A *Mycobacterium tuberculosis*-Infected Patient Who Could Not Tolerate Oral Intake Successfully Treated Using an Intravenous Tedizolid-Containing Regimen

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**Patient:** Male, 77-year-old

**Final Diagnosis:** Pulmonary tuberculosis

**Symptoms:** Appetite loss

**Medication:** —

**Clinical Procedure:** —

**Specialty:** Infectious Diseases

**Objective:** Unusual or unexpected effect of treatment

**Background:** *Mycobacterium tuberculosis* (*M. tuberculosis*) is usually treated by oral antimycobacterial agents, including rifampicin, ethambutol, and pyrazinamide, but the treatment regimen with intravenous and/or intramuscular antimycobacterial agents for patients who cannot take medications orally remains unclear.

**Case Report:** A 77-year-old man with chronic renal failure had an esophageal-skin fistula after he had surgeries for removal of esophageal and gastric cancers and reconstruction using jejunum, and he showed a cavity, tree-in-bud formation, and pleural effusions in his left upper lung fields on his chest X-ray after treatment of cellulitis and bacteremia/candidemia by meropenem, teicoplanin, and micafungin. *M. tuberculosis* was isolated from his sputum and exudate fluid from the reconstructed esophageal-skin fistula. Although he could not take antimycobacterial agents orally, treatment was started with intravenous agents combining levofloxacin (LVFX) every other day, isoniazid (INH), and linezolid (LZD). However, his platelets were decreased 21 days after treatment started, and it was thought to be an adverse effect of LZD and/or INH. After changing LZD to tedizolid (TZD), in addition to changing from INH to intramuscular streptomycin twice per week, his platelet counts increased. Intravenous TZD could be continued, and it maintained his condition without exacerbations of thrombocytopenia and renal failure. The *M. tuberculosis* disappeared, and the abnormal chest X-ray shadows were improved 2 months after the start of treatment.

**Conclusions:** Administration of intravenous TZD, in addition to intravenous LVFX and intramuscular SM in combination, might be a candidate regimen for *M. tuberculosis* patients who cannot take oral medications.

**Keywords:** Renal Insufficiency, Chronic • Immunocompromised Host • Anti-Bacterial Agents

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/937485
Background

Tuberculosis remains the leading cause of death from an infectious disease in adults worldwide, with more than 10 million people becoming newly sick from tuberculosis each year. Although little has changed in the treatment of drug-susceptible tuberculosis, data on increased efficacy with new and repurposed drugs led the World Health Organization (WHO) to recommend all-oral therapy for drug-resistant tuberculosis for the first time ever in 2018 [1].

However, some tuberculosis patients, such as elderly persons, aspiration pneumonia cases, and postoperative patients, cannot be treated with oral antimycobacterial drugs; therefore, intravenous and/or intramuscular administration of the drugs must be selected for the treatment of their tuberculosis, although Mycobacterium tuberculosis (M. tuberculosis) shows good susceptibility to the standard and first-line antimycobacterial drugs, including rifampicin (RIP), ethambutol (EB), and pyrazinamide (PZA), which could be administered orally alone [2]. Levofloxacin (LVFX) and streptomycin (SM) are usually selected for the treatment of patients who cannot be treated with oral antimycobacterial drugs in the clinical setting, but they are second-line drugs and might not provide clinical and microbiological cure.

Recently, M. tuberculosis was reported to show good susceptibility to oxazolidinone antibiotics, including linezolid (LZD) and tedizolid (TZD), in vitro and in vivo, and TZD, rather than LZD, shows greater safety and tolerability with respect to hematological and nephrological toxicity [3-6]. We present the case of a tuberculosis patient who could not be treated with an oral drug regimen but was successfully treated by a combination regimen with intravenous administration of LVFX, intramuscular SM, and intravenous tedizolid (TZD).

This case and the related study were approved by the Institutional Review Board of Saitama Medical University International Center on May 27, 2022 and registered as UMIN000047689.

Case Report

A 77-year-old man with chronic kidney disease (CKD) underwent surgeries in our hospital for removal of esophageal and gastric cancers 2 years earlier along with reconstruction of the esophagus by jejunum several times, but he had developed an esophageal-skin fistula. He could not take food orally and had been started on intravenous hyperalimentation (IVH). In 2019, he developed a high fever and an erosion around the esophageal-skin fistula and was admitted to our hospital again. Laboratory data on admission were as follows: white blood cell (WBC) count, 14.5×10⁹/µL, with 94.0% neutrophils, 3.8% lymphocytes, 2.0% monocytes, 0.1% eosinophils, and 0.1% basophils; platelet count, 224×10⁹/µL; hemoglobin, 10.6 g/dL; blood urea nitrogen, 114.2 g/L; serum creatinine, 3.98 mg/dL; aspartate aminotransferase (AST), 15 U/L; alanine aminotransferase (ALT), 8 U/L; and C-reactive protein, 10.794 mg/dL. Cellulitis was suspected, and he was started on cefazolin 1 g/day followed by meropenem 1 g/day. Meticillin-resistant Staphylococcus epidermidis (MRSE) and Candida albicans were also isolated from blood cultures, and teicoplanin 400 mg every other day and micafungin 150 mg/day were also added on day 6.

