Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-alpha antagonist therapy: safe re-initiation of TNF-alpha blockers after appropriate anti-tuberculous treatment.

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Longterm follow-up of patients with tuberculosis complicating TNF-α antagonist therapy: safe reinitiation of TNF-α blockers after appropriate antituberculous treatment.

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ABSTRACT

The goal of this study was to describe the longterm outcome of patients with tuberculosis (TB) complicating TNF-α blocker therapy. All cases of tuberculosis (21) complicating TNF-α blocker therapy from French University Hospitals were collated between January 2000 and September 2002. Patient outcome was assessed via a postal questionnaire in September 2005. After 4 years of follow-up, the mortality rate was 4.8%, 1 patient had relapsed and 6 patients (29%) had restarted TNF-α antagonist treatment after appropriate antituberculous therapy, without reactivation.

Our data support the concept that TNFα antagonists can be restarted in patients diagnosed with TB provided adequate antituberculous treatment has been completed.

Tumor Necrosis Factor α (TNF-α) induces intracellular death of *Mycobacterium tuberculosis*, macrophage apoptosis and granuloma formation [1-3]. Keane et al. [4] were the first to describe an increased incidence of TB in patients with rheumatoid arthritis (RA) treated with TNF-α blockers. The relative risk of developing TB whilst on this therapy in this patient group has been estimated in the USA and Europe at ≥4 [4-7]. In France, a national multidisciplinary group called RATIO (Research Axed on Tolerance of bIOtherapies) was set up to further the knowledge, prevention and care of opportunistic infections associated with TNF-α antagonists. We report here the long-term outcome of 21 patients in France who developed TB whilst on TNF-α blockers. All cases of TB in patients treated with TNF-α blockers between 1st January 2000 (first TNF-α antagonist use in France) and 30th September 2002 were collected from the gastroenterology, rheumatology, infectious diseases and internal medicine units of all French University hospitals. A Clinical Research Assistant then collected all the available data for each TB case. On-site visits took place from 15th October 2002 to

22st January 2003. Postal questionnaires regarding the patients' outcomes were sent in September 2005 and information collected up to January 2006.

Overall, 25 definite or probable TB cases were reported. 21 cases from 19 different centers were retained for analysis (2 cases could not be validated by an on-site visit, the same patient was declared twice in one case and the diagnosis of TB was not retracted in the last case).

The underlying inflammatory disease, patients' demographic characteristics and concomitant immunosuppressive treatments are shown in Table 1. Most patients had RA and they were all receiving infliximab. Seventeen patients were also treated with corticosteroids at diagnosis with a median daily dosage of prednisolone of 10 mg [range 4-65mg]. Additional immunosuppressive factors included chronic hepatitis C in 1 case and neoplasia in 4 cases: 1 thyroid carcinoma diagnosed after starting infliximab and treated surgically, 1 endometrial carcinoma treated and cured 7 years before starting TNFα blocker therapy, 1 breast carcinoma treated 11 years before starting TNFα blockers and 1 chronic lymphoid leukaemia (CLL) diagnosed one month after the initiation of TNFα blocker therapy. These patients received TNFα blockers because they had very severe forms of RA.

Nine patients (43%) reported at least one of the following previous events: contact with a patient with TB or primary infection or microbiologically confirmed TB treated with antituberculous treatment (Table 2). Fever was the initial symptom in 16 patients. The mean duration between first symptoms and the diagnosis of TB was 38 days [range 3-153 days]. In 8 patients (38%), lung was the only organ involved (5 with a prolonged cough). Four patients (19%) had only extra-pulmonary involvement consisting of lymphadenitis in all cases. In eight patients (38%), the lung and at least one other system were involved - lymphadenitis in 3 cases, peritonitis in 1 case, urinary tract infection in 1 case, bone (elbow) involvement in 1 case, spleen in 1 case and the combination of lymphadenitis, spleen and hepatic involvement

in the remaining case. One patient had no precise clinical localization. As previously observed [4], the frequency of extra-pulmonary and disseminated forms were particularly high in these patients treated with TNF-α blockers (57% of patients). The direct staining examination of the specimen was positive for acid-fast bacilli in 6 out of 21 patients and the culture was positive for *M. tuberculosis* for 19 patients. For the two patients with negative culture, one diagnosis was obtained by positive specific *M. tuberculosis* complex PCR in the bronchoalveolar lavage fluid and the other by a positive Mantoux's test (from 6 to 20 mm) with compatible clinical symptoms and a good response to antituberculous treatment.

Patients received antituberculous therapy for 8.5 months range 1-14 months]: 7 started with triple therapy (6 with isoniazid, rifampin, ethambutol, 1 with isoniazid, rifampin, ofloxacin), 13 (61.9%) with quadruple therapy (isoniazid, rifampin, ethambutol, pyrazinamide) and 1 died before initiation of antituberculous treatment.

