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Puljiz, Ivan; Begovac, Josip

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Tuberculosis in HIV-Infected Patients in Croatia between 1986 and 2005

Ivan Puljiz and Josip Begovac

University Hospital for Infectious Diseases »Dr. Fran Mihaljević«, Zagreb, Croatia

A B S T R A C T

A retrospective medical chart review was performed on 65 HIV-infected patients with tuberculosis hospitalized between 1986 and 2006 at the University Hospital for Infectious Diseases »Dr Fran Mihaljević«, Zagreb. Thirty two patients presented with pulmonary involvement, 13 with extrapulmonary, and 20 patients had disseminated tuberculosis. Forty five patients had an abnormal chest X-ray. Mycobacterium tuberculosis was identified in 35 (53.9%) patients. Ten (15.3%) of 65 patients had already been receiving antiviral therapy, while another 31 (47.7%) initiated antiviral therapy after antituberculosis therapy. Tuberculosis-associated immune reconstitution inflammatory syndrome was observed in 11/27 (40.7%) patients. Forty one patient received the standard six month course of antituberculous therapy, while in 12 patients the therapy was prolonged. Twenty one patient (32%) experienced an adverse event to antituberculosis drugs. Twelve patients died (18.5%). After the introduction of highly active antiviral therapy (HAART) the mortality decreased. The incidence of tuberculosis in HIV-infected patients in Croatia is increasing, and tuberculosis is still an important opportunistic infection in our HIV-infected patients.

Key words: *Croatia, M. tuberculosis, HIV, AIDS, immune reconstitution inflammatory syndrome*

Introduction

Tuberculosis and human immunodeficiency virus (HIV) are the leading causes of death from infectious diseases among adults in the world[1]. Patients with HIV infection are at increased risk for tuberculosis, and tuberculosis is a major cause of morbidity and mortality in HIV-infected patients, particularly in the developing world. Parallel to the increasing use of highly active antiretroviral therapy (HAART), a substantial decrease in the incidence of HIV-associated illnesses has been observed, as well as tuberculosis. However, some patients may not show an immunological response when treated with antiretroviral therapy and therefore remain at high risk of developing opportunistic infections[2]. On the other side, cases of tuberculosis with deterioration were reported also in patients showing an augmented immunological and/or virological response to therapy, known as the immune reconstitution inflammatory syndrome -IRIS[3].

HIV infection is still relatively uncommon in Croatia. The majority of cases are believed to be imported, hence Croatia can be defined as a »pattern III country«[4]. The Epidemiology Service of the Croatian National Institute of Public Health Zagreb reported 553 HIV-infected persons in Croatia in the period 1985 to 2005. The first cases of AIDS have been diagnosed in 1986 and until December 2005 a total of 239 AIDS patients were treated at the University Hospital for Infectious Diseases »Dr. Fran Mihaljević» Zagreb. Out of them 118 AIDS patients died. The incidence of tuberculosis cases in Croatia decreased during the last twenty years. In 2005 there were 1,144 newly detected tuberculosis cases in Croatia rendering an incidence of 26 rates per 100,000 inhabitants.

The aim of our study was to describe the clinical features of tuberculosis in HIV-infected patients in Croatia.

Patients and Methods

We retrospectively analyzed all HIV-infected patients with tuberculosis hospitalized at the University Hospital for Infectious Diseases »Dr. Fran Mihaljević», Zagreb, between January 1, 1986 through December 31, 2005. A case of tuberculosis was defined as the presence of clinicoradiological features and histological findings suggestive of tuberculosis, confirmed by the isolation of *Mycobacterium tuberculosis* in culture or by clinical and radiological improvement in response to specific antitu-

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beruculosis therapy[5]. Culture negative cases were included only if antituberculous therapy was given for at least 6-months. Disseminated tuberculosis indicated the spread of disease from lungs to other organs of the body by blood or lymphatic system. AIDS-defining illnesses were defined according to the 1993 Centers for Disease Control and Prevention revised case definition[6]. The patients were tested for tuberculin reactivity with 5 tuberculin units of purified protein derivate (PPD), using the Mantoux procedure. An induration in response to PPD of at least 5 mm was considered a positive response. IRIS was classified according to the French et al.[7]. Viral load and CD4 cell count were recorded from medical notes at tuberculosis diagnosis. HAART was defined as the use of at least 3 antiretroviral drugs in combination.

