Enf Emerg 2002;4(2):62-65

Treatment of Latent Tuberculosis Infection in injecting drug users co-infected by HIV

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Summary

Clinical assays in injecting drug users (IDU) and HIV infected people with a tuberculin skin test (TST) ≥ 5 mm are intended to evaluate safety and effectiveness of two preventive strategies for tuberculosis (TB). Study protocol compares two treatment arms for M. tuberculosis infection, or latent TB infection (LTBI), as follows: 9 months daily-therapy with isoniazid (9H) vs. 2 months daily-therapy with rifampin and pyrazinamide (2RZ) administered randomly. Present data shows an enhanced adherence concerning the 2RZ-treatment group. Preliminary results of adverse events are not different from another studies or between the two treatment arms either.

Resumen

Ensayo clínico destinado a evaluar la seguridad y la efectividad de dos tratamientos preventivos para la tuberculosis (TB) en usuarios de drogas por vía parenteral (UDVP) infectados por VIH y con induración ≥ 5 mm en la prueba de la tuberculina. Se comparan 9 meses de tratamiento diario con isoniacida *versus* 2 meses de rifampicina más piracinamida. Los datos preliminares demuestran mayor adherencia en el segundo grupo y que no hay diferencias en relación a efectos adversos.

Introduction

Prior to HIV/AIDS epidemic, the main risk factor for developing active TB in persons with positive tuberculin skin test (TST-positive) was having recent TB infection with an approximate rates of 12.9 cases per 1000 person-year[1] and accumulate risk of 10% lifetime. In the AIDS era, TST-positive patients co-infected with HIV are up to fifty-fold more likely to develop active TB than seronegative people[2,3] and this hazard seems to be unremitting. In addition, the rate of active TB among TST-positive and HIV+ injecting drug users (IDU) was estimated as 76 cases/1000 person-year[4]. In Spain, where more than 50,000 HIV+ and *M. tuberculosis* co-infected people are calculated, TB is the first AIDS-related disease[5]. In our setting, imprisonment is strongly associated to having TST-positive, as well as heroin addiction for more than 10 years is the major risk behavior for acquiring HIV infection[6]. These would summarize that in Spanish big cities, such as Barcelona, more than 23% of TB patients were IDU and HIV+[7].

It has been suggested that LTBI, in patients co-infected with HIV, might be efficiently treated with 2RZ[8], although, out of our knowledge, there were not studies validating short-therapies to treat LTBI in IDU. The aim of this work was to compare the safety and effectiveness of two therapy strategies for LTBI to avoid active TB among HIV-infected and IDU people.

Patients and methods

Design

Clinical assays in IDU and HIV infected population with a TST-positive, multicentre, randomized, controlled, comparative and prospective.

Inclusion criteria

HIV infected persons older than 18 years, with TST ≥ 5 mm and no clincal evidence of active TB as follows:

- no cough or fever of unknown origin,
- normal chest x-ray,
- acid-fast bacilli smear negative, as a minimum of three samples, when patients presented productive cough.

Exclusion criteria

- Previous otherwise active TB;
- LTBI treated before;
- Chronic liver disease, defined by transaminase levels almost three times upper limit; or

– Regular alcohol use.

Subjects

N = 1926 (963 patients by arm, needed), recruited from methadone maintenance programs (MMP), prisons and hospitals.

Variables

1. Demographic: age, gender, living conditions.
2. Clinical:
   – Evaluation of adherence by treatment arm.
   – Notification of adverse events by treatment arm.
   – *Follow-up, including visits and blood tests every two weeks and* registering incidence of TB along the 1st year of follow-up.

Treatment

Compliance ≥ 90% was required. Administration as directly observed therapy with a) isoniazid, 5 mg/Kg per day for 9 months (9H); or b) Rifampin, 10 mg/Kg per day and pyrazinamide, 25 mg/Kg per day for 2 months (2RZ). In those patients receiving protease inhibitors or NNRTIs, rifampin was substituted by rifabutin 150 to 300 mg/daily, depending on antiretroviral drugs concurrently administered.

Results (Tables 1, 2)

Along the first year of study, about 37% of those co-infected individuals evaluated were included. Follow-up was completed in 120 of them, 59 in 9H and 61 in 2RZ. The male/female ratio was 4/1. The distribution by age (37 ± 6 year old), the median of CD4+ (687 cell/mL) and the viral load of the HIV by PCR (1.9 log) were similar in both treatment arms. Three patients from 2RZ and 14 from 9H gave up (p = 0.03). Four patients withdrawn because of side effects: one from 9H (1.7%) and 3 from 2RZ (4.9%) (p = 0.60). Two toxic hepatitis were detected, one for each treatment arm. In both cases, transaminase level returned to baseline four weeks after therapy discontinuation with no additional measures required. Rash in one patient and drug-related fever in another were the additional side effects observed among individuals receiving 2RZ. Down the first year of follow-up, no TB cases were detected in patients who had concluded the LTBI treatment.

