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ORIGINAL ARTICLE

Risk of Tuberculosis in Patients Treated With Tumor Necrosis Factor Antagonists Due to Incomplete Prevention of Reactivation of Latent Infection

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Objective. **To evaluate the causes of new cases of active tuberculosis (ATB) in patients treated with tumor necrosis factor (TNF) antagonists included in the national registry BIOBADASER (Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología) after the dissemination of recommendations to prevent reactivation of latent tuberculosis infection (LTBI).**

Methods. **Incidence rate of ATB per 100,000 patient-years and 95% confidence intervals (95% CIs) were calculated in patients entering BIOBADASER after March 2002 and were stratified by compliance with recommendations (complete or incomplete). ATB rates in BIOBADASER were compared with the background rate and the rate in the rheumatoid arthritis cohort EMECAR (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide) not treated with TNF antagonists. In addition, rates of ATB among patients treated with adalimumab, etanercept, and infliximab were estimated and compared only for treatments started after September 2003, when all 3 drugs became fully available.**

Results. **Following March 2002, a total of 5,198 patients treated with a TNF antagonist were registered in BIOBADASER. Fifteen ATB cases were noted (rate 172 per 100,000 patient-years, 95% CI 103–285). Recommendations were fully followed in 2,655 treatments. The probability of developing ATB was 7 times higher when recommendations were not followed (incidence rate ratio 7.09, 95% CI 1.60–64.69). Two-step tuberculosis skin test for LTBI was the major failure in complying with recommendations.**

Conclusion. **New cases of ATB still occur in patients treated with all available TNF antagonists due to lack of compliance with recommendations to prevent reactivation of LTBI. Continuous evaluation of recommendations is required to improve clinical practice.**

KEY WORDS. Infliximab; Etanercept; Adalimumab; Tuberculosis; Compliance; Guidelines.

INTRODUCTION

The use of tumor necrosis factor (TNF) antagonists is accompanied by an increased risk of active tuberculosis (ATB). In February 2000, the Spanish Society of Rheumatology (SER) launched an active pharmacovigilance registry of patients treated with TNF antagonists for rheumatic diseases, named BIOBADASER (Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología). The risk of ATB in this registry was reported previously (1). In February 2002, a collaborative effort between the SER and health authorities resulted in recommendations for the screening and treatment of patients with latent

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tuberculosis infection (LTBI) who were going to be treated with TNF antagonists. The recommendations include 9 months of isoniazid (INH) treatment for patients falling into one of the following categories: 1) a tuberculin skin test (TST) result ≥5 mm or a 2-step TST result ≥5 mm (if the first result was <5 mm); 2) a chest radiograph showing evidence of past tuberculosis; and 3) exposure to ATB or prior partially treated ATB. The significant impact of these recommendations was published elsewhere (2). Following this salient impact, new ATB cases were reported at a much lower rate. Lack of compliance with recommendations was identified in some ATB cases, and therefore a full investigation of all cases registered in BIOBADASER from February 2002 to date was conducted, with special attention to the management of ATB risk prior to initiation of TNF antagonists.

Although the risk of ATB seems to pertain to all 3 available agents, it has been suggested that infliximab and adalimumab carry a higher risk than etanercept. Nevertheless, direct comparison has never been reported. At the time of our first report (1), all patients with ATB had been treated with infliximab, which was accessible earlier than etanercept and adalimumab in our setting. Interestingly, the most recent ATB cases occur in patients treated with all 3 antagonists.

The present guidelines for the use of TNF antagonists in patients with rheumatoid arthritis (RA) proposed by the SER do not include specific indications for the selection of one antagonist over another. Therefore, indication for the use of any TNF antagonist is based on patient and/or physician preferences. In addition, TNF antagonists are provided free of charge to all patients by the national health system in Spain. We believe that the distinct risks of ATB in this population treated with the different agents would correspond to a head-to-head comparison rather than a selection bias in the setting of a homogenous background and free prescription. In the present report, we present the results of the investigation of the impact of compliance with recommendations to prevent reactivation of LTBI and the comparison of the risk of ATB among patients treated with adalimumab, etanercept, and infliximab. Participating investigators and centers are listed in Appendix A.