On day 12, the fever was decreased, but dyspnea appeared, and his chest X-ray and computed tomography (CT) showed a cavity, tree-in-bud appearance, infiltration shadows, and pleural effusions (Figure 1). No bacteria and fungi were detected, but acid-fast bacilli were detected from his sputum and slight pus from the esophageal-skin fistula. M. tuberculosis was identified by polymerase chain reaction (PCR) and collected after culture of the sputum and pus, and it was confirmed by amino acid analysis using time-of-flight mass spectrometry (TOF-MS). Pulmonary and skin M. tuberculosis infections were definitively diagnosed.

Because the patient appeared to be severely ill and could not tolerate oral intake, the first-line regimen, which includes oral RIP, EB, and PZA, could not be given; therefore, combination antibiotic therapy with intravenous INH 200 mg/day, LVFX 250 mg every other day, and LZD 1200 mg/day was started, because it is known to have anti-mycobacterial effects, is immunomodulatory, and dose adjustment is not necessary even in CKD patients (Figure 2).

His condition subsequently improved, and blood tests showed that WBC decreased to 3110/µL, and C-reactive protein returned to 6.001 mg/dL. However, platelet counts decreased, which is an adverse effect of LZD, from 224×10⁹/µL to 23×10⁹/µL more than 2 weeks later. Therefore, LZD was changed to intravenous TZD, an oxazolidinone similar to LZD but not known to cause thrombocytopenia [5,6]. In addition, intravenous administration of INH was also suggested as the cause of thrombocytopenia [7], and it was changed to intramuscular administration of SM 300 mg twice/week. The patient’s condition remained stable; his platelet count increased to 167×10⁹/µL, and serum C-reactive protein decreased to 1.41 mg/dL. M. tuberculosis was found to be susceptible to INH, LVFX, SM, and TZD (Table 1).

M. tuberculosis disappeared 2 months after the start of treatment, and the tree-in-bud appearance and cavity disappeared on computed tomography (CT) (Figure 3). Treatment with the same regimen was continued for half a year, but the patient died suddenly of cardiopulmonary arrest due to a lethal cardiac arrhythmia. Exacerbation of the CKD due to transient dehydration was finally suspected as the cause of death.
Figure 1. Chest X-ray (A) and computed tomography (B) showing cavity, tree-in-bud appearance, infiltration shadows, and pleural effusions (arrows).

Figure 2. Clinical course of the patient. The line graph shows the platelet counts of the patient. Smear and culture of *M. tuberculosis* from sputum are expressed as 2+, 1+, +, and −.
There is a need for newer compounds and regimens that have a sterilizing effect not only in patients with drug-resistant *M. tuberculosis* infection, but also in patients who cannot take the drugs orally even though the causative organism is shown to be susceptible to the usual oral agents.

In the present case, an *M. tuberculosis*-infected patient could not take oral antimycobacterial agents, but improved with a regimen containing intravenous TZD, LVFX, and intramuscular SM, RIP, EB, and PZA, which have been considered the most important key drugs and indispensable in the standard regimen for *M. tuberculosis* infection, can only be administered orally; therefore, alternative, second-line intravenous/intramuscular agents must be selected for patients who cannot tolerate oral intake.

SM, an aminoglycoside, has good activity against mycobacteria, with susceptibilities usually greater than 90% [8,9]. Intramuscular administration of SM was finally used in this case, and it might be considered an alternative candidate drug for *M. tuberculosis* infection, can only be administered orally; therefore, alternative, second-line intravenous/intramuscular agents must be selected for patients who cannot tolerate oral intake.

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In addition, fluoroquinolones have been available most widely, but there is evidence that resistance to drugs of this class increases after repeated use [9]. In the present case, LVFX was used because the causative organism was found to be susceptible to LVFX later (Table 1), and it was one of the few agents that could be used intravenously. Moxifloxacin (MFLX) might be a good alternative candidate, but the intravenous formulation of MFLX is not available in Japan.

