Novel Ribosome Inhibitors are Efficacious in a Murine Skin and Soft Tissue Infection Model Caused by Klebsiella pneumoniae

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Abstract

Background

There is a dearth of new antibiotic agents with which to treat serious Gram-negative and Gram-positive infections. Of particular concern are hospital-acquired and bloodstream infections caused by methicillin-resistant Staphylococcus aureus (MRSA). The latest trend in antibiotic development has been to target bacterial translation and generate novel compounds to inhibit protein synthesis at the 30S ribosomal subunit. Despite these advances, and the advent of high-throughput screening strategies, generating new antibiotics with broad activity against Gram-negative and Gram-positive pathogens remains a daunting task.

Methods

Antimicrobials were studied in a murine skin and soft tissue infection (SSTI) model caused by Klebsiella pneumoniae. RX-04 compounds were orally administered at 1, 2, and 4 log10 cfu compared with untreated controls at the start of therapy. Efficacy was defined as a 4-log10 cfu decrease in bacterial burden compared with untreated controls at 24 hours post-inoculation.

Results

Exemplar RX-04 compounds from a novel chemical series have demonstrated efficacy in a murine SSTI model caused by K. pneumoniae. Bacterial load reductions of 1–4 log10 cfu were observed between 24 and 48 hours post drug administration using an LC/MS/MS assay. In addition, we examined the plasma and tissue pharmacokinetics of select compounds to determine the tissue exposures. For each compound, the ratio of tissue (AUC) to plasma AUC (tissue:plasma ratio) was calculated to determine plasma-supplied areas of high concentration, potentially increasing drug delivery to antimicrobial target sites.

Conclusions

• Four RX-04 compounds were used to demonstrate efficacy in the 5.0 log10 cfu murine SSTI model.
• In order of best efficacy, RX-P569 > RX-P770 > RX-P907 > RX-P724.
• RX-P569 had the lowest MICs against this organism, as well as the highest plasma exposures, correlating with the best efficacy.
• Tissue exposure levels of RX-P569 were superior in a go/no go model of in vitro efficacy demonstrated by this compound.

Keywords: antibiotics, Gram-negative, Gram-positive, MRSA, SSTI, pharmacokinetics, structure-based drug design

Introduction

Antibacterial agents to treat serious Gram-negative and Gram-positive infections often fall short due to bacterial resistance, poor tissue penetration or toxicity, leaving clinicians with few therapeutic options. To address this issue, we have used structure-based drug design to generate compounds in these chemical classes to address the bacterial disease and target a broad range of clinically relevant bacterial pathogens. These compounds have demonstrated efficacy in murine and neutropenic murine thigh infection models.

Materials and Methods

Antimicrobials agents to treat serious Gram-negative and Gram-positive infections were selected based on their tissue penetration or toxicity, leaving clinician with few therapeutic options. To address this issue, we have used structure-based drug design to generate compounds in these chemical classes to address the bacterial disease and target a broad range of clinically relevant bacterial pathogens. These compounds have demonstrated efficacy in murine and neutropenic murine thigh infection models.

Microorganisms and compounds

Klebsiella pneumoniae strain ATCC 5732 was used as a positive control in these studies. The bacterial strain used in these studies was K. pneumoniae (ATCC 700603). RX-P569, RX-P770, RX-P724, and RX-P907 demonstrated a log10 cfu reduction of 1.0, 4.2, 4.0, and 3.7, respectively (Figure 1A and 1B).

We also determined the plasma AUC for these compounds. When dosed at 10 mg/kg, the exposures for these compounds were found to be between 10 and 50 µg*hr/mL. In contrast, Ciprofloxacin had a plasma exposure of ~200 µg*hr/mL (Table 1). These data demonstrate the potential anti-infective effect of these compounds.

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC vs. K. pneumoniae (µg/mL)</th>
<th>Plasma AUC (µg*hr/mL)</th>
<th>Thigh muscle AUC (µg*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX-P569</td>
<td>0.06</td>
<td>21.3</td>
<td>ND</td>
</tr>
<tr>
<td>RX-P770</td>
<td>0.125</td>
<td>9.8</td>
<td>ND</td>
</tr>
<tr>
<td>RX-P724</td>
<td>0.25</td>
<td>20.0</td>
<td>0.35</td>
</tr>
<tr>
<td>RX-P907</td>
<td>0.5</td>
<td>16.5</td>
<td>ND</td>
</tr>
</tbody>
</table>

Results

The plasma concentrations reached a peak at ~1 hour post dosing and decreased rapidly over time in all cases. The plasma AUCs were highest at 10 mg/kg and decreased with increasing dose. In this model, the efficacy was determined by monitoring bacterial burden in thigh tissue at 24 hours post drug administration using an LC/MS/MS assay.

Materials

Female CD-1 mice (weighing 20 – 25 g) were used for all studies. Mice were held in quarantine for one week after arrival to the facility prior to being put on study. The bacterial strain used in these studies was K. pneumoniae (ATCC 700603). RX-P569, RX-P770, RX-P724, and RX-P907 demonstrated a log10 cfu reduction of 1.0, 4.2, 4.0, and 3.7, respectively (Figure 1A and 1B).

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References


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