PATIENTS AND METHODS

A detailed description of BIOBADASER has been previously published (3) and is also available at http://biobadaser.ser.es/. In brief, BIOBADASER is a registry established in February 2000 for active long-term followup of the safety of biologic response modifiers. The registry, which is supported by the SER and funded, in part, by the Spanish Medicines Agency, notes relevant adverse events occurring during and after treatment.

BIOBADASER registers patients with rheumatic diseases being treated with any of the currently approved biologic response modifiers, and comprises ~50% of this group of patients in Spain. Patients treated with adalimumab, etanercept, infliximab, anakinra, and rituximab have been included up to the present. The following data

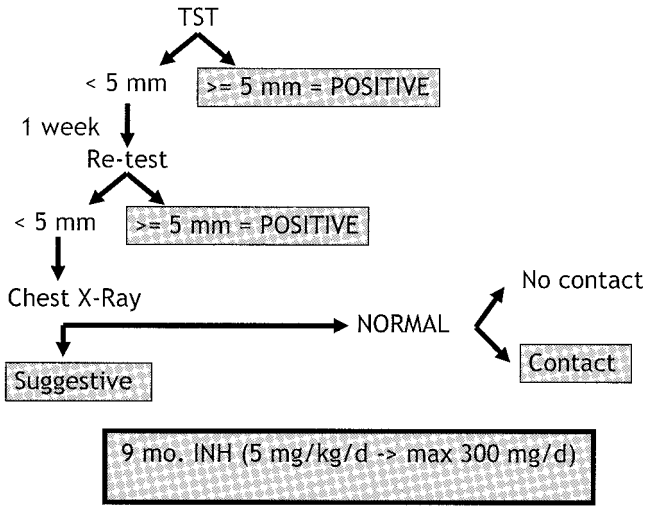

Figure 1. Algorithm of recommendations of the Spanish Society of Rheumatology to prevent active tuberculosis infection in patients to be treated with tumor necrosis factor antagonists. Shaded areas indicate where treatment with isoniazid (INH) is recommended. TST = tuberculin skin testing.

are collected systematically: 1) patient data including sex, date of birth, diagnosis, and date of diagnosis; 2) data on treatment, including type, start date, and discontinuation date together with reason for discontinuation, if applicable; and 3) data regarding adverse events, such as type, date of occurrence, outcome, comorbid conditions, and concomitant medication. Starting March 1, 2002, when recommendations from the SER regarding prevention of reactivation of LTBI in patients treated with TNF antagonists were issued (Figure 1), results from TST, chest radiograph, and therapy for LTBI were also registered.

To guarantee confidentiality, BIOBADASER does not include data that can possibly identify individual patients. The registry protocol and materials were approved by the Spanish Medicines Agency, and data regarding patients are gathered according to the present official regulations on data protection.

Incompleteness and agreement of data with patient charts are assessed on site by annual audits of random samples of 10% of all registered patients. A total of 665 clinical records from 82 centers were reviewed in the last audit before the present analysis; 14% of the records contained errors. All errors were corrected accordingly, yielding an expected underreporting of 11% of discontinuations or adverse events. Data on 12 centers that did not report relevant data actively in the last 2 years and that were detected after random monitoring were censored at the last valid data entry.

For the purpose of the present analysis, full compliance was considered when 1) INH treatment was started in patients with a TST result >5 mm (either the first test or the retest); 2) INH treatment was started in patients with a chest radiograph compatible with past tuberculosis; and 3) TST retest was performed following a negative TST result, or chest radiograph was performed despite negative TST and TST retest results. In all other cases, recommendations were considered to be incompletely followed.

