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Case Report

RECHALLENGING TREATMENT PLAN FOR MULTIDRUG-RESISTANT TUBERCULOSIS IN DIABETIC PATIENT: A CASE REPORT

AHMED ALAA AL-TEMIMI[1]*, MUHAMMAD ZHARIF M NIZAM[1], YAHAYA HASSAN[1], NOORIZAN A AZIZ[1], MOHD FADLI MOHD ASMANI[2], IBRAHIM ABDULLAH[2]

[1]Clinical Pharmacy Unit, Management and Science University, Shah Alam, Selangor, Malaysia. [2]Pharmacy Practice Unit, School of Pharmacy, Management and Science University, Shah Alam, Selangor, Malaysia. Email: Dr.Ahmedpharma@yahoo.com

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) currently considers as the biggest issue and its subcategory, rifampicin-resistant TB (RR-TB). MDR-TB is defined as a resistant to isoniazid (H) and rifampicin (R), while the latter is resistant to rifampicin (R) only. Poorly controlled diabetes mellitus increases the risk of TB and leads to poor TB treatment outcomes as well it is consider potentially threating TB control. Difference in patients' response and side effect developments toward anti-TB (ATB) medications requires rechallenging procedure that can be complicated at times. The management of MDR-TB can be complicated, especially, when the patient cannot tolerate the short regimen. Difference in patients' response and side effect developments toward ATB medications requires rechallenging procedure which can have prolonged treatment time, hospital stay, and make patients exposed to hospital-acquired infection. This challenges and obstacles, however, could be prevented earlier by having strong DOTS strategy to prevent the development of resistance and reactivation of TB.

Keywords: Diabetes mellitus, Multidrug resistant, Pulmonary tuberculosis, Rechallenge multidrug-resistant tuberculosis.

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INTRODUCTION

Tuberculosis (TB) is an infectious disease, highly contagious disease as well considering as a super major public health issue worldwide caused by a mycobacterium called *Mycobacterium TB* (MTB). According to the World Health Organization (WHO), in 2016, Malaysia reported an incidence and mortality of dying 5 per 1000 people. Following from 2000, the mortality rate is decreasing steadily; however, the incidence of new and relapse cases is increasing.In 2016 alone, 370 cases in Malaysia are reported as MDR-/rifampicin-resistant (RR)-TB [1].

Type 2 diabetes mellitus (DM) currently has a very detrimental impact toward the health of Malaysians. It is defined as a condition where the pancreas does not produce enough insulin or the body's cells do not react to insulin. National studies from 1996 to 2015 in Malaysia reported that the current prevalence in 2015 is 17.5%, over double since 1996. This huge increase was probably contributed by the doubling of the prevalence of undiagnosed DM. It is of serious concern that about half of the total reported DM is contributed by individuals with undiagnosed DM [2,3]. The WHO guideline has assigned MDR-TB short regimen and individualized treatment as the effective approach to cure the disease, by the usage of sensitivity tests and five different groups of drugs [4]. In addition, the management of DM in patient currently being treated with anti-TB (ATB) medications is based on efficiency and clinical experience due to many potential interfering factors between ATB and DM medications [5].

This report will present a patient with MDR-TB with underling DM who is currently receiving MDR-TB individual treatment and insulin regimen, respectively, for 36 days. Challenges in the management of these conditions are discussed.

CASE REPORT

A 47-year-old male Malay patient, with known medical history of RR-TB (pulmonary tuberculosis [PTB]) and uncontrolled DM, was referred to Institut Perubatan Respiratori (IPR) (Respiratory Medicine Institute) from a Hospital Kuala Lumpur. He was diagnosed with PTB and DM in May 2016. First-line ATB fixed-dose combination; Akurit-4 (per tablet ethambutol HCl 275 mg, rifampicin 150 mg, isoniazid 75 mg, and pyrazinamide 400 mg) and oral hypoglycaemic agents (OHA); metformin 1 g BD and gliclazide 80 mg BD. The regimen showed improvement as the patient coughs occasionally. However, he defaulted his TB regimen in 2016. A MTB culture and sensitivity test in May 2017 evidenced rifampicin resistance and susceptibility to pyrazinamide (Z), streptomycin (S), and ethambutol (E).

