A CONTROLLED TRIAL OF ISONIAZID IN PERSONS WITH ANERGY AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION WHO ARE AT HIGH RISK FOR TUBERCULOSIS

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ABSTRACT

Background Patients with human immunodeficiency virus (HIV) infection and latent tuberculosis are at substantial risk for the development of active tuberculosis. As a public health measure, prophylactic treatment with isoniazid has been suggested for HIV-infected persons who have anergy and are in groups with a high prevalence of tuberculosis.

Methods We conducted a multicenter, randomized, double-blind, placebo-controlled trial of six months of prophylactic isoniazid treatment in HIV-infected patients with anergy who have risk factors for tuberculosis infection. The primary end point was culture-confirmed tuberculosis.

Results The study was conducted from November 1991 through June 1996. Over 90 percent of the patients had two or more risk factors for tuberculosis infection, and nearly 75 percent of patients were from greater New York City. After a mean follow-up of 33 months, tuberculosis was diagnosed in only 6 of 257 patients in the placebo group and 3 of 260 patients in the isoniazid group (risk ratio, 0.48; 95 percent confidence interval, 0.12 to 1.91; P = 0.30). There were no significant differences between the two groups with regard to death, the progression of HIV disease or death, or adverse events.

Conclusions Even in HIV-infected patients with anergy and multiple risk factors for latent tuberculosis infection, the rate of development of active tuberculosis is low. This finding does not support the use of isoniazid prophylaxis in high-risk patients with HIV infection and anergy unless they have been exposed to active tuberculosis. (N Engl J Med 1997; 337:315-20.)

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TUBERCULOSIS is the only opportunistic infection related to infection with the human immunodeficiency virus (HIV) that threatens the general public. The spread of HIV-related tuberculosis has been well documented, with transmission to both HIV-infected and uninfected persons.¹³ Persons infected with HIV are estimated to be over 100 times as likely as uninfected persons to have tuberculosis,¹ primarily as a result of the reactivation of a latent tuberculosis infection. Tuberculosis develops each year in 7 to 10 percent of persons with positive tuberculin skin tests.⁵⁷ HIV infection accounted for a substantial proportion of the excess cases of tuberculosis in the United States from the mid-1980s through the early 1990s.⁸⁹ The World Health Organization estimated that in 1990 more than 3 million people in the world were coinfected with HIV and Mycobacterium tuberculosis, with more than 100,000 of them living in the United States.¹⁰ According to the Centers for Disease Control and Prevention (CDC), identifying these people so that prophylaxis with isoniazid can be given is an important public health measure.¹¹¹² However, the tuberculin skin test, the only available tool with which to diagnose latent M. tuberculosis infection, has low sensitivity in HIV-infected persons because of their high rate of anergy.¹³ To prevent tuberculosis from spreading in the United States, the CDC suggested in 1991 that preventive therapy be considered for HIV-infected persons who have anergy but belong to “groups in which the prevalence of tuberculosis infection is ≥10 percent.”¹¹ This suggestion has since been supported by the American Thoracic Society¹⁴ and the Infectious Disease Society of America.¹⁵ Although observational data support the conclusion that certain HIV-infected people with anergy are at high risk for active tuberculosis,¹⁶⁻¹⁸ no study has investigated the benefit of providing preventive therapy to this population. We conducted a randomized, placebo-controlled clinical trial to assess the effectiveness of six months of isoniazid prophylaxis in HIV-infected patients with anergy who were at high risk for tuberculosis.

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*Participants in the Terry Beirn Community Programs for Clinical Research on AIDS are listed in the Appendix.
METHODS

Study Patients

Patients were enrolled at 11 units of the Terry Beirn Community Programs for Clinical Research on AIDS. Six units were in greater New York — four in New York City, one in Newark, New Jersey, and one in New Haven, Connecticut. The units outside greater New York were located in New Orleans; Wilmington, Delaware; San Francisco; Washington, D.C.; and Detroit. All the patients had diagnosed HIV infection and characteristics placing them at high risk for tuberculosis infection.11

All the patients received 5 tuberculin units of Tween-stabilized purified protein derivative (PPD), applied by the Mantoux method; the tests were read 48 to 72 hours after the application. In addition, the patients underwent delayed-type—hypersensitivity skin testing with mumps antigen and also with tetanus toxoid in a 1:10 dilution with allergenic extract. Only patients with anergy, defined by a reaction to PPD of less than 5 mm induration and a reaction to both the other antigens of less than 2 mm induration, were eligible for the study.

