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Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

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***Objective*. With rising numbers of anti-tumour necrosis factor α (TNF-α) treatments for rheumatoid arthritis (RA), Crohn's disease and other conditions, physicians unaware of potential pitfalls are increasingly likely to encounter associated severe infections. Our purpose was to assess the incidence and nature of severe infections in our RA patients under anti-TNF-α therapy.**

***Methods*. We reviewed patient charts and records of the Infectious Disease Unit for serious infections in patients with RA in the 2 yr preceding anti-TNF-α therapy and during therapy.**

***Results*. Serious infections affected 18.3% of patients treated with infliximab or etanercept. The incidence was 0.181 per anti-TNF-α treatment year *vs* 0.008 in the 2 yr preceding anti-TNF-α therapy. In several cases, only a few signs or symptoms indicated the severity of developing infections, including sepsis.**

***Conclusions*. A high level of suspicion of infection is necessary in patients under anti-TNF-α therapy. We suggest additional strategies for the prevention, rapid identification and pre-emptive therapy of such infections.**

KEY WORDS: TNF-α, anti-TNF-α therapy, Infection, Complications, Rheumatoid arthritis.

The efficacy of the anti-tumour necrosis factor α (TNF-α) agents infliximab and etanercept in the treatment of rheumatoid arthritis (RA) has been demonstrated in large-scale trials [1–4]. Their results indicate a superior effect of these agents compared with conventional disease-modifying anti-rheumatic drugs (DMARDs). Among the undesired effects of anti-TNF-α agents, infections have been a primary concern. Under study conditions, 53% of patients in the group treated with 3 mg/kg infliximab together with methotrexate had an infection compared with 40% in the placebo group [1]. For any given infection, the difference between the groups was statistically significant. However, the incidence of serious infections, defined as life-threatening or requiring hospitalization, was not statistically different over the dose ranges studied (6% for placebo *vs* 1% for 3 mg/kg every 8 weeks to 6% for 10 mg every 4 weeks). With etanercept, infections occurred in 51% of the patients in the active treatment group compared with 63% in the placebo group [3]. On the basis of these data, it was assumed that the incidence and severity of infections were not markedly increased under treatment with these agents when compared with other data on infections in RA [5–7].

Recently, anti-TNF-α therapy has been associated with the reactivation of tuberculosis, again raising concerns that infections may pose a significant threat [8]. In addition to the existing warnings of potential infections under etanercept and infliximab contained in the package insert, in the case of the latter the FDA (Food and Drug Administration, USA) requested the addition of a 'black box' with recommendations concerning tuberculosis. So far, postmarketing surveys have not revealed significant problems with serious infections under anti-TNF-α therapy. However, because the nature and course of infectious disease may be altered by anti-TNF-α therapy, it is of critical importance to consider this aspect in the care of patients. We evaluated a series of serious infections from our institution which highlight the potential pitfalls and difficulties with infections under infliximab and etanercept.

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Methods

From the onset of compassionate use and after approval for clinical use in RA, all RA patients receiving the anti-TNF-α agents etanercept and infliximab at our institution gave written consent to be followed prospectively in a central national data registry approved by the nationwide ethics committee of the Swiss Academy for Medical Sciences [9]. In addition to the data entered into the registry, other clinical information, including all undesired effects after the beginning of anti-TNF-α therapy, were recorded in the patient charts. The charts of all patients were reviewed for any serious infection in the 2 yr preceding anti-TNF-α therapy. A cross-check with the computerized records of consultations by the Infectious Disease Unit and all microbiology records at the University Hospital Basel was performed on all patients with RA to identify any severe infections that may have been missed in the patient charts. Patients on anti-TNF-α therapy were managed by designated physicians under close supervision by experienced board-certified rheumatologists. We report all events classified as a serious infection, defined as requiring hospitalization and/or intravenous antibiotic therapy, which occurred from the beginning of the anti-TNF-α programme in December 1999 up to May 2002 in patients followed at our out-patient unit. The incidence of infections meeting these criteria was compared with that during the last 24 months of conventional therapy in the same patients before the beginning of anti-TNF-α therapy.

Infliximab was given on an out-patient basis as an intravenous infusion at 3 mg of infliximab/kg body weight over 2 h, following the manufacturer's instructions. Infusions were given at time 0, 2 weeks and 6 weeks, and every 8 weeks thereafter, except when indicated otherwise. In all cases, infliximab was combined with methotrexate, which was given at a dose between 7.5 and 20 mg once weekly. Etanercept was given as twice-weekly subcutaneous injections of 25 mg except when indicated otherwise. Initial injections were performed by specialized nurses of the out-patient unit, and afterwards by the patients themselves once they achieved adequate proficiency.

