Adalimumab, Etanercept, Infliximab, and the Risk of Tuberculosis: Data from Clinical Trials, National Registries, and Postmarketing Surveillance

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ABSTRACT. This review evaluates the risk of tuberculosis (TB), adherence with recommendations for TB prevention, and host-related risk in patients with rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis receiving infliximab (IFX), adalimumab (ADA), and etanercept (ETN) through an analysis of phase III randomized controlled trials (RCT), postmarketing surveillance, and national registries. Ten (0.21%) TB cases occurred among 4590 patients in 16 RCT of IFX, 9 (0.12%) among 7009 patients in 21 RCT of ADA, and 4 (0.05%) among 7741 patients in 26 RCT of ETN. Overall, 19/23 (83%) TB cases occurred in patients with RA. Data from national registries and postmarketing surveillance showed an increased risk of TB in patients receiving any of the 3 anti-tumor necrosis factor (TNF) drugs, with a 3–4 times higher risk associated with IFX and ADA than with ETN. Deviations from recommended TB prevention procedures were observed in up to 80% of patients, and most registries did not include data on host-related risk factors for TB. TB occurrence was reduced in recent RCT but not in real-life practice. TB risk was lower for ETN than for monoclonal antibody anti-TNF agents. More complete data collection, including host-related TB risk factors, is advisable to avoid biased results. (J Rheumatol Suppl. 2014 May; 91:47–55; doi:10.3899/jrheum.140102)

Key Indexing Terms:
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During the past 15 years, 3 inhibitors of tumor necrosis factor-α (TNF-α) — infliximab (IFX), adalimumab (ADA), and etanercept (ETN) — have emerged as effective therapies in patients with rheumatic disorders including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Significant pharmacological characteristics differentiate the 3 TNF-α inhibitors. Both IFX and ADA are monoclonal antibodies (mAb, the former chimeric and the latter fully humanized) directed against TNF, while ETN is a fusion protein that functions as a soluble receptor blocking TNF-α interaction with cell surface receptors[1]. Because TNF blocking facilitates the progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB) by interfering with different steps in the immune response against *Mycobacterium tuberculosis*[2], the risk of active TB development could be increased in association with the use of TNF inhibitors. Over a few years following approval of IFX for treatment of RA, 84 cases of active TB occurred in about 170,000 patients treated worldwide between August 1998 and June 2001[3]. Consequently, the drug labeling was revised by Centocor Inc. in October 2001 with the addition of a boxed warning containing the recommendation to evaluate patients for LTBI before starting IFX therapy. Successively, ADA and ETN were also demonstrated to increase the risk of TB reactivation[4,5]. However, probably owing to different pharmacological properties, data from clinical trials seem to indicate a higher TB risk for the mAb anti-TNF agents, IFX and ADA, than for ETN[6].

To reduce the risk of TB reactivation, various countries have proposed several sets of recommendations/guidelines for the management of patients before starting anti-TNF therapy[7,8,9,10,11,12,13,14,15,16,17,18,19]. These recommendations may not be appropriate for countries other than the ones in which they originated because of different social and economic conditions and the variable prevalence of TB infection. In addition, most of the current recommendations raise some concerns because they do not take into account host-related risk factors or risks related to previous or concomitant therapy. Moreover, there are some differences regarding the duration of therapy for TB reactivation and the delay in starting anti-TNF-α treatment after initiation of prophylaxis.

The objective of this review is to evaluate the risk of TB reactivation in patients with RA, PsA, or AS treated with

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IFX, ADA, or ETN after introduction of LTBI screening recommendations. Data were extracted from published randomized controlled clinical trials (RCT), their open-label extension phases, national registries or databases of biologics, and postmarketing surveillance records. Moreover, we assessed adherence to current recommendations for LTBI detection and active TB prevention as resulting from the clinical trials and registries. Finally, because several host-related characteristics have been identified as increasing the probability of the occurrence of TB[20], we also evaluated the available information related to these additional risk factors.

