Tuberculosis prophylaxis in patients with steroid treatment and systemic rheumatic diseases. A case-control study

B. Hernández-Cruz[1], S. Ponce-de-León-Rosales[2], J. Sifuentes-Osornio[3], A. Ponce-de-León-Garduño[3], E. Díaz-Jouanen[4]

[1]Department of Internal Medicine; [2]Department of Internal Medicine and Clinical Epidemiology; [3]Department of Infectious Diseases; [4]Teaching Division, Instituto Nacional de la Nutrición Salvador Zubirán, Mexico D.F., Mexico

Abstract

Objective

The aim of this study was to assess the impact of isoniazid prophylaxis in patients with systemic rheumatic diseases who attended a teaching hospital in Mexico City between 1987 and 1992.

Methods

In this case-control study, patients with systemic rheumatic diseases and tuberculosis (cases) were compared with patients with systemic rheumatic diseases without tuberculosis (controls). The groups were matched by year of hospital admission and rheumatic disease. Clinical charts were reviewed for: 1) isoniazid prophylaxis, defined as the administration of isoniazid 300 mg/day for 6 or more months in patients with exposure to steroids (prophylaxis with isoniazid was defined as complete, incomplete or any prophylaxis); 2) exposure to steroids: defined as the administration of prednisone > 15 mg/day (or its equivalent of another steroid) for 3 or more months before tuberculosis or recruitment into the study; 3) exposure to immunosuppressants, defined as the administration of any dose of azathioprine, methotrexate, cyclophosphamide, and/or 6-mercaptopurine, before tuberculosis in the cases or recruitment date in the controls; 4) reactivity to PPD; and 5) other relevant variables.

Results

Twenty cases and 66 controls were studied. A 70% decrease in the risk of developing tuberculosis was found among patients who received any prophylaxis with isoniazid as compared to controls: OR 0.31, 95% CI 0.09 - 0.98, p = 0.03. A 97% decrease was seen in those patients who received complete prophylaxis: OR 0.034, 95% CI 0.0001 - 0.216, p < 0.0001. The protective effect of complete prophylaxis persisted even after controlling for other potential confounders, such as age, gender, rheumatic disease, duration of rheumatic symptoms, and exposure to steroids and/or immunosuppressants.

Conclusion

The results of this study suggest that in countries with a high prevalence of tuberculosis the use of isoniazid (300 mg/day for 6 months) in rheumatic patients with exposure to prednisone (> 15 mg/day for three or more months) may be useful to prevent tuberculosis, independently of the results of the PPD reactivity test. However, a controlled clinical trial will be required to confirm these results.

Key words

Tuberculosis, SLE, rheumatic diseases, prophylaxis, isoniazid.

Blanca Hernández-Cruz, MD, Rheumatologist, Staff Researcher; Sergio Ponce-de-León-Rosales, MD, MSc, Staff Researcher, Clinical Epidemiologist; José Sifuentes-Osornio, MD, Infectologist, Staff Researcher; Alfredo Ponce-de-León-Garduño, MD, Infectologist, Staff Researcher; Efraín Díaz-Jouanen, MD, FACR, FACP, Chairman.

Please address correspondence and reprint requests to: Efraín Díaz Jouanen, MD, Teaching Division, Instituto Nacional de la Nutrición Salvador Zubirán, Vasco de Quiroga no. 15, D.F. Mexico CP 14000, Mexico.

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Introduction

Patients with systemic rheumatic diseases are more likely to develop tuberculosis, because of the depressed immunity caused either by their disease (1) or by its treatment (2). The exact prevalence of tuberculosis in patients with systemic rheumatic diseases is unknown, but is estimated to be between < 1% and 5% (3, 4), the higher rates prevailing in countries with a greater prevalence of tuberculosis (5). Although the mortality attributable to tuberculosis in patients with systemic rheumatic diseases is unknown, in patients with systemic lupus erythematosus (SLE) and miliary tuberculosis the rate has been estimated to be between 40% and 100% (3-5).

Since 1986 the American Thoracic Society has recommended the use of isoniazid prophylaxis for patients with a positive PPD reaction who have been receiving >15 mg/day of prednisone for long periods of time (6). However, patients receiving steroids (7) or those with systemic rheumatic diseases (8) frequently have a false negative PPD reaction. Furthermore, conclusive evidence of the benefit of isoniazid prophylaxis in rheumatic patients being treated with steroids is lacking.