A TB relapse was observed in 1 patient in 2004 (microbiologically-confirmed lymph node localization); initial antituberculous treatment had been taken for 6 months and the isolate remained susceptible to all four drugs taken. The patient was retreated for 9 months and cured but he did not resume TNF-α blocker therapy.

The most recent information concerning the health status of patients was obtained via a postal questionnaire sent approximately 4 years after the commencement of antituberculous treatment. At this time, 15 patients were alive and all of them were cured. Among the 6 cases who died, death was formally attributed to TB in 1 patient (4.8%). Five deaths were not related to TB: cardiac failure in 2 cases, acute respiratory failure in 2 cases and a cerebrovascular accident in 1 case. Patients received the following treatments: corticosteroids in 4 patients, methotrexate in 4 patients, leflunomide in 4 patients, salazopyrine in 1 patient, thalidomide in 1 patient, polyvalent immunoglobulins in 1 patient, infliximab in 3 patients,

etanercept in 2 patients (initially 3 patients but 1 switched afterwards for infliximab) and adalimumab in 1 patient.

Six patients restarted TNF-α blockers: 12 months after the initiation of anti tuberculous treatment for 3 patients and 2, 3, and 7.5 months after for the 3 others respectively. Treatment consisted of infliximab for 2 patients, etanercept for 3 patients and adalimumab for 1 patient. One in the etanercept group was later switched to infliximab. None of the 6 patients restarted on TNF-α antagonist treatment developed a reactivation of TB or developed another opportunistic infection and their subjective quality of life improved. The mean follow-up for these 6 patients since commencing antituberculous treatment was 42.7 months (18-60).

The guidelines of the British Society of Rheumatology [8, 9] recommend continuation of TNF-α blockers (with treatment of TB) for patients who develop active TB while on TNF-α blockers, if the expected benefit for the inflammatory disease is strong. To our knowledge, this is the first description of the long-term surveillance of patients having developed TB whilst treated with TNF-α blocker therapy who are then safely resumed on TNF treatment once successfully treated with appropriate antituberculous therapy.

Our data strongly suggest that TB is not a contraindication to restarting anti-TNF-α therapy if the underlying inflammatory disease requires it.

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Table 1. Underlying conditions and immunosuppressive therapy in 21 patients treated with TNF-α blockers who developed tuberculosis in France

	Rheumatoid arthritis	**Ankylosing spondylitis**	**Crohn's disease**	**Other diseases: Polymyositis Psoriatic arthritis**	**Total**	**%**
	(N = 14, 66.7%)	(N = 2, 9.5%)	(N = 2, 9.5%)	(N = 3, 14.3%)	**(N = 21)**	
Male / Female	6 / 8	1 / 1	1 / 1	1 / 2	9 / 12	
Median age (range) at the 1st symptom (yrs)	65 (45-85)	50 (46-54)	34 (28-40)	67 (53-63)		
Mean (± SD) duration of disease (yrs)	10.1 ± 5.0	32.2 ± 2.7	12.4 ± 4.1	12.6 ± 6.6		
Type of treatment at diagnosis of tuberculosis:						
I	1	0	0	2	3	14.3
I + azathioprine	0	0	1	0	1	4.8
I + cyclosporine	1	0	0	0	1	4.8
I + leflunomide	2	0	0	0	2	9.5
I + leflunomide + hydroxychloroquine	1	0	0	0	1	4.8
I + methotrexate	9	2	0	1	12	57.1
I + purinethol	0	0	1	0	1	4.8
Corticosteroids*	12	1	1	3	17	81
Infliximab treatment :						
-Mean (± SD) infliximab dosage (mg/kg)	3.3±0.5	3.0±0.0	5.1±0.2	6.5±3.0	3.9±1.7	-
-Mean (± SD) number of infliximab perfusions at first symptoms	3.5±1.9	3.0±0.0	3.0±0.0	3.0±1.0	3.3±1.6	-
-Mean (± SD) duration of treatment with infliximab (weeks)	13±12.5	12±3.1	26.5±13	9.4±3.6	13.5± 11.4	-
Mean (± SD) duration of immunosuppression (years)	8.1±4.5	7.6±12.8	6.6±2.5	7.4±9.2	7.8±6.0	-

I: infliximab**;** *corticosteroids were combined to immunosuppressive therapy

Table 2. Past medical history in 21 patients with tuberculosis occurring during treatment with TNF-α blockers

	Present *	Absent	Undetermined
Vaccination (BCG)	5 (24%)	7 (33%) **	9 (43%)
Previous exposure to *M. tuberculosis*	6 (29%)	13 (62%)	2 (10%)
Past history of tuberculosis primary infection	7 (33%)	12 (57%)	2 (10%)
Treatment of tuberculosis primary infection (TPI)	2 (29%)	2 (29%)	3 (42%)
Past history of tuberculosis disease	1 (5%)	19 (90%)	1 (5%)

* All of them had received vaccination at least 10 years before diagnosis
** 3 foreigners, others born in France in 1920, 1942 (past history of TPI), 1946 (past history of TPI), 1955 (past history of TPI)