Case Report

Use of bedaquiline in the treatment of a patient with extensively drug-resistant pulmonary tuberculosis

Soultana Kostanta[1], Katerina Manika[1], Apostolos Papavasileiou[2], Panagiotis Ioannidis[3], Eleni Papadaki[1], Konstantinos Zarogoulidis[1], Ioannis Kioumis[1]

[1]Respiratory Infections Unit, Pulmonary Department, Aristotle University of Thessaloniki, G. Papanikolaou Hospital, Exohi, Thessaloniki, Greece
[2]TB Department, Sotiria Chest Diseases Hospital, Athens, Greece
[3]National Reference Center for Mycobacteria, Sotiria Chest Diseases Hospital, Athens, Greece

Key words:
- Bedaquiline
- Extensively resistant tuberculosis

Correspondence:
Katerina Manika, "G. Papanikolaou" Hospital, 57010 Exohi, Thessaloniki,
Tel.: 2313307858, Fax: 2313307253,
e-mail: ktmn05@yahoo.gr

ABSTRACT

A 27-year-old man from the former Soviet Union with unremarkable medical history was diagnosed with pulmonary tuberculosis and was initially treated with the standard antituberculosis regimen (R, H, E, Z). Based on the sputum molecular analysis for *M. tuberculosis* the diagnosis of multidrug-resistant tuberculosis (MDR-TB) at first and later of extensively drug-resistant tuberculosis (XDR-TB) was made. The patient received a complex antituberculosis regimen, which included ethionamide, pyrazinamide, capreomycin, imipenem /cilastatin, linezolid and an increased dose of moxifloxacin at 600 mg. Due to the limited number of drugs that were active *in vitro* in the above regimen, bedaquiline was added for six months, and moxifloxacin was discontinued. The patient showed significant clinical and radiological improvement, increase in body weight, reduction of his cavities' size and culture conversion, without severe side effects. After one year of hospitalization, the patient was discharged on a regimen of capreomycin, linezolid, clofazimine, pyrazinamide, ethionamide and moxifloxacin and is still followed up in the outpatient clinic for tuberculosis of AUTH's Pulmonary Department on a weekly basis. Treatment time is estimated at 18 months after culture conversion.

Pneumon 2016, 29(1):53-57.

INTRODUCTION

Bedaquiline represents the first novel class of antituberculosis drugs, since the release of rifampicin in 1968. Chemically, it is a diarylquinoline which specifically inhibits mycobacterial adenosine triphosphate (ATP) synthase, preventing the energy production and the replication of *Mycobacterium tuberculosis*.[1-3] Bedaquiline has a bactericidal action on both actively multiplying and non-multiplying mycobacteria. In line with the recent recommendations

by the World Health Organization (WHO), bedaquiline is indicated for the treatment of MDR-TB in adults, when, due to extensive resistance, no other effective treatment can be achieved, i.e. four active drugs, and for the treatment of MDR-TB when resistance to quinolones is also detected.[1] Bedaquiline should always used as part of an appropriate multidrug antituberculosis regimen and in accordance with WHO recommendations.[1-6] This report presents the case of a young patient with XDR–TB, who was treated with an antituberculosis regimen containing bedaquiline in order to achieve the necessary number of active antituberculosis drugs, with a favorable outcome.

CASE PRESENTATION

A 27-year-old man from the former Soviet Union, with unremarkable medical history, who has been living in Greece for 10 years, admitted to G. Papanikolaou Hospital due to productive cough and purulent sputum. He also reported low-grade fever and night sweats over a 5-month period. The patient had previously received amoxicillin/clavoulanate and azithromycin with no improvement. Laboratory tests showed no pathological findings, except of an increased erythrocyte sedimentation rate (ESR) to 40mm. The Mantoux test was positive at 15 mm. Infiltrations and cavities of the right lung were detected on the chest x-ray (Figure 1) whereas the patient's chest CT scan revealed radiological findings suggestive of tuberculosis, such as cavitary formations, nodules and tree-in-bud lesions (Figure 2). The Ziehl-Neelsen sputum stain was positive for acid-fast bacilli, while *M. tuberculosis* DNA was detected in sputum by PCR.