We analysed demographic and epidemiological data (age, sex, place of birth, place of residence, HIV transmission category, AIDS-defining illnesses, current antiretroviral therapy regimen, date of tuberculosis diagnosis), laboratory findings (CD4 cell count, plasma viral load /HIV-RNA values/, tuberculin skin test status, chest X-ray), microbiology examination (sputum culture, urine culture, culture of lymph node), locality of disease (pulmonary, extrapulmonary, disseminated) course and outcome of the disease (antituberculous therapy, adverse events, IRIS, recovery or death).

Statistical analysis

To describe the internal data, median and range are given. For categorical variables percentages are used. Differences in categorical variables were analyzed with the use of Fisher's exact two-tailed test. Comparison between continuous variables was done by the Mann-Witney test (two groups), and Kruskall-Wallis test (three groups). The results were considered significant at $p< 0.05$. Survival times were compared by the Cox proportional hazard model. Patients alive were censored as of June 1st 2006. All tests were performed with the STATISTICA for Windows software package.

Results

During the last two decades the incidence of tuberculosis in Croatia has declined from 65 cases per 100,000 in the period 1986–1990 to 31 cases per 100,000 in the period 2001–2005 (Table 1). On the other side, in the same period the number of newly diagnosed HIV-infected persons increased from 62 to 230 (Table 1). Out of 553 HIV-infected patients in Croatia, 65 (11.8%) were coinfected with tuberculosis. The number of tuberculosis cases in HIV-infected individuals increased from 1.5 cases per 1,000 tuberculosis cases in the period from 1986 to 1990 to 9.1 cases per 1,000 in the period from 2000–2005.

We found 17 different major opportunistic infections in our 239 AIDS patients (Table 2). Tuberculosis is the second most frequent opportunistic infection, after *Pneumocystis jiroveci* pneumonia (PCP).

The demographic and baseline characteristics of the 65 individuals with tuberculosis are shown in Table 3. The median age of patients was 40 years, 87.7% were men. Sixty patients (92.3%) were born in Croatia, of whom 27 resided in the Mediterranean coastal region, 25 in the Center mountains, and 8 in the Pannonian continental region of Croatia. The leading risk factor for HIV acquisition was heterosexual sex and sex between men (84.6%).

Thirty two patients presented with pulmonary involvement, 13 with extrapulmonary (lymph nodes 10, CNS 2, liver 1), and 20 patients had disseminated tuberculosis (Table 4). The median CD4 cell count and viral load at the time of tuberculosis diagnosis were 57 cells/μL and 229.082 copies/μL, respectively. Patients with pulmonary form of disease had a median of 57 CD4 cells/μL (range, 3–602 cells/mL), extrapulmonary 152 cells/μL (range, 13–648 cells/μL), and disseminated disease 42 CD4 cells/μL (range, 1–566 cells/μL). Patients with pulmonary and disseminated form of illness had a lower CD4 cell count than extrapulmonary tuberculosis, but the difference was not statistically significant ($p= 0.12$). Forty five (71.4%) patients had an abnormal chest X-ray; 15 had a diffuse and 16 had a focal infiltrate. Other pulmonary abnormalities included miliary, nodular, and reticular patterns of the infiltrates. Five patients had cavities, while pleural effusion was recorded in seven patients.

The average period from the first symptoms to diagnosis of tuberculosis was 18 days. Out of 65 patients *M. tuberculosis* was identified in 35 (53.9%) patients. There were no drug-resistant strains of *M. tuberculosis*. Twen-

TABLE 1
INCIDENCE OF TUBERCULOSIS AND HIV-ASSOCIATED TUBERCULOSIS IN CROATIA FROM 1986 TO 2005*

Years	New cases of TB in total population	Incidence/100.000 individuals	Newly diagnosis HIV-infected patients	Number of TB in HIV-infected patients
1986–1990	15,091	65	62	5
1991–1995	10,957	46	96	14
1996–2000	9,746	41	155	20
2000–2005	6,910	31	230	26

* Data from Epidemiology Service, Croatian National Institute of Public Health Tuberculosis Register.
In 1985 were diagnosed 10 HIV-infected patients

TABLE 2
TUBERCULOSIS CASES AND OTHER OPPORTUNISTIC INFECTIONS (AIDS-DEFINING ILLNESSES) IN 239 AIDS PATIENTS TREATED AT THE UNIVERSITY HOSPITAL FOR INFECTIOUS DISEASES »DR. FRAN MIHALJEVIĆ«, ZAGREB FROM 1986 TO 2005

