Infections during tumour necrosis factor-α blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients

C. Salliot, L. Gossec, A. Ruyssen-Witrand, M. Luc, M. Duclos, S. Guignard and M. Dougados

Objective. To evaluate the rate of infections in rheumatic patients treated with tumour necrosis factor (TNF)-α blockers in daily practice and to determine potential risk factors of infections.

Methods. Systematic retrospective study was conducted in a tertiary-referral centre of all patients receiving at least one TNF-α blocker, between 1997 and December 2004. Serious infections were defined as life-threatening, requiring hospitalization or sequelae. The incidence of infections during the first TNF-α blocker course was compared with the incidence during the period just before such therapy, in the same patients and a number needed to harm was calculated. Univariate and multivariate analysis between patients who suffered from at least one infection during treatment or not, was conducted in order to determine potential associated risk factors.

Results. Among the 709 patients treated with at least one TNF-α blocker, 57.7% had rheumatoid arthritis; a total of 275 infectious events in 245 patients (34.5%) were reported during all treatment courses. Among these infections, 47 infections in 44 patients (6.2%) fulfilled the definition of serious infections. The incidence rate of serious infections was 3.4 ± 38.7 per 100 patient-yrs before TNF-α blocker therapy *vs* 10.5 ± 86.9 during the first TNF-α blocker course ($P = 0.03$, number needed to harm = 14). The single risk factor picked up by multivariate analysis to explain infections was previous joint surgery [odds ratio (OR) = 2.07, 95% confidence interval (CI) = (1.43–2.98), $P < 0.0001$] and, if surgery was taken out of the model, the cumulative dose of steroids [OR = 1.28 (1.04–1.59), $P = 0.02$].

Conclusion. The rate of serious infections during TNF-α blocker treatment observed in daily practice conditions was much higher than in phase III trials evaluating TNF-α blockers. Serious infections are frequent in daily practice and close monitoring is required.

KEY WORDS: TNF-α blockers, Rheumatic diseases, Serious infections, Retrospective.

Tumour necrosis factor (TNF)-α is a pro-inflammatory cytokine that plays a major role in rheumatic diseases. Since 1997, TNF-α blockers have been used in refractory rheumatoid arthritis (RA) [1–7], Crohn's disease [8] and more recently in spondylarthropathies [9, 10] with a proven efficacy. At the present time, three TNF-α antagonists are available: two monoclonal antibodies (infliximab and adalimumab) and one soluble TNF-α receptor (etanercept).

Before the TNF-α blocker era, it was reported that the incidence rate of infections in the RA population was nearly twice as high as in matched non-RA controls. This is thought to be related to the disease itself, which alters immunological functions, decreases mobility and causes skin defects, and also to immunosuppressive drugs (especially concomitant use of steroids) [11, 12].

In placebo-controlled trials evaluating the three TNF-α blockers, for patients with RA, the rate of any infection did not exceed the rate in the placebo groups [1–7]. Concerning serious infections (defined, according to the authors, as life-threatening or requiring intravenous antibiotics or hospitalization), the incidence rate has been reported as 4–6 events per 100 patient-yrs in placebo groups, without significant increase in TNF-α blockers groups (around 4 events) [1, 5, 7]. In a long term safety study, there was also no increase of serious and non-serious infections in patients with RA while taking etanercept during a median time of 25 months [5]. In post-marketing surveillance, two studies, from Sweden and the UK, suggested that the risk for developing serious infections was not increased in patients receiving TNF-α blockers for rheumatic diseases: around 5 events per 100 patient-yrs for the three TNF-α blockers [13, 14].

However, numerous case reports or small series of serious infections, including opportunistic infections have been reported world-wide, and one post-marketing study [15] showed an increased risk of serious infections during TNF-α blocker therapy, compared with the period preceding such treatment, in 60 RA patients.

Tuberculosis, especially extrapulmonary and disseminated, was the most frequently reported granulomatous infection and it occurred with the three TNF-α blockers [16–18]. Other invasive opportunistic infections occurring with the three TNF-α blockers have been reported, such as listeriosis, candidosis, histoplasmosis, nocardiosis, aspergillosis or pneumocystosis [16–22].