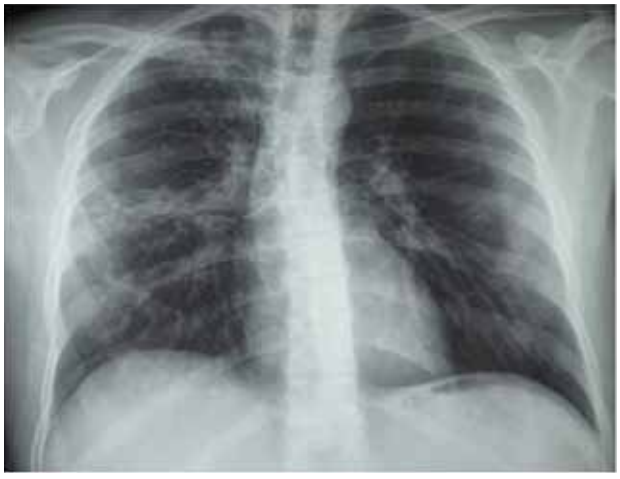

FIGURE 1. Chest x-ray on admission.

The patient was initially treated with the standard antituberculosis regimen of rifampicin, isoniazid, ethambutol and pyrazinamide. However, the molecular drug susceptibility test detected resistance to isoniazid, rifampicin, quinolones and second-line injectable drugs, thus diagnosing XDR-TB. The phenotypic drug susceptibility test on Löwenstein-Jensen medium confirmed resistance to rifampicin, isoniazid, ethambutol, ethionamide, cycloserine, ofloxacin, amikacin and capreomycin. Susceptibility was observed only to para-aminosalicylic acid and linezolid. The anti-tuberculosis regimen was subsequently modified by discontinuation of rifampicin, isoniazid and ethambutol, continuation of pyrazinamide and addition of capreomycin, moxifloxacin at an increased dosage of 600 mg, cycloserine, linezolid, ethionamide,

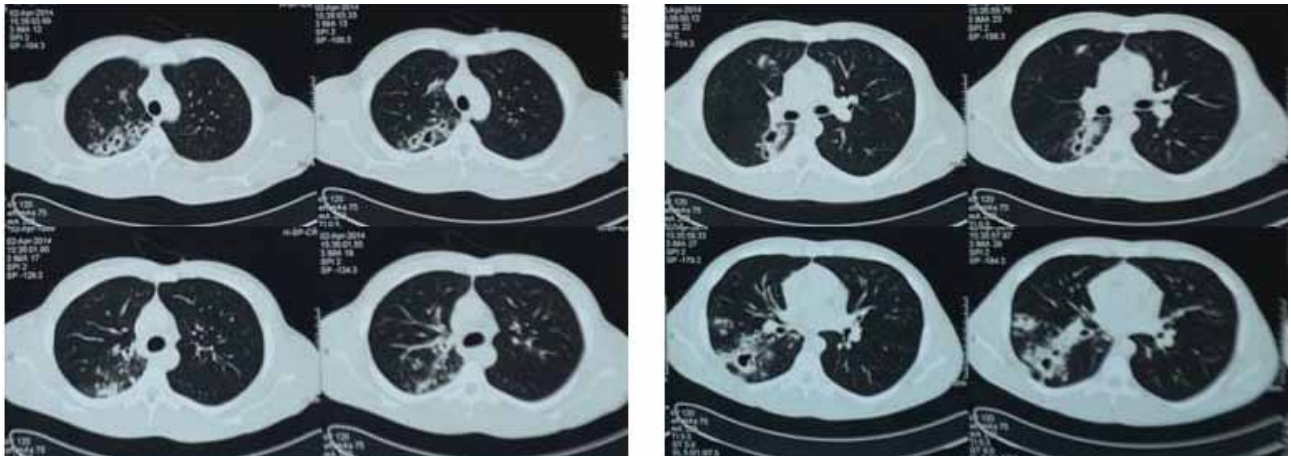

FIGURE 2. Chest CT scan before treatment initiation.

imipenem/cilastatin and para-aminosalicylic acid. Para-aminosalicylic acid was permanently discontinued due to episodes of severe diarrhea. Ethionamide, capreomycin, moxifloxacin and cycloserine were included in the regimen despite the detected drug resistance, because susceptibility testing may not be fully reliable in the case of second-line antituberculosis drugs and the regimen options were extremely limited.

