ORIGINAL RESEARCH

Importance of Therapeutic Drug Monitoring in the Treatment of Active Tuberculosis
A Retrospective Study of 4 Cases

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ABSTRACT
Background: In the treatment of active tuberculosis, therapeutic drug monitoring (TDM) is used to optimize dosing that maximizes therapeutic benefit while minimizing toxicity. In Morocco, TDM is not routinely used, yet low levels of anti-TB drugs can be associated with poorer treatment outcomes.
Methods: We retrospectively checked our archives for patients with active TB for whom TDM was performed during 2014. Medical records were reviewed to abstract demographic, clinical, radiographic and microbiological data including time until smear and culture conversion. Then, we looked for cases with delay of TB conversion.
Results: In total, 24 patients were identified, for whom TDM was performed, they all had low serum drug levels. Among them, 4 patients showed delayed bacteriological conversion.
Conclusions: Our study cases are showing the benefit of serum dosage in the follow-up of the patients showing a delay of sputum examination conversion, both direct and culture, during their evolutions. TDM is potentially useful for the treatment of active TB, but is currently underused in Morocco.

KEY WORDS: Therapeutic Drug Monitoring - Active Tuberculosis - delay of TB conversion

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INTRODUCTION

The WHO estimated that 9.2 million persons worldwide developed active tuberculosis (TB) in 2008, and 1.4 million deaths have occurred (1, 2). In the vast majority of countries, patients with newly diagnosed active TB received standardized treatment with a six-month 4 drugs regimen containing rifampin throughout, which is recommended for low- and middle-income countries (3), as well as high-income countries such as Canada (4) and the United States (5). In adults with drug-sensitive TB, this regimen, with weight adjusted dosing, has shown high efficacy in a large number of randomized trials (6). The therapeutic drug monitoring (TDM) is used to adjust the dosage and allow an optimization of the therapeutic benefit while minimizing toxicity. In the treatment of active tuberculosis, TDM is not systematic, but low levels of antibacillary treatment can lead to poorer outcome.

METHODS

We retrospectively checked our archives for patients with active TB for whom TDM was performed during 2014. Medical records were reviewed to abstract demographic, clinical, radiographic and microbiological data including time until smear and culture conversion. Then, we looked for cases with delay of TB conversion.

RESULTS

In total, during 2014, 24 patients were identified for whom TDM was performed. This represented 3.6% of the total of 665 patients treated over the same interval. The average age of these 24 patients was 37.6 years, with 71% being men. The most significant comorbidity was diabetes which we found in 7 cases (29.1). No patient was HIV-infected. All the 24 cases had drug-sensitive TB. All cases had low serum drug levels. Among them, 4 patients showed delayed bacteriological conversion:

Case 1

A 15 years old Moroccan student, never treated for tuberculosis, with no family history of tuberculosis and with uneventful medical history, showed symptoms a month earlier, with a recurrent bronchitis. Tests showed a positive AFB smear testing. Antibacillary treatment was started with 4pills per day of combined treatment (ERIP) for a weight of 57kg, each pill contained 150mg Rifampicin (R) , 75mg isoniazid (I) , 400mg pyrazinamid (P) and 275mg Ethambutol(E). Bacteriological control of the 2nd and the 4th month were negative with a weight gain of 7kg, whereas the direct examination of sputum at the end of treatment was positive with a weight loss of 3kg. Chest X-ray showed the presence of a right apical excavated opacity with micronodules in the upper third of the right hemithorax. Biology showed inflammation syndrome with SR=87 and CRP= 45; Hepatitis (B, C) and HIV serologies were negative. Liver function tests and ionogram were normal as well, Lipid profile showed total cholesterol= 1.57, HDL=0.18 LDL=1.16, TG=1.16. Sputum culture showed sensitivity to Rifampicin and isoniazid. Genotype MTBDR confirmed sensitivity to Rifampicin. Anti-bacillary Serologic testing revealed an under dosage of rifampicin 2.9 mg, while therapeutic dosing ranges between 8 and 24 mg which required the addition of 150mg of Rifadine. Several controls showed low rates of 0.5 mg/l and 2.4mg/l and 7 mg/l. We decided to restart antibacillary treatment as follows: 3ERIP /5ERI with adaptation of rifampicin doses. Correct serum dosage of rifampicin of 8.4mg/l was obtained with a high dose of rifampicin reaching 15 mg/kg/day. Clinical radiological and bacteriological evolution was favorable.