Thus it is clear that TNF-α blockers can induce the emergence of infections in rheumatic patients. However most of the data available comes from phase-III trials or epidemiological studies, and concerns RA patients. For rheumatic diseases, data about

```
┌─────────────────────────────────────────────────────────────────┐
│ Patients followed-up for rheumatic diseases between 1997 and 2004 = 4589: │
│                                                                   │
│ - Rheumatoid arthritis = 2707.   - Spondylarthropathies = 1460    │
│                                                                   │
│ - Other inflammatory rheumatisms = 422                            │
└─────────────────────────────────────────────────────────────────┘
                               │
                               ▼
        ┌──────────────────────────────────────────────────┐
        │ TNF-α blocker treatment mentioned in patient file = 1571 │
        └──────────────────────────────────────────────────┘
                │                  ┌──────────────────────────────────┐
                │                  │ - TNF-α blocker not initiated = 539 │
                │                  │                                  │
                │                  │ - TNF-α blocker not indicated = 161 │
                │                  │                                  │
                │                  │ - Contraindication = 26          │
                │─────────────────▶│                                  │
                │                  │ - Insufficient data = 43         │
                │                  │                                  │
                │                  │ - Clinical trials for which the  │
                │                  │                                  │
                │                  │ study drugs were undisclosed = 19 │
                │                  │                                  │
                │                  │ - Patient refusal of treatment = 13 │
                │                  └──────────────────────────────────┘
                ▼
        ┌──────────────────────────────────────────────────┐
        │ Patients receiving TNF-α blockers treatment = 770  │
        └──────────────────────────────────────────────────┘
                │
                ▼
        ┌──────────────────────────────────────────────────────────────┐
        │ **709 patients receiving TNF-α blocker therapy and with follow-up*** │
        └──────────────────────────────────────────────────────────────┘
                │
                ▼
        ┌──────────────────────────────────────────────────┐
        │ **623 patients with a control period**** │
        └──────────────────────────────────────────────────┘
```
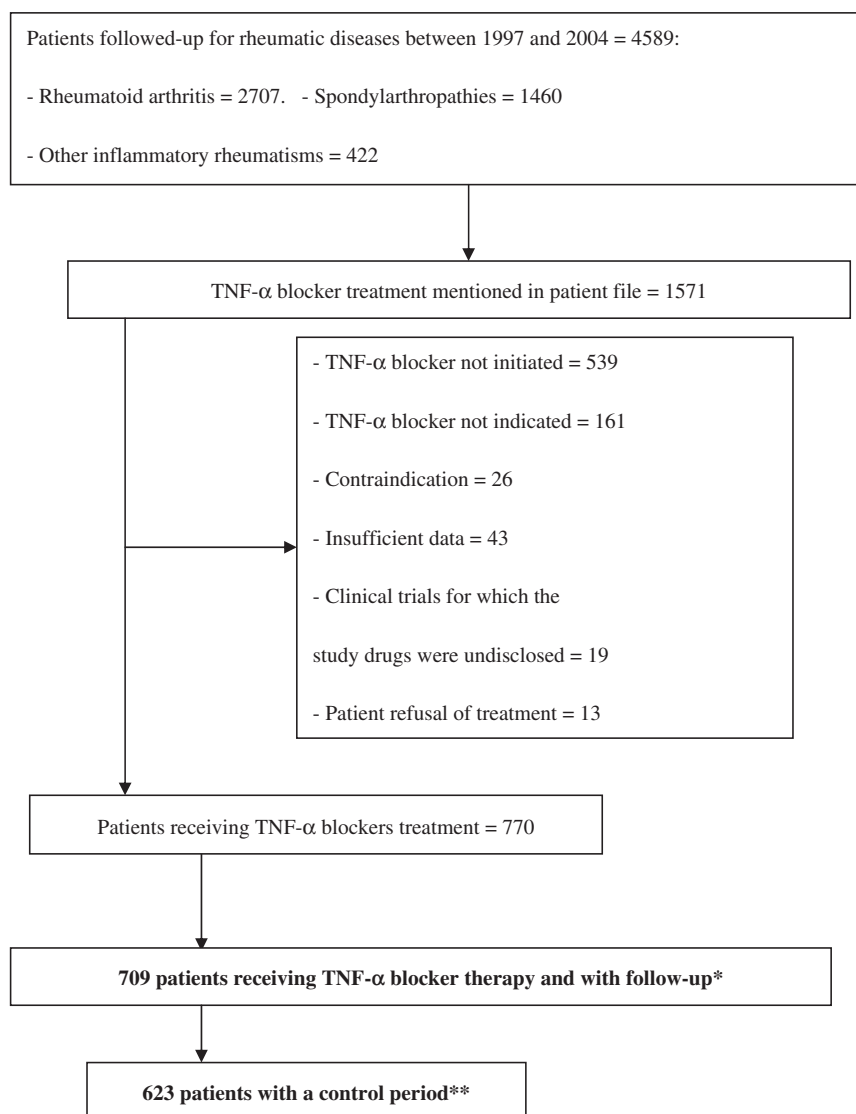
FIG. 1. Flow chart of patient selection process. *Patients with follow-up were those seen at least once after the initiation of the first TNF-α blocker. **Control period is defined as the period immediately preceding the initiation of the first TNF-α blocker course.

serious infections in daily practice and potential differences between infectious patterns according to the TNF-α blocker are missing.

Our purpose was to assess and compare the incidence rates of any infections and serious infections in patients with rheumatic diseases before and during treatment with TNF-α blockers, to describe and to compare infectious patterns according to the TNF-α blocker and finally to determine other potential risk factors of infection for patients taking TNF-α blockers.

Patients and methods

Study design

Retrospective, observational study.

Setting

Monocentre tertiary-referral clinic.

Selection of patients

Figure 1 shows the selection process. All patients who received or had received treatment with TNF-α blockers between 1997 and December 2004 were selected through a computer survey of patients' files (using key-words 'infliximab', 'etanercept', 'adalimumab' and 'TNFα blocker' in full text). With this exhaustive selection, we obtained 1571 patients' files.

