

Regarding treatment there are no consensus guidelines. Because acquired resistances are of concern, combination treatment is recommended with two or three antibiotics to which the agent is susceptible and at least one drug should have good intracellular activity.³ First line drugs in humans include rifampicin, levofloxacin, erythromycin, imipenem, vancomycin and aminoglycosides.⁵ For immunocompromised patients at least six months of antibiotic therapy are advised.¹⁰ The placement of a central venous catheter allows intravenous treatment on an outpatient basis, reducing risks of nosocomial infection and costs. Side-effects from multi-drug treatment over such a long period of time may be a concern and should be closely monitored. Antibiotics withdrawal and substitution may be needed, making *R. equi* infection treatment a dynamic process.

Relapse may occur requiring close surveillance. We scheduled hospital medical consultation whenever the patient presented any complaint and every three months with hemogram, serum biochemistry, blood and sputum cultures and chest computed tomography. After relapse with a brain abscess, brain magnetic resonance was performed every three months until its resolution. No further bronchoscopy was performed following endoscopic treatment of tracheal pseudotumor as the patient refused further invasive examinations and remained asymptomatic.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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First case report in Latin America: Oral treatment of multidrug-resistant tuberculosis with delamanid and bedaquiline in combination with linezolid, moxifloxacin and clofazimine following a DRESS syndrome in a peruvian patient



Dear Editor,

The World Health Organization recommends the use of oral medications for the treatment of multidrug-resistant (MDR)

and extensively drug-resistant (XDR) tuberculosis (TB).^{1–3} However, few countries have adopted these recommendations, either due to lack of medication or because of outdated local recommendations, as in the case of Peru.⁴ The combination of some medications for the treatment of MDR TB such as delamanid (Dlm) with bedaquiline (Bdq) has been associated with a potential risk of cardiovascular symptoms such as prolongation of the QT interval corrected by Fridericia interval (QTcF).⁵ Other medications that may enhance the prolongation of this interval are fluoroquinolones, especially moxifloxacin (Mfx) and clofazimine (Cfz). We present a case of the simultaneous use of these medications in a patient who provided informed consent. There was no prolongation of the QTcF interval, and no sig-

nificant cardiac symptoms were observed throughout the entire treatment. (1) This patient was the first Peruvian to receive a completely oral combination of medications for the treatment of MDR tuberculosis.⁸ (2) This was the first Peruvian case to receive a combination of 4 drugs (Mfx, Bdq, Cfz, and Dlm) considered potentially dangerous because of their sum effects on QTcF.

The patient was a single, nulliparous 23-year-old female with no pathological history living in Lima, Peru. At the beginning of August 2018, she presented hemoptysis and malaise and underwent a chest tomography on August 4th, 2018 showing exudative lesions in the right upper pulmonary lobe associated with a cavity of 3 cm in diameter. On August 14th, 2018, bronchofibroscope was performed, obtaining a smear-positive in bronchial lavage. Tuberculosis treatment was initiated on August 15th with isoniazid, rifampicin, ethambutol and pyrazinamide.⁴ The patient weighed 64 kg at this time. This treatment was suspended on September 10th, 2018 following results of a Line Probe Assay study (Line Probe Assay, Genotype[®] MTBDR Plus Version 2.0) of a sputum sample from August 16th, 2018 showing the presence of primary resistance to rifampicin and isoniazid (Gen KatG). On September 12th, 2018, a new empirical treatment was begun with ethambutol, pyrazinamide, kanamycin, levofloxacin, ethionamide and cycloserine.⁴ On October 16, 2018, the patient presented cervical lymphadenopathy (>3 cm in diameter) and axillary lymphadenopathy, in addition to a temperature of 38.5 °C and rash in the following days. On October 23, 2018, eosinophils in peripheral blood were found to be elevated (7%) and proteins were also found in a urine sample. On October 28th, 2018, antituberculosis treatment was suspended. Eosinophils in peripheral blood continued to increase to a maximum of 21% on November 19th and then normalized on January 17th, 2019. Aspartate aminotransferase (AST) values increased to 78 IU/L on November 19th and normalized on December 3rd (AST: 26 IU/L). Alanine aminotransferase (ALT) values reached a maximum of 152 IU/L on November 10th and normalized on December 3rd (ALT: 34 IU/L). The patient was diagnosed with Drug Rash and Eosinophilia with Systemic Symptoms (DRESS) syndrome, with a score of 6 points in the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) secondary to the treatment received.⁶

