Reduction of clinical tuberculosis in HIV-infected males with isoniazid prophylaxis

K. Alaei,[1,2] A. Alaei[2] and D. Mansouri[2]

تقليص الإصابة بالسل السريري (الإكلينيكي) في الذكور المصابين بعدوى فيروس العَوَز المناعي البشري بواسطة العلاج الوقائي بالأيزونيازيد

كاميار علائي، آرش علائي، داوود منصوري

الخلاصة: للوقاية الكيميائية بالأيزونيازيد أثر إيجابي في الحد من تطوُّر السل السريري. ونظراً لزيادة انتشار السل بين المصابين بفيروس العَوَز المناعي البشري، فقد قمنا بتقييم تأثير الوقاية الكيميائية بالأيزونيازيد على اتقاء حدوث السل السريري (الإكلينيكي) لدى المصابين بالفيروس. أعطينا 300 مليغرام من الأيزونيازيد يومياً لمدة 12 شهراً لـ 246 مصاباً بفيروس العَوَز المناعي البشري ممن كان اختبار التوبركولين الجلدي لديهم إيجابياً. وأثناء سنوات المتابعة الثلاث، توفي 41 شخصاً من المدرجين في الدراسة وانقطع 94 شخصاً عن المتابعة. ومن بين الـ 111 مريضاً الذين تمت متابعتهم لمدة ثلاث سنوات، ظهر السل لدى 12 شخصاً وهذا أقل من المتوقع حدوثه في مجموعة لم تُعَالَج بالأيزونيازيد. يتضح أن الوقاية بالأيزونيازيد وسيلة فعالة لمنع حدوث السل السريري (الإكلينيكي) لدى المصابين بفيروس العوز المناعي البشري والإيجابيين لاختبار التوبركولين الجلدي.

ABSTRACT Isoniazid (INH) chemoprophylaxis has a positive impact on the development of clinical tuberculosis. Due to the increased prevalence of tuberculosis among HIV-infected individuals, we evaluated the effect of INH on the prevention of clinical tuberculosis in HIV-infected patients. We administered 300 mg of INH daily to 246 HIV-infected, tuberculin skin test-positive patients for 12 months. During 3 years of follow-up, 41 participants died and 94 were lost to follow up. Of the 111 patients followed for the 3 years, 12 developed tuberculosis which is lower than might be expected in an untreated group. INH prophylaxis appears to be an effective method to prevent clinical tuberculosis among HIV-infected, tuberculin skin test-positive patients.

Réduction de la tuberculose clinique chez des hommes infectés par le VIH grâce à une prophylaxie par isoniazide

RESUME La chimioprophylaxie par isoniazide a un impact positif sur l'évolution de la tuberculose clinique. Etant donné l'augmentation de la prévalence de la tuberculose chez les individus infectés par le VIH, nous avons évalué l'effet de l'isoniazide sur la prévention de la tuberculose clinique chez des patients séropositifs. Nous avons administré 300 mg d'isoniazide par jour pendant 12 mois à 246 patients séropositifs chez lesquels le test cutané à la tuberculine était positif. Durant les trois années de suivi, 41 participants sont décédés et 94 ont été perdus de vue. Sur les 111 patients suivis pendant trois ans, 12 ont développé une tuberculose qui était moins forte que celle à laquelle on pouvait s'attendre dans un groupe de patients n'ayant pas eu de traitement. La prophylaxie par isoniazide semble être une méthode efficace de prévention de la tuberculose clinique chez les patients séropositifs qui ont une réaction positive au test cutané à la tuberculine.