All medical files were checked in order to exclude patients who had not received a TNF-α blocker and to select patients receiving a TNF-α blocker and with a follow-up in our department, i.e. seen at least once during out-patient visits or hospitalizations after the initiation of the TNF-α blocker. All patients with follow-up were analysed to describe infectious patterns and evaluate potential associated risk factors of infections.

To compare infections rates before and during TNF-α blocker therapy, a more restricted population was analysed: among patients with follow-up, patients with a control period, i.e. those seen in the department before the initiation of the first TNF-α blocker were selected.

To assess the different objectives of this study, three periods of time were defined. First, the period for all TNF-α blocker courses of treatment between the dates of initiation and of interruption of each TNF-α blocker (date of end of this period was December 2004 for patients still receiving a TNF-α blocker at this date). For this period, a patient receiving successively two TNF-α blockers was entered twice, once for each treatment course. Second, the duration of the first TNF-α blocker was defined as the period between the date of its initiation and its discontinuation or December 2004. Finally, the control period before TNF-α blocker initiation was defined as the period between the date of the first out-patient visit in our department of rheumatology and the date of initiation of the first TNF-α blocker.

Data collection

Five residents performed the file search between December 2004 and March 2005. In medical files and during out-patient visits, the following data were collected.

Demographic characteristics were collected: gender, underlying disease and its duration, age at the initiation of the first TNF-α blocker and several potential associated risk factors [previous joint surgery, diabetes mellitus, obesity, lymphopenia, neutropenia, prior and concomitant steroid therapy and disease-modifying anti-rheumatic drugs (DMARDs)]. Underlying diseases were RA, spondylarthopathies and others (unclassified inflammatory rheumatisms, Still's disease, idiopathic periosteitis, etc.). They fulfilled the American College of Rheumatology criteria for RA [23] and Amor's criteria for spondylarthropathy [24].

Previous joint surgery was recorded as joint arthroplasty or arthrodesis, obesity was defined as body mass index $>30 \text{ kg/m}^2$, lymphopenia as lymphocyte count $<1300/\text{mm}^3$ and neutropenia as neutrophilic polynuclear cell count $<1700/\text{mm}^3$ at any time during follow-up.

Each patient could have been treated with several TNF-α blockers and thus have several treatment courses. The first three TNF-α blocker treatment courses were collected and, for each one, doses and duration. Concomitant therapies, i.e. at the initiation of the TNF-α blocker, with their dosage (steroids, DMARDs), were also collected for all TNF-α blocker courses.

Only infectious events reported in medical files or during out-patient visits were available; they were categorized as 'serious' (defined as life-threatening or requiring hospitalization or sequelae) and 'not serious' infections. For each one, site of infection, micro-organism and outcome were collected.

Statistical analysis

Double data entry was performed and all data were analysed anonymously. The database was analysed using SAS, the statistical analysis system, version 8.0.

Incidence rates. The incidence rate was defined as the number of events (infections) per 100 patient-yrs. It was calculated during all treatment courses, during the first TNF-α blocker and during the control period. The incidence rate of infections during the first TNF-α blocker course was compared with the rate during the control period in the same patients, for those with a control period (case-cohort design), by paired *t*-test. To compare these incidence rates, the relative risk ratio (incidence rate during the first TNF-α blocker/incidence rate during the control period) and the number needed to harm (NNH) of serious infections were calculated. The NNH reflects the number of patients who, if they received the TNF-α blocker treatment for 1 yr, would lead to one additional patient being harmed (i.e. having a serious infection), compared with control patients (in this case, the same patients before TNF-α blocker treatment). The NNH is calculated as (1/absolute risk increase), the latter defined as (experimental event rate-control event rate). The advantage of the NNH is that it reflects an absolute risk increase, and because it is related to the control event rate, it reflects the true baseline or underlying risk of the study population [25]. For rational decision-making in daily clinical practice, absolute measures such as NNH may be more meaningful than relative measures [26]. Because of the large confidence intervals (CIs) around the serious infection rates, CIs were not reported for the NNH, as proposed by Mc Quay and Moore [27].

Infectious patterns. Descriptive analysis was performed for infectious patterns in all patients during all treatment courses and according to the TNF-α blocker. To avoid multiple statistical testing, and also because this aspect was perceived as an exploratory analysis, no formal statistical comparisons were performed.

Potential associated risk factors. In order to determine potential associated risk factors of infections among patients who suffered from at least one infection during treatment or not, univariate and multivariate analysis were performed, with any infection, yes *vs* no, as dependent variable. For univariate analysis, Chi-square and *t*-tests were used. Multivariate analysis was performed with stepwise logistic regression with inclusion of all variables with a *P*-value <0.3 in univariate analysis. The level of significance was set at 5% bilaterally.

Results

The selection process of medical files is shown in Fig. 1. Among the 770 patients who received at least one TNF-α blocker, 709 were followed in the department after the initiation of TNF-α blocker therapy. There was no difference between the characteristics of patients with and without follow-up (data not shown). Among these 709 patients, 623 had a control period before the initiation of the first TNF-α blocker course, as defined earlier.

