Effects of HIV Status and Other Variables on the Outcome of Tuberculosis Treatment in Spain

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OBJECTIVE: To analyze the effect of human immunodeficiency virus (HIV) status and other variables on the outcome of tuberculosis treatment in Spain.

PATIENTS AND METHODS: Multicenter retrospective cohort study in 6 autonomous communities of Spain (from May 1996 to April 1997). Data on treatment outcome were collected for new cases of tuberculosis in accordance with European guidelines. Follow up of patients continued for 3 months after scheduled end of treatment.

RESULTS: Of the 4899 patients included, 3417 (69.7%) had a satisfactory outcome, 438 (8.9%) died before or during treatment, and 1044 (21.4%) had a potentially unsatisfactory outcome. On stratification by HIV status, satisfactory outcome, mortality, and potentially unsatisfactory outcome were reported for 43.4%, 21.5%, and 35.1%, respectively, of HIV-positive patients; 71%, 6.2%, and 22.8%, respectively, of HIV-negative patients; and 74.3%, 7.5%, and 18.2%, respectively, of patients with no HIV status available. HIV modified the effect of several variables on the outcome of treatment, and so separate logistic regression models for each HIV category were constructed. Among HIV-positive patients, mortality increased in patients with neoplastic disease and in users of drugs by nonintravenous routes of administration, whereas potentially unsatisfactory outcomes increased in intravenous drug users and in women.

CONCLUSIONS: In Spain, the outcome of tuberculosis treatment is much worse in HIV-positive patients. Drug use and presence of neoplastic disease substantially affect mortality.

Key words: *Outcome of tuberculosis treatment. Potentially unsatisfactory outcome. HIV status.*

Efectos del VIH y otras variables sobre el resultado del tratamiento antituberculoso en España

OBJETIVO: Analizar el efecto del virus de la inmunodeficiencia humana (VIH) y otras variables sobre el resultado del tratamiento antituberculoso en España.

PACIENTES Y MÉTODOS: Estudio multicéntrico de cohorte retrospectivo en 6 comunidades autónomas (de mayo de 1996 a abril de 1997). Se recogió información sobre el resultado del tratamiento en casos nuevos de tuberculosis siguiendo la normativa europea. Se realizó seguimiento de los casos hasta 3 meses después de la fecha prevista de finalización del tratamiento.

RESULTADOS: De los 4.899 pacientes incluidos, se observó un resultado satisfactorio en 3.417 (69,7%), 438 (8,9%) murieron antes o durante el tratamiento y 1.044 (21,4%) tuvieron un resultado potencialmente insatisfactorio. Estratificando por el estado de la infección por el VIH, las cifras fueron, respectivamente: para los que la presentaban, del 43,4, el 21,5 y el 35,1%; para los seronegativos, del 71, el 6,2 y el 22,8%, y para aquellos en quienes no constaba, del 74,3, el 7,5 y el 18,2%. El VIH modificaba el efecto de diversas variables sobre el resultado del tratamiento, por lo que se ajustaron modelos de regresión logística separados para cada categoría VIH. Entre los seropositivos, la mortalidad aumentó en enfermos con neoplasias y en usuarios de drogas por vías distintas de la parenteral, mientras que los resultados potencialmente insatisfactorios aumentaron en usuarios de drogas por vía intravenosa y en las mujeres.

CONCLUSIONES: En España, el resultado del tratamiento antituberculoso es mucho peor en enfermos infectados por el VIH. El uso de drogas y el hecho de padecer neoplasias tienen un papel importante sobre la mortalidad.

Palabras clave: *Resultados del tratamiento antituberculoso. Resultado potencialmente insatisfactorio. Estado VIH.*

Introduction

One of the priorities in the control of tuberculosis is to cure patients with the disease, given that the most effective way to prevent transmission and avoid the appearance of drug-resistant strains is to detect cases of tuberculosis early and treat them appropriately. The World Health Organization (WHO) has set a goal of

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curing at least 85% of infectious patients as part of the program to control tuberculosis. To achieve this goal, the organization recommends a directly observed treatment, short-course (DOTS) strategy, in which surveillance of the treatment outcome makes an essential contribution to the assessment of the effectiveness of control programs.[1]

In 1997, a joint working group of the WHO and the International Union Against Tuberculosis and Lung Disease drew up guidelines for monitoring the outcomes of tuberculosis treatment in the European region of the WHO.[2] Given that the overall goal is to attain satisfactory outcomes in 85% of the patients treated, and that a mortality rate of 5% is considered acceptable, an investigation should be undertaken when potentially unsatisfactory outcomes exceed 10% (treatment failure, transfer, and withdrawal from treatment).