[1]*HIV/STI/DU Counselling and Care Centre, Medical University of Kermanshah, Kermanshah, Islamic Republic of Iran.*

[2]*HIV/TB Counselling and Care Centre, National Research Centre of Tuberculosis and Lung Diseases, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Teheran, Islamic Republic of Iran.*

Introduction

HIV infection has recently become one of the most important risk factors for the development of *Mycobacterium tuberculosis* infection into active tuberculosis (TB) [*1*]. The rate of disease progression for HIV-infected patients ranges between 1.6 and 9.7 per 100 person-years (py) in purified protein derivative (PPD)-positive cases [*2–5*]. Isoniazid (INH) chemotherapy has been highly effective among HIV-negative individuals at curtailing the progression to clinically active TB [*6,7*]. Also, in HIV-infected cases, INH prophylaxis reduces the rate of disease progression [*2,4,8,9*]. In a study from Haiti, 12 months of INH preventive chemotherapy (IPT) was significantly protective [*10*]. We studied the efficacy of 12 months INH prophylaxis in HIV-infected individuals voluntarily attending the HIV/STI care centre in the city of Kermanshah, Islamic Republic of Iran from October 1997 to December 2001.

Methods

In this prospective study, 290 HIV-positive individuals identified in prison were tested with tuberculin skin test (TST) from 1 October 1997 until 1 April 1998. All HIV-positive cases were male and injecting drug users (IDUs). The patients were classified as TST-positive with a PPD reaction > 5 mm and TST-negative with PPD ≤ 5 mm. After excluding active TB patients, all TST-positive cases received INH preventive chemotherapy (300 mg/day) daily for 12 months under observation [recommended regimen of the World Health Organization (WHO)] [*11*]. During the term in prison and after release, they were followed up in the HIV/STI care centre for more than 3 years. TB incidence was calculated as the number of confirmed TB cases occurring during the follow-up period expressed as cases/100 py. The efficacy of preventive therapy among the TST-positive patients was measured as the relative risk based on TB incidence in patients who took INH prophylaxis.

The chi-squared test was used to calculate statistical significance.

Results

Of 290 HIV-positive males tested with TST, 255 individuals (87.9%) had PPD > 5 mm. The median age was 37 years. Five of these cases had a previous history of clinical TB. Four cases had active TB at the first visit and were treated with a 6-month regimen of INH . There was no evidence of clinically-active TB in 246 cases (84.8%) and all of them received INH preventive chemotherapy for 12 months. During the 3-year follow-up, 41 participants (16.7%) died and 94 cases (38.2%) were lost to follow up. The remaining 111 cases (45.1%) were evaluated completely. Of 115 HIV-infected, TST-positive patients, 4 (3.5%) developed active TB every year for 3 years following the completion of INH preventive chemotherapy. Of these 12 cases, 8 (66.7%) were smear positive and 3 (25.0%) smear negative for pulmonary TB and 1 had extrapulmonary TB (liver). Eight cases occurred in the 20–40-year-old age group and the remainder were older than 40 years (Table 1).

Discussion

M. tuberculosis infection in HIV-infected injecting drug users in our study was very high (87.9%). This rate is more than the estimated rate in the general population (12%) and in HIV-infected persons (23%) between the ages of 15 and 49 years in the

Table 1 **Prevalence of clinical tuberculosis in HIV-infected patients following isoniazid prophylaxis, by age group**

Age group (years)	No.	%
<20	0	0.0
20–40	8	66.7
>40	4	33.3
Total	12	100.0

Eastern Mediterranean Region [*12*]. According to one study, the prevalence of active TB in TST-positive HIV patients was 7.9/100 py without INH prophylaxis [*13*]. INH chemoprophylaxis in two large randomized, placebo-controlled series afforded 60% to 90% protection [*6,7*]. In the present study, the incidence of clinically active TB was 3.5/100 py after 12 months INH preventive chemotherapy. In one study from Haiti on 58 HIV-positive cases the incidence was 1.7/100 py [*10*]. The rate was 1.2/100 py in the multi-site study by Gordin and colleagues [*14*], and 1.6/100 py in Spain [*15*].

One reason for the higher rate of development of clinical TB in our study is the high prevalence (87.9%) of *M. tuberculosis* infection in our HIV patients versus 53.3% in the Haiti study [*10*]. Without INH preventive chemotherapy, the prevalence of active TB in that study was 10.0/100 py.

