Clinical and bacteriologic efficacy of telithromycin in patients with bacteremic community-acquired pneumonia

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Summary This retrospective analysis was performed to determine the clinical and bacteriologic efficacy of the ketolide antibacterial telithromycin in patients with community-acquired pneumonia (CAP) with pneumococcal bacteremia. Patients ≥ 13 years old with radiologically confirmed CAP and a positive blood culture for Streptococcus pneumoniae at screening were analyzed from eight multicenter Phase III/IV clinical trials. In four open-label, non-comparative studies, patients received telithromycin 800 mg once daily for 7–10 days. In four randomized, controlled, double-blind, comparative studies, patients received telithromycin 800 mg once daily for 5–10 days or a comparator antimicrobial (amoxicillin 1000 mg three times daily, clarithromycin 500 mg twice daily, or trovafloxacin 200 mg once daily) for 7–10 days. In total, 118 patients (telithromycin, 94/1061 [8.9%]; comparator, 24/244 [9.8%]) had documented pneumococcal bacteremia. Those who were treated with telithromycin achieved a clinical cure rate of 90.2% (74/82, per-protocol population); S. pneumoniae was eradicated in 77/82 (93.9%) bacteremic patients who received telithromycin and 15/19 (78.9%) comparator-treated patients. Clinical cure was also observed among telithromycin-treated bacteremic patients who were infected with penicillin- or erythromycin-resistant strains of S. pneumoniae (5/7 and
8/10, respectively). In conclusion, telithromycin achieves high clinical and bacteriologic cure rates in CAP patients with pneumococcal bacteremia.

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Introduction

Community-acquired pneumonia (CAP) causes considerable morbidity, with one of the most serious complications being the progression to bacteremia and further septic complications. Studies conducted by Fang et al. established that bacteremia occurs more frequently in patients with pneumonia caused by Streptococcus pneumoniae (16/55 [29%]) compared with other etiologies, while work reported by Bishara et al. confirmed that the microorganism most frequently isolated from patients with CAP bacteremia is S. pneumoniae (46% [n = 4548]). Recent estimates suggest that the annual incidence of pneumococcal bacteremia in the USA is about 15–30 cases/100,000 population, 60–87% of which are associated with pneumococcal pneumonia in adults.6 Data from some studies have indicated that up to 50% of all patients with bacteremic pneumococcal pneumonia may develop complications, such as respiratory failure, meningitis, pleural effusions, and empyema.4 Furthermore, mortality rates in studies of bacteremic pneumococcal CAP patients were considerably higher (18.6%) than in studies of hospitalized and ambulatory patients with pneumococcal CAP (8.1%).5 The relative risk of bacteremia is significantly higher in young children (aged ≤ 2 years), the elderly (aged ≥ 65 years), and those with impaired immunity, asplenia, or comorbid conditions, such as diabetes mellitus.4 Cigarette smoking and alcohol abuse are also known risk factors for bacteremic pneumococcal pneumonia.6–8

With the increasing shift towards outpatient therapy, there is a growing risk that some outpatients will have bacteremia. In a study by Campbell et al. of 760 patients with CAP, 43 (5.7%) patients had positive blood cultures. However, severity of illness as measured by Fine score9 correlated poorly with the incidence of bacteremia in these patients. Thus, while 32/622 (5.1%) patients in Fine classes III–V were bacteremic, 11/138 (8.0%) patients in the lower-risk classes (Fine classes I and II)—patients whom physicians might be encouraged to treat on an outpatient basis—also had positive blood cultures. To add to this risk, the rising incidence of antimicrobial resistance among strains of S. pneumoniae is a growing concern. Current estimates suggest that up to 40% of S. pneumoniae isolates worldwide show resistance to penicillin, although considerable regional variation exists.10 Resistance to macrolides among isolates of S. pneumoniae is also increasing worldwide,10 with the prevalence of resistance to erythromycin exceeding the rates of penicillin resistance in most countries.11 Emergence of pneumococcal resistance to fluoroquinolones is a more recent concern and is associated with increased use of these agents.12,13 Thus, there is an appreciable risk that some patients with CAP will not only be bacteremic but also have a resistant pathogen. If cultures are not obtained—as is often the case with outpatients—and if the efficacy of the prescribed antibiotic is hampered by resistance or marginal potency, these patients may progress to sepsis with rapid clinical deterioration or suppurative complications. It is therefore of great importance that empiric treatment given for CAP in the outpatient setting provides reliable first-line efficacy.