Patients' characteristics

The characteristics of the 709 and 623 patients are summarized in Table 1. There was no difference between these two groups of patients. Among the 709 patients, 60.4% were women and the mean age at the beginning of the first TNF-α blocker was 46 yrs. The underlying disease was mainly RA (57.7%) or spondylarthropathies (29.6%). The mean duration of rheumatic disease was 12 yrs before the initiation of TNF-α blocker therapy. Twenty-three percent had had previous joint surgery. Nearly 20% of patients had at least one comorbidity factor such as diabetes mellitus (4%), obesity (11%), lymphopenia (7%) and neutropenia (1%). Before initiation of the first TNF-α blocker, 78% of the patients received steroids and the mean number of previous DMARDs was three per patient.

Of the 709 patients, 204 received more than one TNF-α blocker resulting in 913 treatment courses (etanercept 50%, infliximab 30% and adalimumab 20%). In association with biotherapy, 58.5% of patients received steroids with a mean dose of 8.4 mg daily and 53.7% received at least one DMARD. The mean follow-up while taking TNF-α blocker was 1.5 ± 1.2 yrs for the 709 patients and all treatment courses and 1.3 ± 1.3 yrs for the 623 patients during the first TNF-α blocker.

Incidence rates of any and serious infections

A total of 275 infectious events in 245 patients were reported during all treatment courses (34.5% of the 709 patients). Among these infections, 47 infections in 44 patients (6.2%) fulfilled the definition of serious infections.

For all treatment courses, the incidence rates were 48.2 ± 138.3 per 100 patient-yrs for any infections and 10.4 ± 82.1 per 100 patient-yrs for serious infections.

TABLE 1. Characteristics of patients receiving TNF-α blockers for rheumatic diseases between 1997 and 2004

	Patients with follow-up[a] $n = 709$	Patients with follow-up and control period[b] $n = 623$
Age at initiation of TNF-α blocker in yrs, mean (S.D.)	45.9 (13.7)	46.5 (13.5)
Men, n (%)	281 (39.6)	247 (39.6)
Duration of follow-up in yrs, mean (S.D.)	1.7 (1.4)	1.7 (1.4)
Underlying disease:		
Rheumatoid arthritis n (%)	409 (57.7)	363 (58.2)
Spondylarthropathies n (%)	264 (37.2)	231 (37.1)
Others, n (%)	36 (5.1)	29 (4.6)
Duration of disease in yrs before TNF blocker therapy, mean (S.D.)	11.8 (9.6)	12.1 (9.7)
Previous joint surgery, n (%)	159 (22.4)	145 (23.4)
Comorbidity:		
At least one comorbidity factor, n (%)	141 (20.0)	130 (21.0)
Obesity[c], n (%)	79 (11.1)	72 (11.6)
Body mass index, mean (S.D.)	24.4 (4.7)	24.4 (4.7)
Diabetes mellitus, n (%)	30 (4.2)	28 (4.5)
Lymphopenia[d], n (%)	48 (6.7)	45 (7.2)
Neutropenia[e], n (%)	7 (1.0)	6 (0.8)
Previous immunosuppressive therapy:		
Previous steroid therapy, n (%)	549 (77.9)	486 (78.5)
Cumulative dose of steroid in g[f], mean (S.D.)	21.3 (22.5)	21.5 (22.7)
Number of DMARDs[g] per patient, mean (S.D.)	3.0 (2.7)	3.1 (2.1)
First course of TNF-α blocker:		
Etanercept, n (%)	375 (52.9)	329 (52.8)
Infliximab, n (%)	237 (33.4)	205 (32.9)
Adalimumab, n (%)	97 (13.7)	89 (14.3)
Mean duration of follow-up during TNF therapy in yrs, mean (S.D.)	1.3 (1.2)	1.3 (1.2)
Concomitant therapy at initiation of the first TNF-α blocker:		
Steroid, n (%)	415 (58.5)	363 (58.3)
Dose of steroid[f] (mg per day), mean (S.D.)	8.4 (5.1)	8.3 (5.3)
At least one DMARD[g], n (%)	379 (53.4)	333 (53.7)
Methotrexate, n (%)	310 (43.7)	272 (43.6)
Steroids + methotrexate, n (%)	214 (30.2)	187 (30.0)

S.D.: standard deviation.

[a]Patients with follow-up were those seen at least once after the initiation of the first TNF blocker. [b]Control period was defined as the period just before the initiation of the first TNF blocker. [c]Body mass index >30 kg/m^2. [d]Lymphopenia = lymphocytes count <1300/mm^3. [e]Neutropenia = neutrophilic polynuclear cells count <1700/mm^3. [f]For patients who had taken steroids during the first TNF blocker. [g]DMARD, disease-modifying anti-rheumatic drug.

TABLE 2. Incidence rates of any infections and serious infections in 623 patients (patients taking their first TNF-α blocker were compared with themselves before starting therapy)

	Patients with at least one infection n (%)	Follow up in yrs mean (S.D.)	Incidence rate of any infections[b] mean (S.D.)	Incidence rate of serious infections[b] mean (S.D.)
Before TNF-α blocker therapy[a]	42 (6.7)	1.1 (1.2)	9.3 (50.8)	3.4 (38.7)
During the first TNF-α blocker	215 (34.5)	1.3 (1.2)	54.1 (153.6)	10.5 (86.9)
P-value comparing rates before and during therapy			<0.0001	0.03

S.D.: standard deviation.

