Increased Risk of Tuberculosis in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To quantify the risk of tuberculosis (TB) in an unselected sample of patients with rheumatoid arthritis (RA) compared to the risk in the general population.

Methods. The incidence of TB in the general population of Spain was obtained from the National Network of Epidemiological Surveillance reports. The incidence of TB was ascertained from a cohort of 788 patients with RA selected randomly from the registries of 34 participating centers throughout Spain. A patient was considered a TB case only if information about disease symptoms, microorganism identification, and TB treatment were confirmed in the clinical records. The relative risk of TB in RAwas calculated by dividing the standardized mean incidence of TB from 1990 to 2000 in the RAcohort by the mean incidence of TB in Spain during the same years.

Results. The mean incidence of TB in the general population of Spain from 1990 to 2000 was 23 cases per 100,000. Seven cases of TB were identified in the RAcohort, yielding a mean annual incidence (1990–2000) of 134/100,000 patients. The incidence risk ratio of pulmonary TB in patients with RAcompared to the general population is 3.68 (95% CI 2.36–5.92).

Conclusion. We found a 4-fold increased risk of TB infection in patients diagnosed with RA. These results might help to interpret the magnitude of the problem attributable to the introduction of new therapies in RA. (J Rheumatol 2003;30:1436–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TUBERCULOSIS RISK ASSESSMENT COMORBIDITY

Tuberculosis (TB) affects over 8 million people and causes 2 million deaths each year world-wide[1]. After a period of diminished activity in industrialized countries, TB emerged again as an enormous health problem with considerable social implications due to aging of population, migratory movements, and immunocompromised states caused by human immunodeficiency virus infection, various debilitating diseases, and the use of immunosuppressive drugs[2,3].

Patients with autoimmune rheumatic diseases, mainly systemic lupus erythematosus, but probably also rheumatoid arthritis (RA), are at higher risk of infections, including TB[4]. This increased risk is thought to be related to the immune disturbances caused by the disease itself, as well as to the treatment with immunosuppressive drugs[4]. There are many reports of opportunistic and non-opportunistic infections in patients treated with methotrexate, azathioprine, cyclophosphamide, cyclosporine, or corticosteroids[5-9]. Generalization in the use of these drugs has been accompanied by a clear rise in the rate of new and relapsing cases of TB in the last decade all over the world[10]. Introduction of new tumor necrosis factor (TNF)-alpha blockers for the treatment of rheumatic diseases has raised concerns about the risk of TB in these patients[11]. The problem arises when trying to quantify the risk of TB attributable to these new biological agents, as to date the risk of TB in typical patients with RA has not been measured.

Our objective was to quantify the rate of TB in an unselected RA sample before the widespread use of anti-TNF blockers compared to the rate of TB in the general population. The results might indicate the magnitude of the problem attributable to the introduction of new therapies in RA.

MATERIALS AND METHODS

In Spain, the National Network of Epidemiological Surveillance reports yearly the number of TB cases (pulmonary and meningeal) that come to the attention of the system. The incidence of TB is calculated each year by dividing the number of cases by the Spanish population. The mean incidence of TB in adults during the years 1990 through 2000, 23 cases per 100,000 population, was used as a reference[12,13] (Figure 1).

EMECAR (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide) is a mixed cohort study (prospective and retrospective)

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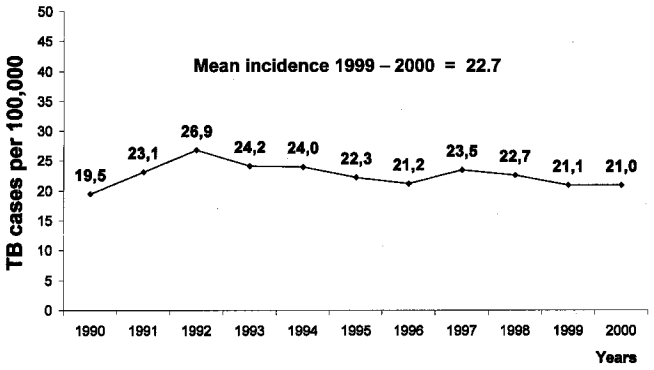

Figure 1. Incidence of pulmonary tuberculosis in adults from the general population in Spain over the last decade[12,13] (and data from the National Centre of Epidemiology).

