

Treatment of Rheumatoid Arthritis With Tumor Necrosis Factor Inhibitors May Predispose to Significant Increase in Tuberculosis Risk

A Multicenter Active-Surveillance Report

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Objective. The long-term safety of therapeutic agents that neutralize tumor necrosis factor (TNF) is uncertain. Recent evidence based on spontaneous reporting shows an association with active tuberculosis (TB). We undertook this study to determine and describe the long-term safety of 2 of these agents, infliximab and etanercept, in rheumatic diseases based on a national active-surveillance system following the commercialization of the drugs.

Methods. We analyzed the safety data actively collected in the BIOBADASER (Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología) database, which was launched in February 2000 by the Spanish Society of Rheumatology. For the estimation of TB risk, the annual incidence rate in patients treated with these agents was compared with the background rate and with the rate in a cohort of patients with rheumatoid arthritis (RA) assembled before the era of anti-TNF treatment.

Results. Seventy-one participating centers sent

data on 1,578 treatments with infliximab (86%) or etanercept (14%) in 1,540 patients. Drug survival rates (reported as the cumulative percentage of patients still receiving medication) for infliximab and etanercept pooled together were 85% and 81% at 1 year and 2 years, respectively. Instances of discontinuation were essentially due to adverse events. Seventeen cases of TB were found in patients treated with infliximab. The estimated incidence of TB associated with infliximab in RA patients was 1,893 per 100,000 in the year 2000 and 1,113 per 100,000 in the year 2001. These findings represent a significant increased risk compared with background rates. In the first 5 months of 2002, after official guidelines were established for TB prevention in patients treated with biologics, only 1 new TB case was registered (in January).

Conclusion. Therapy with infliximab is associated with an increased risk of active TB. Proper measures are needed to prevent and manage this adverse event.

Clinical trials of tumor necrosis factor (TNF) inhibitors have demonstrated significant efficacy in patients with rheumatoid arthritis (RA) refractory to existing disease-modifying antirheumatic drugs (1–3). Although no major side effects were reported during the clinical trials, a recent report (4) on the relationship between active tuberculosis (TB) and treatment with the TNF α inhibitor infliximab for Crohn's disease and RA stressed the need for long-term scrutiny of patients treated with these biologic response modifiers.

The wide use of TNF inhibitors for the treatment of RA and other conditions is based on a trade-off between benefit and risk. Hence, estimating the risk of

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TB associated with this treatment, together with designing strategies to prevent this worrisome complication, warrants serious consideration.

In close coincidence with the approval of infliximab for treating RA patients in Europe, the Spanish Society of Rheumatology (Sociedad Española de Reumatología [SER]) launched a database for the registration and active followup of patients with rheumatic diseases treated with biologic response modifiers. In the present report, we describe the adverse events registered over the last 2 years in a large cohort of patients with rheumatic diseases who have been treated with the 2 TNF inhibitors currently available, etanercept and infliximab. Special attention was given to the description of cases of active TB and to the risk for the infection compared not only with background rates in the population (5), but also with the infection risk for RA patients not treated with these biologic response modifiers (6).

PATIENTS AND METHODS

The BIOBADASER database. BIOBADASER (Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología) is a database established by the SER in February 2000 for the active long-term followup of patients with rheumatic diseases to assess the safety of biologic response modifiers in diseases. The registry, which is supported by the SER and funded in part by the Agencia Española del Medicamento, notes relevant adverse events occurring during treatment.

All hospital- and community-based Rheumatology Units in Spain were invited to participate. The protocol and notification materials with clear instructions were sent to the Chief-of-Service of every Rheumatology Unit in the country. The SER has maintained maximum dissemination of information regarding the project among all Spanish rheumatologists through 1) personal letters, 2) posting on the SER Web page, 3) notes in the Web distribution list in rheumatology, 4) the Society's *SER Bulletin*, 5) the Society's official journal (*Revista Española de Reumatología*), and 6) The Annual Meetings of the National and Regional Societies of Rheumatology in Spain. Full information regarding BIOBADASER can be found online at www.biobadaser.ser.es. A list of participating investigators and centers appears in Appendix A.

Patients registered in BIOBADASER are those with rheumatic diseases who are starting treatment with a biologic response modifier as well as those who were treated before the database was created (but for whom retrospective data are available [the earliest data are from January 1999]). At the time of this report, only the records of patients treated with infliximab and/or etanercept were entered into the database, since these were the only drugs available for clinical use in Spain.