[a]Same patients before introduction of the first TNF-α blocker. [b]Per 100 patient-yrs.

Comparison of incidence rates before and during the first TNF-α blocker course

During the first TNF-α blocker course, 222 infections occurred in 215 of the 623 patients (34.5%). Among them, 38 serious infections occurred in 36 patients (5.7%). During the control period, 47 infectious events were collected in 42 patients (6.7%) with 13 (2.1%) serious infections. The incidence rates (Table 2) of any infections during the control period *vs* the first TNF-α blocker course were 9.3 ± 50.8 *vs* 54.1 ± 153.6 per 100 patient-yrs ($P < 0.0001$), respectively. For serious infections, the incidence rates were 3.4 ± 38.7 *vs* 10.5 ± 86.9 per 100 patient-yrs, respectively ($P = 0.03$). The relative risk ratio of serious infections during the first TNF-α blocker was 3.1 compared with the control period without TNF-α blocker, and the NNH was 14, i.e. 14 patients would need to be treated 1 yr to observe one additional serious infection.

Rates of infections according to the TNF-α blocker

During the first treatment course, mean rates of serious infections were 10.2 ± 69.3, 12.3 ± 102.2 and 5.3 ± 26.2 per 100 patient-yrs, respectively during treatment with infliximab (16 of 237 patients, mean follow-up 1.5 ± 1.2 yrs), etanercept (15 of 375 patients, mean follow-up 1.2 ± 1.1 yrs) and adalimumab (5 of 97 patients, mean follow-up 1.3 ± 1.3 yrs). During the first treatment course, mean rates of any infections were 69.8 ± 152.8, 44.1 ± 161.1 and 37.3 ± 64.9 per 100 patient-yrs, respectively during treatment with infliximab (106 patients), etanercept (95 patients) and adalimumab (35 patients).

TABLE 3. Comparison of infectious patterns according to TNF-α blocker for 913 treatment courses in 709 patients

	All treatment courses $n = 913$	Infliximab $n = 276$	Etanercept $n = 455$	Adalimumab $n = 182$
Any infections n (%[a])	275	139 (50.5)	94 (34.2)	42 (15.3)
Sites of infection n (%[b]):				
Upper respiratory tract	98 (10.7)	37 (13.4)	43 (9.4)	18 (9.9)
Lung	59 (6.4)	37 (13.4)	20 (4.4)	2 (1.1)
Skin	58 (6.3)	32 (11.6)	14 (3.1)	12 (6.6)
Urinary tract	22 (2.4)	14 (5.1)	5 (1.1)	3 (1.6)
Gastrointestinal tract	16 (1.7)	8 (2.9)	4 (0.9)	4 (2.2)
Genital tract	5 (0.5)	3 (1.1)	1 (0.2)	1 (0.5)
Osteoarticular	3 (0.3)	0 (0)	3 (0.6)	0 (0)
Neurological	0 (0)	0 (0)	0 (0)	1 (0.5)
Other	14 (1.5)	8 (2.9)	4 (0.9)	2 (1.1)
Micro-organisms n (%[b]):				
Bacterial	148 (16.2)	78 (28.2)	54 (11.8)	16 (8.8)
Viral	84 (9.2)	43 (15.5)	25 (5.5)	16 (8.8)
Mycobacterial	2 (0.2)	2 (1.1)	0 (0)	0 (0)
Fungal	18 (1.9)	7 (2.5)	7 (1.5)	4 (2.2)
Parasitic	1 (0.1)	1 (0.3)	0 (0)	0 (0)
Not defined	22 (2.4)	8 (2.9)	8 (1.7)	6 (3.3)
Outcome n (%[c]):				
Death	1 (0.3)	0 (0)	1 (1.0)	0 (0)
Cured	272 (98.9)	139 (100)	91 (96.8)	42 (100)
Sequelae	2 (0.7)	0 (0)	2 (2.1)	0 (0)

[a]Percentage for all infections. [b]Compared with the number of all treatment courses, the number of the infliximab, etanercept or adalimumab therapies, respectively. [c]compared with the number of any infections during all treatment courses, infliximab, etanercept and adalimumab therapies, respectively.

Infectious patterns

Infectious patterns are shown Table 3. For all infections merged, the most frequent sites of infections were upper respiratory tract (35.6%), lung (21.4%) and skin (21.0%). Bacteria were responsible in 53.8%, virus in 30.5% and fungi in 6.5% of cases. For the 47 serious infections, the most frequent sites of infection were skin and skin-associated tissues (40.4%), lung (19.1%), urinary (12.7%), upper respiratory (10.6%), gastrointestinal tracts (10.6%) and osteoarticular (6.4%). Serious infections were caused mainly by bacteria (74.5%), virus (10.6%), mycobacteria (4.2%), parasites (2.1%) and fungi (2.1%). They occurred during treatment with infliximab ($n = 20$, 7.2% of infliximab treatment courses), etanercept ($n = 18$, 4.0%) and adalimumab ($n = 9$, 4.9%). The two mycobacterial infections reported during TNF-α blocker therapy occurred with infliximab (one pulmonary tuberculosis and one skin infection due to non-tuberculosis mycobacteria). Five patients were hospitalized in intensive care department, for bacterial pulmonary infections (four patients) and digestive infection (one patient). One patient, receiving etanercept for RA, died of pneumococcal septicaemia.