On admission, the patient was well but reported to have hemoptysis, fever, night sweats, and consistent dry cough as initial symptoms. His blood glucose level was 24.1 mmol/L. The chest X-ray showed consolidation in the base of the left lung. Laboratory investigation showed low albumin level of 27.2 g/L. The MTB culture and sensitivity test evidenced a positive result. Based on patient's history and current symptoms, MDR-TB short regimen and insulin therapy were immediately started on day 1 which are composed in Table 1.

The MDR-TB short regimen lasted for only 6 days when the patient started to develop nausea, vomiting, fever, and urticaria rash. The patient was given chlorpheniramine tablet 4 mg and loratadine tablet 10 mg once daily. The short regimen was suspended for 7 days to prevent worsening of side effects. The patient was started on chlorpheniramine 4 mg and loratadine 10 mg once daily, and betamethasone cream 1:4 locally applied twice daily. As the patient had become intolerant to the short regimen, the individualized regimen was planned.

On the day 13, the patient was started on streptomycin (S) 250 mg once daily. The dose was increased to 500 mg and then 750 mg for the next 2 days. Patient's renal function was monitored to avoid nephrotoxicity. On day 17, levofloxacin (Lfx) 750 mg once daily rechallenge was started but then stopped 3 days later when the patient experienced swelling on his face. It was later diagnosed as secondary angioedema. The reaction resolved 3 days after the medication was stopped.

On the day 22, pyrazinamide (Z) 1500 mg once daily rechallenge was started, and the patient uric acid level was monitored for gout. On the day 27, ethambutol (E) was administered for rechallenge with daily

dosage increments of 400 mg, 800 mg, and 1200 mg for the next 3 days. On day 29, ethionamide (Eto) 750 mg once daily rechallenge was started. However, the next day, the patient complains of dizziness. His blood pressure also reduced from the usual day-to-day reading. Eto was withheld for 3 days before being stopped.

The latest MTB culture and sensitivity result obtained after 26 days of admission showed no improvement. Resistance to isoniazid and rifampicin was observed while amikacin, kanamycin, capreomycin, viomycin, and fluoroquinolones showed susceptibility. As per the last day, this patient was followed up (day 35), and he was started on high-dose isoniazid (H^H) 1000 mg once daily despite the resistance status. Thus, his current treatment regimen now consists of streptomycin (S) 750 mg once daily, ethambutol (E) 1200 mg once daily, pyrazinamide (Z) 1500 mg once daily, and high dose isoniazid (H^H). The patient decided to continue his treatment which will last for 20–24 months until the resolution of the disease.

The patient blood glucose level was controlled by the administration of insulin actrapid and insulatard 8 iu. The patient's blood glucose was monitored 4 times a day: Pre-breakfast, pre-lunch, pre-dinner, and at night before sleep (Fig. 1). However, the patient still does not know how to administer insulin by himself as this is his 1st time receiving it. The patient and caregiver education on this matter was later given to ensure that his blood glucose level is controlled, and the ATB medications are effective (Table 2).

DISCUSSION

Risk associated with defaulted TB treatment

Many factors such as a drug resistance that obstacles to successful directly observed therapy short-course that lead to delay disease control. Treatment default is known to be associated with misuse, foreign birth, male gender, previous default, low socioeconomic status, psychiatric illness, unemployment, migration, side effects, long distance to the clinic, social stigma, and poorly-implemented therapy short course. Category II cases is classified by the WHO for the patients who did not success, default from, or relapse after completion of standard first-line TB treatment and present for retreatment [6].

Table 1: Current medication history

Medication name	Dose	Frequency	Route of administration
Kanamycin	100 mg	OD	IM
Clofazimine	750 mg	OD	PO
Ethionamide	250 mg	BD	PO
Ethambutol	1200 mg	OD	PO
Levofloxacin	500 mg	OD	PO
Pyrazinamide	1500 mg	OD	PO
Isoniazid	1500 mg	OD	PO
Insulin Actrapid	8 iu	TDS	IM
Insulin Insulatard	8 iu	OD	PO