Results

A total of 60 patients were treated at our out-patient unit during the period after October 1999. Thirty-six treatment courses were started with etanercept and 28 with infliximab, of which 34 and 18 respectively are ongoing. Five patients switched from infliximab to etanercept, and one from etanercept to infliximab. The median age was 52.98 yr (range 21.3–85.4 yr), 13 were males and 47 were females. The median duration of RA was 12.4 yr (range 1.7–39.4 yr) and the median number of DMARDs was 3 (range 1–8). The median number of treatment months per patient was 19.6 (range 4.0–33.14) for infliximab and 20.69 (range 2.14–32.1) for etanercept. The principal features of the 11 patients with a serious infection are summarized in Table 1. In the following, brief comments are provided.

Patient 1 presented with pneumonia due to *Streptococcus pneumoniae* and *Pneumocystis carinii*, and patient 10 with pneumonia due to *Staphylococcus aureus*. In both cases onset was abrupt, with chest pain and dyspnoea. This was preceded by a slight cough without discomfort or general symptoms. Patient 1 had an isolated elevation of C-reactive protein (CRP) 4 days before the onset and patient 10 had normal clinical, laboratory and chest radiographic examinations only 2 days before the acute symptoms began. *P. carinii* was detected in bronchial washings. Patient 10 had extensive necrotizing abscesses of both lungs. Patient 2 had bilateral *Legionella pneumophila* pneumonia and fever but felt no distress.

Patient 3 was admitted because of nausea, loss of appetite and failure to provide a urine sample in the morning. Leucocytes were 18.0×10^9/l and CRP was 249 mg/l (normally <5.0 mg/l). After admission, intense abdominal pain and deterioration of her general condition evolved rapidly in the late afternoon. A CT scan excluded diverticulitis, but catheter urine and all blood cultures were positive for *Escherichia coli*. Patient 4 had normal clinical and laboratory examinations 2 days before the acute onset of a foot abscess, probably originating from a plantar bunion, with chills and fever. Surgical drainage fluid and all blood cultures grew *S. aureus*. In patient 6, a meniscal tear with prominent effusion of the right knee was present. Joint fluid showed scant growth of coagulase-negative staphylococci after several days. A second and third joint aspirate showed increasingly rapid growth and an increasing number of leucocytes. Upon differentiation, *Staphylococcus lugdunensis* was identified, a coagulase-negative species with pathogenic potential similar to *S. aureus* in the bloodstream [10]. Despite i.v. flucloxacillin, her condition worsened until an open, extensive synovectomy was performed, whereupon recovery began [11]. Patients 7 and 11 developed severe diverticulitis with systemic manifestations within hours; i.v. antibiotics were initiated without delay and blood cultures remained negative. Patient 8 had an unexpectedly rapid systemic extension of a bladder infection.

These cases illustrate the variety of clinical presentations of serious infections associated with anti-TNF therapy, the propensity to behave relatively innocuously for an extended time, and their life-threatening nature. There was no apparent predilection for a specific bacterial agent. No tuberculosis or serious viral infections were recorded. With the exception that the shortest interval between initiation and infection was 22 weeks, we found no relationship with the duration of infliximab or etanercept therapy. Also, there was no clustering of infections at any point in the interval between infliximab infusions. Temperature, erythrocyte sedimentation rate and leucocyte counts were not consistently altered, whereas CRP was uniformly elevated, in several cases before the infection became evident locally or systemically.

In seven of the 11 cases, it was possible to attribute the clinically apparent infection to specific organisms, exceptions being two patients with pneumonia and two patients with diverticulitis. A broad variety of agents and the possibility of multiple infections must be considered in the diagnostic work-up. Coagulase-negative staphylococci from patients under anti-TNF-α therapy should be interpreted similarly to those in

Table 1. Clinical features of patients with complications under anti-TNF-α therapy