Case definition and data analysis. Adverse events, their relative frequency per unit of time, and total numbers of patients and treatment starts (with either infliximab or etanercept), as well as time to treatment discontinuation, are

reported. Survival analysis was conducted with the use of life tables and reported as the cumulative percentage of patients still receiving medication (drug survival rate).

In BIOBADASER, a patient was classified as a TB case when *Mycobacterium tuberculosis* was isolated from any specimen obtained from a patient with an appropriate clinical picture. When necessary, physicians who reported a TB case were interviewed regarding the clinical presentation of the patient, results of the purified protein derivative (PPD) test and chest radiographs prior to starting therapy, previous treatment of latent TB infection, and concomitant medications at the time of active TB infection. The incidence rate (per 100,000 patient-years) and 95% confidence intervals (95% CIs) were calculated.

National rates of TB were obtained from the National Network of Epidemiological Surveillance (5). In order to compare the national (background) rate of TB with the rate of TB in the BIOBADASER population, the BIOBADASER sample was standardized by age and sex using the same strata for which there was information in the general population. TB rates in patients with RA not treated with the biologic agents were obtained from EMECAR (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide), which is a cohort study funded by the SER. The EMECAR cohort (6), descriptive of the RA patient population of Spain, was assembled in 1999 by random sampling from the clinical databases of 34 Rheumatology Units and is currently in the third year of followup. The sample includes 788 patients about whom information concerning clinical presentation, activity of the disease, progression of the disease, and comorbidity is prospectively collected. EMECAR patients are representative of the RA patient population of Spain, and their disease covers the entire spectrum of severity. To compare background TB rates in RA patients receiving versus those not receiving biologic treatment, only RA patients in the BIOBADASER database were compared with patients in the EMECAR cohort. No standardization was needed in this analysis, since the samples were comparable in age and sex.

RESULTS

As of February 2002, a total of 1,540 patients from 71 centers had been registered in the BIOBADASER database. The data prior to the initiation of the registry in February 2000 were retrospectively collected for 61 patients. Mean \pm SD followup was 1.1 ± 0.6 years; 840 patients were followed up for at least 1 year and 109 for at least 2 years. Seventy-two percent of the patients were women and had a mean \pm SD age of 51 ± 15 years and a diagnosis of RA (1,265 patients). Other common diagnoses were psoriatic arthritis (89 patients) and ankylosing spondylitis (76 patients). There are data on 1,578 treatment starts. In 38 patients, discontinuation of one agent was followed by initiation of therapy with the other. Most treatment starts were with infliximab (86%).

Therapy with the TNF inhibitor was discontinued

Table 1. Characteristics of patients with tuberculosis (TB) identified and reported to the BIOBADASER database*

Age/sex	Diagnosis	Location of TB	PPD test result†	Chest radiograph†	Prophylaxis	Evidence of previous TB‡	Months to active TB§	Concomitant medication
61/F	PsA	Lymph node	–	Normal	ND	–	3	MTX, CS
58/F¶	RA	Disseminated	–	Normal	ND	A	3	MTX, CS
70/F	RA	Lymph node	ND	Normal	ND	–	1	MTX, CS
54/F	RA	Lymph node	ND	ND	?	B	2	MTX, CS
52/M	RA	Pulmonary	ND	ND	ND	–	6	MTX
61/M	RA	Liver–spleen	–	Apical thickening	ND	–	4	MTX
56/F	RA	Pulmonary	ND	Normal	ND	–	12	MTX, CS, warfarin sodium
74/M	RA	Disseminated	–	Normal	?	–	3	MTX, CS
41/F	PsA	Pulmonary	?	?	?	–	4	MTX
56/F	RA	Lymph node	ND	Normal	ND	–	16	MTX
65/F	RA	Pulmonary	ND	Atelectasy	ND	–	17	MTX, CS, paroxetine
78/F¶	RA	Disseminated	?	?	?	–	2	MTX, CS
81/F	RA	Pulmonary	ND	ND	ND	C	3	MTX, CS
51/F	RA	Pulmonary	+	Apical granuloma	ND	D	7	MTX
60/F	RA	Lymph node	ND	ND	?	E	1	MTX
71/F	RA	Disseminated	ND	Normal	ND	–	3	MTX, CS
71/F	RA	Disseminated	–	Normal	ND	–	3	MTX, CS

* See Patients and Methods for a description of the BIOBADASER database. PPD = purified protein derivative; PsA = psoriatic arthritis; ND = not done; MTX = methotrexate; CS = corticosteroids; RA = rheumatoid arthritis; ? = unknown.