In the present case, LZD, which is an oxazolidinone antibiotic to which the organism showed good susceptibility in vitro, was selected initially. LZD has been used both orally and intravenously for systemic mycobacterial infections as an emerging treatment option, including for multi-drug-resistant *M. tuberculosis* infection [11,12]. In addition, LZD shows immunomodulatory effects, and inhibitory effects on cytokines and inflammation have been reported [13]. Decreased levels of proinflammatory cytokines IL-1β, IFN-γ and TNFα, and the chemokines MIP-2 and KC were detected in the lungs of influenza-related community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia animal models after treatment with LZD compared to treatment with vancomycin [13]. It might have been sufficient in the present case due to these effects, similar to macrolide antibiotics such as azithromycin and clarithromycin, which are also known to have immunomodulatory

### Table 1. Drug susceptibility of *Mycobacterium tuberculosis* isolated from exudate fluid from the esophageal-skin fistula.

<table>
<thead>
<tr>
<th>No.</th>
<th>Drugs</th>
<th>MIC</th>
<th>R/I/S</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>INH</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>RIP</td>
<td>N/A</td>
<td>S</td>
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<tr>
<td>3</td>
<td>EB</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>SM</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>KM</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>EVM</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>PAS</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>CS</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>TZD</td>
<td>0.5</td>
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INH – isoniazid; RIP – rifampicin; EB – ethambutol; SM – streptomycin; KM – kanamycin; EVM – enviomycin; PAS – para-aminosalicylic acid; CS – cycloserin; TZD – tedizolid; MIC – minimum inhibitory concentration; R/I/S – resistant, intermediate, susceptible, respectively.

### Discussion

There is a need for newer compounds and regimens that have a sterilizing effect not only in patients with drug-resistant *M. tuberculosis* infection, but also in patients who cannot take the drugs orally even though the causative organism is shown to be susceptible to the usual oral agents.

In the present case, an *M. tuberculosis*-infected patient could not take oral antimycobacterial agents, but improved with a regimen containing intravenous TZD, LVFX, and intramuscular SM, RIP, EB, and PZA, which have been considered the most important key drugs and indispensable in the standard regimen for *M. tuberculosis* infection, can only be administered orally; therefore, alternative, second-line intravenous/intramuscular agents must be selected for patients who cannot tolerate oral intake.

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effects [14,15]. In addition, LZD has very good penetration into most tissues in humans, and a decreased dose is not necessary when used even in patients with renal failure [16,17].

Furthermore, TZD has become available as an oxazolidinone with immunomodulatory effects similar to LZD, but showing more effectiveness at half the dose of LZD [18,19]. The sterilizing effect of intermittent TZD for pulmonary tuberculosis was shown, and a TZD dose of 200 mg/day or 700 mg twice a week is recommended for testing in patients; the intermittent TZD dosing schedule is suggested to be much safer than daily LZD [4]. In vivo activity of TZD against 120 M. tuberculosis strains, including susceptible, first-line-resistant, and multi-drug-resistant isolates, was also examined, and very good susceptibility was seen, with MIC90 and MIC50 of 0.5 and 0.25 ug/mL, respectively [3]. In addition, the clinical efficacy and safety of long-term use of TZD were reported in an adolescent patient with pulmonary tuberculosis who underwent liver transplantation [20]. In total, TZD might be able to be used more safety and effectively for the long-term treatment of M. tuberculosis patients with chronic renal failure and thrombocytopenia than LZD. TZD can also be administered intravenously. Therefore, TZD was selected and used in addition to LVFX and SM after thrombocytopenia was found, which might have been due to LZD and/or INH. Although the possibility of thrombocytopenia due to bacteremia/candidemia and micafungin was also considered, the platelet count recovered after termination of LZD and INH. It might be possible to treat pulmonary tuberculosis more successfully with intravenous TZD, LVFX, and intramuscular SM instead of standard oral regimens comprising combinations of INH, RIP, EB, and PZA.

Conclusions

We present the case of a CKD patient with pulmonary M. tuberculosis infection with an esophageal-sk in fistula. The patient was unable to tolerate oral medications, which thus excluded use of the standard first-line regimen for M. tuberculosis, but improvement was achieved in this patient by treatment with intravenous TZD, consistent with the results of drug susceptibility testing in vitro. TZD was combined with intravenous LVFX and intramuscular SM. Oxazolidinone antibiotics, especially TZD, might have immunomodulatory activity and show better tissue penetration, antibacterial activities, and longer half-life reduction time than LZD. Therefore, the regimen of the combination of intravenous TZD, LVFX, and intramuscular SM might be a good candidate for the treatment of M. tuberculosis in patients with chronic renal failure when there is concern about thrombocytopenia, especially when the patients cannot take the standard drugs orally.

Acknowledgments

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Declaration of Figures’ Authenticity

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