Case 2

A 42 years old Moroccan patient, treated for smear positive tuberculosis for 4 months by ERIP 3pills/day with a weight of 42kg, was admitted to the emergency room for acute dyspnea with sharp stabbing thoracic pain. On auscultation, there were no breath sounds on the right side with hyperresonance on percussion. Chest X-rays showed a large right pneumothorax. An emergency chest tube was placed and the lung re-expanded after 10 days. Complete blood count (CBC) showed: Hemoglobin=12.7, white blood cell (WBC)=13300, platelets=335000, CRP =170 mg / l, and ionogram was normal. After 4 months of antibacillary treatment, TB testing was repeatedly positive. The genetic study using PCR XPERTMTB / RIF detected mycobacterium tuberculosis which was complicated with the absence of resistance to rifampicin. Serologic testing for antibacillary revealed rifampicin dosage of 4.8 mg/l (therapeutic range between 8 and 24 mg) requiring the addition of 150mg of Rifampicin. Several controls showed low rate at 4.86 mg/l and 1.51mg/l and 5.25 mg/l. Correct serum dosage for rifampicin (13.02 mg/l) was obtained at 750mg/day that is 14.42 mg/kg/day. The antibacillary treatment was extended for 6 months with good clinical and radiological evolution.

Case 3

An 18 years old Moroccan patient, never treated for tuberculosis but with recent family history of TB for his father was treated for smear-positive tuberculosis, showed a chronic cough of more than 2 years with interscapular pain. Chest X-rays showed excavated bilateral alveolar condensations with necrotic mediastinal lymph nodes. Smear sputum tests for TB were negative. Staff decision was to treat the patient for smear negative TB and antibacillary treatment was introduced: ERIP: 3pills a day for an initial weight of 47 kg. The clinical evolution was favorable during the first two months with a weight gain of 10Kg. However, on the third month, the patient showed a reoccurrence of coughing, fever with night sweats and 10Kg loss of weight. Chest X-rays and CT scan performed at the end of anti-TB treatment showed an aggravation of the pulmonary condensations with persistence of lymphatic nodes. The smear sputum search at the end of treatment was negative. The patient was re-admitted to hospital with bronchial endoscopy performed. Biopsies were in favor of noncaseating granulomas, bronchoalveolar lavage: showed absence of TB in direct examination but culture was positive. Antibiogram showed no resistance to RIF, INH, Strep, PZA, and ETB. A second line TB treatment was proposed to the patient: streptomycin: 750mg/day, Oflocet: 800mg/day, PZA: 1200mg/day Etionamide: 750mg/day, Rifampicin: 450 mg/day. TB smear tests remained positive both on direct exam and culture. We decided to put the patient back on ERIP: 3pills/day for a weight of 46 kg. CBC tests showed a microcytic hypochromic anemia, ferritin: 93ng / L, serum iron = 0.13mg / l, SR= 103mm, CRP: 53mg/l, liver function tests: ALT = 10 IU/L, AST = 12ui/L, alkaline phosphatase: 33ui / l, renal function tests: creatinin: 6mg/l urea: 0.19g/l; Hepatitis (B,C) and HIV were negative, albumin 26 g /l, vitamin B12: 836pg / l, Parasitological exploration of the feces (-), TB Test in stool (-), and GenXpert (-). The serum assay of anti-TB treatment found: INH: 0.59mg/l, Rifampicin: 3.85mg/l. We increased the dose by adding 150mg of rifampicin and 75mg of isoniazid reaching 16.30mg/kg/day of rifampicin and 8.15mg/kg/day of isoniazid reaching a serum concentration of INH: 4.11 mg/l and Rifampicin 14.43 mg/l. The evolution was favorable with disappearance of general signs and weight gain and normalization of X-rays.

Case 4

A 76 years old Moroccan patient, former smoker 35P/year who stopped 10 years ago, with 4-month history of productive cough with purulent sputum associated with low volume hemoptysis. Smear positive tuberculosis was diagnosed and treatment began. The evolution was marked by non-clinical improvement and positivity of smear tests on direct examination on the fourth month after being negative on the 2nd month. Clinical examination found the patient to be cachectic, weight 33 kg, with diffuse reils. Chest X-rays showed worsening bilateral nodular and micronodular opacities compared to the initial X-rays. An antibiogram showed no resistance for the ERIP drugs. Tests showed an inflammatory syndrome with normal renal and hepatic function SR=110 mm/1h, negative HIV serology. Genexpert confirmed the presence of Mycobacterium tuberculosis with absence of resistance to rifampicin. The serum concentration of rifampicin was at 1.79mg/l, then at 2.08mg/l, then at 5.57mg/l. Increasing doses of rifampicin with liver function control allowed the normalization of rifampicin concentration. Clinical, radiological and bacteriological improvement was obtained after an treatment extension for six more months.