The patients were also required to be at least 13 years old, to have no clinical or radiologic evidence of active tuberculosis, and to have total bilirubin concentrations of 2.5 mg per deciliter (43 μmol per liter) or less and serum concentrations of aspartate aminotransferase and alkaline phosphatase that did not exceed five times the upper limits of normal. Patients were excluded from the study if, during the preceding year, they had lived in a household with a person with active tuberculosis or if they were currently receiving any agent with potential activity against tuberculosis. They were also excluded if they had evidence of acute hepatitis or peripheral neuropathy or a history of a positive PPD test, intolerance to the study medication, or treatment for one month or more with agents with potential antituberculous activity.

The study protocol was approved by the institutional review board at each participating site, and written informed consent was obtained from all patients.

Study Design and End Points

The study was a randomized, placebo-controlled, double-blind trial of isoniazid for the prevention of tuberculosis. The patients received 300 mg of isoniazid or a matching placebo plus, in either trial of isoniazid for the prevention of tuberculosis. The patients

The primary end point was active tuberculosis, pulmonary, extrapulmonary, or both; confirmation by a positive culture for M. tuberculosis from any source was required. Cultures and susceptibility tests were performed at local laboratories. Secondary end points were probable tuberculosis, clinical progression of HIV disease, and death. Clinical disease progression was defined as the first occurrence of an acquired immunodeficiency syndrome (AIDS)—defining condition according to a description adapted from the 1987 CDC classification or as a recurrence of any of the following: Pneumocystis carinii pneumonia, esophageal candidiasis, herpes simplex infection, disseminated herpes zoster, and septicemia due to nontyphoidal salmonella. The diagnosis of probable tuberculosis required clinical evidence from a physical examination and diagnostic tests, plus either a response to antituberculous therapy or evidence at autopsy of granulomas with organisms positive for acid-fast bacilli. Cases of tuberculosis that were not confirmed by culture were reviewed by the Clinical Events Committee, which was unaware of the treatment assignments. Sputum smears positive for acid-fast bacilli were in themselves not sufficient for a diagnosis of confirmed or probable tuberculosis. Data on other opportunistic and adverse events were also collected.

Follow-up

The initial follow-up visits were scheduled for months 1, 2, 4, and 6. At months 1, 2, and 6, serum aspartate aminotransferase, total bilirubin, and alkaline phosphatase were measured. The patients were next seen at month 12 and every 4 to 6 months thereafter. At each follow-up visit there was a clinical assessment to detect tuberculosis, hepatitis, peripheral neuropathy, and new HIV-related diseases. Patients thought to have active tuberculosis were studied by chest radiography, sputum evaluation, and other tests as appropriate to the presumed site of infection. Clinicians monitored compliance with treatment by interviewing the patients.

Data Analysis

During the study, the investigators were kept unaware of the interim results. Data on toxicity and efficacy were reviewed periodically by an independent Data and Safety Monitoring Board. The treatment groups were compared with use of the chi-square test, Fisher’s exact test, Student’s t-test, and the Wilcoxon rank-sum test. Time-to-event analyses were performed with proportional-hazards regression. Because of the low number of events, an unstratified, unadjusted analysis was done to evaluate tuberculosis-related end points. Both unadjusted and adjusted analyses, all stratified according to unit, were performed to assess mortality and the progression of HIV disease; these analyses were adjusted for the base-line variables shown in Table 1. Subgroup analyses were also performed with these same variables. All P values were two-sided.

RESULTS

Study Patients

From November 29, 1991, through January 7, 1994, 517 patients were enrolled in the study; 260 were randomly assigned to isoniazid, and 257 to placebo. All the patients were followed through June 30, 1996.

The base-line characteristics of the study groups are shown in Table 1. The two groups were similar. The mean age was 38 years (range, 21 to 64). The majority of the patients were black (47 percent) or Latino (33 percent), 32 percent were women, and 58 percent reported having used injection drugs. Overall, the median CD4 count was 240 cells per cubic millimeter (interquartile range, 100 to 417), and 23 percent of the patients had AIDS.

