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SHORT REPORT

High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis

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ABSTRACT: Pyrazinamide (PZA) combined with either ethambutol (EMB) or a fluoroquinolone for 6–12 months is one of the treatments recommended for latent tuberculosis infection (LTBI) in contacts exposed to multidrug-resistant tuberculosis (MDR-TB). The aim of the present study was to describe the side effects related to combined PZA and EMB treatment given for LTBI, in contacts previously exposed to MDR-TB.

In total, 12 consecutive contacts, all of African origin and aged 38±5 yrs, were treated with daily PZA (23±4 mg·kg^{-1}) and EMB (17±4 mg·kg^{-1}) at Geneva University Hospital outpatient clinic (Switzerland), as a result of contact-tracing procedures for two patients with contagious MDR-TB.

Clinical status and liver function tests (aspartate aminotransferase (ALAT) and alanine aminotransferase (ASAT)) were monitored monthly. In seven cases (58%) treatment was discontinued after a median of 119 days, due to hepatic toxicity in six cases (ALAT or ASAT elevation more than four times the upper normal limit), and gastrointestinal symptoms in one case.

In conclusion, combined pyrazinamide and ethambutol for latent tuberculosis infection may be associated with a high risk of hepatic toxicity, and warrants close monitoring. There is clearly a need for alternative preventive treatments for contacts exposed to multidrug-resistant tuberculosis.

KEYWORDS: Ethambutol, hepatotoxicity, latent tuberculous infection, multidrug-resistant tuberculosis, pyrazinamide, treatment

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Multidrug-resistant tuberculosis (MDR-TB) is defined as a tuberculous infection by bacilli showing simultaneous resistance to at least isoniazid (INH) and rifampicin (RIF). In Switzerland, between 1999–2000, 1.2% of all declared cases of tuberculosis (TB) were MDR-TB, and all were foreign-born [1]. Maintaining a high index of suspicion in patients with risk-factors for MDR-TB, rapid identification (whenever possible through genotyping for resistance to RIF), isolation of active cases, directly observed therapy implementation, and treatment of latent tuberculosis infection (LTBI) caused by exposure to cases of MDR-TB are all essential to control the spread of resistant bacilli. The current USA guidelines recommend the use of pyrazinamide (PZA) and either ethambutol (EMB) or a fluoroquinolone as a first-line treatment (before results of susceptibility testing for infecting strain are available) for adults with LTBI related to MDR-TB, for 6–12 months [2]. These recommendations are supported by expert opinion, but not by controlled trials [3].

Recent reports have highlighted the potential hepatotoxicity of combined treatment with RIF and PZA for LTBI (5.8%) [4–6]. Due to the lower hepatic toxicity of RIF alone, rather than that of PZA, the question of the toxicity of PZA and its' acceptability in a prophylactic treatment has been raised [7, 8]. To date, information as to the toxicity of PZA in combination with either EMB or a fluoroquinolone is scarce [9–11].

This case series describes the high prevalence of drug-induced hepatitis associated with treatment of latent MDR-TB infection by PZA and EMB in adults.

PATIENTS AND METHODS

Contact-tracing procedures performed for two cases of MDR-TB treated in Geneva University Hospital (Switzerland) during 2003 led to the

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identification of 18 subjects considered at risk for LTBI. The first index case was a young HIV-positive female from Angola, Africa, with cavitary pulmonary TB. The second index case was a young HIV-negative female from Eritrea (Africa) with multiple pulmonary cavitary lesions. Both cases had a productive cough, and positive sputum smears showing numerous acid-fast bacilli and were consequently strongly infectious.

In total, 12 out of the 18 contacts identified were followed in Geneva University Hospital, while six left the Geneva area and were lost to follow-up. All contacts originated from either sub-Saharan Africa (n=9) or Eritrea (n=3). All contacts identified had a tuberculin skin test (TST) induration >10 mm (17±4 mm; TST 2 units of RT 23® Tuberculin; Statens Serum Institut, Copenhagen, Denmark), and definite close contact with either of the two index cases. None of the contacts were aware of a previous TST.