Telithromycin is the first of a new class of semisynthetic antibacterials—the ketolides—structurally related to the macrolides, and was developed specifically to provide a spectrum of antibacterial activity targeted for the effective treatment of community-acquired respiratory tract infections (RTIs) caused by either common or atypical/intracellular pathogens. Importantly, telithromycin shows potent in vitro activity against S. pneumoniae, including strains that are resistant to penicillin and erythromycin.14 The clinical and bacteriologic efficacy of telithromycin in patients with CAP has been demonstrated in eight recent multinational Phase III/IV clinical trials15–21 (sanofi-aventis, data on file). Data from six of these trials have previously been assessed by Barman Balfour and Figgitt.22 The aim of this analysis is to review the clinical and bacteriologic efficacy of telithromycin among the subset of patients with pneumococcal bacteremia who were included in the eight trials.

Methods

Patient population and design of studies

Data from eight international, multicenter Phase III/IV clinical studies conducted between February 1998 and February 2002 were pooled and analyzed
Efficacy of telithromycin in bacteremic CAP

Clinical and bacteriologic outcomes

In the Phase III/IV studies, clinical and bacteriologic assessments were made at five visits: Day 1 (pretherapy/entry), Days 3–5 (on-therapy), Days 11–13 (end of therapy), Days 17–24 (post-therapy/test of cure), and Days 31–45 (late post-therapy).

Clinical outcome was assessed by the investigator, based on clinical signs and symptoms and X-ray findings, and classified as cure, failure, or indeterminate. Clinical cure was defined as the disappearance or return to pre-infection state of all signs and symptoms, together with radiologic improvement, such that further antibacterial therapy was unnecessary; clinical failure was defined as unchanged or worsened symptoms, requirement for additional antibacterial agents, or an adverse event leading to treatment discontinuation; and indeterminate clinical outcome was defined as missing post-treatment information, early discontinuation for reasons unrelated to study drug, requirement for additional antibacterials for non-RTI-related reasons, or identification of a laboratory measurement fulfilling exclusion criteria and leading to treatment discontinuation after initiation of treatment.

In patients with bacteremia, blood cultures were repeated at the on-therapy visit and at post-therapy/test of cure only if the patient remained febrile or was assessed as a clinical failure. A satisfactory bacteriologic outcome was reported where the infecting pathogen was either shown to have been eradicated or where the patient’s clinical improvement was such that a follow-up culture was not obtained. In these latter cases, it was presumed that the pathogen had been eradicated successfully. If the bacteriologic response could not be categorized, the outcome was classed as indeterminate. If the infection was caused by more than one pathogen and the bacteriologic outcome was persistence, presumed persistence, recurrence, or reinfection for at least one pathogen, the outcome was classed as unsatisfactory.

The clinical and bacteriologic efficacies of telithromycin and comparator antibacterials were determined in patients with documented pneumococcal bacteremia in the mITT population (patients with indeterminate responses were classified as clinical failures) and PPb populations.

Descriptive statistics were used in this retrospective pooled analysis.
Results

Patient population

Of the 2289 patients with CAP who received telithromycin (mITT population), 1061 had an investigator-defined causative pathogen identified at pretherapy/screening and were therefore included in the bmITT population (Table 1). Of these, 94 telithromycin-treated patients (8.9%) had documented pneumococcal bacteremia compared with 24/244 (9.8%) comparator-treated patients included in this analysis compared with comparator-treated patients reflect the inclusion of data from four open-label studies with telithromycin. In the telithromycin and comparator groups, 82 and 19 patients were evaluable in the PPb population, respectively. In most patients, S. pneumoniae was present as the sole pathogen; 23/82 (28.0%) telithromycin-treated patients and 6/19 (31.6%) comparator-treated patients had mixed-pathogen infections (additional pathogens identified in samples cultured from these patients included Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, and Klebsiella pneumoniae). Among telithromycin-treated patients with pneumococcal bacteremia, there were 13 S. pneumoniae isolates that were resistant to penicillin and/or erythromycin (PPb population; Table 1). Of these, three were resistant to penicillin alone (MIC ≥2 μg/mL), six were resistant to erythromycin alone (MIC ≥1 μg/mL), and four S. pneumoniae isolates were resistant to both penicillin and erythromycin. In the comparator group, one of the bacteremias was documented as being erythromycin resistant. All S. pneumoniae isolates were susceptible to telithromycin (MIC ≤1 μg/mL) at the start of therapy.