The distribution of risk factors for tuberculosis infection is shown in Table 2. The two study groups were similar, except that the placebo group included higher proportions of people who had been unemployed for one year or more (P = 0.06) or who had lived with a person with active tuberculosis more than one year before enrollment (P = 0.08). Over 90 percent of the patients had two or more risk factors for tuberculosis, and 74 percent lived in the New York City area.
TABLE 1. Base-Line Characteristics of the Study Patients.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ISONIAZID (N = 260)</th>
<th>PLACEBO (N = 257)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>33.8</td>
<td>30.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>37.4</td>
<td>38.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Race or ethnic group (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>46.2</td>
<td>47.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Latino</td>
<td>32.7</td>
<td>33.1</td>
<td></td>
</tr>
<tr>
<td>White or other</td>
<td>21.2</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>History of injection-drug use (%)*</td>
<td>57.1</td>
<td>58.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Male homosexuality or bisexuality (%)†</td>
<td>28.8</td>
<td>29.3</td>
<td>0.92</td>
</tr>
<tr>
<td>AIDS (%)†</td>
<td>21.5</td>
<td>24.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Median CD4+ count (cells/mm³)</td>
<td>233.0</td>
<td>247.0</td>
<td>0.48</td>
</tr>
<tr>
<td>Use of antiretroviral drugs (%)</td>
<td>72.7</td>
<td>73.2</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Data are based on 240 patients in the isoniazid group and 242 patients in the placebo group.
†Data are based on 250 patients in the isoniazid group and 246 patients in the placebo group.
‡AIDS was defined according to the 1987 CDC classification.

TABLE 2. Risk Factors for Exposure to Tuberculosis.

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>ISONIAZID</th>
<th>PLACEBO</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PERCENT WITH RISK FACTOR</td>
<td>NO. STUDIED</td>
<td>PERCENT WITH RISK FACTOR</td>
</tr>
<tr>
<td>Birth outside U.S.*</td>
<td>20.8</td>
<td>260</td>
<td>18.8</td>
</tr>
<tr>
<td>Residence in high-risk area for ≥1 yr†</td>
<td>95.4</td>
<td>260</td>
<td>95.7</td>
</tr>
<tr>
<td>Drug or alcohol abuse for ≥1 yr</td>
<td>81.9</td>
<td>254</td>
<td>78.0</td>
</tr>
<tr>
<td>Unemployed for ≥1 yr</td>
<td>68.8</td>
<td>256</td>
<td>76.5</td>
</tr>
<tr>
<td>Homeless for ≥1 yr</td>
<td>13.6</td>
<td>257</td>
<td>16.3</td>
</tr>
<tr>
<td>Household contact before the past yr with someone with active tuberculosis</td>
<td>5.5</td>
<td>217</td>
<td>10.2</td>
</tr>
<tr>
<td>No. of risk factors</td>
<td></td>
<td>260</td>
<td>257</td>
</tr>
<tr>
<td>1</td>
<td>9.6</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.7</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42.7</td>
<td>45.1</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>25.0</td>
<td>26.1</td>
<td></td>
</tr>
</tbody>
</table>

*This risk factor refers to birth in a country with a high prevalence of tuberculosis.
†High-risk areas included the inner city, areas with a high prevalence of tuberculosis, long-term care facilities, and correctional institutions.

Treatment and Follow-up

In both groups, 63 percent of the patients completed six months of treatment. Adverse events led to the permanent discontinuation of the study drug in 9 percent of the patients in each group. Among those who discontinued treatment in each group, approximately half did so during the first two months. At the end of the study, 6.2 percent of the isoniazid group (16 patients) and 7.0 percent of the placebo group (18 patients) were lost to follow-up with respect to whether they had tuberculosis. The average duration of follow-up was 34 months in the isoniazid group and 33 months in the placebo group.

Tuberculosis, Survival, and Progression of HIV Disease

Table 3 shows the rates of tuberculosis, death, and progression of HIV disease or death (as a combined variable), with the associated relative risks. Confirmed tuberculosis developed in 3 of the 260 patients in the isoniazid group and 6 of the 257 patients in the placebo group (rates per 100 patient-years of follow-up, 0.4 and 0.9, respectively; relative risk, 0.48; 95 percent confidence interval, 0.12 to 1.91; P = 0.30). Susceptibility testing was performed on isolates from eight of nine patients, including all three in the isoniazid group; the eight isolates were all found to be susceptible to isoniazid. All three patients in the isoniazid group had pulmonary tuberculosis. Four of the patients in the placebo group had pulmonary tuberculosis, one had extrapulmonary tuberculosis, and one had both. There was one patient with probable pulmonary tuberculosis in the isoniazid group, as compared with none in the placebo group. All the cases of tuberculosis occurred six months or more after randomization and after the study drug had been discontinued. Of the three patients in the isoniazid group who had tuberculosis, two completed all six months of therapy and one completed only four months.