Mexico is a country with high rates of tuberculosis. In 1994, 19.2 new cases of lung tuberculosis (9) and 22 new cases of all forms of tuberculosis per 100,000 inhabitants (10) were detected. The estimated incidence rate is even higher. In 1994, 51.7 new cases of all forms of tuberculosis per 100,000 inhabitants were calculated (11). In our hospital, it is common practice to administer isoniazid to rheumatic patients who have been taking > 15 mg/day of prednisone (or its equivalent) for 3 or more months, whether the patient is PPD positive or PPD negative. We decided to undertake a case-control study to evaluate the usefulness of this prophylactic approach.

Patients and methods

Cases were patients with systemic rheumatic diseases and tuberculosis. Controls were patients with systemic rheumatic diseases without tuberculosis. Cases were found by reviewing: (i) the microbiology laboratory records; (ii) the lists of discharge diagnoses for in-patients; and (iii) the institute's database of rheumatic patients with rheumatic disease, which included both in- and out-patients. Controls were found by reviewing: (i) the lists of discharge diagnoses for in-patients; and (ii) the institute's database of in- and out-patients with rheumatic diseases. One case was match with three controls. The selection of the controls was made by matching to the case by "year of admission". The second step was to match by rheumatic disease. In cases where diagnosis matching was a problem, controls with similar systemic diseases were found. In cases with more than 3 possible controls, these were selected using a random number stable (12).

The following variables were sought for in the medical records: demographic information, tuberculosis, administration of isoniazid, steroid exposure, and/or immunosuppressant exposure. These variable were defined as follows. Exposure to steroids: the administration of prednisone > 15 mg/day (or its equivalent of another steroid) for 3 or more months. Exposure to immunosuppressive drugs: administration of any dose of azathioprine, methotrexate, cyclophosphamide, and/or 6-mercaptopurine. Time of exposure: for steroids and immunosuppressive drugs two periods of time exposure were considered: (i) the time period from the diagnosis of the systemic rheumatic disease to either tuberculosis (for cases) or the date of recruitment into the study (for controls); and (ii) within the last 6 months before tuberculosis (cases) or the recruitment date (controls).

Prophylaxis with isoniazid was classed as complete, incomplete or any prophylaxis, as follows. Complete prophylaxis was assumed when the patient with exposure to steroids received 300 mg/day of isoniazid continuously for 6 to 12 months at any time during the follow-up in our hospital and before the onset of tuberculosis (cases) or the recruitment date (controls). Incomplete prophylaxis was assumed when the patient with exposure to steroids received less than 300 mg/day of isoniazid, or for less than six months (because of the development of tuberculosis or for any other reason) before the appearance of tuberculosis (cases) or the recruitment date (controls). "Any prophylaxis" meant that the patient

with exposure to steroids had received either complete or incomplete isoniazid before the onset of tuberculosis (cases) or the recruitment date (controls).

Patients with AIDS, primary hypocortisolism, or those who had been diagnosed with tuberculosis before the development of the systemic rheumatic diseases were excluded. The degree of malnutrition was assessed according to the patient's weight deficit in relation to his/her ideal weight (13). The diagnoses of rheumatic diseases were formulated according to standard criteria (14-20).

Tuberculosis was diagnosed based on the patient's clinical history, the therapeutic response to 6 months of antimicrobial therapy, and one of the following: a positive culture for *Mycobacterium tuberculosis*, characteristic histopathologic findings, detection of mycobacteria by fluorochrome staining and confirmation by Ziehl-Nielsen in tissue biopsies or appropriate clinical samples (21). A positive culture for *M. tuberculosis* was required for a diagnosis of urinary tract tuberculosis (22).

Statistical analysis

For descriptive purposes we used the means, standard deviations, medians, ranges, or percent relative frequencies, as appropriate. Odds ratios were calculated as association indexes with their exact 95% confidence intervals (CI 95%). Statistical significance was evaluated using Pearson's χ^2 test, Fisher's exact test, Student's t-test or the Mann and Whitney's U statistic, as appropriate. The two-tailed alpha level was set at $p = 0.05$. The Mantel Haenszel procedure was used for the matched analysis of the odds ratios and their confidence intervals (23).