In our study after 12 months of INH preventive chemotherapy only 3.5/100 py had active TB. If we consider the estimated rate of active tuberculosis in the absence of INH prophylaxis in the Haitian study (10%), we might have expected far more cases of clinical tuberculosis during the 3-year follow-up period. It would seem therefore that INH prophylaxis is successful in reducing the number of clinical TB cases. In addition, it has been reported that administration of INH preventive chemotherapy to TST-positive, HIV-infected patients both increases life expectancy and reduces medical costs [*16,17*].

In conclusion INH prophylaxis provides protection against both endogenous reactivation and exogenous reinfection with *M. tuberculosis* [*17*]. We recommend further studies evaluating the efficacy of 6 months of INH prophylaxis and two-drug prophylaxis regimens in HIV-infected patients in our country.

Acknowledgements

The authors wish to acknowledge the cooperation of Dr R. Rezaei, prision health staff and staff of the province health centre in data collection.

References

1. Sackoff JE, Torian LV, Frieden TR. TB prevention in HIV clinics in New York City. *International journal of tuberculosis and lung disease*, 2001, 5:123–8.
2. Selwyn P et al. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *Journal of the American Medical Association*, 1992, 268: 504–9.
3. Markowitz N et al. Incidence of tuberculosis in the United States among HIV-infected persons. *Annals of internal medicine*, 1997, 126:123–32.

4. Daley CL et al. Incidence of tuberculosis in injection drug users in San Francisco: impact of anergy. *American journal of respiratory and critical care medicine*, 1998, 157:19–22.

5. Gourevitch MN et al. Effectiveness of isoniazid chemoprophylaxis for HIV-infected drug users at high risk for active tuberculosis. *AIDS*, 1999, 13:2069–74.

6. Ferebee SH et al. A controlled trial of isoniazid prophylaxis in mental institutions. *American review of respiratory disease*, 1963, 88:161–275.

7. Krebs A et al. Five years of follow-up of the IUAT trial of isoniazid prophylaxis in fibrotic lesions. *Bulletin of the international union against tuberculosis*, 1979, 54:65–9.

8. Guelar A et al. A prospective study of the risk of tuberculosis among HIV-infected patients. *AIDS*, 1993, 7:1345–9.

9. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *Morbidity and mortality weekly report*, 1998, 47(RR-20):1.

10. Pape JW et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet*, 1993, 342:268–72.

11. Sudre P et al. *Tuberculosis: a global overview of the situation today*. Geneva, World Health Organiztion, 1991 (WHO/TB/91.158).

12. Morris K. HIV epidemic could number 40 million by year 2000. *Lancet*, 1997, 350:1683 (News).

13. Klein NC et al. Use of mycobacterial smears in the diagnosis of pulmonary tuberculosis in AIDS/ARC patients. *Chest*, 1989, 95:1190–2.

14. Gordin F et al. *A randomized trial of 2 months of rifampin (RIF) and pyrazinamide (PZA) versus 12 months of isoniazid (INH) for the prevention of tuberculosis (TB) in HIV-positive (+), PPD+ patients*. Paper presented at the Fifth Conference on Retroviruses and Opportunistic Infections, 1–5 February 1998.

15. Moreno S et al. Isoniazid preventive therapy in human immunodeficiency virus-infected persons. Long-term effect on development of tuberculosis and survival. *Archives of internal medicine*, 1997, 157:1729–34.

16. Alaei K et al. *The prevalence rate of clinical TB in HIV-infected patients in Kermanshah province from March 1998 until April 2001*. Presented at the Sixth International Congress on AIDS in Asia and the Pacific, Melbourne, Australia, 5–10 October 2001 (Ref. No. Tu. 1586).

17. Iseman MD. *A clinician's guide to tuberculosis*. Philadelphia, Lippincott Williams & Wilkins, 2000:202.