Due to the insufficient number of available active drugs in the regimen, administration of bedaquiline was decide at a dosage of 400 mg once daily for 2 weeks, followed by 200 mg 3 times per week for 22 weeks. During this period moxifloxacin was discontinued, due to the additive effects of both drugs on the QT interval.[1,4] The treatment was well-tolerated under strict surveillance. When the prescribed treatment time was completed, bedaquiline was discontinued. Moxifloxacin was then reintroduced at an increased dosage of 600 mg once daily. The patient developed signs of depression soon after the initiation of cycloserine administration, thus necessitating the discontinuation of the drug.

During hospitalization, the patient showed significant clinical improvement and the time to sputum stain and culture conversion was 3 and 5 months respectively. After one year of hospitalization imipenem/cilastatin was discontinued and the patient was discharged on a regimen of capreomycin, linezolid, clofazimine, pyrazinamide, ethionamide and moxifloxacin.

The patient has been followed up weekly for the last six months in the TB outpatient clinic. He is in excellent condition while his new chest CT scan showed improvement of the radiological findings including the elimination of cavity formations and concomitant reduction in nodules (Figure 3). The patient has gained weight, while his only abnormal laboratory finding is a mild elevation of transaminase levels, which did not require treatment modification. The patient's compliance is excellent and he is estimated to continue antituberculosis treatment for 18 months after culture conversion.

DISCUSSION

For more than forty years no new TB drugs had become available, while WHO estimates that up to half a million new MDR-TB cases occur worldwide every year.[1] The resistance to antituberculosis drugs has been known since the time of the first TB drugs, i.e. streptomycin in 1943 and para-aminosalicylic acid in 1949. The difficulty in building up an effective antituberculosis regimen is enhanced by the considerable number of side effects of the currently available drus.[2,7,8] A new era in the fight against tuberculosis seems to be the approval of two new drugs: bedaquiline for the treatment of MDR-TB on December 28, 2012 by the U.S. Food and Drug Administration (US FDA) and recently the conditional approval of delamanid by the European Medicines Agency.[1,9] Bedaquiline, as already mentioned, is a diarylquinoline with bactericidal activity against both actively replicating and non-replicating mycobacteria. By inhibiting the ATP synthesis in *Mycobacterium* species, it eliminates even non-replicating cells, while the precise mechanism of action is not fully understood.[5,10,11] It is possible that bedaquiline, by targeting the cell's energy metabolism, could be effective even against less metabolically active organisms, probably via ATP exhaustion.[6,10] Diarylquinolines have a different structure and mechanism of action from that of fluoroquinolone antibiotics. This means that antibiotic resistance to fluoroquinolones, which are a part of the MDR-TB standard treatment regimen, does not entail resistance to bedaquiline.[11]

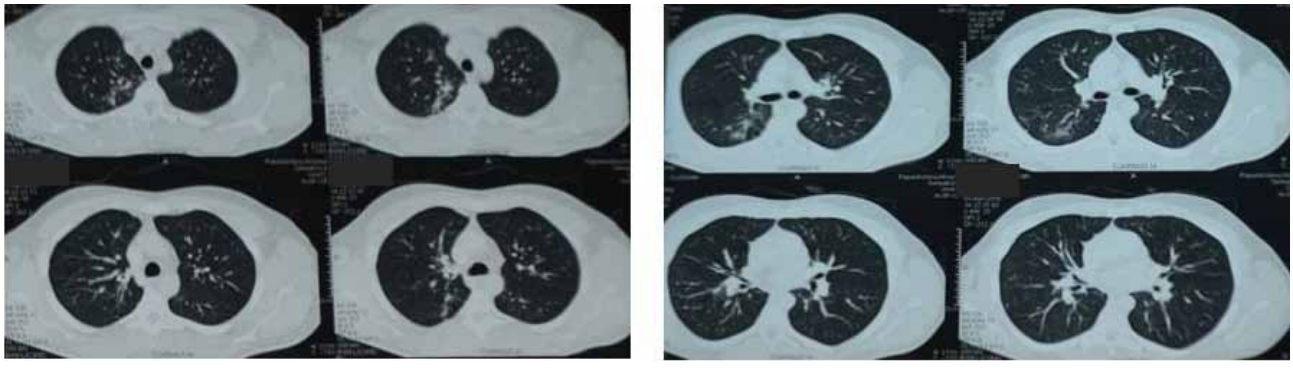

FIGURE 3. Chest CT scan 18 after treatment initiation.