The severity of infection was comparable between bacteremic patients and those of the overall CAP population. Among telithromycin-treated patients in the mITT population, 50.9% had a Fine score of I, 33.6% had a Fine score of II, and 15.5% had a Fine score of ≥III (23.1% of whom were hospitalized); in the bacteremic bmITT population, these values were 41.5%, 41.5%, and 17.0%, respectively (Table 1).

Clinical and bacteriologic outcomes

Patients with pneumococcal bacteremia who were treated with telithromycin achieved clinical cure rates of 90.2% (74/82) in the PPb population and 80.9% (76/94) in the bacteremic bmITT population. Clinical cure rates for patients with bacteremia were numerically lower for comparator-treated subjects (Table 2), although the small numbers involved make statistical differentiation impossible. The clinical cure rates for telithromycin in bacteremic patients were comparable to those observed for the overall CAP population: 91.2% (1755/1925) for the PPb population and 83.1% (1902/2289) for the mITT population.

Eradication of S. pneumoniae was achieved in 77/82 (93.9%) bacteremic patients who received telithromycin (documented eradication, n = 25; presumed eradication, n = 52) and 15/19 (78.9%) bacteremic patients who received a comparator agent (S. pneumoniae was presumed eradicated in all comparator-treated patients) (PPb population; Table 2). In the overall CAP PPb population, eradication of S. pneumoniae was observed in 305/318 (95.9%) patients treated with telithromycin and 63/70 (90.0%) patients treated with comparators. The clinical and bacteriologic success rates among telithromycin- and comparator-treated patients with pneumococcal bacteremia are summarized in Table 2. Clinical cure rates were comparable for telithromycin-treated bacteremic patients infected with isolates of S. pneumoniae resistant to either penicillin alone (3/3) or erythromycin alone (6/6; mef(A) 3/3, erm(B) 3/3), while 2/4 patients infected with S. pneumoniae resistant to both penicillin and erythromycin failed treatment.

Overall, in the PPb population, eight telithromycin-treated patients and four comparator-treated patients (two amoxicillin and two clarithromycin) with bacteremia were categorized as clinical failures. Of the eight telithromycin patients, five received additional antibacterial treatment. Four of these five patients received treatment with a combination of ≥2 antibacterial agents (including amikacin, piperacillin, vancomycin, penicillin, gentamycin, cefotin, and cefuroxime axetil) while the fifth patient was initially treated with amoxicillin followed by amoxicillin–clavulanate. All eight patients were subsequently assessed as cured with or without additional antibacterial treatment. In all eight cases, the blood isolates of S. pneumoniae obtained at baseline were susceptible to telithromycin and—of the six patients who had blood cultures repeated on-therapy or following treatment discontinuation—only one patient was a documented microbiologic failure. This telithromycin-treated patient who failed microbiologically had S. pneumoniae resistant to both erythromycin (MIC 4.0 μg/mL) and penicillin (MIC 2.0 μg/mL) at baseline. A blood culture performed on Day 4 was positive for S. pneumoniae and the patient had some mild to moderate respiratory symptoms but no fever.
Table 1  Key pretherapy/entry characteristics of patients with community-acquired pneumonia (CAP) bacteremia in eight Phase III/IV clinical trials who received telithromycin or a comparator antibacterial.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Treatment regimen</th>
<th>No. of patients (bmiITT)*</th>
<th>No. of patients (bacteremic bmiITT)*</th>
<th>No. of patients with penicillin- and/or erythromycin-resistant S. pneumoniae [bacteremic bmiITT (PPb)]</th>
<th>% (n) of bacteremic bmiITT patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind, randomized, active-controlled, two-arm, parallel-group</td>
<td>TEL 800 mg qd 10 days</td>
<td>62</td>
<td>13</td>
<td>2 (1)</td>
<td>23.1 (3)</td>
<td>23.1 (3)</td>
</tr>
<tr>
<td></td>
<td>AMX 1000 mg tid 10 days</td>
<td>63</td>
<td>14</td>
<td>0 (0)</td>
<td>64.3 (9)</td>
<td>21.4 (3)</td>
</tr>
<tr>
<td>Double-blind, randomized, active-controlled, two-arm, parallel-group</td>
<td>TEL 800 mg qd 10 days</td>
<td>48</td>
<td>5</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CLA 500 mg bid 10 days</td>
<td>45</td>
<td>2</td>
<td>0 (0)</td>
<td>50.0 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Double-blind, randomized, active-controlled, two-arm, parallel-group</td>
<td>TEL 800 mg qd 7–10 days</td>
<td>32</td>
<td>3</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TVA 200 mg qd 7–10 days</td>
<td>34</td>
<td>2</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Double-blind, randomized, active-controlled, three-arm, parallel-group</td>
<td>TEL 800 mg qd 5 days</td>
<td>111</td>
<td>12</td>
<td>0 (0)</td>
<td>16.7 (2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TEL 800 mg qd 7 days</td>
<td>123</td>
<td>7</td>
<td>0 (0)</td>
<td>14.3 (1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CLA 500 mg bid 10 days</td>
<td>102</td>
<td>6</td>
<td>1 (1)</td>
<td>16.7 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Open-label</td>
<td>TEL 800 mg qd 7–10 days</td>
<td>67</td>
<td>12</td>
<td>3 (2)</td>
<td>33.3 (4)</td>
<td>16.7 (2)</td>
</tr>
<tr>
<td>Open-label</td>
<td>TEL 800 mg qd 7–10 days</td>
<td>98</td>
<td>12</td>
<td>3 (3)</td>
<td>16.7 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Open-label</td>
<td>TEL 800 mg qd 7 days</td>
<td>255</td>
<td>8</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Open-label</td>
<td>TEL 800 mg qd 7 days</td>
<td>265</td>
<td>22</td>
<td>5 (4)</td>
<td>18.2 (4)</td>
<td>4.5 (10)</td>
</tr>
<tr>
<td>Total TEL</td>
<td>TEL 800 mg qd 7 days</td>
<td>1061</td>
<td>94</td>
<td>16 (13)</td>
<td>17.0 (16)</td>
<td>6.4 (6)</td>
</tr>
</tbody>
</table>