IFX-related Risk of TB

Since October 2001, data from 9 RCT involving 3578 patients with RA[21,22,23,24,25,26,27,28,29], 3 RCT involving 419 patients with PsA[30,31,32], and 4 RCT involving 593 patients with AS[33,34,35,36] have been published.

As a consequence of LTBI screening recommendations, a relatively low number of cases of TB reactivation were recorded in clinical trials of IFX in RA, PsA, and AS, including the open-label extension phase studies[37,38,39]. Overall there were 10 (0.21%) cases of TB, 8 in patients with RA[21,25,37], and 1 case each in those with PsA[32] and AS[33]. A careful analysis of these cases raises some considerations. First, most of the multicenter trials were conducted worldwide, with marked differences in TB risk among the different countries, hence overshadowing the additional risk for developing TB. In this regard, even when the trials were designed to assess the safety of IFX[27], the description of TB cases was generally poor without indications of the country in which the adverse event was recorded and without information on the coexistence of additional TB risk factors. Second, most TB cases were recorded in RA trials, suggesting that the underlying disease and probably the previous immunosuppressive treatment may constitute adjunctive risk factors for TB reactivation. Indeed, patients with PsA and AS usually have a less heavy background of immunosuppressive therapies compared to patients with RA. Finally, defective screening procedures for LTBI were reported in 3 patients[25,32], and 1 case occurred in a country at intermediate risk of TB (Argentina)[25].

Nevertheless, in spite of the reduced risk recorded in clinical trials after introduction of procedures to detect LTBI and prophylaxis against TB, as shown in Table 1, an increased risk of TB reactivation in patients treated with IFX was confirmed by data from national registries and postmarketing surveillance. With the exclusion of data from BIOBADASER 2003[40], ARTIS 2005[41], Pharmetrics 2006[43], and LOHREN 2009[46], including patients treated before the October 2001 recommendations, an incidence rate was recorded ranging from 17 to 716 cases/100,000/year (median: 284.5), with a significantly increased relative risk compared to the incidence of active TB in the respective countries. However, there are some concerns regarding possible biases in these data. In general terms, the reports from registries and postmarketing surveillance do not provide details about host-related risk factors including ethnicity, malnutrition, drug abuse, comorbidities, contact with infected persons, correct adherence to LTBI screening procedures, and therapy to prevent active TB. These factors, with the exception of data on LTBI screening procedures, were carefully analyzed in a recent study based on data from the Kaiser Permanente Northern California registry[51]. Confirming previous data[20], a 2- to 3-fold increased risk of active TB was found in patients with RA of Hispanic ethnicity or with comorbidities such as diabetes or chronic renal disease. Unfortunately, the risk associated with current assumption of nonbiologic therapies was not calculated in that study.

When reported[44,45,46,47,48,49], defective LTBI screening procedures, inadequate TB prophylaxis, or both were detected in up to 80% of the cases, with those patients having an estimated 7 times higher probability of developing active TB compared to patients undergoing appropriate investigations[44].

Despite some relevant biases concerning data collection and adherence to local recommendations for TB prevention, data from postmarketing surveillance and national registries indicate that IFX consistently increases the risk of TB reactivation, and a careful evaluation of additional risk factors together with proper screening for LTBI is mandatory before IFX therapy is started.

ADA-related Risk of TB

The efficacy and safety of ADA have been investigated in 14 RCT involving 5658 patients with RA[52,53,54,55,56,57,58,59,60,61,62,63,64,65], 5 RCT involving 936 patients with AS and axial SpA[66,67,68,69,70], 2 RCT involving 415 with PsA[71,72], and 7 open-label extension phases of RCT[73,74,75,76,77,78,79]. All these trials were conducted after the October 2001 recommendations had been issued and all patients were screened for LTBI before study entry.

