TP-434 Has Potential to Treat Complicated Urinary Tract Infections (cUTI)

J. SUTCLIFFE1*, T. GROSSMAN1, M. RONN1, X. XIAO1, A. LEIGHTON2
1Tetraphase Pharmaceuticals, Inc., Watertown, MA; 2Medical Consultant, San Francisco

Background: TP-434 is a novel broad-spectrum fluorocycline being developed by Tetraphase Pharmaceuticals for a wide range of infections, including both Gram-negative and Gram-positive bacteria. TP-434 could be an important addition to treatment of cUTI.

Methods: MBCs of TP-434 were done using CLSI standard procedures. Female BALB/c mice were infected with 10^8 bacteria in 0.2 ml of 0.9% saline into the bladder to establish pyelonephritis. TP-434 was administered IV and orally in urine and in healthy subjects after IV or oral administration were evaluated using validated biochemical assay procedures.

Results: TP-434 has an excellent spectrum: empiric treatment of cUTI caused by either gram-negative or gram-positive bacteria, with MBC/MIC values of 0.065 to 0.65 and 0.006 to 0.03 µg/ml against 176 Escherichia coli and 219 Klebsiella pneumoniae isolates, respectively, and MBC/MIC at 1:1 µg/ml, except anecdotally in resistant (multiple isolates) in MRSA and admission for 24 hours. In vitro studies showed that TP-434 is bactericidal against uropathogens. After 2 hours of treatment with 1.5 mg/kg IV fluoroquinolone, the uropathogen rate, the rate of infection increased by 30 days or 10 days. A single mouse dose of 2 mg/kg provided urine levels in excess of 1 µg/ml over the 24-hour period following ingestion.

Conclusions: The combination efficacy of TP-434 for key uropathogens such as enterococci in pyelonephritis along with its ability to provide urine levels at multiplicities above target MICs support further evaluation for use in an oral/IV step-down therapy for cUTI/pyelonephritis.

Abstract

Introduction

Incidence of uropathogens and pyelonephritis. A recent population-based study showed a rapid rise of pyelonephritis, the most severe complication of UTIs (3). The current treatments for UTIs are often inadequate because of the high rate of resistance, and the cost of treatment is too high. In a recent study, 43% of patients with UTIs were treated with antibiotics, which is an important reason for the high rate of resistance. In a recent study, 43% of patients with UTIs were treated with antibiotics, which is an important reason for the high rate of resistance. In this study, we evaluated the efficacy and safety of TP-434 in the treatment of cUTI.

Methods

TP-434 MIC, MBC, Values for Organisms of Major cUTI (gram-negative and gram-positive isolates)

<table>
<thead>
<tr>
<th>Number of Isolates</th>
<th>Organism</th>
<th>MBC (µg/ml)</th>
<th>MBC/MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>E.coli</td>
<td>0.006</td>
<td>0.001</td>
</tr>
<tr>
<td>15</td>
<td>K.pneumonia</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

References