On the basis of the joint American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) guidelines for treatment of LTBI in contacts exposed to MDR-TB cases, a combined treatment of PZA and EMB was initiated for 9 months [2]. Intended doses were 20–25 $mg \cdot kg^{-1} \cdot day^{-1}$ and 15–20 $mg \cdot kg^{-1} \cdot day^{-1}$ for PZA and EMB, respectively. This choice was in agreement with susceptibility testing of *Mycobacterium tuberculosis* strains of index cases. All treatments were initiated between September 2003 and March 2004. Cases were announced to the Swiss national registry of pharmacovigilance.

Liver function testing (ASAT: aspartate aminotransferase; and ALAT: alanine aminotransferase) was performed before the beginning of the chemoprophylaxis, after 2 weeks and then on a monthly basis.

Treatment was discontinued if increase in ALAT or ASAT was greater than four times the upper limit of normal (ALAT: 42 $U \cdot L^{-1}$; ASAT: 42 $U \cdot L^{-1}$), or if the patient presented drug-related adverse effects.

Systematic serology for viral hepatitis was not performed, since initial ASAT and ALAT were within normal values in all subjects.

RESULTS

Details of the clinical and laboratory follow-up are summarised in table 1. Median age of contacts was 38 yrs (range 31–48 yrs). All had baseline values of ALAT and ASAT within the normal range. None had any comorbidity or medication, albeit for one patient with chronic (undiagnosed) hepatitis B infection and systemic hypertension, treated by diltiazem, hydrochlorothiazide and valsartan. Daily doses of PZA and EMB were mean±SD (range): 23±4 $mg \cdot kg^{-1}$ (17–33) and 17±3 $mg \cdot kg^{-1}$ (13–22), respectively.

Only five out of the 12 (42%) contacts completed their treatment. Six contacts (50%) discontinued because of an increase in ALAT or ASAT above the threshold of four times the upper normal value after 152±69 days (median: 119 days; table 1) and two of these cases had gastrointestinal (GI) symptoms. One patient had a mild elevation of liver enzymes associated with GI symptoms requiring discontinuation of medication. No other side-effects were reported, albeit for unspecific visual disturbances in one case with normal visual evoked potentials.

Among the six patients with liver toxicity, peak values ranged from 82–1,338 $U \cdot L^{-1}$ for ALAT and 164–2,030 $U \cdot L^{-1}$ for ASAT. For all contacts, liver enzyme values returned to normal after discontinuation of medication.

DISCUSSION

In this case series, combined treatment with PZA and EMB for LTBI after exposure to MDR-TB was associated with a remarkably high rate of drug-induced hepatitis (50%; occurring after a median of 4 months of treatment), and, to a lesser extent, GI symptoms, leading to discontinuation of treatment in a total of 58% of contacts treated. ASAT and ALAT levels returned to normal after PZA and EMB were discontinued. No

TABLE 1 Characteristics, symptoms and liver tests of contacts treated by pyrazinamide (PZA) and ethambutol (EMB) for latent tuberculosis infection

Case	Age	Sex	Origin	PZA dosage $mg \cdot kg^{-1} day^{-1}$	EMB dosage $mg \cdot kg^{-1} \cdot day^{-1}$	Symptoms	ASAT peak value $U \cdot L^{-1}$	ALAT peak value $U \cdot L^{-1}$	HIV serology	HBV	HCV	Discontinued treatment
1	33	F	Congo	21	22	None	251	134	NA	NA	NA	After 89 days
2	35	M	Angola	24	14	None	164	358	NA	NA	NA	After 87 days
3	34	M	Angola	24	15	Nausea	60	110	NA	NA	NA	After 99 days
4	32	F	Angola	24	19	Nausea and vomiting	182	125	Neg.	Neg.	Neg.	After 229 days
5	36	F	Congo	19	16	None	357	115	Neg.	Neg.	Neg.	After 119 days
6	43	M	Congo	23	14	Loss of appetite	2030	1338	Neg.	Healed	Neg.	After 193 days
7	46	M	Congo	20	16	None	175	82	Neg.	Chronic active	Neg.	After 247 days
8	41	M	Angola	17	13	Dizziness	53	32	Neg.	NA	NA	No
9	48	F	Congo	22	18	None	41	46	NA	NA	NA	No
10	31	M	Eritrea	22	18	None	28	25	NA	NA	NA	No
11	36	F	Eritrea	24	19	None	30	18	Neg.	NA	NA	No
12	40	M	Eritrea	33	20	Visual disturbances, normal VEP	26	19	NA	NA	NA	No