Spain has the second highest incidence of both tuberculosis and acquired immune deficiency syndrome (AIDS) within the European Union.[3,4] Moreover, tuberculosis has consistently been the disease that has most often led to diagnosis of AIDS, with a peak in the association of the two diseases in 1994, when 41.9% of patients with AIDS had first been diagnosed with tuberculosis.[5] According to the results of the Multicenter Project on Tuberculosis Investigation (abbreviated as PMIT in Spanish), at least 18% of all patients with tuberculosis diagnosed between May 1996 and April 1997 were also infected with the human immunodeficiency virus (HIV).[6]

As noted by other authors, the overlap between populations infected by HIV and tuberculosis points to a marked interaction between these 2 diseases in Spain, and HIV infection has led to an increase in the number of patients with tuberculosis in Spain in recent decades.[7] Nevertheless, we have little information on how HIV infection affects the outcome of tuberculosis treatment in Spain in the community at large. This article analyzes this effect through the information obtained from a cohort of almost 5000 tuberculosis patients identified by the PMIT in 6 autonomous communities. The study patients came from a general population that represented 32% of the entire Spanish population.[8]

Patients and Methods

The PMIT identified a cohort of tuberculosis patients through case finding in different registers of 6 Spanish autonomous communities, namely, Asturias, Galicia, Basque Country, La Rioja, Murcia, and Catalonia. Tuberculosis cases were defined as patients with a positive sputum smear and/or culture for *Mycobacterium tuberculosis* complex, or a physician's prescription that included 2 or more tuberculosis drugs. Subjects who met the second condition but not the first were included as cases only if the prescription was maintained for 3 months, whereas those with cultures positive for *M tuberculosis* who had not received treatment, whether due to death or some other exceptional cause, were included.

Patients previously infected with tuberculosis and those in prison at diagnosis were excluded from the study for logistical reasons. Patients with no medical history available at the time of diagnosis were also excluded because this document, along with death registers, was the source of data used in this study.

Clinical and epidemiological data and data on treatment outcomes were taken from the medical history. If patients were lost to follow up, their medical history was lost, or the information on the treatment outcome in the medical history was incomplete, we searched the death registries of the autonomous communities to determine whether the patient had died.

For the purposes of the study, patients were classed as HIV positive when it was so indicated in their medical history. Otherwise, given that HIV testing is not routine in tuberculosis patients, they were classed as HIV negative when their medical history stated that the HIV test result was negative or that they were HIV negative, or as having unknown HIV status.

Treatment for the patients started between May 1996 and April 1996, and follow up lasted until 3 months after the scheduled end of treatment.

The categories for treatment outcome were defined according to European guidelines as follows[2]: *a)* satisfactory outcome, patients who completed treatment and who were discharged by the treating physician not longer than 3 months after the scheduled end of treatment; *b)* death, patients who died of any cause during the scheduled treatment period; *c)* transfer out, patients who changed center before finishing treatment and so no information on treatment outcome was available; *d)* treatment failure, patients who had not attained negative cultures or smears 5 months after starting treatment, or who had positive sputum cultures after an initial conversion to negative, and whose first-line therapy had been replaced by a second-line one; and *e)* treatment interrupted (default), patients who had interrupted treatment for more than 2 consecutive months, who had not completed therapy 3 months after the scheduled end of treatment, or who had taken less than 80% of the prescribed doses.

These categories were subsequently pooled into 3, namely: *a)* satisfactory outcome; *b)* death; and *c)* potentially unsatisfactory outcome, which included transfer to a different center, treatment failure, and treatment interruption.

For the purposes of the study, lack of information on the treatment outcome in the medical histories or missing medical histories were also classed as a potentially unsatisfactory outcome.

Statistical Analysis

Frequency distributions were calculated for the treatment outcomes by different variables and possible associations were investigated using the χ^2 test. To assess associations between different independent variables and death or potentially unsatisfactory outcome, the odds ratio (OR) and its 95% confidence interval (CI) were used. Logistic regression was used in the multivariate analysis to analyze the relationship between the treatment outcome and the variables of interest. To construct the model and verify the goodness of the fit, we used the Hosmer and Lemeshow[9] approach, in which an initial model was constructed that included all significant variables in the bivariate analysis ($P \leq .25$). By working backwards, irrelevant variables were eliminated using the likelihood ratio test to compare successive models. Epidemiological variables were added one by one to the model resulting from this process, even if they were not statistically significant, and assessed for inclusion the final model.

The statistical program used was STATA (version 6.0).[10]