy) was a key secondary end point. Response rates to therapy were compared between tedizolid and linezolid with and without the presence of specified measures of disease severity at screening.

RESULTS. Among the 1333 patients in the pooled intent-to-treat population, there was no difference in the specified measures of disease severity between patients randomized to tedizolid (N = 664) and linezolid (N = 669). Early clinical response rates were similar between the tedizolid and linezolid treatment groups across all evaluated severity subgroups. Similar response rates between the 2 antibacterials were also maintained for investigator-assessed clinical response at PTE across all evaluated measures of severity.

CONCLUSIONS. In the pooled data for these 2 Phase 3 trials for ABSSSI, 6 days of tedizolid was consistently noninferior to 10 days of linezolid, regardless of the measure of disease severity used.

INTRODUCTION

- The high prevalence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) as a cause of acute bacterial skin and skin structure infections (ABSSSI) in some regions of the world underscores the need for novel treatment options.[1]
- Although there is no consensus on defining disease severity in ABSSSI, a number of baseline markers have been used as disease severity criteria in clinical trials, including lesion size, fever, leukocytosis, sepsis criteria (Systemic Inflammatory Response Syndrome [SIRS] plus known or suspected infection), lymphadenopathy, and presence of immature neutrophils (bands).[2,3]
- 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.[4-6]
- 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.[7,8]
- In June 2014, the US Food and Drug Administration (FDA) approved tedizolid phosphate for treatment of ABSSSI caused by susceptible Gram-positive pathogens, including MRSA.[9]
- In the present prespecified pooled subgroup analysis of tedizolid Phase 3 studies, we assessed the effect of different baseline disease severity markers on clinical response in patients with ABSSSI.

METHODS

- ESTABLISH-1 and ESTABLISH-2 were randomized, double-blind, noninferiority Phase 3 clinical trials in patients with ABSSSI; the study designs of both trials have been described in detail previously.[7,8]
- Patients were randomized 1:1 to tedizolid 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days.
- ESTABLISH-1 patients received oral therapy exclusively, whereas ESTABLISH-2 patients first received intravenous therapy for 24 hours, then could be switched to oral study drug when prespecified clinical improvement criteria were met.
- Key inclusion criteria
  - Cellulitis/erysipelas, wound infection, or major cutaneous abscess, each with a surface lesion area ≥75 cm^2; wound infections and abscesses also required erythema extending ≥5 cm from the edge of the wound or abscess to the lesion margin
  - At least 1 regional or systemic sign of infection (lymphadenopathy, temperature ≥38°C [fever], white blood cell count ≥10 000 cells/mm^3 or <4000 cells/mm^3, or ≥10% immature neutrophils)
  - Suspected/documented Gram-positive pathogen
  - Age ≥18 years (ESTABLISH-1) and ≥12 years (ESTABLISH-2)
- Key exclusion criteria
  - Uncomplicated or Gram-negative ABSSSI
  - Use of any systemic or topical antibiotic with Gram-positive activity within 96 hours before the first dose of study drug
  - Previous treatment failure of same infection site
  - Infections close to prosthetic devices, severe sepsis, or known bacteremia at time of enrollment
  - Confirmed immunocompromised status (recent history of opportunistic infections with active underlying cause or receipt of systemic immunosuppressive therapy)

End Points

- The primary end point was early clinical response, defined as a reduction in lesion area of ≥20% at 48 to 72 hours after start of the study drug.
- A key secondary end point was investigator-assessed clinical response at the posttherapy evaluation (PTE; 7 to 14 days after end of therapy).

Analyses

- Data from both studies were pooled and the effect of the following specified measures of disease severity at baseline on clinical response was evaluated:
  - Lesion area (>300 cm^2 vs ≤300 cm^2)
  - Fever (temperature ≥38°C) at baseline (Yes vs No)
  - Increased WBC (≥10 000 cells/mm^3) at baseline (Yes vs No)
  - SIRS (Yes vs No)
    - SIRS defined as 2 or more of the following: temperature <36°C or >38°C; heart rate >90 beats/min; respiration rate >20 breaths/min; WBC <4000 cells/mm^3 or 12 000 cells/mm^3; or >10% bands
  - Lymphadenopathy (Yes vs No)
  - Presence of immature neutrophils (bands; >10% vs ≤10%)

RESULTS

- Pooled efficacy data from 1333 patients in the intent-to-treat (ITT) population (tedizolid, N = 664; linezolid, N = 669) were included in the current analysis.
  - No difference in the proportions of patients with specified baseline disease severity markers was seen between the 2 treatment groups (**Table 1**).

