Effect of NSAID/Corticosteroid Use on the Efficacy of Tedizolid in Acute Bacterial Skin and Skin Structure Infection: Pooled Data From the Phase 3 ESTABLISH-1 and ESTABLISH-2 Studies

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ABSTRACT

INTRODUCTION. Tedizolid is a novel oxazolidinone with potent activity against a wide range of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and with a favorable safety profile. 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 acute bacterial skin and skin structure infections (ABSSSI). Use of nonsteroidal anti-inflammatory drugs (NSAID) and/or corticosteroids (CS) is common in patients with ABSSSI. Due to their anti-inflammatory properties, it is possible that concomitant use of these agents may reduce lesion size and confound the primary outcome of ≥20% reduction in lesion size at the 48- to 72-hour visit. This subgroup analysis of pooled data from ESTABLISH-1 and ESTABLISH-2 examined the effect of concomitant NSAID/CS use on early clinical response in patients with ABSSSI receiving tedizolid or linezolid.

METHODS. Patients with ABSSSI (lesion surface area ≥75 cm^2 and ≥1 regional or systemic sign of infection) received tedizolid 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days. The use of NSAID/CS was documented for each patient and the primary outcome for both therapies at the 48- to 72-hour visit was compared between patients with and without NSAID/CS use.

RESULTS. A total of 1333 patients were randomly assigned to receive tedizolid or linezolid. Patients were mostly male (63.1%); the average age was 44 years. The most common ABSSSI was cellulitis (45.3% and 45.9% in tedizolid and linezolid treatment groups, respectively), followed by major cutaneous abscess (25.3% and 24.8%) and wound infections (29.4% and 29.3%). Overall, 44 of 664 patients (6.6%) in the tedizolid treatment group and 63 of 669 patients (9.4%) in the linezolid group received NSAID or oral CS during the first 72 hours of treatment. Among patients receiving NSAID/CS, early clinical response rates at 48 to 72 hours were similar between the tedizolid and linezolid groups (70.5% vs 69.8%), but lower overall compared with patients not receiving NSAID/CS (82.4% with tedizolid vs 80.4% with linezolid).

CONCLUSION. Early clinical response rates were similar in patients treated with either tedizolid or linezolid for ABSSSI in the ESTABLISH-1 and ESTABLISH-2 trials, regardless of NSAID/CS use. This finding suggests that there is an absence of bias with anti-inflammatory drug use in assessing early clinical response rates in ABSSSI clinical trials.

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]
- 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.[4,5]
  - The primary outcome of these trials—early clinical response—was defined as ≥20% reduction in lesion size at the 48- to 72-hour visit.
- Nonsteroidal anti-inflammatory drugs and corticosteroids (NSAID/CS) are a frequently prescribed adjunctive treatment for patients with skin infections, particularly cellulitis, to reduce signs of inflammation.[6]
  - In patients with cellulitis, evidence suggests that supplemental anti-inflammatory therapy might hasten the resolution of infection, thereby confounding the primary outcome of clinical response, as measured by change in lesion size.[6,7]
- This subgroup analysis of pooled data from the Phase 3 trials analyzed the effect of NSAID/CS use on early clinical response in patients with ABSSSI being treated with tedizolid or linezolid.

METHODS

Study Design

- ESTABLISH-1 (NCT01170221) and ESTABLISH-2 (NCT01421511) were randomized, double-blind, double-dummy, multicenter, multinational, noninferiority Phase 3 clinical trials in patients with ABSSSI.
- 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 could then be switched to oral study drug when prespecified clinical improvement criteria were met.

Patient Selection

- Key inclusion criteria
  - Diagnosis of ABSSSI (cellulitis/erysipelas, major cutaneous abscess, or wound infection)
  - Lesion surface 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 immature neutrophils >10%)
  - 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
  - Use of monoamine oxidase inhibitors or serotonergic agents
  - Previous unsuccessful treatment 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)

Select End Point

- The primary end point was ≥20% reduction in lesion area 48 to 72 hours after the first dose of drug (early response) without having received nonstudy systemic antibacterial treatment for any reason for a period of 72 hours from the first dose of study drug.

Analysis Population

- This subgroup analysis used pooled data from the intent-to-treat populations of both Phase 3 clinical trials to compare the primary end point in patients who used NSAID/CS up through 72 hours after the first dose of study drug versus patients who did not.

RESULTS

- When the primary end point for clinical response was assessed, less than 10% of patients had received an NSAID or oral CS through the 72 hours after the first dose of study drug (**Table 1**).
- NSAID/CS were used by 44 of 664 patients treated with tedizolid (6.6%) and by 63 of 669 patients treated with linezolid (9.4%).
- Other baseline characteristics (**Table 1**):
  - Cellulitis was the most common ABSSSI (45.3% in the tedizolid group and 45.9% in the linezolid group).
  - Median lesion area was 197.1 cm^2 and 210.0 cm^2 in the tedizolid and linezolid groups, respectively.
  - At baseline, approximately 25% of patients had a temperature ≥38°C (fever), and 40% to 50% had a white blood cell count ≥10 000 cells/mm^3 or <4000 cells/mm^3.
  - The majority of patients for whom a pathogen was isolated had *S. aureus* infection (81.0% to 83.0%), of which more than one third was caused by MRSA.