Recording of adverse events is done online. An ATB

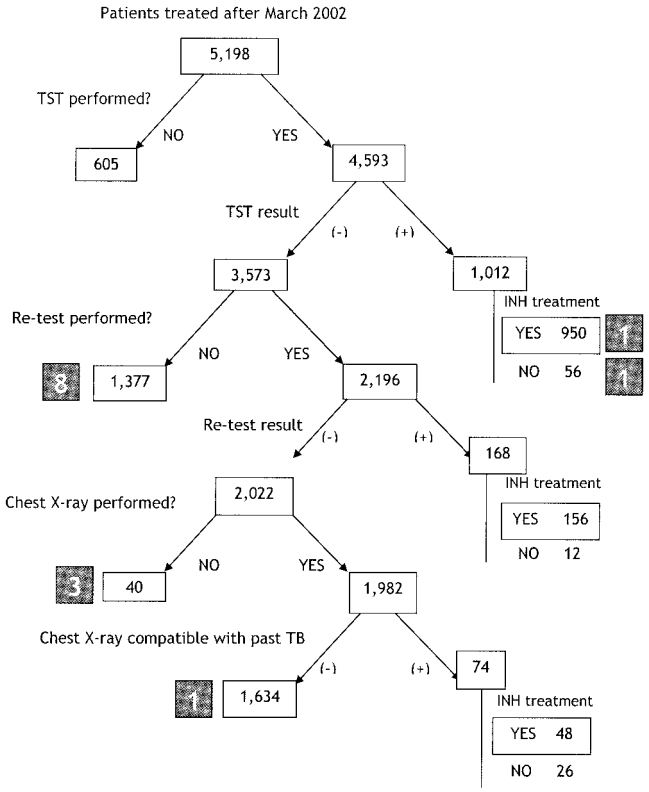

Figure 2. Compliance with Spanish Society of Rheumatology recommendations (February 2002) to prevent active tuberculosis (ATB) with tumor necrosis factor antagonists. Cases of ATB are shown in the shaded boxes. TST = tuberculin skin testing; INH = isoniazid.

case was considered when *Mycobacterium tuberculosis* isolated from any specimen was noted in a patient with an appropriate clinical picture. When necessary, physicians who reported a tuberculosis case were questioned regarding the clinical presentation of the patient, results of the TST, chest radiograph status prior to starting therapy, previous treatment of LTBI, and concomitant medications at the time of ATB infection. The incidence rate (IR) of ATB per 100,000 patient-years and 95% confidence intervals (95% CIs) were calculated in patients entering BIOBADASER after March 2002 and were stratified by compliance with recommendations (complete or incomplete). ATB rates in BIOBADASER were compared with the rate in Spain (4) and the rate in a previously described cohort of patients with RA not exposed to TNF (5). In any case, rates were compared to estimate the relative risk of ATB. Incidence rate ratio (IRR) was calculated as IR of the exposed group divided by IR of the nonexposed group. In addition, the rate of ATB among patients treated with adalimumab, etanercept, and infliximab was estimated and compared only for treatments started after September 2003, when all 3 drugs became fully available.

RESULTS

A total of 5,198 patients were treated with a TNF antagonist after March 2002, and 3,088 were treated for the first time after September 2003.

ATB cases after dissemination of recommendations for screening and treatment of patients with LTBI to be treated with TNF antagonists. TST was performed in 4,593 patients (Figure 2), and TST results were ≥5 mm in 1,012. Of these 1,012 patients, 950 were treated with INH. Of 950 patients, 1 developed ATB. There was an additional ATB case among the 56 patients not treated with INH.

TST retest was performed in 2,196 of the 3,573 patients (Figure 2) who had a TST result <5 mm, and the TST retest result was ≥5 mm in 168 patients. Of these 168 patients, 156 were treated with INH and 12 were not treated. There was 1 case of ATB in this latter group. Among those 1,377 patients in whom retest was not performed, there were 8 ATB cases.

Chest radiograph was performed in 1,982 of the 2,022 patients with a TST retest result <5 mm (Figure 2). Chest radiograph showed evidence of prior tuberculosis infection in 74 patients. Of these, 48 were treated with INH. There were no cases of ATB in the 74 patients. None of the patients with normal chest radiograph and TST test result <5 mm developed ATB. Three cases of ATB also occurred in 40 patients in whom chest radiograph was not performed.