Opportunistic infections	No	%
Pneumocystis jiroveci pneumonia (PCP)	70	15.8
Mycobacterium tuberculosis	65	14.7
Candidiasis of esophagus, trachea, bronchi or lungs	60	13.6
HIV-encephalopathy	48	10.8
Cytomegalovirus (CMV) chorioretinitis	29	6.6
HIV wasting syndrome	28	6.3
Kaposi's sarcoma	27	6.1
Cryptococcosis extrapulmonary	25	5.6
Malignant lymphoma	22	5.0
Toxoplasmosis of brain	19	4.3
Central nervous system diseases, undetermined	16	3.6
Progressive multifocal leucoencephalopathy	11	2.5
Herpes simplex virus ulcers (duration > 1 month)	9	2.0
Recurrent bacterial pneumonia	5	1.1
CMV – other location	4	0.9
Cervical malignancies	3	0.7
Salmonella bacteriaemia (> 2 episodes)	2	0.5
Summary	443	100.00

ty one patient had sputum-culture proven *M. tuberculosis* (five were smear positive), while in 10 patients bacterium was cultured from the lymph node. Two patients had positive urine culture for *M. tuberculosis*, while in one patient the bacterium was detected in pleural effusion and spinal fluid, respectively. Patients with microbiological confirmed disease had a median of 125 CD4 cells/μL (range, 1–648 cells/μL), while patients with unconfirmed disease had 54 CD4 cells/μL (range, 1–602 cells/μL) (p=0.42).

At the time of tuberculosis diagnosis, twenty eight patients had another AIDS-defining illness, 22 esophageal candidiasis, three PCP, and one patient had recurrent-bacterial pneumonia, Kaposi's sarcoma and *Cryptococcocus* meningitis, respectively. Ten (15.3%) of 65 patients had already been receiving antiviral therapy, while another 31 (47.7%) initiated antiviral therapy after anti-tuberculosis therapy, median of 27 days (range 1–96 days). Of the 41 patient who received antiretroviral therapy, 5 recieved one drug (zidovudine), 9 two drugs (zidovudine plus didanosine), and 27 HAART. Seven HAART regimens, involving nine different combinations of drugs were prescribed. Twelve patients received a combination of nucleoside reverse transcriptase inhibitor with non-nucleoside reverse transcriptase inhibitor, while other 15 nucleoside reverse transcriptase inhibitors with protease inhibitor. Eleven of 27 (40.7%) patients receiving HAART were diagnosed with IRIS. IRIS occured at a median of 17 days (range 8–24) after initiating HAART. Seven of 11 patients who developed IRIS had disseminated tuberculosis.

Of the 65 patients, 53 completed therapy whereas 12 (18.4%) patients died during treatment. Tuberculosis was diagnosed prior to 1999 (HAART was introduced in Croatia in April, 1998) in 32 patients, while in 33 patients after that period. Of the 32 patients diagnosed before 1999, 19 died and of 33 patients diagnosed in the period 1999–2005, 5 died. The hazard ratio of death was 0.27 (95% confidence interval 0.1 to 0.7) lower in the period 1999–2005 compared to the period 1986–1998 (p= 0.009). Of the 53 patients who completed therapy, 41 re-

TABLE 3
DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF 65 PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS

Median age (range) years	40 (16–74)
Sex, male (%)	57 (87.7)
Place of birth (%)	
Croatia	60 (92.3)
Other	5 (7.7)
Place of residence in Croatia (%)	
Mediterranean coastal	27 (45.0)
Pannonian continental	8 (13.3)
Center mountains	25 (41.7)
HIV transmission category (%)	
Injecting drug users	8 (12.3)
Man who have sex with man	27 (41.5)
Heterosexual	28 (43.1)
Other/undefined	2 (3.1)

TABLE 4
CLINICAL, RADIOLOGICAL AND LABORATORY CHARACTERISTICS OF 65 PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS AT THE TIME OF TUBERCULOSIS DIAGNOSIS