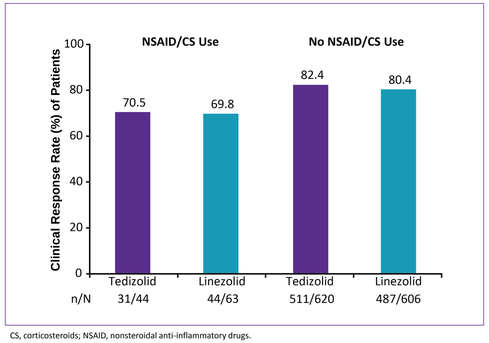
Table 1. Demographic and Clinical Characteristics of Pooled Phase 3 Study Population Were Similar Between Treatment Groups (ITT Population)

Characteristic	Tedizolid 200 mg once daily for 6 days (N = 664)	Linezolid 600 mg twice daily for 10 days (N = 669)
Age, median (range) (years)	44.5 (17–86)	44.0 (15–100)
Male, n (%)	429 (64.6)	412 (61.6)
Temperature ≥38°C (fever), n (%)	155 (23.3)	157 (23.5)
White blood cell count ≥10 000 cells/mm^3 or <4000 cells/mm^3, n (%)	316 (47.6)	284 (42.5)
Type of ABSSSI, n (%)		
Cellulitis/erysipelas	301 (45.3)	307 (45.9)
Major cutaneous abscess	168 (25.3)	166 (24.8)
Infected wound	195 (29.4)	196 (29.3)
Lesion area, median (range) (cm^2)	197.1 (22.5–5572.8)	210.0 (627.0–5220.0)
At least 1 Gram-positive ABSSSI identified at baseline, n	406	412
Staphylococcus aureus, n (%)[a]	329 (81.0)	342 (83.0)
MRSA	141 (34.7)	146 (35.4)
MSSA	188 (46.3)	198 (48.1)
β-hemolytic streptococci, n (%)[a]	43 (10.6)	29 (7.0)
Streptococcus anginosus-milleri Group, n (%)[a]	30 (7.4)	28 (6.8)
Enterococcus spp, n (%)[a]	10 (2.5)	6 (1.5)
NSAID/CS use, n (%)[b]	44 (6.6)	63 (9.4)

ABSSSI, acute bacterial skin and skin structure infection; CS, corticosteroids; ITT, intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; NSAID, nonsteroidal anti-inflammatory drugs.
[a]Percentages for bacterial isolates were calculated using number of patients with at least 1 Gram-positive ABSSSI identified at baseline as the denominator.
[b]Up through 72 hours after the first dose of study drug.

- In patients using and not using NSAID/CS, early clinical responses rates were similar between tedizolid and linezolid treatment groups (**Figure 1**).

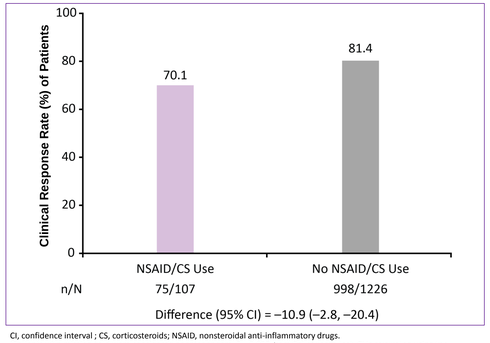
Figure 1. Early Clinical Response Rates Were Similar Between Treatment Groups With or Without NSAID/CS Use[a]



CS, corticosteroids; NSAID, nonsteroidal anti-inflammatory drugs.
[a]Patients with missing data were considered nonresponders.

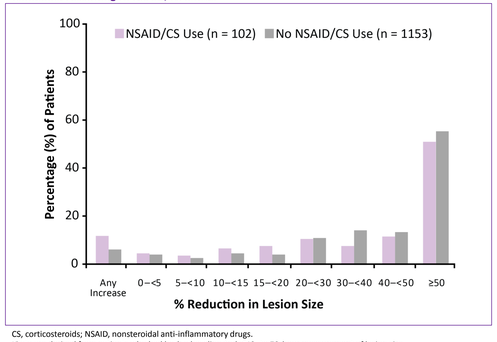
- Early clinical response rates were lower overall among patients using NSAID/CS compared with those not using NSAID/CS (**Figures 2** and **3**).

Figure 2. Early Clinical Response Across Treatment Groups (Combined) Was Lower Among Patients Using NSAID/CS[a]



CI, confidence interval ; CS, corticosteroids; NSAID, nonsteroidal anti-inflammatory drugs.
[a]Patients with missing data were considered nonresponders. *P* = 0.025 from Chi-squared test. CI is calculated using the methodology of Miettinen and Nurminen.

Figure 3. Distribution of Reductions in Lesion Size at 48 to 72 Hours in Both Treatment Groups Combined According to NSAID/CS Status[a]



CS, corticosteroids; NSAID, nonsteroidal anti-inflammatory drugs.
[a]Data are derived from patients who had both a baseline and a 48- to 72-hour measurement of lesion size.

CONCLUSIONS

- Early clinical response rates were similar between tedizolid and linezolid treatment groups in patients with and without NSAID/CS.
  - This finding suggests that use of anti-inflammatory agents did not bias the assessment of early clinical response in the ESTABLISH-1 and ESTABLISH-2 Phase 3 ABSSSI studies.
- Patients taking anti-inflammatory agents had lower response rates, defined by a ≥20% reduction in lesion size at 48 to 72 hours, across both arms, challenging previous findings that anti-inflammatory agents hastened improvement of ABSSSI lesions, defined as reduction in lesion size.

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