supported by the Spanish Society of Rheumatology. EMECAR's objectives are to provide references of average measures of disease activity and progression of RA in our country, and to describe the frequency of comorbid diseases in rheumatoid patients, for comparison with other populations and to quantify the risk of specific comorbidity in RA. The cohort was assembled in 1998-99 by random selection of patients with RAfrom the clinical registries of 34 centers throughout Spain. RApatients ever diagnosed and registered in the participating clinics were randomly selected (total eligible population 13,260). A minimum sample size of 673 was calculated after a pilot study. Clinical records were reviewed to confirm RA classification criteria[14]. A strict contact protocol was followed to ensure participation of eligible patients. Ineligible patients (135 did not qualify as having RAby the inclusion criteria, 96 had died, and 328 were impossible to locate) were replaced by the next patients in the random list. Eighty-two successfully contacted patients expressed unwillingness to participate and were not replaced (response rate 90.5%). The study was approved by the Ethics Committee of Hospital La Princesa, Madrid. Participant rheumatologists were instructed in collecting the data and performing all measurements, according to standard definitions and procedures. Patients'clinical records were reviewed for all past and present relevant diseases including infections (by site and microorganism) and date of diagnosis. All data were cross-checked with the patients in personal interviews.

The definition of a TB case in both data sources was based either on documentation of a positive culture for *Mycobacterium tuberculosis* or on a compatible clinical picture responding solely to TB therapy.

Statistical analysis. The mean standardized incidence of TB during the last 10 years (1990 to 2000) in the EMECAR cohort was calculated. The standardization of each year's incidence by age and sex was performed using the Spanish population over age 16 (as no RApatients were below this age) in year 2000 as a reference. This standardization permitted estimation of an expected TB incidence rate if the patients were the same age and sex as the general population. To obtain each cohort year estimate, only patients who had already been diagnosed with RAby that year and had not previously been diagnosed with TB were included in the calculations.

The relative risk of TB in RAand 95% confidence intervals were calculated by dividing the standardized mean incidence of TB in the last 10 years in EMECAR (expected incidence) by the mean incidence of TB in the general population over age 16 reported in the same period. All analyses were performed in Stata, v.7 (Stata Corp., College Station, TX, USA).

RESULTS

Table 1 shows the characteristics of the 788 patients included in the EMECAR cohort. Seven TB cases were identified after the diagnosis of RA. Table 2 gives data for the incident TB cases, most of whom were women over age 60 with few years of formal education. The mean TB incidence in the EMECAR cohort (1990-2000) is 134 per 100,000 patients (95% CI 50–218). After standardization by age and sex, the mean incidence is 95 cases per 100,000 patients. If only pulmonary cases are considered, the incidence is 85 per 100,000. The mean incidence of TB (pulmonary and meningeal) in the 1990-2000 decade in the general population over age 16 is 23 per 100,000 (Figure 1), with 94% corresponding to pulmonary TB. When compared to the rate in the general population during the same period, the incidence risk ratio (IRR) of TB (any location) in RA is 4.13 (95% CI 2.59–6.83), and for pulmonary TB, the IRR is 3.68 (95% CI 2.36–5.92).

DISCUSSION

Our results reveal a 4-fold increased risk of tuberculous disease in patients diagnosed with RA compared to the risk in the general population of Spain. This quantification is particularly useful to estimate the risk of TB attributable to new therapies for RA. If we found that the risk of TB in RA patients undergoing biological therapies were greater than 4, and clearly if greater than 7, when compared to the general population rates, this should be interpreted as attributable to the new treatment, and not to RA.

A better study design to investigate this question would have been either a prospective or a case-control study, but a quantification of the risk of TB in a baseline RApopulation was needed urgently, following reports of the number of TB cases in RA patients taking TNF-α blockers[12]. Actually, the EMECAR initiative was undertaken before the marketing of these drugs in Spain, and was designed to assess the risk of TB, among other comorbidities, prospectively. All risk estimations will very probably be compromised to some extent in the coming years by the increasing use of TNF-α blockers in rheumatoid patients.

The strengths of a study rely on the country where it was carried out. Spain has universal coverage by the public health system, thus any random selection of patients ever registered at public centers will likely yield a representative sample of Spanish patients with RA. Moreover, the rate of TB in Spain is higher than in other Western countries, and consequently the exposure of RA patients to tuberculosus bacilli is high as well, providing a sufficient number of events to allow quantification. This is probably the reason why a US study did not find a clear association of TB with RA[15], as the rate of TB reported in the US is low compared to the Spanish rate, only 6.8 cases per 100,000.

The real incidence of TB in Spain may be slightly higher than that reported, due to under-reporting of pulmonary cases and non-obligation to declare extrapulmonary TB other than meningeal[16]. In the EMECAR cohort, we take into account all cases of TB, irrespective of the location. If the percentage of unreported extrapulmonary TB in Spain were around 20% as described[17-19], we could recalculate the

Table 1. Sociodemographic and clinical characteristics of patients included in the EMECAR cohort.