Concerning infectious patterns and for the three TNF-α blockers, upper respiratory tract was the site where infection was observed most frequently. Few differences were observed according to the type of TNF-α blocker (Table 3). Nevertheless, lung infections occurred more frequently during infliximab therapy (13.4% of infliximab treatment courses) and skin localizations under infliximab (11.6% of infliximab treatment courses) and adalimumab (6.6% adalimumab treatment courses). The type of TNF-α blocker did not seem to influence the nature of the micro-organism responsible for infection.

Associated risk factors of infections in patients taking TNF-α blocker

In univariate analysis, previous joint surgery ($P = 0.0003$), number of previous DMARDs ($P = 0.04$) and concomitant use of steroids ($P = 0.03$) appeared as associated risk factors of presenting with any infection in patients receiving TNF-α blocker (Table 4).

However, age at the initiation of biotherapy, gender, comorbidity factors, nature of the underlying disease and its duration, previous use of steroids, cumulative dose of steroids and concomitant use of DMARDs did not appear to be (Table 4). Twenty patients older than 70 yrs received TNF-α blocker therapy. For these patients, the incidence rate of infections was 35.0 ± 67.0 per 100 patient-yrs and similar to the one of younger patients (39.0 ± 67.0 per 100 patient-yrs). None had serious infections during TNF-α blocker therapy.

The following variables: previous joint surgery, underlying disease, number of previous DMARDs, previous use of steroids and cumulative dose, concomitant use of steroids and lymphopenia were entered in the multivariate model. The single risk factor picked up by logistic regression to explain infections was previous joint surgery [odds ratio (OR) = 2.07, 95% CI = 1.43–2.98, $P < 0.0001$] and, if surgery was taken out of the model, a high previous cumulative dose of steroids (if >60 g, OR = 1.28, 95% CI 1.04–1.59, $P = 0.02$).

Discussion

This study conducted in daily practice conditions suggests that, in contradiction with the findings in phase-III trials, infections are frequent adverse events of TNF-α blockers and serious infections are also much more frequent during treatment than before treatment in the same patients. Moreover, it seems that such adverse events are more frequently observed with infliximab than with etanercept or adalimumab. Finally, such infections are likely to occur in more severe patients with previous joint surgery and treated with higher doses of steroids.

Thus, four types of information issue from this study. The first important information concerns infection rates, the second concerns potential differences between TNF-α blockers, the third relates to infection characteristics, and the fourth to risk factors of infections.

Concerning infection rates, this study shows that serious and non-serious infections were much more frequent during TNF-α blocker therapy than before this therapy, in the same patients.

TABLE 4. Risk factors of infections in 709 patients treated with TNF-α blockers, univariate analysis

	Patients with infectious events ($n = 245$) Mean ± s.d. or n (%)	Patients without infectious events ($n = 464$) Mean ± s.d. or n (%)	P
Age at the initiation of TNF-α blocker	45.7 ± 13.7	46.0 ± 13.8	0.79
Women	151 (61.6)	277 (59.7)	0.62
Previous joint surgery	74 (30.2)	85 (18.3)	0.0003
Rheumatic disease:			
Rheumatoid arthritis	152 (62.0)	257 (55.4)	0.15
Spondylarthropathies	82 (33.4)	182 (39.2)	
Others	11 (4.5)	25 (5.4)	
Duration of rheumatic disease in yrs	12.2 ± 9.3	11.4 ± 9.7	0.31
Previous use of steroids	196 (80)	353 (76.0)	0.25
Previous cumulative dose of steroid (g)	23.5 ± 24.7	20.1 ± 21.1	0.11
Number of previous DMARDs	3.2 ± 2.1	2.9 ± 2.0	0.04
Concomitant use of steroids	157 (64.1)	258 (55.6)	0.03
Concomitant use of DMARDs	133 (54.3)	246 (53.0)	0.84
Concomitant use of steroids + methotrexate	76 (31.0)	138 (29.7)	0.72
At least one comorbidity factor	43 (17.5)	82 (17.6)	0.97
Diabetes mellitus	11 (4.5)	19 (4.1)	0.80
Obesity	28 (11.4)	51 (11.0)	0.86
Neutropenia	3 (1.2)	4 (0.8)	0.64
Lymphopenia	20 (8.1)	28 (6.0)	0.28

Patients receiving their first TNF-α blocker were compared with themselves before the initiation of this treatment. Thus, the two groups of patients were matched for sex, age and the severity of rheumatic diseases. However, in this retrospective study, because of potential underreporting of non-serious infections during the control period, a conclusion should not be made about the increased incidence rate of any infections during the first TNF-α blocker. On the other hand, the definition of 'serious' infections used here was comparable with that of the phase III trials (as given in the introduction of this article). Moreover, the incidence rate of serious infections during the control period (3.4 per 100 patient-yrs) was comparable with the rate given in the placebo groups in phase-III trials for RA [1, 5, 7]. Thus, serious infections during the control period seem to be neither over-estimated nor underreported in the present study, which gives strength to our results.