† Within the 2 months prior to starting infliximab therapy.

‡ A = interstitial fibrous tracts and calcified adenopathy on chest radiograph years before starting therapy; B = exposure to TB in childhood; C = interstitial pattern on chest radiograph in the past (a question of TB infection in childhood); D = treated previously for TB; E = underwent hysterectomy for TB 12 years prior to starting therapy.

§ From initiation of infliximab to diagnosis of active TB.

¶ Deceased.

on 228 occasions (14%), essentially due to adverse events. Drug survival rates for infliximab and etanercept pooled together were 98% at 1 month, 96% at 2 months, 91% at 6 months, 85% at 12 months, and 81% at 24 months. There were no differences in drug survival rates between infliximab and etanercept, although the number of patients treated with the latter agent was small.

There were infections in 118 patients, skin-related adverse events in 44, and postinfusion reactions to infliximab in 31. The lower respiratory tract was the leading site of infection (21% of patients), followed by the skin (13%), urinary tract (11%), and upper respiratory tract (9%). Ten patients developed sepsis. The microorganisms implicated in the infections were *M tuberculosis* in 17 patients, herpes zoster virus in 8, *Staphylococcus* species in 5, *Salmonella* species in 4, and unspecified bacteria in 15. No microorganism was reported in the remaining patients.

Fifteen patients with TB were diagnosed as having RA, and 2 additional patients with TB had psoriatic arthritis. All patients with active TB were being treated with infliximab, and 59% were diagnosed as having TB within 3 months of treatment initiation. Table 1 summarizes the main features of these patients. The site of active infection was extrapulmonary in 65% of patients. In 6 patients, the chest radiograph and PPD test results

were missing in the 2 months prior to starting therapy with the TNF inhibitor. Both the PPD test and chest radiographs had been performed in only 6 patients. In 4 patients, the chest radiographs showed normal results and the PPD test result was negative. Five patients had clinical or radiographic evidence of prior TB infection. The two-step PPD testing was not performed in any of the patients. Two patients died of their infections.

The estimated incidence of TB associated with infliximab was 1,893 cases per 100,000 patients in the year 2000 and 1,113 cases per 100,000 patients in the year 2001. Background TB incidence in Spain in the year 2000 was 21 cases per 100,000 inhabitants (5). In the EMECAR cohort (6), the estimated annual incidence of TB among RA patients not exposed to TNF inhibitors was 95 cases per 100,000 patients (age- and sex-adjusted with the Spanish population as reference and using the standardized mean incidence of TB between the years 1990 and 2000 [inclusive] in the EMECAR cohort). From these data, the calculated risk ratio (RR) of TB in patients with rheumatic diseases treated with infliximab compared with the background rate in the Spanish population was 90.1 (95% CI 58.8–146.0) in the year 2000 and 53.0 (95% CI 34.5–89.0) in the year 2001. This calculation assumes the same incidences in both years, since the report for 2001 was not available. In RA

patients who did not receive TNF inhibitors, the estimated RR of TB (adjusted for age and sex) was 4.13 (95% CI 2.59–6.83) relative to the background rate (6). The RR of TB in infliximab-treated RA patients versus RA patients not exposed to this therapy was 19.9 (95% CI 16.2–24.8) in the year 2000 and 11.7 (95% CI 9.5–14.6) in the year 2001.

DISCUSSION

To our knowledge, this is the largest observational study (based on a national registry) on the safety aspects of TNF inhibitors used in the clinical management of rheumatic conditions. The 81% drug survival rate after 2 years is similar to, or even greater than, that reported in extensive clinical trials (1–3). A recent study in an academic clinical center in the US estimated a 1-year survival rate of 50–70% for patients taking the soluble TNF receptor etanercept (7). Patients in our cohort are covered by the Spanish National Health System, which provides comprehensive care at no end-user cost to almost 100% of the population, and which includes free access to the clinical specialist. In some countries, the costs of the medication and followup care by specialists impose a significant economic burden on many patients and may contribute to early discontinuation of this expensive therapy. Whether the excellent drug survival rates reported in the present study reflect these issues remains to be confirmed.