Multiple logistic regression models were developed, where the dependent variable was the presence of tuberculosis, and the independent variable was prophylaxis. Age, sex, rheumatic diagnosis, duration of the rheumatic disease, and the use of steroids or other immunosuppressants were potential confounders, which were controlled for in this part (24). In our use of the logistic regression procedure, we adopted both conditional and non-conditional approaches. Given that the results always pointed in the same direction, and the matching criteria (rheumatic diagnosis and year of diagnosis) were not exhaustive from our point of view, we chose to assume a conservative attitude and thus to present the results of the non-conditional analysis. Otherwise the point and interval estimates and their statistical significance would have been more extreme. Statistical analyses were performed using the STATA package, version 3.0, 1992 (25).

Results

A total of 578 charts were reviewed and 22 cases of systemic rheumatic diseases in association with tuberculosis were detected. Two patients were excluded because they had tuberculosis prior the rheumatic disease: one with RA and the other with primary antiphospholipid syndrome (APS). Another 3 cases were excluded because a diagnosis of tuberculosis could not be made. Sixty-six controls were selected.

Table I shows the characteristics of the

Table I. Clinical characteristics of patients with systemic rheumatic disease and tuberculosis, and controls.

A.

Variable	Cases (n = 20) Mean	Median	SD	Limits	Controls (n = 66) Mean	Median	SD	Limits	p
Age (years)	40.9	41.5	16.5	12 - 66	34	29.5	16.5	15 - 83	0.16*
Duration of rheumatic disease before TB (cases) or recruitment date (controls) (in mos.)	23.05	9	34.6	0 - 144	43.4	19.5	60.4	0 - 310	0.093**
Follow-up after TB or recruitment date (mos.)	27.3	26	16.8	6 - 72	28.9	28	16.6	6 - 76	0.111**
Years of formal education	5.7	6	4.5	0 - 15	10.1	9	4.9	0 - 24	0.001**

Limits: min - max. * Student's t-test; ** Mann and Whitney's U statistic.

B.

Variable	Cases (n = 20) no.	%	Controls (n = 66) no.	%	Odds ratio, and 95% confidence internal	P
Sex (male)	7	41	7	11	5.84, 1.5 – 21.7	0.003*
Socioeconomic level						
Low	11	61	32	52		0.55**
Medium	7	39	27	43		
High	0	0	3	5		
Malnutrition	12/20	60	24/65	37	2.56, 0.82 – 8.11	0.077*
Type of rheumatic disease						
Systemic lupus erythematosus	8	40	38	57		0.82**
Rheumatoid arthritis.	4	20	11	17		
Polymyositis-dermatomyositis.	4	20	9	14		
Mixed connective tissue disease	2	10	2	3		
Others	2	10	6	9		

Others: 1 case of Wegener vasculitis and 1 of Henoch-Schönlein vasculitis; Controls = scleroderma (n = 5), CREST (n = 1).* Fisher exact test; ** Pearson's χ^2 test

cases and controls. The cases were younger and had a shorter rheumatic disease duration than the controls, although the difference was not statistically significant. Furthermore, the case patients showed a lower level of formal education (p = 0.001), a higher frequency of malnutrition (p = 0.07), and were predominantly male (p = 0.003). The rheumatic diseases observed were similar between the cases and controls. SLE was the most frequent rheumatic disease in both cases and controls, followed by RA and polymyositis-dermatomyositis (Table Ib). Seven cases (35%) and 19 controls (29%) had at least one associated disease. The most relevant were: alcoholism in 4 cases and 4 controls (OR= 3.88, 95% CI = 0.63 - 22.85, p = 0.08); type II diabetes mellitus in 3 and 6, respectively (OR = 1.76, 95% CI = 0.26 - 1.76, p = 0.42); and chronic renal failure in 2 and 5 respectively (OR = 1.36, 95% CI = 0.12 - 9.14, p = 0.66). PPD reactivity was ≥ 10 mm of induration in 4 of 15 cases (27%) (it was not evaluated in 5 cases) and in 1 of 17 controls (6%) p = 0.161 (not evaluated in 49 controls). In most of the patients, the PPD test was carried out as part of a routine tuberculosis screening when the patients were on steroids.