Compared with phase III trials evaluating TNF-α blockers in RA, the incidence rate of serious infections was much higher in the present study: 10.5 *vs* 3–4 events per 100 patient-yrs (for comparable definitions of 'serious infections'). Unlike clinical practice, the patients included in phase-III trials are selected according to inclusion and exclusion criteria. This methodological difference could explain in part this high rate of infections. Unlike in placebo-controlled trials, the incidence rate of serious infections during the TNF-α blocker was three times higher than during the control period [1, 5, 7]. Furthermore, the NNH was evaluated at 14 in this study. A highly harmful intervention may have an NNH as small as 5. However, the clinical relevance of the harmfulness obviously depends not only on the numerical value of the NNH but also on the severity of the outcome. In this case, serious infection being a severely harmful outcome, an NNH of 14 can be considered as highly clinically relevant [25].

There are few data for infection rates in daily practice in the literature. In a post-marketing study, Kroesen *et al.* [15] evaluated prospectively serious infections (defined as requiring hospitalization and/or intravenous antibiotic therapy) in 60 patients with RA receiving infliximab or etanercept and found much higher incidence rates than during the 24 months before initiation of TNF-α blocker in the same patients (18.1 per 100 TNF blocker treatment years *vs* 0.8 events in the 2 yrs preceding the initiation of TNF blocker therapy, respectively). Recently, Listing *et al.* [28] compared the incidence rate of serious infections between 858 RA patients receiving infliximab or etanercept treatment and 601 RA

controls treated with DMARDs. The rates per 100 patient-yrs were 6.4, 6.2 and 2.3 for etanercept, infliximab and controls, respectively; the relative risk of serious infections for patients receiving TNF-α blocker therapy was 2 [28]. Thus, results of the present study are opposed to phase III trials but comparable with the two published daily practice studies.

The second important aspect of this study's results concerns potential differences between TNF-α blockers. In this study, infection rates for serious infections seemed to be higher for infliximab therapy than for the other two molecules, etanercept and adalimumab. For any infections, rates appeared higher for infliximab and comparable for etanercept and adalimumab. The clinical relevance of these differences in rates remains to be determined. Furthermore bias cannot be excluded, i.e. perhaps patients treated with these molecules were not strictly comparable; this limitation is common to all non-randomized studies. Moreover, the patients receiving infliximab therapy might be monitored more frequently (e.g. every 8 weeks) by their physicians comparing with those treated with subcutaneous TNF-α blocker. Thus, they may have a greater opportunity to report an infection especially non-serious one.

TNF-α plays a major role in the defense against micro-organisms, especially intracellular bacteria for which it prevents dissemination by activating the formation of granulomas [21, 29–34]. Wallis *et al.* [19] observed that the risk of granulomatous infections was 3.25-fold greater during infliximab therapy than during etanercept treatment. This difference may reflect the ways in which infliximab and etanercept neutralize TNF-α. Infliximab seems to have a much higher affinity for both soluble TNF-α and transmembrane TNF-α and to induce apoptosis of monocytes and T-cells. Thus, the neutralization of TNF-α and the defects in host immunity could explain the increased risk of granulomatous infections during infliximab therapy comparing etanercept treatment [31–37]. However, it is difficult to hypothesize on the mechanisms since it appeared that the infection rates were rather low with adalimumab, even though it is, like infliximab, a monoclonal antibody. The literature lacks data concerning the difference between rates of infections during adalimumab *vs* etanercept therapies. These results should perhaps be interpreted with caution, as exploratory results, pending further confirmation by other studies.

This study gives some indications concerning infectious patterns in daily practice during TNF-α blocker therapy.

As reported in the literature, bacterial and viral infections were the most frequent in the present study and the most common localizations were skin, upper respiratory tract and lung [1, 5, 7, 15]. Perhaps, at the initiation of such therapy, the patients might be educated about dental hygiene, self-survey of fever and skin lesion. In the present study, only two tuberculosis infections were reported, which may be due to the systematic screening for tuberculosis before initiation [38].

Associated risk factors to explain infections, in the present study, were previous joint surgery and a high cumulative dose of steroids. Curiously, age, underlying disease and its duration did not appear as associated risk factors. Nevertheless, previous joint surgery and a high cumulative dose of steroids are more frequent in severe RA. In 609 patients with RA followed during 12.7 yrs before the TNF-α blocker era, Doran et al. [39] found increased age, presence of extra-articular manifestations of RA, leucopenia, use of steroids and comorbidity as strong predictors of serious infections. In association with adalimumab, concomitant use of DMARDs was not associated with an increased risk of infections [7].

Some strengths and shortcomings of this study are the following. This study was retrospective. Thus, the potential underreporting of non-serious infections during the control period did not allow us to conclude about the increase of any infections occurring under TNF-α blocker therapy; furthermore, some patterns of infections could have been detailed fully. However, phase-III efficacy clinical trials cannot adequately study adverse effects: only observational studies may assess such a risk [40]. The present study focused on the use of TNF-α blockers in daily practice, was systematic and exhaustive without selection of patients, thus avoiding bias. Moreover, all patients treated with a TNF-α blocker whatever their rheumatic underlying disease were included, whereas most data in the literature concerns patients receiving TNF-α blocker for refractory RA.