Compared with an RA cohort from a similar patient population in the era before the approval of anti-TNF therapy, we observed a significant increase in the risk of TB in RA patients treated with infliximab. For RA patients in the pre-TNF inhibitor era, the data are somewhat equivocal (8–12). In our reference cohort of RA patients in Spain (the EMECAR study), a significant increase occurred (6). Patients included in this latter study were recruited from some of the hospitals that are currently providing data for BIOBADASER; hence, this cohort represents a valid group for comparison purposes. It seems that the major difference between the EMECAR and BIOBADASER cohorts is the nonexistence of biologic response modifiers when the former cohort was assembled.

The annual incidence rate of TB in Spain is in the upper range of what is considered a low rate by most investigators, but it remains 3–5 times higher than the rates in other European countries and the US. Genetic factors favoring disease reactivation or progression of the infection may be involved and can vary among ethnic groups. The Spanish Health Authorities

stress mandatory notification about TB cases. Still, there is the suspicion of certain undernotification. Nevertheless, studies in geographic regions where TB was actively sought did not show a significantly greater rate of TB compared with that from the National Network of Epidemiological Surveillance (13), and the rate of TB was clearly lower than that seen in the BIOBADASER cohort. It should be noted that the case definition in all data sets explored in the present report (BIOBADASER, EMECAR, and national rates from the National Network of Epidemiological Surveillance) is symptomatic TB infection.

In the present study, most of the reported cases of TB involved extrapulmonary sites of infection, and 2 resulted in death. In our study (Table 1), 7 patients could, in retrospect, have been considered to have latent TB. In 7 of the remaining 10 patients, a proper assessment of this infection was limited by the absence of relevant data. In the other 4 patients, the PPD test results were reported to be negative and the chest radiograph results were reported to be normal. Thresholds of 5-, 10-, and 15-mm diameters for a positive PPD skin test result have been proposed for different at-risk populations (14), with a diameter of ≥ 5 mm being considered positive for high-risk groups. The use of a higher cutoff point (>10 mm) for a case to be considered positive could have been the cause of the reported negative results in the present study, or perhaps, the patients may have lost their ability to react to tuberculin. In such a situation, two-step testing could produce a positive skin reaction (booster phenomenon). Nevertheless, exogenous reinfection can happen in heavily exposed, but otherwise healthy, individuals in geographic locations with a high background incidence of TB.

Of overriding concern arising from the findings of the present study is that patients with RA treated with

Table 2. Recommendations of the Spanish Health Authorities and the Spanish Society of Rheumatology regarding the management of TB risk in RA patients who are to undergo treatment with tumor necrosis factor inhibitors*

Patients in any of the following categories should be treated for 9 months with 5 mg/kg body weight (up to a maximum of 300 mg) of isoniazid daily:
History of untreated or partially treated TB, or exposure to an active case of TB
Chest radiograph showing residual changes indicative of prior TB infection
Reaction of >5 mm in diameter on PPD skin testing or on 2-step testing procedure (when initial PPD result is <5 mm in diameter), with an interval of 7–10 days between steps

* See Table 1 for definitions.

infliximab are at high risk for active TB and should be managed appropriately. In May 2001, the SER alerted Spanish rheumatologists and proposed recommendations regarding the management of latent TB in patients who were to undergo treatment with TNF inhibitors. Subsequently, in February 2002, the Spanish Health Authorities in collaboration with the SER presented their guidelines and recommendations (Table 2). It is noteworthy that our latest review of the BIOBADASER data in December 2002 showed no new cases of TB among the patients who had started treatment after February 2002. It is hoped that this signifies the success of the initiatives. Whether etanercept treatment shares this increased risk of TB is not known, because to date, our database includes only small numbers of patients treated with etanercept. Nevertheless, it has recently been reported that in the US, the number of TB cases in patients receiving etanercept is similar to the background incidence of TB (15).

Finally, the present study underscores the value of independent, active surveillance of new drugs following their introduction to the market. It also highlights the crucial role of cooperation between biomedical societies in the improvement of patient care.

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APPENDIX A: CONTRIBUTORS TO THE BIOBADASER DATABASE

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