Variable	Frequency, %	Mean ± SD	Median*
Women	72.1		
Positive rheumatoid factor	73.7		
Age at baseline visit, yrs		61 ± 13	64 (54–71)
Age at RAonset, yrs		48 ± 15	49 (37–59)
Disease duration, yrs		10.1 ± 7.9	9 (4–13)
Early arthritis, < 2 yrs	14.4		
Disease activity, DAS28 3		4.09 ± 1.39	4.06 (3.12–5.11)
Functional status, HAQ		1.6 ± 0.4	1.6 (1.2–1.9)
DMARD treatment	72		

* 25th–75th percentile. DAS: Disease Activity Score. HAQ: Health Assessment Questionnaire. DMARD: disease modifying antirheumatic drug.

Table 2. Characteristics of the 7 TB cases found in the RAcohort.

Sex	Age at RA Diagnosis, yrs	Age at TB Diagnosis, yrs	Location of TB	RF	Rheumatoid Nodules	Extraarticular RA	Smoker (yrs)	Time Taking CS if > 3 mo	DMARD	Concomitant Disease
F	71	75	Lung	+	No	Yes	No	5–10yrs	GSim, CLQ, MTX, CF, CLO	Cytopenia
F	67	74	Lung	–	No	No	No	5–10yrs	GSim, CLQ, D-PEN, MTX, CF, CLO	Leukopenia
F	55	75	Lung	+	No	Yes	No	5–10yrs	GSim, CLQ, MTX oral GS, GSim	Anemia
F	51	65	GD	–	No	Yes	No	> 10yrs	HCQ, MTX	None
M	33	63	Pleural	+	Yes	Yes	Yes (30)	0	CLQ	DM, COPD
M	29	76	Lung	+	Yes	Yes	Yes (50)	0	MTX	Anemia, cancer
F	42	45	Lung	+	Yes	Yes	No	> 10yrs	SSZ, MTX	Anemia

TB: tuberculosis; RF: rheumatoid factor, CS: corticosteroids, DMARD: disease modifying antirheumatic drugs, GS: gold salts (oral or intramuscular), CLQ: chloroquine, HCQ: hydroxychloroquine, MTX: methotrexate, CYC: cyclosporine, CLO: chlorambucil, D-PEN: D-penicillamine, AZA: azathioprine, CF: cyclophosphamide, SSZ: sulfasalazine, GD: gastroduodenal, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease.

risk of TB in RA by increasing the incidence in the general population to 29 cases per 100,000, and the risk ratio would still be greater than 4-fold. It is also possible that some patients in our cohort had undiagnosed TB disease or, if diagnosed and treated elsewhere, that the patient had forgotten the episode when asked about infections, especially if mild. This means that errors may occur in both data sources, and likely in the same direction; therefore obtaining a risk ratio is the optimal measure of the likelihood of TB in patients with RA.

The number of TB cases in the cohort was too small to draw any conclusion on the underlying reason for the increased risk, and no further analysis to test associations with any variable was attempted. This would be more adequately addressed by a case-control study. There are, however, 2 possible explanations for the increased rate of TB in RA. First, a causal relationship between mycobacterial infection and RA remains to be elucidated[20-24]. On the other hand, the debilitating and chronic nature of RA, the presence of comorbidity, the treatments used, or most likely a combined effect of all these factors, could predispose to TB infection. All but 2 patients with TB in our cohort had anemia or other cytopenias by the time of TB diagnosis, and one had diabetes and chronic obstructive pulmonary disease (Table 2). One patient developed a malignancy, but several years after the diagnosis of TB. No other known risk factors such as recent infection, chronic renal disease, or acquired immune deficiency syndrome were present. Regarding treatment, all TB cases in the cohort had received disease modifying antirheumatic drugs, although it is remarkable that one patient had received only chloroquine as single treatment when TB was diagnosed, and 2 had not received prolonged or high doses of corticosteroids. The risk of TB attributable to corticosteroid use has not been determined and remains controversial[7,25], although most authorities consider that patients taking more than 15 mg/day prednisone for 2–4 weeks are at risk for developing TB disease[26,27].

Patients with RAare at increased risk for developing TB. The potential reasons must be analyzed with a different study design, although it is likely that immunosuppression from medication and from debilitation secondary to longstanding RA are important risk factors. The implications of this risk require awareness both when initiating any

immune-suppressive medication, and when uncontrolled inflammation is debilitating the patient with RA.

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APPENDIX

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