Overall, 9 cases of TB were identified, most of which occurred in patients with RA. Indeed, 7 of the 9 cases were observed in patients with RA[57,58,63,74,76]; 1 case occurred in a patient with PsA[78] and 1 in a patient with AS[70]. Of the recorded TB cases, only 2 occurred in trials lasting 24 weeks or less[63,70], and no details are available on 3 cases[63,70,78]. Of the remaining, 1 case occurred in a patient with negative screening for LTBI[57], and of the 2 cases observed in the 5-year extension phase of the PREMIER study[74], 1 occurred in a 49-year-old woman from the United States with a history of TB during childhood who had a positive tuberculin skin test (TST) and received only 6 months of isoniazid prophylaxis. Except for 1 case reported in a Chinese study[70], no information regarding the occurrence in TB-endemic countries could be identified.

Table 1. Infliximab and tuberculosis (TB) risk: data from postmarketing surveillance and national registries.

Source/Year [Reference]	No. TB Cases/ No. Patients	TB IR IFX/Country, No. Cases/100,000 Population/year	RR	Defective LTBI Screening/TB Prophylaxis	Data on Host-related TB Risk Factors (%)
BIOBADASER, Spain, 2003 [40]	15/1324	90	NA	Pre-LTBI scr*	NA
ARTIS, Sweden 2005, [41]	11/1565	145/NA	NA	Pre-LTBI scr*	NA
RABBIT, Germany 2005, [42]	1/346	289/8	36.1	NA	NA
Pharmetrics, Canada, 2006 [43]	19/1074	NA	NA	Pre-LTBI scr*	NA
BIOBADASER, Spain, 2007 [44]	5/1137	383/25	15.3	49%	NA
Japan, 2008 [45]	14/5000	280/25	11.2	0%	NA
LOHREN, Italy, 2009 [46]	3/519	278/8	34.7	Pre-LTBI scr*, 15.3%	NA
RATIO, France, 2010 [47]	41/NA	187/8.7	21.4	80%	66%
BSRBR, UK, 2010 [48]	39/3718	123/14	8.8	5%	70%
South Korea, 2011 [49]	2/78	540/69.8	7.7	50%	NA
GISEA, Italy, 2012 [50]	6/837	716/8	89	NA	NA
Northern California, USA 2013 [51]	8/5320	17/5	3.4	NA	NA

*Pre-LTBI screening: includes patients treated before 2001 recommendation for latent TB infection detection. NA: not available; LTBI: latent tuberculosis infection; RR: relative risk; IR IFX: incidence ratio in infliximab-treated patients.

Similarly to IFX, the paucity of TB cases recorded in clinical trials of ADA reflects the rigorous safety measures that are usually observed in these studies.

Data from clinical practice, a rather different context, show some discrepancies between the results from clinical trials and those of published, large cohorts of patients receiving ADA, postmarketing surveillance and national registries, settings in which the adherence to LTBI screening procedures is weak. Indeed, 21 patients developed active TB in a large cohort of 6610 patients with RA enrolled in a real-life, 12-week open-label study[80] conducted in 12 countries at low risk of TB[81]. Confirming the defective application of recommendations for TB prevention, 8 patients had a TST > 5 mm in diameter but only 3 of them received a complete course of isoniazid, while 1 stopped isoniazid after 6 months. According to local recommendations, isoniazid prophylaxis was not started in the other 4 patients because they had a TST < 10 mm in diameter.

As summarized in Table 2, the risk of TB in patients treated with ADA has been extensively evaluated in several reports based on data from postmarketing surveillance and national registries of biologics. All the registries showed an increased risk of active TB, with incidence rates ranging between 91 to 308 cases/100,000/year (median 203), significantly higher than the TB incidence rates recorded in the respective countries.

As previously discussed for data from national registries on the use of IFX, also for ADA the paucity of information concerning host-related risk factors and the correct procedures for LTBI detection and TB prophylaxis could have created some biases in the results, leading to an overestimation of the related TB risk. However, ADA-exposed patients are at increased risk of TB, and clinicians should carefully evaluate patients for LTBI and additional risk factors for TB before starting ADA therapy.

ETN-related Risk of TB

Evaluating articles published from 2002, we identified 26

Table 2. Adalimumab and tuberculosis (TB) risk: data from postmarketing surveillance and registries.