In a phase IIb trial of 160 patients with MDR-TB, the addition of bedaquiline to the antituberculosis regimen, reduced the median time of culture conversion, as compared with placebo, from 125 days to 83 days and increased the rate of culture conversion to 79% vs. 58% at 24 weeks and 62% vs. 44% at 120 weeks of treatment. In addition, cure rates at 120 weeks were 58% in the bedaquiline group and 32% in the placebo group.[1,12]

Possible side effects of bedaquiline include headache, nausea, vomiting, arthralgias, myalgias, diarrhea, elevated transaminases and corrected QT interval (QTc) prolongation. Bedaquiline should not be co-administered with drugs such as quinolones, which also prolong the QT interval. Co-administration with clofazimine can lead to severe, potentially life-threatening cardiac arrhythmias. Bedaquiline is metabolized primarily by the hepatic enzyme CYP3A4, therefore co-administration with moderate or strong inducers of this enzyme should be avoided. Bedaquiline should be administered with food, because this is how its bioavailability is increased 2-fold, while dose adjustment is not required in patients with mild or moderate renal or hepatic dysfunction.[1-6]

Interestingly, in the randomized phase IIb trial a higher death rate was recorded in the bedaquiline group (12.7%, 10/79 patients) compared to the placebo group (2.5%, 2/81 patients).[1] Tuberculosis was the cause for the five out of the ten deaths in the bedaquiline group, while the remaining five deaths were attributed to various causes such as alcohol poisoning, hepatitis with liver cirrhosis, peritonitis and septic shock, cerebrovascular accident and road accident. The causes of death could not be interpreted or associated with response to treatment, relapse of tuberculosis or co-administration of other drugs.[1] Nevertheless, due to the increased number of deaths in the bedaquiline group, its use should be strictly limited to cases where there are no alternatives. Particular care is required when the drug is administered to elderly, to HIV patients who receive antiretroviral treatment and to pregnant women.[1] Use of bedaquiline is strictly limited as a part of a WHO-recommended antituberculosis regimen in adult patients with pulmonary MDR-TB and never as monotherapy. WHO guidelines were published in order to avoid the development of resistance to the new drug and to identify possible side effects.[1-6,15]

In the UK, the conclusions from a series of a cost-benefit analyses indicate that the addition of bedaquiline to the regimen proved to be less costly and more effective than the current MDR-TB standard of care. Cost-savings resulted especially from reduction in hospitalization time, which offsets bedaquiline drug costs.[13]

Although bedaquiline has not been clinically tested for non-tuberculous mycobacterial (NTM) disease, it was administered in a small trial of 10 patients who experienced treatment failure and advanced lung disease caused by *M. avium complex* or *M. abscessus*.[14] The patients had been treated for 1 to 8 years and eight of them had macrolide-resistant mycobacterial isolates. As a result of treatment with bedaquiline for 6 months, a microbiological response was observed in 60% of patients (six out of 10), while 50% (five out of 10) showed one or more negative cultures. The findings and the potential benefit of bedaquiline in patients with advanced NTM lung disease must be confirmed by larger studies.[14]

The patient presented here received a complex antituberculosis regimen which included medications with dubious or unknown activity, like quinolones, cycloserine, ethionamide and imipenem. According to the World Health Organization, the recommended XDR-TB treatment regimen is typically composed of at least pyrazinamide and four second-line antituberculosis drugs, which are considered effective. Many of the drugs in the patient's regimen were of unknown efficacy. The patient had received pyrazinamide as part of his initial regimen and this turned out to be monotherapy. In addition, despite the resistance to ofloxacin, moxifloxacin was included in his regimen. Capreomycin was also administered although in vitro resistance was documented. Due to serious side effects, the administration of para-aminosalicylic acid was discontinued, despite the fact that it was the only effective bacteriostatic agent. Linezolide and imipenem/cilastatin were used as a supplement to the regimen, even though their antituberculosis effect is not completely documented (WHO group 5 TB drugs). As a consequence of the above mentioned restrictions, it became evident that a reasonably effective regimen could not be achieved and it was considered necessary to augment treatment. Therefore, bedaquiline was introduced in the regimen.

The patient was hospitalized for one year and after that he is on a weekly outpatient follow-up. Throughout this period, special attention has been given to his complete compliance, development of mutual confidence and cooperation in order to ensure the best possible outcome.

In conclusion, the management of multidrug resistant tuberculosis is complex and cumbersome. In the face of this challenge both the release of new drugs and the proper use of those available at present, are of extreme importance.

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