Tuberculin skin test status [n=44] (%)	
Positive	12 (27.3)
Negative	32 (72.7)
Site (%)	
Pulmonary	32 (49.2)
Extrapulmonary	13 (20.0)
Disseminated	20 (30.8)
CD4+ T lymphocytes × 106/l [n=56] (range)	56.5 (1–648)
≥ 500(%)	4 (7.1)
200–499	8 (14.3)
0–199	44 (78.6)
Plasma viral load – RNA copies/ml [n=35] (range)	299.082 (2.540–4,960.000)
< 100.000/mL (%)	9 (25.7)
100.000–500.000/mL	12 (34.3)
500.001–1,000.000/mL	8 (22.9)
> 1,000.000/mL	6 (17.1)
Chest X-ray pattern (%)	
Normal	18 (27.7)
Focal infiltrate	15 (23.1)
Diffuse infiltrates	12 (18.5)
Pleural effusion	7 (10.8)
Cavities	5 (7.7)
Nodular pattern	3 (4.6)
Reticular pattern	3 (4.6)
Miliary	2 (3.1)

ceived the standard six months course, whereas 12 patients received prolonged treatment. The reason for a prolonged tuberculosis course was tuberculosis meningitis (1 patient) and disseminated disease (11 patients). In our patients most commonly recommended regimen was a four-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol given for the first 2 months, and isoniazid and rifampin continued for another 4 months. Adverse events led to a cessation and modification of their tuberculosis therapy in 21 (32.3%) patients. The most common side effects noted were hepatitis (11 patients), gastrointestinal disturbances (7 patients), fever (6 patients) and rash (2 patients).

Discussion

Croatia is country with a moderate incidence of *M. tuberculosis* infection in the indigenous population and with a relatively small number of HIV-infected persons. The incidence of tuberculosis is much lower than in the developing countries, but is higher than in the Western European countries. The incidence of tuberculosis in Croatia has been declining during the last two decades nearly threefold, from 72 cases per 100,000 in 1986 to 26 cases per 100,000 inhabitants in 2005. On the other side, the incidence of HIV infection had a slow increase over time. Therefore, a relative rise in the number of HIV-related tuberculosis compared to non-HIV related tuberculosis in the last two decades is not surprising. Comparison of tuberculosis incidence in general populations and HIV-infected persons shows that the incidence of tuberculosis is 20 to 30 times higher among HIV-positive persons. We found that 14.7% of our AIDS patients had tuberculosis. In the USA about 5% of AIDS patients developed tuberculosis, while in the Western European countries the frequency of tuberculosis in AIDS patients has been estimated between 5 to 15%[8]. Much higher numbers of AIDS patients contract tuberculosis in developing countries, where up to 50% of the total population may be infected with *M. tuberculosis*[9].

A significant proportion of our patients (72.7%) had a negative skin test. It is not surprising because more than half of our patients (50.5%) are in advanced immunosuppression (CD4 cell count <100/μL). With the recommended cut-off point for HIV-infected patients of 5 mm induration at 48 hours after intradermal injection of 5 units of PPD, skin testing is consistently negative only in patients with advanced immunosuppression[10].

About one half of our patients had pulmonary involvement. Several other studies reported pulmonary in-

volvement in 70–90% of the total number of HIV-infected patients with tuberculosis[11,12]. Jones et al. found that extrapulmonary tuberculosis becomes more common as the CD4+ count falls[10]. Low CD4 cells count in disseminated form of illness is to be expected as well. Pulmonary tuberculosis infection has become more commonly reported in the post-HAART era, possibly resulting from increased cases due to IRIS.

HIV-infected patients with pulmonary tuberculosis exhibit atypical radiological presentation and negative sputum smear more frequently than their HIV-negative counterparts[13,14]. Chest X-ray findings in HIV-associated tuberculosis vary with the CD4+ count. The upper lobe infiltrates, which are typical of reactivated disease, occur in approximately one third of patients[13]. However, in HIV-infected patients with pulmonary tuberculosis chest X-ray may be normal, especially in those with advanced immunosuppression. In autopsy studies, up to 50% of HIV-related tuberculosis deaths go undiagnosed[15,16].

More than half (53.8%) of our patients were already diagnosed with active tuberculosis when HIV testing was performed.

In Croatia, a dual combination antiretroviral therapy was introduced during 1995 and triple combination with protease inhibitors in April 1998. In our study, the risk of death decreased by 73% among HIV-infected persons treated in the HAART era. However, a significant proportion of HIV-infected patients presented with tuberculosis while already undergoing HAART[17].