As shown in Table II, most of the patients had been exposed to steroids or immunosuppressants before the development of their tuberculosis. No significant difference was observed between the cases and controls in exposure to steroids either at any time or with in the last six months before tuberculosis. Methylprednisolone boluses were used in 1 case and 5 controls. The exposure to immunosuppressive drugs was higher in the controls than in the cases, these differences being primarily due to treatment with azathioprine at any time before tuberculosis or the inception date. Azathioprine was used more commonly in the control group, follow by methotrexate. Other drugs used but not included in the table were chloroquine (4 cases and 19 controls), D-penicillamine (0 and 7, respectively) and colchicine (0 and 3, respectively), none of which showed any statistical significance between the cases and controls.

Table II. Exposure to steroids and immunosuppressants before the development of tuberculosis in the patients with systemic rheumatic diseases, and as of the inception date of their rheumatic disease in the controls.

Drug	Time	Cases (n = 20)		Controls (n = 66)		P*
		no.	%	no.	%	
Any drug	Any time	16	80	60	92	0.203
	6 months	16	80	57	88	0.464
Steroids**	Any time	13/18	72	55/63	89	0.126
	6 months	13/18	72	51/62	82	0.338
Immunosuppressants	Any time	5	20	42	64	0.004
	6 months	5	25	26/65	40	0.292
Azathioprine	Any time	3	15	31	47	0.017
	6 months	3	15	17	26	0.382
Methotrexate	Any time	2/12	17	18/54	33	0.385
	6 months	1/19	5	5/61	8	0.692
Cyclophosphamide PO	Any time	1	5	2	3	0.553
	6 months	0	0	2	3	1.0
Cyclophosphamide IV	Any time	1	5	5/64	9	1.0
	6 months	1	5	5/65	8	1.0
6-mercapthopurine	Any time	1	5	3	5	1.0
	6 months	1	5	2	3	0.553

* Fisher exact test

** In 5 patients (2 cases and 3 controls), the time and dose of prednisone could not be quantified. For explanations, see Patients and methods.

The effect of isoniazid prophylaxis is shown in Table III. The reasons for incomplete prophylaxis were the development of tuberculosis during isoniazid administration (3 cases), inadequate dose or duration (1 case and 2 controls) and isoniazid-related hepatitis (2 cases). The remaining 13 cases had received prednisone before admittance to our hospital and never received prophylaxis. All patients with prophylaxis had been exposed to steroids before their tuberculosis or the recruitment date. Any prophylaxis resulted in a 70% decrease in the risk of tuberculosis, and complete prophylaxis decreased this risk by 97%. However, after adjustment for exposure to immunosuppressive drugs (either within the last 6 months or at any time during the disease), the statistical significance persisted only for those patients who received complete prophylaxis. No significant changes were observed when analyzing the frequency of prophylaxis during the study period (data not shown).

Complete prophylaxis always showed a protective effect, with an OR ranging from 0.008 to 0.037 in the multiple logistic regression models adjusted for age, gender, exposure to steroids, immunosuppressants or both, length of rheumatic disease, and rheumatic diagnosis (Table IV). The protective effect of complete prophylaxis persisted when both steroids and/or immunosuppressive drugs were included in the model, either at any time or in the last six months from the diagnostic of the systemic rheumatic disease to tuberculosis (cases) or the recruitment date (controls). The same analysis for any prophylaxis showed a tendency for a protective effect ranging from OR = 0.179 to 0.38, although with a variable statistical significance.

Four cases died during follow-up: one of tuberculosis and three due to their rheumatic disease. Seven of the controls died as a consequence of their rheumatic disease. Although the prognosis tended to be consistently worse among the cases and among the patients without prophylaxis, the difference from the controls was not statistically significant (p = 0.759, p = 0.436, respectively).

Discussion

This study shows that in patients with

Table III. Effect of isoniazid prophylaxis adjusted for exposure to steroids and immunosuppressive drugs (drug treatment).