One hundred twenty-nine of the 260 patients in the isoniazid group died, as compared with 126 of the 257 patients in the placebo group (relative risk, 0.96; P = 0.76). The reported causes of death did not differ between the groups. In one of the six patients in the placebo group who had tuberculosis, the tuberculosis was discovered at autopsy but was not considered to have been the primary cause of death. No other patient in either group died from tuberculosis-related causes. One hundred fifty-five of the 260 patients in the isoniazid group died or had progression of HIV disease, as compared with 154 of the 257 patients in the placebo group (relative risk, 0.97; P = 0.78).

Various subgroups were studied with regard to the combined end point of death or the progression of HIV disease, and no differences were found between the study groups. In both groups, the patients with 100 or fewer CD4+ cells per cubic millimeter reached the combined end point at substantially higher rates than did the patients with higher counts. After adjustment for base-line covariates, the relative risks of both death and the combined end point of death or progression of HIV disease remained nonsignificant.
Adverse Events

Twenty-nine patients in the isoniazid group (11.2 percent) and 30 patients in the placebo group (11.7 percent) had reportable adverse events (Table 4). During the first six months, no patients in the isoniazid group and two patients in the placebo group had reportable events related to peripheral neuropathy. Three patients in the isoniazid group and no patients in the placebo group had grade III neuropathy that did not meet the criteria for an adverse event. In each group there was one case of grade IV hepatitis (requiring substantial medical intervention or therapy and possible hospitalization); in addition, in the isoniazid group there were 23 cases of suspected hepatitis of lesser severity that did not result in study-drug discontinuation, as compared with 19 cases in the placebo group. On the basis of laboratory data collected in the first six months, 11 patients in the isoniazid group and 6 patients in the placebo group had grade III or higher serum aspartate aminotransferase values (more than five times the upper limit of normal) (P = 0.32). We found no differences between groups in the occurrence of adverse events according to age, race, or sex.

DISCUSSION

Isoniazid has been used successfully to prevent reactivation tuberculosis for the past 40 years. More recently, several investigators have shown the ability of isoniazid to reduce the incidence of tuberculosis markedly among HIV-infected persons with positive PPD tests. In an observational study of HIV-infected drug users in New York City, persons with positive PPD tests who did not receive isoniazid acquired tuberculosis at a rate of 9.7 cases per 100 person-years, whereas no tuberculosis developed in coinfectected patients who received isoniazid. In a randomized study of PPD-positive, HIV-infected patients in Haiti, isoniazid reduced the incidence of tuberculosis from 10.0 to 1.7 cases per 100 person-years. Similar reductions have been reported in other studies.

The ability to diagnose latent tuberculosis in HIV-infected persons has been hindered by their reduced response to delayed-type–hypersensitivity skin tests. Attempts to increase the sensitivity of the tuberculin skin test in this population through the use of a two-stage or “booster” test have not been successful. Therefore, many persons with dual infection cannot be identified by the clinical tests currently available. To prevent reactivation tuberculosis in such persons, the CDC suggested in 1991 that isoniazid prophylaxis “be considered” for patients with anergy who are in groups at high risk for tuberculosis.

Our study showed that among such patients, six
months’ treatment with isoniazid, although safe, was not effective in preventing tuberculosis or improving survival. We went to great lengths to identify patients at substantial risk for tuberculosis. Over 90 percent had two or more risk factors for the disease, and almost three fourths were from the New York City area, where HIV-infected persons are known to have tuberculosis at high rates. Nevertheless, the incidence of tuberculosis in the placebo group was only 0.9 per 100 person-years. This finding is particularly important, since it may reflect a lower-than-expected rate of latent tuberculosis infection or an environment in which the risk of acquiring new tuberculosis infections has decreased because of effective public health measures of control.

Recently, Whalen et al. reported the preliminary results of a trial of isoniazid prophylaxis among HIV-infected persons with anergy in Uganda. Their study was also unable to show a benefit of isoniazid in patients with anergy, because tuberculosis developed in the patients receiving placebo at a rate of 3.06 per 100 person-years, as compared with 2.53 per 100 person-years for the patients receiving isoniazid (P = 0.68).