The patient was hospitalized on January 25th, 2019 with the aim of designing a new tuberculosis treatment schedule. She was stable with normal vital signs and with a weight of 65 kg. Laboratory tests showed a normal blood count, mild anemia, normal renal, hepatic and cardiac function (normal echocardiogram, electrocardiogram, QTcF, and cardiac enzymes), normal glycosylated hemoglobin, and negative viral hepatitis studies (HAV, HBV, HCV). Antibiotic susceptibility testing showed sensitivity to: ethambutol, pyrazinamide, streptomycin, kanamycin, capreomycin, ethionamide, cycloserine, ethionamide, para-aminosalicylic acid (PAS), levofloxacin and Mfx. The MDR TB unit decided to use new tuberculosis drugs that had not previously been combined in Peru, and the new antituberculosis treatment was begun on March 13th, 2019. This treatment consisted of linezolid (Lzd) at a dose of 600 mg/day, Mfx 400 mg/day, Cfz 200 mg/day, Bdq at a dose of 400 mg/day for the first 14 days and then 200 mg 3 times/week for 22 weeks for a total of 24 weeks, and Dlm at 100 mg bid for

24 weeks. After 24 weeks of treatment, Bdq and Dlm^{2,7} were suspended. The patient continued to receive Lzd at the dose described. Cfz was decreased to 100 mg daily from the fourth month due to changes in skin color. The dose of Mfx was increased from 400 mg to 800 mg daily from week 24. Throughout this period laboratory tests were normal. There was no prolongation of the QTcF interval, and no significant cardiac symptoms were observed during the entire treatment. Fig. 1 shows the results of the periodic controls of the QTcF Interval in the timeline of this case. Direct sputum smear and cultures taken monthly were negative from the first month of treatment and throughout the treatment. The 2 tomographic controls taken at months 4 and 8 of treatment showed no lung lesions.

Several aspects are of note in the present case: (1) This patient was the first Peruvian and the first Latin American patient to receive a completely oral combination of medications for the treatment of MDR tuberculosis.⁸ (2) This was the first Peruvian and the first Latin American case to receive a combination of 4 drugs (Mfx, Bdq, Cfz, and Dlm) considered potentially dangerous because of their sum effects on QTcF.¹ (3) According to the study of Borisov et al.⁹ only 39 out of a total of 658 cases (6.1%) have received Bdq and Dlm consecutively or in combination, none being from Peru. In addition, of the 9 cases presenting severe cardiological events, none had received the same combination as our patient. (4) In Latin America, only Chile and Mexico together have reported 4 cases treated with the combination of Bdq and Dlm, with apparently none using Cfz and Mfx simultaneously.⁹ The treatment was well tolerated by our patient, with no adverse cardiovascular events like those reported in other series of patients using this combination.^{5,10} Cfz produced slight pigmentation of the skin that did not bother the patient. Lastly, clinical response was excellent with notable radiological improvement.

This drug combination was demonstrated to be safe and effective and well tolerated. None of the frequent adverse reactions that occur with the use of kanamycin injectable medications that are still used in Peru for the treatment of MDR tuberculosis⁴ were observed. Moreover, this treatment is highly effective since the sensitivity of bacteria to Bdq, Dlm and Lzd is high.¹¹ The patient will be followed every 3 months for 2 years to record possible development of relapse. The results of this case are important for demonstrating that oral treatment of MDR tuberculosis is possible and can be carried out safely with suitable monthly clinical controls and periodic QTcF controls.

Statement of ethics

The authors have no ethical conflicts to disclose.

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Author contributions

All authors contributed equally to this correspondence.

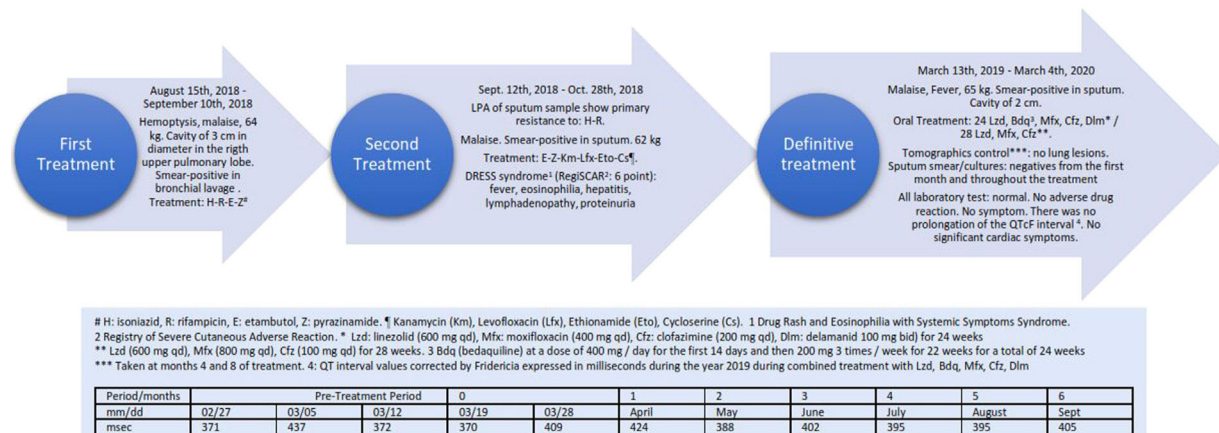


Figure 1 Results of the periodic controls of the QTcF interval in the timeline of this case.

Conflicts of interest

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