Incidence and Risk Factors of Tuberculosis in Patients with Human Immunodeficiency Virus Infection

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Received: 14 July 2012
Accepted: 11 January 2013

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Korea is a low prevalence country for human immunodeficiency virus (HIV) infection and has an intermediate tuberculosis (TB) burden. We previously reported that the incidence of TB in HIV-infected patients was 9.6 cases per 100 person-years (P-Y) between 1988 and 1997. The aims of the present study were to measure any change in incidence from the previous study, and to identify risk factors for TB in HIV-infected patients. We reviewed all medical records of HIV-infected patients who were followed-up in one tertiary hospital between 1998 and 2010. Over the total observation period of 5858.33 P-Y, TB developed in 70 patients (1.19 cases per 100 P-Y; 95% confidence interval [CI], 0.91-1.47 cases per 100 P-Y). Based on Poisson regression, one risk factor associated with TB was an initial CD4+ cell count below 200 cells/μL (relative risk, 2.34; 95% CI, 1.47-3.73). Mean CD4+ cell counts of pulmonary, extrapulmonary, and both pulmonary and extrapulmonary TB were 179.8 cells/μL, 138.3 cells/μL, and 114.2 cells/μL, respectively (P = 0.55). In conclusion, the incidence of TB in HIV-infected patients has decreased since the previous study. An initial CD4+ cell count below 200 cells/μL is an independent risk factor for development of TB in HIV-infected patients.

Key Words: Tuberculosis; Incidence; Risk Factors; HIV

INTRODUCTION

Tuberculosis (TB) is the most common opportunistic disease in human immunodeficiency virus (HIV)-infected patients in Korea (1). HIV-infected patients are at strikingly increased risk of TB (2). The risk of death in HIV-infected patients with TB is approximately three-to-seven times higher than in uninfected individuals (3) and two times higher than in HIV-infected patients without TB (4).

Korea is a low prevalence country for HIV/AIDS and has an intermediate TB burden (5). Recently the Korea Centers for Disease Control and Prevention reported an increase in annual newly-detected HIV and TB co-infected patients from 2000 to 2005 (5). We previously reported that the incidence of TB in HIV-infected patients was 9.6 cases per 100 P-Y (person-year) (95% CI, 6.0-14.5 cases per 100 P-Y) between 1988 and 1997 (6). The aims of the present study were to determine whether there has been any change in incidence since the previous study, and to identify the risk factors for TB in HIV-infected patients.

MATERIALS AND METHODS

Study population

We reviewed the medical records of HIV-infected patients fol-lowed-up at Seoul National University Hospital between January 1998 and December 2010. SNUH is a 1,600-bed, university-affiliated teaching hospital, and the largest referral center for HIV/AIDS in Korea. During the study period, patients were examined every 3 months. Further evaluation, including chest radiographs, was performed in patients with suspicious symptoms of tuberculosis.

Definitions

Tuberculous cases were categorized as 'proven', 'probable', and 'possible' as in our previous study (6). Tuberculous cases were defined as proven if they had clinical symptoms or radiological features and Mycobacterium tuberculosis was identified in a clinical specimen by culture or PCR methodology; as probable, if they had clinical symptoms or radiological features and histopathological findings compatible with tuberculosis; and as possible, if they had clinical symptoms or radiological features and anti-tuberculous treatment was effective.

Tuberculous cases were categorized as having pulmonary TB if the lung was the only organ involved, and as extrapulmonary TB if any other organ was involved (7).

Isoniazid prophylaxis

The tuberculin skin test (TST) was not routinely performed be-

cause most of the population of Korea has received BCG vaccination. Some physicians have recommended that HIV-infected patients receive the TST, but others have not. Isoniazid (INH) prophylaxis (300 mg/day for 9 months) was recommended to patients with a positive TST results.

Statistical methods

The incidence of TB was calculated as the number of cases per 100 P-Y of observation and exact confidence intervals (CI) were calculated based on the Poisson distribution. Follow-up time was calculated for each patient starting from enrollment and continuing until one of the followings occurred: first TB diagnosis, death from any cause, transfer to another hospital or nursing home, last recorded visit if it was before 2010, or 31st December 2010 if the last visit was January 2011 or thereafter. ANOVA was used for continuous variables. All data were analyzed with SPSS 19.0 (SPSS, Inc., Chicago, IL, USA). Univariate and multivariate Poisson regression models were used to determine risk factors related to TB, and were expressed as relative risks (rate ratios). Age, sex, transmission route, CD4+ cell counts, and INH prophylaxis were included as potential confounding variables in the multivariate analysis by Poisson regression. All tests were two-sided and a P value < 0.05 was considered significant.

Ethics statement

The study protocol was approved by the institutional review board of the Seoul National University Hospital (IRB No. H-1205-118-411). Informed consent was exempted by the board.