Eight women and 7 men with ATB (mean ± SD age 54 ± 15 years and 53 ± 15 years, respectively) were registered

Table 1. Evolution of the incidence rate (IR) of active tuberculosis (ATB) per 100,000 patient-years in treatments started before and after the issue of the recommendations*

Treatment started	Patient-years	Cases	IR (95% CI)	IRR vs. general population (95% CI)†	IRR vs. RA not exposed to TNF blockers (95% CI)‡
Before March 2002	8,671	41	472 (384–642)	19 (11–32)	5.8 (2.5–15.4)
After March 2002-January 2006	8,717	15	172 (103–285)	7 (3–13)	2.4 (0.8–7.2)
100% compliance	4,546	2§	43 (11–175)	1.8 (0.28–7.1)	Undetermined¶
<100% compliance	4,170	13	311 (181–536)	13 (6–25)	4.8 (1.04–44.3)

* IRR = incidence rate ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; TNF = tumor necrosis factor.
† IRR compared with the rate of ATB in the general population of Spain (25 cases per 100,000 [4]).
‡ IRR compared with the rate of ATB in an RA cohort not exposed to TNF antagonists (90 per 100,000 [14]). Only patients with RA are compared.
§ In 1 case recommendations were followed but the patient did not take isoniazid properly. In another case, tuberculin skin testing and retest results were negative, and the chest radiograph did not show lesions compatible with past tuberculosis.
¶ No cases of ATB occurred among RA patients (5,209 patient-years).

Table 2. Description of patients treated with tumor necrosis factor antagonists after September 2003*

	Infliximab		Etanercept		Adalimumab	
	No cases (n = 1,137)	ATB cases (n = 5)	No cases (n = 1,336)	ATB cases (n = 2)	No cases (n = 615)	ATB cases (n = 1)
Age, mean ± SD years	49 ± 14	68 ± 7	51 ± 14	48 ± 7	54 ± 13	59
Men, no. (%)	534 (47)	3 (40)	537 (40)	2 (100)	140 (23)	1
Rheumatoid arthritis, no. (%)	453 (40)	4 (80)	670 (50)	1 (50)	542 (88)	1
Time to develop ATB from treatment start		1.2–8.7 months		<2.5 months		1 year, 2 months

* ATB = active tuberculosis.

in BIOBADASER, corresponding to a rate of 172 cases per 100,000 patients-years (95% CI 103–285). Six had active pulmonary infection, 6 had disseminated infection, and 1 had renal infection. Five patients were hospitalized and no patients died. The relative rate of ATB compared with the rate in the general population and the rate in an RA cohort not exposed to TNF antagonists is shown in Table 1. This is an update of a previously published table (2) and includes the rate of ATB stratified by compliance with recommendations. Recommendations were followed in 2,655 treatments started after March 2002 (51.1). The probability of developing ATB was 7 times higher when recommendations were not followed (IRR 7.09, 95% CI 1.60–64.69). The estimate of the risk difference between compliant and noncompliant groups was 268 (95% CI 88–448).

INH treatment was administered to a total of 1,292 patients and 16 had a relevant elevation of liver enzymes leading to discontinuation of the drug. No hospital admissions or deaths secondary to liver toxicity were communicated.

ATB cases by TNF antagonist after September 2003. A brief description of the patients starting TNF therapy for the first time after September 2003 stratified by TNF antagonists is shown in Table 2, and the rate of ATB in these patients stratified by TNF antagonists is shown in Table 3. There was not a significant difference in the rate of all 3 biologic agents. The statistical power for 2-sample comparison to detect differences between infliximab (highest incidence rate) and etanercept (lowest incidence rate) was 0.2264.

DISCUSSION

In the present study, we investigated the impact of adherence to recommendations on preventing reactivation of LTBI and compared the risk of ATB among patients treated with adalimumab, etanercept, and infliximab. We found that lack of compliance with local recommendations—in our setting issued in March 2002 by the SER—was associated with new cases of ATB.