Source/Year [Reference]	No. TB Cases/ No. Patients	TB IR ADA/Country, No. Cases/100,000 Population/year	RR	Defective LTBI Screening/TB Prophylaxis, %	Host-related TB Risk Factors (%)
BIOBADASER, Spain, 2007 [44]	1/615	176/25	7.4	49%	NA
LOHREN, Italy, 2009* [46]	1/303	191/8	23.8	15.3%	NA
RATIO, France, 2010 [47]	23/NA	215/8.7	24.7	80%	66%
BSRBR, UK, 2010 [48]	20/4857	217/14	8.8	5%	70%
South Korea, 2011 [49]	1/66	308/69.8	4.4	50%	NA
GISEA, Italy, 2012 [50]	2/802	249/8	31.1	NA	NA
Japan, 2012 [82]	4/3000	133/25	5.3	NA	NA
Northern California, USA 2013 [51]	7/2338	91/5	18.2	NA	NA

Note: Differently from infliximab and etanercept, data on adalimumab from LOHREN were included because the drug was licensed after the October 2001 recommendations on LTBI and active TB prevention. NA: not available; LTBI: latent tuberculosis infection; RR: relative risk; IR ADA: incidence ratio in adalimumab-treated patients.

RCT assessing the efficacy and safety of ETN, 15 in 5192 patients with RA[83,84,85,86,87,88,89,90,91,92,93,94,95,96,97], 2 in 957 patients with PsA[98,99], and 9 in 1592 patients with AS[100,101,102,103,104,105,106,107,108]. Overall, including RCT open-label extension studies[109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125], 4 (0.05) cases of TB were recorded (3 in patients with RA[97,113,115] and 1 in a patient with AS[122]).

Details are available only for 2 cases: The first occurred after 3 years of therapy in a patient with RA who had screened negative for TB at study entry[115], and the second after 2.8 years of treatment in an patient with AS born in a country at high risk of TB, who had a negative TST and chest radiography at study entry[122].

Available data on occurrence of TB in ETN-treated patients with RA, PsA, or AS from healthcare databases, postmarketing surveys, and national registries of biologics are summarized in Table 3. Previously highlighted findings for IFX and ADA data from real-life indicated an increased risk of TB, although lower in comparison with mAb anti-TNF-α.

TB occurred in 32 of 2349 subjects with RA receiving ETN in the Pharmetrics database with an adjusted rate ratio of 1.2 (0.9–1.8)[43]. However, this database also included patients treated before 2001. With the exception of BIOBADASER 2003[40], RABBIT[42], and the South Korean registry[49], an increased risk of TB reactivation was found in all registries, with an incidence ratio ranging from 9.3 to 233 cases/100,000/year (median 85.5).

Data from clinical trials and real-life practice seem to indicate that the risk of TB is lower with ETN than with mAb anti-TNF agents. However, the results are somewhat conflicting, and particularly data from national registries show a different risk profile, probably due to different populations and to low adherence with recommendations for LTBI screening and TB prevention. Hence, LTBI screening and active TB prophylaxis should be performed before starting treatment with ETN.

Comparison of IFX-, ADA-, and ETN-associated Risk of TB Based on Real-life Data

As shown in Table 4, all 3 anti-TNF agents are associated with increased risk of active TB. However, confirming data in the literature[5], the risk is at least 3 to 4 times higher in patients exposed to monoclonal antibodies IFX and ADA than in those receiving the soluble receptor ETN. The different interference on TB granuloma formation exerted by ADA and IFX with respect to ETN may explain the higher incidence rate of TB cases[2,6]. However, the low number of TB cases in clinical trials carried out after October 2001 suggests the importance of adherence to the recommended LTBI screening procedures and TB prevention therapy.