Table 2: Patient's demographic and current medication in IPR

Patient details	Medication
Age in years at diagnosis/sex	45/male
Regimens received (time)	MDR-TB short regimen K, E, Eto, Lfx, Z, H^H, Cfz (D1–D6) MDR-TB individualized regimen S (D13) Lfx (D17–D20) Z (D22) E (D27) Eto (D29–D32) H (D35) Insulin regimen Insulin actrapid (D1–D35) Insulin insulatard (D1–D35)
Drugs used for MDR-TB	SEZ-H^H
Drug resistance	H and R

K: Kanamycin, E: Ethambutol, Eto: Ethionamide, Lfx: Levofloxacin, Z: Pyrazinamide, H^H: High dose isoniazid, Cfz: Clofazimine, S: Streptomycin, R: Rifampicin, MDR-TB: Multidrug-resistant tuberculosis, IPR: Institut Perubatan Respiratori

A study states that one important risk factor for acquiring MDR-TB is a history of previous TB treatment. In this case, the patient had a defaulted treatment in 2016. Based on the patient history, DOTS was poorly implemented toward this patient. This can be improved by counselling and communication between health staff and patients, decentralization of treatment involving community health workers, flexibility in the choice of DOT supporter, and reinforced supervision activities of remote health posts [7].

Managing patient with MDR-TB and DM

Poorly controlled DM increases the risk of MDR-TB, and diabetes leads to poor MDR-TB outcomes of treatment. The patient had uncontrolled DM since 2016 which can reduce the treatment outcome for ATB medications and increase the chance for mortality. Biologically, DM affects susceptibility to MDR-TB due to the effects of DM on essential and adaptive immunity [8,9]. Minimize ability to clear infection could possibly lead to MDR-TB-related deaths among people with DM explicitly, and it is also possible that these patients face a greater likelihood of death during MDR-TB therapy because of DM associated with some concomitant diseases, such as cardiovascular diseases, stroke, and renal failure.

Treatment wise, the pharmacokinetics of TB drugs also could be affected by disease of DM so that the bactericidal activity is pointed. From the patient medication history, rifampicin was administered as a part of the first-line ATB regimen. Rifampicin administration could interfere with pharmacokinetics of OHA, such as gliclazide, by decreasing its level, which in turn impedes glucose control [10]. This interaction may contribute to poorer outcome in this patient. This patient will express a higher chance of recurrent TB due to reduced immunity that increases the susceptibility to reactivation of the earlier infection, which manifested a year later in 2017. Patients with hyperglycemia levels had significantly reduced levels of rifampicin serum concentrations, thus showing an inversely proportional relationship between blood glucose and rifampicin serum levels [11]. Hence, the importance of controlling blood glucose level cannot be over-emphasized in the presence of TB and DM.

During the patient stay in IPR, repeat testing of glucose levels was performed 4 times per day. The patient was immediately started on insulin on admission to lower his blood glucose level for the ATB medications to work efficiently. Administration of insulin for this patient was reasonable as there is no interaction between insulin and ATB medications.

MDR-TB regimen conversion, adverse drug reactions (ADRs), and rechallenge procedure

According to the WHO guideline, patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens. The intensive phase will be 4–6 months while the continuation phase will be 5 months. Regimen composition will be 4–6 km-Mfx-Pto-Cfz-Z-H^H-E and 5 Mfx-Cfz-Z-E [4]. Modifications using similar medications were made to this patient starting regimen which was Eto and Lfx due to unavailability of prothionamide and moxifloxacin. This was not a problem as those agents showed equivalent efficacy for treating MDR-TB [11,12].

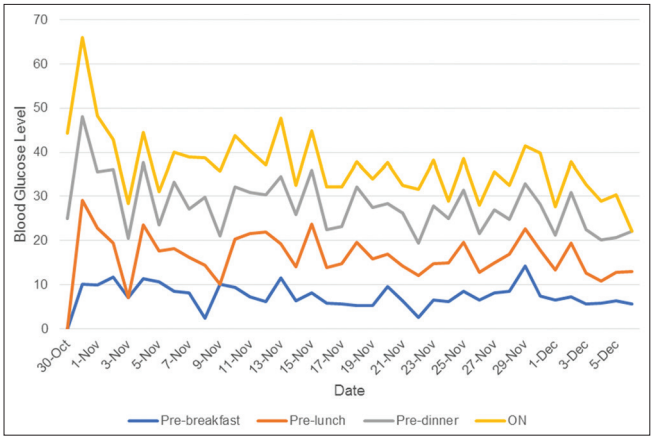

Fig. 1: Patient blood glucose level during hospital stay

In general, side effects are more serious in second-line treatment compared to first-line treatment. In this case, the patient developed nausea, vomiting, and urticaria rash a few days after the regimen was started. This did not permit further use of the short regimen and require changes to long and individualized regimen according to the WHO 2016 conditional recommendation on selecting a treatment plan for MDR-TB. The intensive phase will be up to 8 months and the continuation phase will be up to 12 months.

