Cessation of Spread of Lesion and Absence of Fever at 72 hours in Complicated Skin and Skin Structure Infection (cSSSI): Reanalysis of the Combined ASSIST Phase III Studies Comparing Iclaprim (ICL) and linezolid (LZD)

David Huang, MD, PhD, Mark Wilcox, MD, Matthew Dryden, MD, Paul Hadvary, PhD, Ralph Corey, MD

Background

Iclaprim (ICL), a new generation diaminopyrimidine compound, is a dihydropyrimidine reductase inhibitor antibiotic in clinical development. The efficacy of ICL was tested in two identical randomized double-blind Phase III clinical trials comparing ICL to LZD in the treatment of patients with cSSSI. The endpoint of cessation of spread of lesion and absence of fever was evaluated at a 72 hour visit using the combined data.

Methods

Patients with cSSSI were treated for 10–14 days with IV ICL 0.8 mg/kg q12 hours or IV linezolid (LZD) 600 mg q12 hours. Outcomes were reanalyzed applying cessation of spread of lesion/erythema as well as absence of fever at 72 hours in intent-to-treat (ITT) population.

Results

The total ITT population comprised 911 (ICL: 500; LZD: 411). The distribution of infection types was very similar in both treatment groups and encompassed wound infections (50%), cellulitis (38%), major abcesses (26%), infected ulcers (11%) and first- or second-degree burns (10%). Staphylococcus aureus (591 isolates) accounted for 69% of all Gram-positive isolates, of which 39.9% were methicillin-resistant (MRSA). 73% had a fever >38°C, and 94% had an erythema score of moderate or severe. A high lesion response and fever resolution occurred at 72 hours in the ITT population: 73.6% (95% CI = 69.3–77.4%) for ICL and 72.5% (95% CI = 68.5–76.4%) for LZD recipients (difference 1.1%, 95% CI = –4.5% to 6.6%).

Conclusion: At 72h, ICL achieved a high rate of cessation of spread of erythema and fever resolution in patients with cSSSI. This was comparable to that seen with LZD.

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Early Clinical Response Assessment

A 72 hours early clinical response was defined as at a 72 hour visit by assessing the number of patients who had a cessation of spread of lesion/erythema as well as absence of fever at 72 hours among the ITT population.

Methods

Study Design

Both ASSIST studies were randomized, multi-center, double-blind, Phase III studies of essentially identical design

Based on the identical design of the two ASSIST studies, a combined analyses was possible by merging the datasets into a single database to evaluate the efficacy and safety of ICL compared to LZD.

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Both treatment groups were well-balanced with respect to demographics, infection type, and identified bacteria at baseline.

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In this reanalysis of the ASSIST studies, the endpoint of cessation of spread of lesion and absence of fever was evaluated at a 72 hour visit among the Intent-to-Treat Population (ITT).

The ITT population included all randomized patients who received at least one dose of study medication.

Patient Population

Hospitalized patients diagnosed with cSSSI suspected or proven to be caused by Gram-positive bacteria were included in the ASSIST studies.

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A preliminary early clinical response was defined at a 72 hour visit by assessing the number of patients who had a cessation of spread of lesion/erythema as well as absence of fever at 72 hours among the ITT population.

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Figure 1: Frequency of Infection Type at Baseline in the ITT Population.

Figure 2: Eradication/Presumed Eradication (% of Baseline Pathogens in the MITT Population.

Table 1: Early Clinical Response Assessment in the ITT Population.

<table>
<thead>
<tr>
<th>ASSIST-1</th>
<th>ASSIST-2</th>
<th>Combined</th>
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<tbody>
<tr>
<td>ICL</td>
<td>LZD</td>
<td>ICL</td>
</tr>
<tr>
<td>N</td>
<td>249</td>
<td>249</td>
</tr>
<tr>
<td>Responder</td>
<td>184 (73%)</td>
<td>177 (71%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>69.1–79.2%</td>
<td>68.0–79.7%</td>
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<tr>
<td>Difference</td>
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<td>–4.9%</td>
</tr>
<tr>
<td>95% CI</td>
<td>–5.4%–10.4%</td>
<td>–4.6%–7.7%</td>
</tr>
</tbody>
</table>

Conclusions

• At 72h, ICL achieved a high rate of cessation of spread of erythema and fever resolution in patients with cSSSI. This was comparable to that seen with LZD.

• ICL is a potential important new therapeutic option for treatment of cSSSI, especially those caused by MRSA.

• Pivotal clinical trials are warranted to evaluate ICL for the indication of acute bacterial skin and skin structure infections.

Reference


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