RESULTS

Study population and baseline characteristics

A total of 1,301 HIV-infected patients were observed between January 1998 and December 2010. Eighty-four patients were diagnosed as having TB during the study period, of which 14 had already been diagnosed or treated in another hospital before January 1998. After exclusion of these 14 patients, seventy patients were newly diagnosed during the study period. The majority of these 70 patients were male (90%), had been infected with HIV through sexual contact (87%), were diagnosed as having proven TB (84%), and did not receive INH prophylaxis (92.9%). The mean initial CD4+ cell count of the patients with TB was 185.5 (± 200.2) cells/μL (Table 1). A total of 173 (13.3%) patients received INH prophylaxis. The mean duration of INH prophylaxis was 311 (± 50) days. Of the 173 patients, 5 developed TB during the study period, despite receiving INH prophylaxis for 9 months or more.

Eighteen patients had pulmonary TB, sixteen had extrapulmonary TB, and 36 had both pulmonary and extrapulmonary TB. The most common sites of extrapulmonary TB were lymph node (n = 34), followed by pleura (n = 18), intra-abdominal or-

Table 1. Demographic and clinical of characteristics of the HIV-infected patients with tuberculosis

Characteristics	Value (n = 70)
Age (IQR)	38.5 (33-48)
Sex (%)	
Male	63 (90)
Female	7 (10)
Transmission route (%)	
Homosexual	28 (40)
Heterosexual	33 (47)
Transfusion	2 (3)
Unknown	7 (10)
Initial CD4+ cell counts (cells/μL)	
Mean ± SD	185.5 ± 200.2
Median (IQR)	94.5 (29.7-352.5)
< 200	43 (61.4%)
≥ 200	27 (38.6%)
Tuberculosis diagnosis status (%)	
Proven	59 (84)
Probable	1 (1.7)
Possible	10 (14.3)
Isoniazid prophylaxis (%)	
Yes	5 (7.1)
No	65 (92.9)

IQR, interquartile range.

gan (n = 11), bone marrow (n = 9), central nervous system (n = 7), bone and/or joint (n = 3), and skin (n = 2). Mean CD4+ cell counts at the time of diagnosis of pulmonary, extrapulmonary, both pulmonary and extrapulmonary TB were 179.8 cells/μL, 138.3 cells/μL, and 114.2 cells/μL, respectively. Mean CD4+ cell counts were not significantly different between groups ($P > 0.05$).

TB incidence and risk factors

Over the total observation period of 5858.33 P-Y, new TB developed in 70 patients (1.19 cases per 100 P-Y; 95% CI, 0.91-1.47 cases per 100 P-Y). The incidence was higher among women than men; higher among those infected via transfusion than in sexually transmitted cases; higher in patients with initial CD4+ count < 200 cells/μL; and higher in those not receiving INH prophylaxis (Table 2). In patients with initial CD4+ cell counts < 200 cells/μL the incidence of TB was 2.06 cases per 100 P-Y (95% CI, 1.45-2.67), while in patients with CD4+ cell counts > 200 cells/μL it was 0.72 cases per 100 P-Y (95% CI, 0.45-0.99). Only initial CD4+ cell count < 200 cells/μL at the time of enrollment was independently associated with an increased incidence of TB in the multivariate Poisson regression analysis (Table 3). There was no independent relationship between INH prophylaxis and the incidence of TB.

Mortality rate

All patients with TB received anti-tuberculous medications for 6 months or more. During the follow-up period, 17 patients died, 9 due to TB. The estimated mortality rate due to TB in HIV-infected patients was 0.15 cases per 100 P-Y; 95% CI, 0.08-0.29 cases per 100 P-Y.

Table 2. Incidence of tuberculosis in HIV-infected patients according to baseline characteristics

Baseline characteristics	Total patients (No.)	TB patients (No.)	Observation period (P-Y)	Incidence, cases per 100 P-Y (95% CI)	Relative risk (95% CI)	P value
Overall	1,301	70	5858.33	1.19 (0.91-1.47)		
Sex						
Female	107	7	570.36	1.22 (0.32-2.12)	1.24 (0.58-2.64)	0.577
Male	1,194	63	5287.97	1.19 (1.04-1.34)	1	
Age (yr)						
< 30	312	11	1248.59	0.88 (0.36-1.40)	0.53 (0.25-1.12)	0.096
30-39	462	29	2218.24	1.30 (0.83-1.77)	0.94 (0.52-1.70)	0.841
40-49	287	14	1309.06	1.07 (0.51-1.63)	0.73 (0.37-1.47)	0.379
≥ 50	240	16	987.34	1.62 (0.83-2.41)	1	
Transmission route						
Unknown	259	7	793.28	0.88 (0.23-1.53)	0.32 (0.14-0.75)	0.009
Transfusion	14	2	91.21	2.19 (1.09-7.53)	1.98 (0.53-7.43)	0.311
Homosexual	543	28	2451.32	1.14 (0.72-1.56)	0.69 (0.42-1.12)	0.134
Heterosexual	485	33	2522.52	1.31 (0.87-1.75)	1	
Initial CD4+ count (cells/μL)						
< 200	515	43	2086.70	2.06 (1.45-2.67)	2.43 (1.52-3.89)	0.001
≥ 200	786	27	3771.63	0.72 (0.45-0.99)	1	
INH prophylaxis						
No	1128	65	4535.29	1.43 (1.09-1.77)	1.99 (0.81-4.88)	0.131
Yes	173	5	1323.04	0.38 (0.05-0.71)	1	