Table 1. Measures of Disease Severity at Baseline in the Tedizolid and Linezolid Treatment Groups

Measure of Disease Severity	Tedizolid 200 mg once daily for 6 days (N = 664) n (%)	Linezolid 600 mg twice daily for 10 days (N = 669) n (%)
Lesion area		
>300 cm^2	228 (34.3)	220 (32.9)
≤300 cm^2	436 (65.7)	449 (67.1)
Fever at baseline		
Yes	159 (23.9)	160 (23.9)
No	505 (76.1)	509 (76.1)
Increased WBC		
Yes	316 (47.6)	284 (42.5)
No	348 (52.4)	385 (57.5)
SIRS		
Yes	163 (24.5)	128 (19.1)
No	501 (75.5)	541 (80.9)
Lymphadenopathy		
Yes	524 (78.9)	524 (78.3)
No	140 (21.1)	145 (21.7)
Presence of immature neutrophils (bands)		
>10%	76 (11.4)	56 (8.4)
≤10%	588 (88.6)	613 (91.6)

SIRS, Systemic Inflammatory Response Syndrome; WBC, white blood cell.

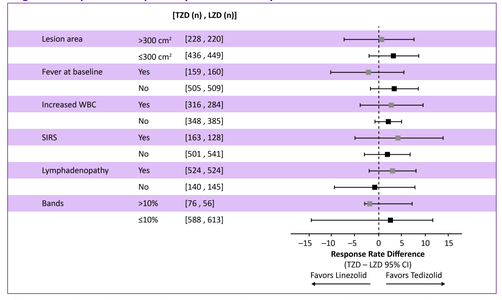
- Early clinical response rates were similar between the tedizolid and linezolid treatment groups across all disease severity subgroups (**Table 2** and **Figure 1**).

Table 2. Early Clinical Response Rates by Disease Severity Subgroups in the Tedizolid and Linezolid Treatment Groups

Measure of Disease Severity	Tedizolid 200 mg once daily for 6 days (N = 664) n/N (%)	Linezolid 600 mg twice daily for 10 days (N = 669) n/N (%)
Lesion area		
>300 cm^2	183/228 (80.3)	176/220 (80.0)
≤300 cm^2	359/436 (82.3)	355/449 (79.1)
Fever at baseline		
Yes	135/159 (84.9)	138/160 (86.3)
No	407/505 (80.6)	393/509 (77.2)
Increased WBC		
Yes	251/316 (79.4)	217/284 (76.4)
No	291/348 (83.6)	314/385 (81.6)
SIRS		
Yes	133/163 (81.6)	100/128 (78.1)
No	409/501 (81.6)	431/541 (79.7)
Lymphadenopathy		
Yes	424/524 (80.9)	408/524 (77.9)
No	118/140 (84.3)	123/145 (84.8)
Presence of immature neutrophils (bands)		
>10%	64/76 (84.2)	48/56 (85.7)
≤10%	475/588 (81.3)	483/613 (78.8)

SIRS, Systemic Inflammatory Response Syndrome; WBC, white blood cell.

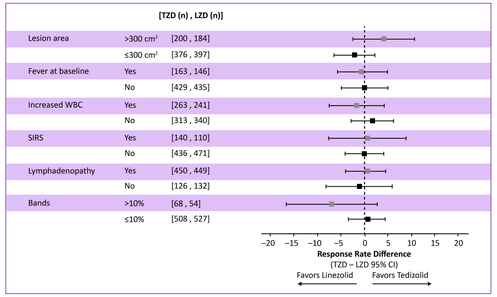
Figure 1. Early Clinical Response by Disease Severity Measures



CI, confidence interval; LZD, linezolid; SIRS, Systemic Inflammatory Response Syndrome; TZD, tedizolid; WBC, white blood cell.
Note: difference is the weight treatment difference (weighted by study) and the CI is adjusted for study.

- Similar clinical response rates between tedizolid and linezolid were also observed at PTE across all evaluated measures of disease severity (**Figure 2**).

Figure 2. Investigator-Assessed Clinical Response at the Posttherapy Evaluation by Severity Measures



CI, confidence interval; LZD, linezolid; SIRS, Systemic Inflammatory Response Syndrome; TZD, tedizolid; WBC, white blood cell.
Note: difference is the weight treatment difference (weighted by study) and the CI is adjusted for study.

CONCLUSIONS

- This subgroup analysis of the pooled efficacy data from ESTABLISH-1 and ESTABLISH-2 showed that early clinical response rates (at 48 to 72 hours) and outcomes 7 to 14 days posttherapy with tedizolid and linezolid were similar, regardless of disease severity at baseline or how disease severity was measured.
- The findings of this pooled analysis suggest that tedizolid once daily for 6 days was noninferior to linezolid twice daily for 10 days for the treatment of ABSSSI, irrespective of disease severity at baseline and timing of end point evaluation.

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