Table 5 shows the wide range (2.6 to 12.4 per 100 person-years) in the rate at which tuberculosis develops among untreated, HIV-infected patients with anergy according to other studies in this country and elsewhere. Even though recent studies have questioned the value and reliability of testing for anergy, it is clear from several studies that patients with anergy constitute a distinct group whose risk for tuberculosis is intermediate between that of tuberculin-positive patients and that of patients who are tuberculin-negative but do not have anergy. Any potential benefit of preventive therapy would be even smaller in a population not selected for anergy. The studies shown in Table 5 differ with regard to the criteria used to define tuberculosis: some used clinical definitions, but ours and some others required cultures positive for *M. tuberculosis.* Moreno et al. reported that if only culture-confirmed cases were considered, the tuberculosis rate would be 8.1, rather than 12.4, per 100 person-years. Papel et al. reported that of 15 cases of tuberculosis they found, only 6 were culture-confirmed. Guéral et al. reported that of the cases in their study, only 65 percent were culture-confirmed. The rates of tuberculosis reported in these studies may therefore be underestimated.

It is not known whether the cases of tuberculosis in our study or the others represent reactivations or new infections. All the studies except one were conducted in the period from the late 1980s to the early 1990s, when tuberculosis-control efforts were ineffective both in the United States and elsewhere. Studies conducted during that period showed that over one third of tuberculosis cases in San Francisco were apparently due to recent infections, as were up to 40 percent of cases in New York City. Our study was largely conducted after tuberculosis-control efforts nationwide had improved, and particularly those in New York City, so that rates of tuberculosis decreased. Thus, it is likely that the low rate of tuberculosis we observed largely resulted from reactivation, whereas the other studies may have included a substantial number of cases due to recent infection.

In considering the possible benefits of isoniazid prophylaxis for any group, the toxic effects of the drug must be considered. Although 12 months of isoniazid therapy is recommended for HIV-infected persons with a known risk of tuberculosis, we elected to use the 6-month regimen recommended for HIV-negative patients in order to reduce the risk of toxic effects for study patients who were not infected with tuberculosis. The rate of adverse events did not differ statistically between the isoniazid group and the placebo group. Thus, isoniazid appeared to be safe in these patients even though many of them had histories of drug or alcohol abuse. Isoniazid has been associated with hepatotoxicity and death, how-
ever. Therefore, its known toxic effects must be taken into account when one considers using it in persons without confirmed latent tuberculosis.

We evaluated the effectiveness of isoniazid prophylaxis for HIV-infected persons with anergy who were at risk for tuberculosis. Because of the low incidence of tuberculosis in our study, we found no significant benefit associated with isoniazid use. Our study population was highly representative of patients perceived to be at risk for tuberculosis in the United States, and without a more accurate method of detecting latent tuberculosis, we believe it would be impossible to identify people likely to benefit from prophylaxis. The results of our study, therefore, do not support the use of preventive therapy with isoniazid among HIV-infected persons with anergy in the United States, except in specific high-risk situations, such as that of people who have recently come in close contact with someone who has active tuberculosis.

Supported by the National Institute of Allergy and Infectious Diseases.

We are indebted to the study patients for their participation and support; to Parke-Davis for providing isoniazid and matching placebo; to Rackley Laboratories for providing vitamin B6; and to the other members of the Community Programs for Clinical Research on AIDS protocol 005 team: Lawrence Deyton, Philip Hopewell, Thomas Kerkering, Geri Maiatico, Keith Dawson, Megan Paye, Carol Webster, Joyce Konnick, Kathleen Daniels, Katherine Math, Jill Chemut, Linda Perry, and Mary Foulke.

APPENDIX

The following institutions and persons participated in the Community Programs for Clinical Research on AIDS: Addiction Research and Treatment Corporation, Brooklyn, N.Y. (J. Ellison and T. Williams); Harlem AIDS Treatment Group, New York (C. Guity, M. Hardy, and E. Medard); Clinical Directors Network, Brooklyn, N.Y. (R. Torres, A. Verdales, and L. Podhurst); Louisiana Community AIDS Program, New Orleans (J. Walker, Sister S. Pablouch, and R. Cropper); North Jersey Community Research Initiative, Newark (V. Taylor, A. Sheridan, and N. Regevski); Delaware Community Program for Clinical Research on AIDS, Wilmington (W. Holloway, M. Matsumoto, and S. Chaptimo); Bronx-Lebanon Hospital Center, Bronx, N.Y. (J. Ernst, R. Duncafé, and E. Doramajian); Hill Health Corporation, New Haven, Conn. (S. Updegrove, J. Burns, and R. Vogel); Community Consortium, San Francisco (K. Clanson, A. Crawford, and C.A. Lewis); Washington Regional AIDS Program, Washington, D.C. (K. Zahnow, A. Labriola, and C. Gibert); and Wayne State University, Detroit (L. Neubauer and C. Czajk).

REFERENCES