	Cases (n = 20) no.	Controls (n = 66) no.	Crude analysis OR (95% CI)	p*	Exposure to steroids and immunosuppressive drugs In the last 6 months* OR (95% CI)	p	At any time* OR (95% CI)	p
Prophylaxis								
Any	7	42	0.31 (0.09 - 0.98)	0.038	0.3 (0.08-1.09)	0.074	0.35 (0.10 - 1.23)	0.119
Complete	1	40	0.034 (0.0001 - 0.216)	0.001	0.0 (0.00 - 0.26)	< 0.001	0.04 (0.00 - 0.29)	< 0.001
None	13	24						

For explanations see Patients and methods. p = two-tailed Fisher's exact test.

rheumatic diseases who have taken steroids the risk of developing clinical tuberculosis was considerably reduced if they also received isoniazid prophylaxis. Although a randomized controlled clinical trial would be the ideal epidemiological design to evaluate the efficacy of a treatment, this would be difficult to apply in the case of isoniazid prophylaxis in rheumatic disease patients because both represent uncommon events with long periods of latency. Furthermore some physicians would find unethical the requirement for the random assignment of treatment. In this case, a case-control study represents an acceptable alternative (26).

We made an effort to achieve maximum comparability between the cases and controls in order to diminish the bias of a case-control study. Cases differed from controls in gender, rheumatic disease duration, years of formal education, malnutrition and rheumatic disease. It was not possible match by gender as well as by year of admission and by rheumatic diseases. Subsequent adjustment for gender in the multivariate analysis, however, did not show any appreciable difference in terms of the protective effect. It was clear from our analysis that gender represented a confounding variable. We have no clear explanation for the predominance of males among our cases. Tuberculosis is more common in males in some populations, including ours (9, 10). The differences in tuberculosis indices by gender vary with age and are not the same from population to population. Among adults, males are afflicted more often than females (at an approximate ratio of 2: 1). The incidence rates of tuberculosis by gender are very similar for young children, but the annual rate of infection is slightly higher for males. These differences probably have both biological and social roots (27).

Differences in the duration of the rheumatic diseases between cases and controls were not statistically significant, although they were clinically important and could have biased our results. Some rheumatic diseases are characterised by higher rates of activity and by treatment with steroids in the early phase of the disease.

The patients who attended our hospital had a low level of formal education and a lower socioeconomic status. In such situations tuberculosis is more prevalent and the effect of prophylaxis may be higher. On the other hand such factors could also affect variables like compliance and the ability to pay, variable that may have influenced our results but which were not evaluated in this retrospective study. In addition, there was a slightly higher degree of malnutrition among our cases compared to the controls. Given the cross-sectional nature of this study, we were not able to estimate the exact relationship in time between the malnutrition and the tuberculosis.

Regarding the matching for rheumatic disease, an identical matching of the diagnoses could not be achieved between the controls and the cases with vasculitis and scleroderma; however, this difference was not statistically significant. Finally, we found a greater exposure to immunosuppressants among the controls. After controlling for the exposure to steroids and/or immunosuppressants in the multivariate analysis (Table IV), the effect of complete prophylaxis persisted, thereby strengthening our conclusion.

Table IV. Adjustment for confounders and the association of isoniazid and TB. Multiple logistic regression models.

Variable(s) controlled in the model	Any prophylaxis OR	p	Complete prophyl. OR	P
None (crude effect)	0.308	0.03	0.034	0.002
Age	0.359	0.098	0.028	0.002
Gender	0.361	0.068	0.037	0.003
Rheumatic disease (RD)	0.237	0.029	0.013	0.001
Exposure to steroids	0.444	0.197	0.037	0.002
Exposure to immunosuppressants (IS)	0.476	0.197	0.049	0.006
Exposure to steroids and/or IS	0.352	0.073	0.035	0.002
RD duration	0.305	0.031	0.036	0.002
Age, gender	0.391	0.143	0.024	0.002
RD duration, steroids and IS (6 months)	0.316	0.054	0.034	0.003
Age, gender, steroid and IS (6 months)	0.380	0.146	0.023	0.002
RD duration, gender, steroids and IS (6 months)	0.373	0.110	0.036	0.003
RD duration, age, gender, steroids and IS (6 mos.)	0.371	0.142	0.026	0.002
RD duration, gender, RD	0.207	0.029	0.009	0.001
RD duration, gender, RD, steroids and IS (6 mos.)	0.179	0.026	0.008	0.001

For explanations see Patients and methods. OR: Odds ratio.