Table 3. Multivariate Poisson regression analysis of factors independently associated with incidence of TB in HIV patients

Variables	Relative risk (95% CI)	P value
Sex		
Female	1.07 (0.50-2.31)	0.859
Male	1	
Age (yr)		
< 30	0.57 (0.27-1.22)	0.147
30-39	0.98 (0.54-1.78)	0.939
40-49	0.75 (0.38-1.50)	0.417
≥ 50	1	
Transmission route		
Unknown	0.29 (0.12-0.68)	0.004
Transfusion	2.05 (0.57-7.40)	0.270
Homosexual	0.73 (0.44-1.21)	0.224
Heterosexual	1	
Initial CD4+ count (cells/μL)		
< 200	2.34 (1.47-3.73)	0.001
≥ 200	1	
INH prophylaxis		
No	2.22 (0.91-5.43)	0.080
Yes	1	

DISCUSSION

This study documents the incidence and risk factors for TB in HIV-infected patients between 1998 and 2010. Our previous study between January 1988 and June 1997 showed a TB incidence of 9.6 cases per 100 P-Y (95% CI, 6.0-14.5 cases per 100 P-Y) (6), which is approximately 8 times higher than the 1.19 cases per 100 P-Y in the present survey. A relatively large reduction in TB incidence in HIV infected patients has also been observed in surveys in Europe; from 1.91 (95% CI, 1.51-2.37 per 100 P-Y) in 1994-1995 to 0.12 (95% CI, 0.07-0.21 per 100 P-Y) in 2002-2003 (9). The reduction observed in this study may be due

to a decrease in the overall prevalence of TB in Korea (10) and/ or the impact of highly active anti-retroviral therapy (HAART) on TB incidence. HAART has been available in Korea since 1997, and after then several new anti-retroviral agents were also introduced (11-13).

The incidence of TB in HIV-infected patients varies greatly according to the extent of HIV progression (6). In our analysis the incidence of TB was higher in patients with initial CD4+ cell counts below 200 cells/μL than in those with counts above 200 cells/μL. In the former the incidence of TB was 2.06 cases per 100 P-Y (95% CI, 1.45-2.67) and in the latter, 0.72 cases per 100 P-Y (95% CI, 0.45-0.99). In the Poisson regression analysis, the unadjusted ratio of the incidence in the two groups was 2.43 (95% CI, 1.52-3.89, P = 0.001), and after adjustment for sex, age, transmission route, and INH prophylaxis, the ratio was 2.34 (95% CI, 1.47-3.73, P = 0.001). This signifies that the patients with initial CD4+ cell counts below 200 cells/μL were at about two times greater risk than those with CD4+ cell counts above 200 cells/μL. Studies before the availability of HAART also found that the incidence of TB was associated with initial CD4+ cell counts (14, 15).

INH prophylaxis was not a significant risk factor for TB incidence in this study. INH prophylaxis is known to be one of the factors which affect the incidence of TB in HIV-infected patients, and it seems to reduce it generally (3, 16, 17). In our study, the incidence of TB in individuals without INH prophylaxis was 1.43 cases per 100 P-Y, higher than in those who received INH prophylaxis. But the risk ratio between two groups was 2.22 (95% CI, 0.91-5.43; P = 0.080), which was not statistically significant. Testing for latent TB is recommended for every HIV-infected patient, and if latent TB is diagnosed by either TST or the interferon-gamma release assay, INH prophylaxis is recommended.

But in Korea, diagnostic tests were not carried out for every HIV-infected patient because most patients had previously received BCG vaccination. Further studies are required to evaluate the effect of INH prophylaxis on the incidence of TB in Korea.

HIV-infected patients are more likely to have extrapulmonary TB than uninfected individuals (18). In our analysis, 52 (74.3%) of the 70 HIV-infected individuals with TB presented with extrapulmonary TB infection. The most common sites of extrapulmonary TB were lymph node and pleura, as also found in a survey of extrapulmonary TB in the United States between 1993 and 2006 (10). Low CD4+ cell counts are recognized as a risk factor for extrapulmonary TB (8, 18, 19). In this study, CD4+ cell counts differed between the three groups of pulmonary TB, extrapulmonary TB and pulmonary TB-extrapulmonary TB, with the highest counts in patients with pulmonary TB, but the differences were not statistically significant.

Our study had some limitations. Firstly, it was only conducted in a single tertiary hospital, albeit the largest referral center for HIV-infected patients in Korea. Hence the results cannot be generalized to all HIV-infected patients in Korea. Secondly, for reasons discussed above, only a small portion of the HIV infected patients in this study received INH prophylaxis (20, 21). We cannot draw any conclusion about the effect of INH prophylaxis on TB incidence.

In conclusion, the incidence of TB between 1998 and 2010 was 1.19 cases per 100 P-Y, which was much lower than found in our previous study between 1988 and 1997. An initial CD4+ cell count < 200 cells/μL is a risk factor for TB.

ACKNOWLEDGMENTS

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