AMX, amoxicillin; bid, twice daily; bmiITT, bacteriologic modified intent to treat; CLA, clarithromycin; COPD, chronic obstructive pulmonary disease; PPb, bacteriologic per protocol; qd, once daily; TEL, telithromycin; tid, three times daily; TVA, trovafloxacin.

*Does not include subjects with a diagnosis of atypical infections.

†There were no patients with Fine scores of IV or V in any of the studies, except the comparator study with amoxicillin in which 7.7% of TEL patients and 14.3% of AMX patients had a Fine score of IV, and one of the open-label studies in which 4.5% of TEL patients had a Fine score of IV.
The investigator switched from telithromycin to another antibiotic regimen on Day 5 (penicillin and cefoxitin). In the comparator PPb treatment group, all four patients classified as treatment failures received additional antibiotics. *S. pneumoniae* was not isolated from the repeat blood culture of the single comparator-treated patient whose blood was re-tested.

A further 10 telithromycin- and five amoxicillin-treated patients excluded from the PPb population, but evaluable in the bmITT population, failed treatment. Eight of these telithromycin-treated patients and four amoxicillin-treated patients received additional antibacterial therapy. None of those patients whose blood was re-tested (six telithromycin- and four amoxicillin-treated patients) had *S. pneumoniae* isolated from the repeat blood culture.

Overall, therefore, with the exception of one patient, none of the telithromycin-treated bacteremic patients (*n* = 11) classified as treatment failures and who had a repeat blood culture was documented as a microbiologic failure.

### Discussion

In patients with CAP caused by *S. pneumoniae*, there is a risk of progression to bacteremia and septic complications.\(^4\) Evidence suggests that some patients who present with CAP and are classified as Fine class I or II are at measurable risk for bacteremia.\(^5\) Based on current guidelines, cost or other socioeconomic factors, many of these patients are likely to be treated as outpatients without blood or respiratory cultures being obtained. However, as inappropriate empiric antibiotic treatment may significantly increase mortality in patients with CAP bacteremia,\(^2\) it is imperative that empiric treatment given for CAP in the outpatient setting provides reliable first-line efficacy.