DISCUSSION

In the present retrospective case control study, 24 patients were identified for whom TDM was performed, with 24 having at least one low drug level, and required dose adjustment. The most frequent low levels were of INH and rifampin. Among TB patients who underwent TDM, low levels were associated with diabetes and more extensive disease.

In our study, patients with low drug levels had longer time to culture conversion, as was reported by others (4). However, final treatment outcomes were not affected because doses were adjusted and therapy was often prolonged. Ultimately, all patients were cured.

Slow response to therapy can lead to prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence of TB after treatment. The causes of slow response are diverse, but measurement of serum anti-TB drug levels, or therapeutic drug monitoring (TDM), are potentially useful tools for uncovering the causes of slow response (5, 6). Low serum levels can be a consequence of malabsorption, inaccurate dosing, altered metabolism, or drug–drug interactions (6), but in most instances, low serum levels can be readily corrected with dose adjustment.

Although published reports describe patients for whom slow response was attributable to low drug levels, questions remain about how to best implement TDM on a programmatic scale (4, 7).

Therapeutic drug monitoring is a standard clinical technique used for many therapeutic cases, including many infectious diseases particularly in tuberculosis. The serum concentration monitoring allows the clinician to make quick decisions regarding the adjustment of therapy. The benefit of the therapeutic monitoring of these drugs is subject to discussion. It might be useful in cases like moderate or severe kidney failures, in case of dialysis or peritoneal dialysis, and for patients co-infected with HIV if they respond poorly or slowly to TB treatment. Another indication is in case of association with treatment containing protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)(3). However, some patients may react late to tuberculosis treatment.

As in our study where we found 7 diabetes, Scott et al. showed that diabetic patients were at significantly increased risk of having a low rifampin level (OR 5.8, 95% CI 1.4–23.1, p = 0.01) (2).

These patients may benefit from the serum assay for early adjustment of treatment regime, thereby preventing the development of drug resistance. According to the reported cases, patients with low levels of drug took more time for conversion of direct examination and/or culture, as was reported in the literature (4). Yet, the final results were more positive because the doses were adjusted earlier and the therapy period was often extended. However, there are proofs published that low levels of drugs lead to poorer treatment outcome (5), failure and relapse (6), and an acquired resistance (8). This suggests that the serum dosage of antibacillary treatments is potentially useful for the treatment of active tuberculosis, but it is at present often underused.

Another important implication is to know if the current administration of rifampicin is adequate; other studies suggested that the current dosage can be less optimal, and trials are necessary for data analysis.

CONCLUSION

In summary, low drug levels were frequent among patients on therapy for active TB. Although low drug levels are difficult to predict, there is evidence – from the current and other studies – that low levels are clinically important.

Our series reinforces the indication of the determination of serum antibacillaries especially given unfavorable negativity, and underlines the benefit of a therapeutic adjustment dose to obtain healing and prevent progression to resistance. Other studies on serum assays especially rifampicin in vivo and in vitro would be interesting to explain cases of under-dosage.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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Declared none.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

(1) Organization WH. Global tuberculosis control: WHO report 2010: World Health Organization; 2010.

(2) 2. Scott K. Therapeutic Drug Monitoring for Slow Response to Tuberculosis Treatment in a State Control Program, Virginia, USA. Therapeutic Drug Monitoring. 2010.

(3) Babalik A, Mannix S, Francis D, Menzies D. Therapeutic drug monitoring in the treatment of active tuberculosis. Canadian respiratory journal: journal of the Canadian Thoracic Society. 2011;18(4):225.

(4) Mehta JB, Shantaveerapa H, Byrd RP, Morton SE, Fountain F, Roy TM. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. CHEST Journal. 2001;120(5):1520-4.

(5) Weiner M, Burman W, Vernon A, Benator D, Peloquin CA, Khan A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. American journal of respiratory and critical care medicine. 2003;167(10):1341-7.

(6) Weiner M, Benator D, Burman W, Peloquin CA, Khan A, Vernon A, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Clinical Infectious Diseases. 2005;40(10):1481-91.

(7) Kimerling ME, Phillips P, Patterson P, Hall M, Robinson CA, Dunlap NE. Low serum antimycobacterial drug levels in non-HIV-infected tuberculosis patients. CHEST Journal. 1998;113(5):1178-83.

(8) Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. Clinical infectious diseases. 2009;48(12):1685-94.