The frequency of tuberculosis IRIS among patients in the present study was 40.7%. The majority of these patients developed IRIS after the second week of initiating HAART. Previous studies reported IRIS rate ranging from 11% to 43%[18,19]. IRIS presents within the first 2 months of HAART, usually in the first few weeks[20]. IRIS has symptoms overlapping with worsening tuberculosis and drug reactions, and can be life-threatening. The majority of patients with IRIS had a disseminated tuberculosis (7/11). Other studies demonstrated that extrapulmonary tuberculosis was one of the possible risk factors associated with the occurrence of IRIS[18,21].

Although highly effective therapy for both HIV and tuberculosis is available, concomitant administration is difficult. To date, the optimal time to start HAART in HIV/tuberculosis coinfected patients is not known. Physicians and patients have to balance the risk of HIV progression against the risk of having to discontinue therapies because of toxicities, side effects or unforeseen drug/drug interaction[22]. Patients who start antiretroviral therapy early in their tuberculosis treatment can be predisposed to IRIS. WHO guidelines suggest starting antiretroviral drugs within 2 months of tuberculosis treatment at a CD4 count between 50 to 200 per μL and for extrapulmonary tuberculosis or other manifestation of severe immunosuppression[23]. For patients with CD4 counts less than 50 per μL, treatment initiation is advised within 2 weeks[23].

The same treatment guidelines as for HIV-uninfected patients can be applied to HIV-infected patients with tuberculosis. Several studies recommending prolonged therapy, particularly in patients with disseminated disease[24,25]. However, there is now evidence that the standard 6-month treatment course may be adequate for all forms of HIV-related tuberculosis, except central nervous system involvement[26,27]. Prolonged therapy is recommended only for patients with a slow or suboptimal response. Between 6% and 24% of patients require a modified drug regimen because of intolerance, usually to isoniazid or, even more frequently to rifampin[28]. Use of rifabutin may be an alternative to therapy with rifampin.

The decline in tuberculosis-related mortality in our patients (73%) in the HAART era is almost identical to the findings reported by Dean et al.[29] where the mortality fell by 72% after the introduction of HAART[29]. Tuberculosis case-fatality rates in Africa are 16–35% in HIV-infected individuals[30].

In conclusion, tuberculosis is still one of the leading opportunistic infections in our HIV-infected patients. The proportion of HIV-related tuberculosis compared to non-HIV related tuberculosis is slowly increasing in the last two decades, however, mainly because of a decline of non-HIV related tuberculosis. After the introduction of HAART the mortality in HIV-associated tuberculosis decreased substantially.

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I. Puljiz

University Hospital for Infectious Diseases »Dr. Fran Mihaljević«, Mirogojska 8, 10000 Zagreb, Croatia
e-mail: ipuljiz@bfm.hr

TUBERKULOZA U BOLESNIKA ZARAŽENIH HIV-OM U HRVATSKOJ U RAZDOBLJU OD 1986. DO 2005. GOD.

S A Ž E T A K

Rad se temelji na retrospektivnoj analizi 65 HIV-pozitivnih bolesnika s tuberkulozom koji su bili hospitalizirani u Klinici za infektivne bolesti »Dr. Fran Mihaljević« u Zagrebu od 1986. do 2005. godine. Trideset i dva bolesnika su imala plućni oblik bolesti, 13 izvanplućni, a 20 je imalo diseminiranu tuberkulozu. Patološki nalaz na rendgenskoj slici pluća otkriven je u 45 bolesnika. *Mycobaterium tuberculosis* je dokazan u 53,9% bolesnika. Deset (15,3%) bolesnika je bilo na antivirusnoj terapiji prije dijagnosticiranja tuberkuloze dok je antivirusna terapija uvedena u 31 (47,7%) bolesnika nakon započinjanja liječenja tuberkulostaticima. Imunorekonstruktivni inflamatorni sindrom je zabilježen u 11/27 (40,7%) bolesnika. Standardno šesto mjesečno liječenje provedeno je u 41 bolesnika, a 12 bolesnika liječeno je dulje. Nuspojave su zabilježene u 21 bolesnika. Umrlo je 12 (18,5%) bolesnika. Nakon uvođena visoko učinkovite antiretrovirusne terapije (HAART) smanjuje se smrtnost. Incidencija tuberkuloze u HIV-pozitivnih osoba u Hrvatskoj je u porastu, a tuberkuloza je važna oportunistička infekcija u naših HIV-pozitivnih bolesnika.