Concerns About National Registries

Several registries are currently updated in different countries and provide useful information on the efficacy and safety of biologics in real-world clinical practice. However, with respect to the specific issue of TB, only 1 report from registries provided information regarding additional risk factors in the single patient, with consequent adjustment of the relative risk[51]. In reports on data from the Pharmetrics database, the LOHREN and GISEA registries, results were adjusted for age, sex, comorbidity, and concomitant therapies including corticosteroids, but not for ethnicity, drug abuse, malnutrition, or exposure to TB-infected subjects[43,46,50]. In the British registry[48], a 6-fold increased risk of TB was observed in patients of non-white ethnicity, but other known risk factors were not captured. In the French registry only variables related to the country of birth

Table 3. Etanercept and tuberculosis (TB) risk: Reported cases of TB from postmarketing surveillance and national registries.

Source/Year [Reference]	No. TB Cases/ No. Patients	TB IR ETN/Country, No. Cases/100,000 Population/year	RR	Defective LTBI Screening/TB Prophylaxis, %	Host-related TB Risk Factors (%)
BIOBADASER, Spain 2003 [40]	0/216	0	NA	Pre-LTBI scr*	NA
ARTIS, Sweden, 2005 [41]	6/NA	80/NA	NA	Pre-LTBI scr*	NA
RABBIT, Germany, 2005 [42]	0/512	0/8	0	NA	NA
Pharmetrics, Canada, 2006 [43]	32/2349	NA	NA	Pre-LTBI scr*	NA
BIOBADASER, Spain, 2007 [44]	2/1336	114/25	4.6	49%	NA
Japan 2009 [126]	8/7091	112/25	4.5	0%	NA
LOHREN, Italy 2009 [46]	1/242	233/8	29.1	Pre-LTBI scr*, 15.3%	NA
RATIO, France, 2010 [47]	5/NA	9.3/8.7	1.1	80%	66%
BSRBR, UK, 2010 [48]	8/5521	53/14	3.8	5%	70%
South Korea, 2011 [49]	0/210	0/69.8	0	50%	NA
GISEA, Italy, 2012 [50]	1/1130	88/8	11	NA	NA
Northern California, USA, 2013 [51]	8/2778	83/5	16.6	NA	NA

*Pre-LTBI screening included patients treated before 2001 recommendation for latent TB infection detection. NA: not available; LTBI: latent tuberculosis infection; RR: relative risk; IR ETN: incidence ratio in etanercept-treated patients.

Table 4. Overall cases of tuberculosis (TB) in infliximab-, adalimumab-, and etanercept-treated patients, pooled incidence ratio, and relative risk: comparison of results from national registries and postmarketing surveillance.

Anti-TNF Agent	No. TB Cases/ No. Patients (%)	Pooled IR Cases/ 100,000/year, mean ± SD	Pooled IR Cases/ 100,000/year, median	Pooled RR, mean ± SD	Pooled RR, median
Infliximab	164/20918 (0.78)	316.87 ± 226.77	284.5	24.1 ± 28.12	13.25
Adalimumab	59/11981 (0.49)	197.5 ± 67.14	203	15.46 ± 10.29	13.5
Etanercept	71/21385 (0.33)	86.53 ± 73.14	85.5	5.2 ± 5.82	4.15

TNF: tumor necrosis factor; RR: relative risk; IR: incidence ratio.

and concomitant traditional therapies were analyzed[47], while in the RABBIT registry patients were evaluated only for body mass index and current therapies. Finally, data on the appropriateness of LTBI screening procedures and TB prophylaxis are available only in the BIOBADASER 2007 and the French Registry[44,47].

Data from both clinical trials and national registries indicate an increased risk of TB reactivation in patients treated with the anti-TNF agents IFX, ADA, and ETN, with a lower risk associated with ETN therapy. Nevertheless, important criticisms may be raised about the data collection and relative risk adjustment reported by national registries. Indeed, neglecting host related risk factors, including country of birth and/or residence, ethnicity, comorbidities, drug abuse, concomitant treatments, defective LTBI screening procedures, and active TB prophylaxis may lead to important biases.

We suggest that precisely structured registries including all risk-related variables would help to better evaluate the risk of TB in patients receiving anti-TNF agents.

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