This study indicates that, in daily practice, serious infections are frequent during TNF-α blocker therapy, and perhaps more during infliximab treatment, with a much higher rate than in phase-III trials. The most frequent site of infections seem to be upper respiratory tract, lung and skin. Thus, at the initiation of TNF-α blocker therapy, patients should be educated about the early symptoms of infection and self-survey of fever, lung symptoms and skin lesions. Patients should be carefully selected and thereafter monitored with regard to TNF-α blocker therapy, in particular for patients treated with previous high dose of steroids. These important results may lead to modifications of the physician's habits when initiating and monitoring a TNF-α blocker, if they are confirmed by further studies.

The two authors contributed equally to the conception, design, analysis, interpretation of data, and to drafting the manuscript.

The authors have declared no conflicts of interest.

References

1. Maini R, St Clair EW, Breedveld F et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932–9.
2. Lipsky PE, van der Heijde DM, St Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med 2000;343:1594–602.
3. Weinblatt ME, Kremer JM, Bankhurst AD et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
4. Moreland LW, Schiff MH, Baumgartner SW et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478–86.
5. Moreland LW, Cohen SB, Baumgartner SW et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 2001;28:1238–44.
6. Furst DE, Schiff MH, Fleischmann RM et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563–71.
7. van de Putte LB, Atkins C, Malaise M et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–16.
8. Targan SR, Hanauer SB, van Deventer SJ et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's disease cA2 study group. N Engl J Med 1997;337:1029–35.
9. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet 2000;356:385–90.
10. van der Heijde D, Dijkmans B, Geusens P et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.
11. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.
12. Singh G, Ramey DR, Rausch PL, Schettler JD. Serious infections in rheumatoide arthritis: relationship to immunosuppressive use. Arthritis Rheum 1999;42(Suppl.):S71–474.
13. Dixon WG, Hyrich KL, Watson K, Symmons DPM, Silman AJ and the BSR Biologics Register. Serious infection rates in patients receiving biologics therapy in the United Kingdom: results from the BSR biologics register. EULAR congress 2005, OP0094.
14. Jacobsson LTH, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, Geborek P. No increase of severe infections in rheumatoid arthritis patients treated with TNF-blockers. EULAR congress 2005, SAT0164.
15. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003;42:617–21.
16. Keane J, Gershon S, Wise RP et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098–104.
17. Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 2004;39:295–9.
18. Keystone EC. Safety of biologic therapies-an update. J Rheumatol Suppl 2005;74:8–12.
19. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261–5.
20. Nestea MG, Radstake T, Joosten LA, van der Meer JW, Barrera P, Kullberg BJ. Salmonella septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and Toll-like receptor 4 expression. Arthritis Rheum 2003;48:1853–7.
21. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2003;48:3013–22.
22. Crum NF, Lederman ER, Wallace MR. Infections associated with tumor necrosis factor-[alpha] antagonists. Medicine 2005;84:291–302.
23. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

24. Amor B, Dougados M, Listrat V *et al.* Are classification criteria for spondylarthropathy useful as diagnostic criteria? Rev Rhum Engl Ed 1995;62:10–5.

25. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. New Engl J Med 1988;318:1728–33.

26. Sierra F. Evidence-base medicine in practice: applying number needed to treat and number needed to harm. Am J Gastroenterol 2005;100:1661–3.

27. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann intern Med 1997;126:712–20.

28. Listing J, Strangfeld A, Kary S *et al.* Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403–12.

29. van der Klooster JM, Bosman RJ, Oudemans-van Straaten HM, van der Spoel JI, Wester JP, Zandstra DF. Disseminated tuberculosis, pulmonary aspergillosis and cutaneous herpes simplex infection in a patient with infliximab and methotrexate. Intensive Care Med 2003;29:2327–9.

30. Haerter G, Manfras BJ, de Jong-Hesse Y *et al.* Cytomegalovirus retinitis in a patient treated with anti-tumor necrosis factor alpha antibody therapy for rheumatoid arthritis. Clin Infect Dis 2004;39:e88–94.

31. Gardam MA, Keystone EC, Menzies R *et al.* Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003;3:148–55.

32. Wallis RS, Ehlers S. Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. Semin Arthritis Rheum 2005;34(Suppl.):34–8.

33. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. Clin Infect Dis 2005;41 (Suppl.):S194–8.

34. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? Clin Infect Dis 2005;41(Suppl.):S199–203.

35. Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol Suppl 2005;74:35–9.

36. Dinarello CA. Differences between anti-tumor necrosis factor-alpha monoclonal antibodies and soluble TNF receptors in host defense impairment. J Rheumatol Suppl 2005;74:40–7.

37. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50:372–9.

38. Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. Ann Rheum Dis 2003;62:791.

39. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.

40. Pincus T, Stein CM. Why randomised clinical trials do not depict accurately long-term outcomes in rheumatoid arthritis: some explanations and suggestions for future studies; Clin Exp Rheumatol 1997;15(Suppl. 17):S27–38.