The treatment of pneumococcal infections is becoming more of a challenge due to the rising incidence of drug-resistant strains of *S. pneumoniae*. In the past, penicillins have been the treatment of choice for pneumococcal infections; however, more recently, guidelines for the empiric treatment of CAP have included macrolides as initial therapy.\(^26,27\) The development and spread of penicillin- and macrolide-resistant strains of *S. pneumoniae*, however, may limit the usefulness of macrolide and \(\beta\)-lactam antibacterial agents for empiric therapy.\(^10,28\) Plouffe et al.\(^29\) observed that, over a 40-month period (1991–1994), the proportion of *S. pneumoniae* isolates obtained from bacteremic patients who were resistant to penicillin, cefazidime, or trimethoprim–sulfamethoxazole increased 1.5–3.5-fold. Furthermore, azalides—such as azithromycin—may not maintain sufficiently high plasma concentrations to adequately treat pneumococcal bacteremic infection.\(^30,31\) Breakthrough pneumococcal bacteremia was recently reported in 9.8% (4/41) of patients who had previously been treated with azithromycin or clarithromycin for 3–5 days. The pneumococcal strains isolated from these four patients were all resistant to erythromycin (MIC 8–16 \(\mu\)g/mL) and three of the four showed reduced susceptibility to penicillin.

### Table 2 Clinical cure and bacteriologic eradication rates in patients with pneumococcal bacteremia associated with community-acquired pneumonia who received telithromycin or a comparator antibacterial at the post-therapy/test of cure visit.

<table>
<thead>
<tr>
<th></th>
<th>Telithromycin n/N (%)</th>
<th>Amoxicillin n/N</th>
<th>Clarithromycin n/N</th>
<th>Trovafloxacin n/N</th>
<th>All comparators pooled n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bmITT population*</td>
<td>76/94 (80.9)</td>
<td>7/14</td>
<td>6/8</td>
<td>2/2</td>
<td>15/24 (62.5)</td>
</tr>
<tr>
<td>PPb population</td>
<td>74/82 (90.2)</td>
<td>7/9</td>
<td>6/8</td>
<td>2/2</td>
<td>15/19 (78.9)</td>
</tr>
<tr>
<td><strong>Bacteriologic eradication†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bmITT population†</td>
<td>79/94 (84.0)</td>
<td>8/14</td>
<td>6/8</td>
<td>2/2</td>
<td>16/24 (66.7)</td>
</tr>
<tr>
<td>PPb population</td>
<td>77/82 (93.9)</td>
<td>7/9</td>
<td>6/8</td>
<td>2/2</td>
<td>15/19 (78.9)</td>
</tr>
</tbody>
</table>

bmITT, bacteriologic modified intent to treat; PPb, bacteriologic per protocol.

*Patients with indeterminate outcomes at the post-therapy/test of cure visit were assessed as clinical failures.

†Documented and presumed eradication.

†Patients with indeterminate outcomes at the post-therapy/test of cure visit were assessed as bacteriologic failures.
The clinical success rate achieved with telithromycin in patients with pneumococcal CAP bacteremia in this analysis is comparable with similar studies using other antibacterial agents. In a study of the fluoroquinolone levofloxacin, 90.7% (98/108) of patients with pneumococcal bacteremia had a successful clinical response, including 91.7% (11/12) of patients infected with a macrolide- or penicillin-resistant strain. Similarly, in studies to evaluate the efficacy and safety of dirithromycin in the treatment of acute bacteremic pneumonia, a favorable clinical response post-therapy was observed in 90.9% (10/11) and 100% (8/8) of pneumococcal bacteremic patients treated with dirithromycin and erythromycin, respectively. All isolates in this study were susceptible to erythromycin.

It should be noted that the present analysis is not a prospective study and does not fulfill the criteria of a formal meta-analysis. However, the similar, standardized design of the eight studies supports the pooling of data obtained from the relatively small number of bacteremia cases identified across these studies. It should also be noted that the prevalence of underlying risk factors (including smoking status, presence or absence of COPD, and age ≥ 65 years) varied between the two groups of bacteremic patients; however, the low numbers of affected patients precluded further analysis of the impact of these underlying risk factors on the clinical and bacteriologic efficacy of the antibacterial treatment regimens. Despite these limitations, the findings from this analysis illustrate there is a risk that patients treated for mild to moderate CAP on an outpatient basis will have bacteremia. The 90.2% cure rate achieved with oral telithromycin in these patients is encouraging. The bacteremic patients included in this analysis had the advantage of close monitoring and having blood and sputum cultures evaluated. However, in community practice CAP therapy is empiric and therefore needs to provide reliable, effective cover against the likely causative pathogens—which, increasingly, will include drug-resistant strains.

**Conclusion**

Telithromycin—the first ketolide antibacterial to be approved for clinical use—achieves high clinical and bacteriologic cure rates in CAP patients with pneumococcal bacteremia. At a dosage of 800 mg given orally once daily for 5–10 days, telithromycin...
provides a convenient, effective treatment option for empiric antibacterial therapy for patients with CAP-associated pneumococcal bacteremia.

References