Table 3. Incidence rate (IR) of active tuberculosis stratified by tumor necrosis factor (TNF) antagonist after September 2003*

TNF antagonist	Patient-years	Cases	IR per 100,000 (95% CI)
Infliximab	1,303	5	383 (159–921)
Etanercept	1,740	2	114 (28–459)
Adalimumab	565	1	176 (24–1,254)

* 95% CI = 95% confidence interval.

We gathered our data from a voluntary registry, a type of registry faced with certain limitations. To be reliable, data must be of high quality (6). The quality of our database is ensured by a clear definition of its purpose, an optimized number of variables, and an easy method of data collection that allows consistency checks. In situ and online audits of collected data disclose 14% incompleteness, predicted in a voluntary event-based registry (7). Considering this 14% incompleteness in our analysis, the lowest IR for the noncompliant group would be 268.1 (95% CI 149.1–481.8) and the highest IR for the compliant group would be 50.1 (95% CI 13.7–183.6). These would produce an IRR of developing ATB for the noncompliant group of 5.346 (95% CI 1.29–22.21). To improve clinical practice based on scientific evidence, the source of the problem to implementation of guidelines or recommendations has to be identified (8). Implementation failures commonly relate to factors extrinsic to the guidelines; however, intrinsic factors contribute as well (9–11). In a previous study, we estimated that in roughly 20% of patients in BIOBADASER, the physician failed to follow recommendations to manage LTBI, and we wondered about the future impact of this setback on the rate of new ATB (2). A straightforward explanation was not identified, although we believed that the increasing surplus of work represented for these new therapies was at play. In our study, TST 2-step testing for LTBI appeared to be the major barrier to complying with recommendations that have been shown to be effective. Interestingly, low compliance with guidelines to prevent ATB among patients with human immunodeficiency virus infection has also been reported, owing also to the low proportion of persons undergoing a TST (12). Ambiguity or softly supported evidences are among the intrinsic reasons that contribute to failure to follow recommendations, and this may be the case regarding the recommendations for TST. In schoolchildren, BCG vaccination does not interfere with diagnostic TST, and TST is a useful tool in assessing the risk of tuberculosis infection (13–15). Furthermore, the effect of BCG vaccination on positive TST in adults ages >30 years is probably negligible (16). Also, in countries with a high prevalence of tuberculosis, positive TST response and positive retest in adults is caused by latent tuberculosis rather than previous vaccination (17). All in all, TST and TST retest seem to be valuable tools for

evaluation of tuberculosis in countries with a high prevalence rate of ATB. In 8% of the patients in whom 2-step testing was performed following a negative TST result, the second test result was positive. In a population such as ours, with a high background annual rate (25 per 100,000), this may represent a true prior exposure to *Mycobacterium* infection rather than vaccination. Nevertheless, this assumption may be questioned and may hamper our recommendations. Cost-effective alternatives to TST in selected populations are the interferon-γ release assays (18). However, these tests have not been validated in populations that are immune compromised by the disease itself or by medications, as is the case in RA. Validation of this test is critical in RA and other chronic inflammatory diseases.

Membrane-bound TNFα seems to provide major protection against *Mycobacterium* infection in mice models (19,20). The dissimilar affinity for this membrane-bound TNFα is proposed to explain the different reported rates of ATB among TNF antagonists in humans. Monoclonal antibodies have both a higher affinity for membrane-bound TNF and a larger risk for ATB than does etanercept (21,22). In our study, there were cases of ATB with all 3 TNF antagonists; however, taking into account the low power (0.22) of our work to detect significant differences in the rates, this issue remains unsettled. We suggest that in populations at high risk for tuberculosis, similar precautions regarding treatment of patients who are going to be treated with all 3 available agents should be taken.

In summary, new cases of ATB still occur in patients treated with all available TNF antagonists due to lack of compliance with recommendations to prevent reactivation of LTBI. Continuous evaluation of recommendations is required to improve clinical practice.

AUTHOR CONTRIBUTIONS

Dr. Gómez-Reino had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study design. Gómez-Reino, Carmona.
Analysis and interpretation of data. Gómez-Reino, Carmona.
Manuscript preparation. Gómez-Reino, Carmona.
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APPENDIX A: PARTICIPATING INVESTIGATORS AND CENTERS

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