ASAT: Aspartate aminotransferase; ALAT: alanine aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus; F: female; M: male; VEP: visual evoked potentials; NA: not available; Neg: negative.

other adverse effects (such as arthralgias or cutaneous reaction) were noted in this study.

As previously mentioned, current USA guidelines recommend the use of PZA with either EMB or a fluoroquinolone as first-line treatment for adults with LTBI related to MDR-TB, for 6–12 months [2]. The present report is, to the current authors' knowledge, the first to describe a high rate of drug-induced hepatitis in contacts treated in this context with a combination of PZA and EMB. Previous publications have described high rates of drug-induced hepatitis in contacts treated by PZA with either levofloxacin (47%) or ofloxacin (25–41%) [9–11]. Median time to peak increase in ASAT and/or ASAT was approximately 4 weeks in these three studies, with a wide variability (drug-induced hepatitis occurring up to 25 weeks after beginning of treatment). Liver tests returned to normal within 3–5 weeks after discontinuing treatment [10].

EMB is not considered as incriminated in drug-induced hepatitis, and, thus, liver toxicity in this series is most probably exclusively PZA related [7, 8]. However, the rate of drug-induced hepatitis in standard treatment for active TB (INH, RIF, PZA and EMB) is ~3% [7]. Thus, rates described for combinations of PZA and either RIF (8–9%) [4–6], fluoroquinolones (25–47%) [9–11], or EMB are surprising and yet unexplained. In the present report, treatment was interrupted after a median period of 4 months, thus, prolonged treatment with PZA when compared with the 2 months of standard treatment for active TB may contribute to the increased incidence of liver toxicity. However, drug-induced hepatitis occurred earlier in cases treated with PZA and a fluoroquinolone. Risk factors for PZA-induced hepatitis have been identified in patients undergoing treatment for active TB, such as sex (female), older age ($\geqslant$60 yrs of age), birth in Asia and HIV infection [7, 12]. However, none of these risk factors were relevant in the present study.

Two additional comments must be made as to the results presented. First, all contacts treated for LTBI underwent monthly monitoring of ASAT and ALAT. This is not recommended as a routine measure in treatment for active TB or LTBI [2, 13]. The relevance of a mild asymptomatic increase in ASAT and ALAT may, thus, be questioned, and could be overestimated in the data presented. However, documenting ASAT or ALAT levels three times or more above the upper limit of normal level (if symptoms present) or five times above (if asymptomatic) is considered as a mandatory reason for interrupting all potentially hepatotoxic tuberculostatic drugs in ATS/CDC guidelines [13]. Thus, the attitude adopted is in agreement with recent recommendations and previous publications [7, 12]. Secondly, all contacts were of African origin, most of them from sub-Saharan Africa. The unexpectedly high rate of drug-induced hepatitis could, thus, be related to the ethnic background of the subjects studied. However, to the present authors' knowledge there is no support for this hypothesis in the previous publications relative to treatment for either active TB or LTBI.

Although any conclusion based on available evidence is preliminary, the frequency of drug-induced hepatitis in published reports of patients exposed to MDR-TB, and treated for LTBI with PZA and either EMB or fluoroquinolones, is preoccupying. Drug-induced hepatitis can occur several months after the beginning of treatment. Furthermore, marked increases in ASAT and/or ALAT can be virtually asymptomatic. Systematic monthly monitoring of patients and their liver enzymes is mandatory in this setting.

Furthermore, alternative regimens to those presently recommended must be envisaged and studied, because of the increasing frequency of multidrug-resistant tuberculosis and, thus, the increasing need for an effective treatment for latent tuberculosis infection in these cases.

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