To stop potential offending drugs, TB consultant often rechallenges drug one by one from the previous regimen. It is, sometimes, not possible to distinguish a reaction as due to the addition of a new drug or due to a flare of the underlying reaction. Stopping and starting medications or treating with a weak regimen can lead to drug resistance and treatment failure, so the balance of preventing harm and providing treatment requires significant clinical skill and experience. Most experts would not recommend rechallenge once a drug is identified as the causative agent.

Lfx and Eto had been identified as the offending agent with Naranjo algorithm score of 8 and 6, respectively, representing probable ADR. Lfx-induced angioedema cases had been reported in several cases in the previous years. Angioedema is defined as sudden swelling of skin, subcutaneous and submucosal tissue, and respiratory or gastrointestinal tracts which can last up to 7-days. In most cases, discontinuation of the drug and administration of antihistamines proved to be effective. Eto has a negative inotropic effect on the heart in which its time course and intensity correspond to the blood pressure reduction. Treatment is mainly supportive. Vital signs should be monitored (sensorium, blood pressure, heart, and respiratory rate) regularly, and hypotension must be corrected with isotonic fluids or inotropic agents [13].

Inclusion of high-dose isoniazid after isoniazid resistance was identified

On discussion with consultant and referring to the WHO guideline, isoniazid is recommended alongside a full MDR-TB regimen in patients with RR strains confirmed or suspected to be susceptible to isoniazid. High-dose isoniazid is one of the core components of the shorter MDR-TB treatment regimen. Strains bearing mutations in the promoter region of the inhA gene may have a minimum inhibitory concentration to isoniazid that is low enough to be overcome by high-dose isoniazid. In such settings, the drug may still add benefit [4].

Monitoring for potential side effects and ADRs

The patient should be monitored for the risk of hypoglycemia and diabetic nephropathy. Changed pharmacokinetic dynamics of ATB medications in patients with DM may warrant adjustments in the TB treatment regimen. Pyrazinamide and ethambutol doses could need to be in sync based on creatinine levels in patients with diabetic nephropathy. Pharmacists play important role in ensuring medications adherence and providing pharmaceutical care management to TB patients with DM [14].

Streptomycin, like other aminoglycosides, possesses the risk of nephron- and ototoxicity. Renal function must be monitored by documenting creatinine at least monthly. Furthermore, documenting baseline and monthly audiology examination is required for audiology examinations. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Pyrazinamide is one of the most hepatotoxic ATB agents and the only ATB agents that have the potential to cause hyperuricemia in the patient. Therefore, monitoring transaminases and uric acid is necessary. For ethambutol, patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and color discrimination monitoring should be performed.

Isoniazid highly necessary needs clinical monitoring for all patients. It is recommended to do baseline liver function testing for the patients receiving multiple TB drugs or other hepatotoxic drugs or with underlying liver disease (including viral hepatitis). Symptoms of hepatotoxicity confirmed by follow-up liver function testing. Since this patient's albumin is low, he was predisposed to the risk of hepatotoxicity due to the increased concentration of free drugs [15].

CONCLUSION

In summary, the management of MDR-TB can be complicated, especially, when the patient cannot tolerate the short regimen. Difference in patients' response and side effects developments toward ATB medications requires rechallenging procedure which can have prolonged treatment time, hospital stay, and make patients exposed to hospital-acquired infection. This challenges and obstacles, however, could be prevented earlier by having strong DOTS strategy to prevent the development of resistance and reactivation of TB.

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AUTHORS' CONTRIBUTIONS

All the authors contributed equally to the conductance of the study, writing, and editing the article.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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