Variable	9H	2RZ	Total
Gender: Male Female	59 53 6	61 47 14	120 100 20
Age*	36 ± 4	37 ± 9	37 ± 6
ALT*/AST* Male Female	36/34 30/32	38/32 40/47	p =n.s.
Alk P*./Bili* Male Female	171/0.86 130/1.3	181/1 190/1.9	p=n.s.

ALT = Alanin-amino-transferase; AST = Asparragin-amino-transferase; Alk P = Alkaline phosphatase; Bili = bilirrubin; p = n.s. not significant.
*Numbers explain mean values

Table 1. Description of demographic and clinical variables

Description	9H	2RZ	p
Abandons n(%):	14 (23.7)	3 (4.9)	0.03
Adverse events n(%)	1 (1.7)	3(4.9)	0.6

Table 2. Abandons and adverse event

Discussion

Among patients co-infected with HIV, preventive therapy is essential to controlling and eliminating TB as much as avoiding AIDS progression[9,10]. A key difference in most preventive therapy trials for TB conducted before and after the beginning of the HIV/AIDS epidemic is that the earlier trials focused on 12-month regimens of isoniazid, whereas five of seven trials[11-15] conducted in HIV-infected populations assessed 6-month regimens of isoniazid. Four of these 6-month isoniazid regimens[12-15], were chosen for study on the basis of the operational feasibility of providing therapy in countries with limited resources where preventive therapy programs were not available; the fifth study[15], an U.S. trial conducted among anergic patients, used a 6-month regimen because of the absence of previous data about optimal duration of therapy for TST-negative, HIV-infected patients. Despite these variations, the expert consultants concluded that the findings from these different preventive therapy studies should apply to most persons with LTBI, regardless of their HIV serostatus, because similar levels of protection have been observed when identical preventive therapy regimens have been administered to persons infected with HIV and those not infected.

Four studies of HIV-infected persons have evaluated 6-month and 12-month regimens of daily isoniazid[10,12,14,15]. Both of the studies that evaluated a 6-month regimen included a placebo comparison

group and demonstrated reductions in the incidence of TB among persons in the treatment group (70% in Uganda[12], and 75% in Kenya[14]). A study of the 12-month regimen[10], which was conducted in Haiti and also included a placebo comparison group, demonstrated an 83% reduction in the incidence of TB among persons in the treatment group. A multicenter trial conducted in the United States, Mexico, Brazil and Haiti[15] proved that the magnitude of protection obtained from a regimen of isoniazid administered daily for 12 months was similar to that obtained from a regimen of rifampin and pyrazinamide administered daily for 2 months. Researchers found identical rates of TB (1.2 per 100 person-years) in two groups TST-positive, HIV-infected persons: those who primarily self-administered isoniazid daily for 12 months and those who primarily self-administered rifampin and pyrazinamide daily for 2 months. Both study groups had similar adverse events and mortality rates; persons taking rifampin and pyrazinamide for 2 months were significantly more likely (80%) to complete therapy than were persons taking isoniazid for 12 months (68%) ($p<0.001$). The two other trials conducted in Haiti and Zambia[10,13] that have also evaluated regimens of rifampin and pyrazinamide for prevention of TB, have not included comparison arms of 12-months isoniazid regimens. Isoniazid preventive therapy regimens of 6 and 12 months' duration have not been compared with each other in the same study conducted among HIV-infected persons. In a study conducted in Uganda[12], investigators observed no statistically significant reduction in TB rates but a high rate of toxicity and drug intolerance among persons who took three drugs (isoniazid, rifampin and pyrazinamide) daily for 3 months compared with persons who took a placebo.

The effects of LTBI on mortality and progression of HIV infection appear to be limited in the literature, with the exception that such therapy can protect against the development of TB disease and its associated consequences. Moreover, the duration of this protective effect has not been clearly established for HIV-infected persons[16]. Despite these limitations and uncertainties, preventive therapy is recommended because its benefits in preventing TB disease are thought to be a greater than the risks of serious treatment-related adverse events, and such therapy benefits society be helping to prevent the spread of infection to other persons in the community.

The implementation of TB preventive therapy programs should be facilitated by the use of newly recommended short-course rifampin-based regimens and twice-weekly isoniazid regimens, especially among patients for whom DOPT (P for Preventive, Directly Observed Therapy) is feasible. As well as published by Gordin et al., related to general HIV-infected population, among IDU co-infected with HIV and TB, the adherence of LTBI treatment shows a tendency concerning positively 2RZ. Preliminary results (up to 900 patients by arm required) of adverse events are not different from another studies or between the two treatment arms either. However, enhance the collaborative centres and increase consistently the number of enrolled patients is needed to set up authoritative conclusions.

Acknowledgements

This work is supported by a national fund for research (Fondo para la Investigación y Prevención del SIDA en España) FIPSE nr 3091/99.

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