Table V. Some estimates of the prophylaxis effect in rheumatic patients.

	Estimated frequency of TB (3 - 0.1%) X	Relative risk reduction of TB with isoniazid A	Risk of TB Y = (X) (a)	Difference of risk reduction X - Y	No. needed to be treated to prevent 1 case of TB 1 / (X - Y)
Any prophylaxis	0.03	0.30	0.009	0.021	47.6
	0.025	0.30	0.007	0.017	57.1
	0.01	0.30	0.003	0.007	142.8
	0.003	0.30	0.0009	0.0021	476.1
	0.001	0.30	0.0003	0.0007	1428.5
Complete prophylaxis	0.03	0.03	0.0009	0.0291	34.3
	0.025	0.03	0.0007	0.0242	41.2
	0.01	0.03	0.0003	0.0097	103.9
	0.003	0.03	0.00009	0.00291	343.6
	0.001	0.03	0.00003	0.00097	1030.9

For explanations see Patients and methods.

In order to estimate the benefit of the systematic use of isoniazid prophylaxis, we calculated the number of patients who would have had to be treated to prevent one case of tuberculosis, following the procedure of Guyatt *et al.* (28) (Table V). In 1994 we had 12 new cases of tuberculosis among 480 patients with rheumatic diseases attending our hospital. The frequency of tuberculosis was 2.5%, and the number of patients that had to be treated to prevent one case of tuberculosis was 57.1 and 41.2 for any prophylaxis and complete prophylaxis, respectively. This rate could represent an underestimation because we had a survival cohort and some cases of undiagnosed tuberculosis were not included in the estimation. Staples *et al.* reported 4 cases of tuberculosis in 223 patients with SLE; with this figure the frequency of tuberculosis was 1.79% (1) and the numbers of patients with SLE that had to be treated to prevent one case of tuberculosis were 142 and 103 for any prophylaxis and complete prophylaxis, respectively. These figures support the use of isoniazid prophylaxis in patients with rheumatic diseases in countries with high rates of tuberculosis.

A satisfactory balance between benefits and risks must be obtained when considering the use of prophylaxis. Isoniazid is an inexpensive drug (300 mg/day for 6 months has a total cost of US$ 28 in Mexico). It is easily administered once a day, its use does not add any significant costs to the follow-up, and adverse reactions to isoniazid are infrequent, with the majority reverting upon discontinuation of the treatment. Alterations in liver functioning occurred in 2 out of the 7 cases and in none of the 42 controls taking isoniazid; none of the deaths documented were attributable to isoniazid. The observed frequency of hepatotoxicity was 4%, which is higher than that reported in a large series drawn from the general population (0.1 to 2.8%) (29). The existence of concomitant diseases, hypoalbuminemia, and multiple drug use could explain the higher toxicity seen in our study.

A special comment should be made with regard to PPD reactivity in patients with rheumatic diseases, especially patients with SLE. Such patients frequently have a false negative PPD result due to immune system dysfunctions and the drugs they are taking for treatment, primarily steroids (7). Therefore, we evaluated the effect of isoniazid prophylaxis in patients with rheumatic diseases and exposure to steroids, independently of whether they were PPD positive or PPD negative.

A special comment should also be made regarding exposure to the bacillus Calmette-Guérin (BCG) vaccine. In a retrospective study such as ours, based on clinical records, it is difficult to evaluate BCG vaccine exposure. However, in Mexico the BCG vaccine is administered at birth. In addition, results concerning the protective effect of the BCG vaccine are conflicting. A recent meta-analysis has shown that its efficacy against pulmonary tuberculosis may range from 0% to 80% in children (30). There is undisputed evidence that BCG protects against tuberculosis meningitis. This protective effect decreases with time, and is probably lost after ten years. In our study, the effect of BCG vaccine was not evaluated, but we estimate that it was low.

The results of this study suggest that, in countries with a high prevalence of tuberculosis, the use of isoniazid (300 mg/day for 6 months) in rheumatic patients with exposure to prednisone (> 15 mg/day for three or more months) is useful to prevent tuberculosis, independently of the results of the PPD test. However, a clinical controlled trial will be required to confirm this.

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