Patient	Age (yr), sex	Diagnosis; DMARDs	Date of diagnosis	Comorbidity	IFX/ETC	Concomitant therapy	Infection	Microorganism
1	30, F	RA, RF^-; MTX, CYS, AU, LEF	2/1999	Bronchial asthma	IFX 3 mg/kg	MTX 15 mg/w, PRD 30 mg/d	Pneumonia, secondary bloodstream infection	*S. pneumoniae*, *P. carinii*
2	49, M	RA, RF^-; MTX, CYP, CYS	1991	Psoriasis	IFX 3 mg/kg	MTX 15 mg/w	Pneumonia	*L. pneumophila* (antigen only)
3	73, F	Erosive RA, RF^+; HCL, MTX p.o., SAL, CYS, AU	3/1996	None	ETC 1×25mg/w	MTX 15 mg/w, PRD 10 mg/d	Urosepsis, secondary bloodstream infection	*E. coli*
4	66, F	Erosive RA, RF^+; AU, SAL, MTX	1987	None	IFX 3 mg/kg	MTX 10 mg/w, PRD 7.5 mg/d	Foot abscess, secondary bloodstream infection	*S. aureus*
5	42, F	Rapidly progressive, erosive RA, RF^+; MTX, SAL, HCL	1992	None	IFX 3 mg/kg	MTX 10 mg/w	Pneumonia	n.d.
6	72, F	RA, RF^-; HCL, SAL, AU, PEN, CYS, CYP	1988	Heart failure	ETC 2×25 mg/w	None	Septic knee arthritis, secondary bloodstream infection	*S. lugdunensis*
7	57, F	RA, RF^-; MTX, SAL, CYS	1995	None	IFX 3 mg/kg	MTX 20 mg/w, PRD 10 mg/d	Diverticulitis	n.d.
8	38, F	RA, RF^+; PEN, MTX, AZA, CYP, SAL, HCL	7/1993	Diffuse systemic sclerosis	ETC 2×25 mg/w	CYS 100 mg/d PRD 5 mg/d	Pyelonephritis	*Proteus mirabilis*
9	52, F	RA; PEN, HCL, SAL, MTX	1976	Hypertension, osteoporosis	ETC 2×25 mg/w	PRD 5 mg/d, diclofenac 2×50 mg	Pneumonia	n.d.
10	61, F	RA, RF^+; MTX, SAL, HCL, CYS	1966	Hypertension	IFX 3 mg/kg	HCL 1 × 200mg/d, MTX 12.5 mg/w, PRD 10 mg/d	Pneumonia	*S. aureus*
11	66, F	Erosive RA, RF^+; MTX	8/1999	CHD, hypertension Graves disease, osteoporosis	ETC 2×25 mg/w	PRD 5 mg/d	Diverticulitis	n.d.

Infliximab and etanercept were administered as described under Methods.

AU, gold; CHD, coronary heart disease; CYP, cyclophosphamide; CYS, cyclosporin; d, day; ETC, etanercept; HCL, hydroxychloroquine; IFX, infliximab; LEF, leflunomide; MTX, methotrexate; n.d., not determined; p.o., orally; PEN, D-penicillamine; PRD, prednisone; RF, rheumatoid factor; SAL, salazopyrin (sulphasalazine); w, week.

TABLE 2. Treatment years before and after anti-TNF-α therapy and incidence of serious infections

	Before anti-TNF-α	After start of anti-TNF-α
Years of observation	123.0	60.65
Serious infections	1	11
Serious infections/yr	0.008	0.181

Treatment years were determined as described under Methods.

patients with severe immunosuppression, and the species should be identified.

The total number of months of treatment with etanercept and infliximab, the number of months of treatment with DMARDs before starting anti-TNF-α therapy and the number and incidence of serious infections are shown in Table 2. There was a clear difference in the incidence of serious infections before compared with after anti-TNF-α therapy. Of all patients under anti-TNF-α therapy, 18.3% had a serious infection.

Discussion

From the onset of clinical trials, a central concern of cytokine blockade has been a potential increase in susceptibility to infections. This was due to the central role of cytokines, especially TNF-α and interleukin 1, in mounting the inflammatory response. TNF-α in soluble form increases the expression of adhesion molecules on endothelial cells and activates neutrophils and macrophages. Surface-bound TNF-α is likely to be involved in cell-to-cell interactions, possibly potentiating the activation of specific and non-specific immune effective cells. Finally, it may also play a role in winding down inflammation once surface-bound TNF-α receptors are expressed. In spite of these considerations, no significant increase in serious infections has been reported in studies performed to evaluate the efficacy of anti-TNF-α agents [12]. However, it is noteworthy that there may be a dose-dependent increase in serious infections under anti-TNF-α therapy [2]. Postmarketing surveys have not shown a clear increase in the rate of serious infections, apart from the reactivation of tuberculosis, though this is infrequent [8].

Both in relation to the number of treatments started and of patient-years of treatment, the rates of serious infections in our patients are approximately twice as high as those reported in the efficacy studies [1–4] or registered in postmarketing surveys. The difference in incidence under anti-TNF-α agents cannot be explained by different definitions of serious infections, because all of our cases required hospitalization. In postmarketing surveys, under-reporting, or a lack of reporting, may be a significant factor. Given the highly effective reduction in disease activity achieved by these agents, which also occurred in our patient population, some adverse outcomes may be acceptable. However, patient and physician awareness must be tuned to recognize that the course of infections may be fulminant and that every effort must be made to clarify even slight alterations in well-being. This is necessary because clinical and laboratory signs may be blunted by TNF-α blockade and by concomitant immunosuppressive medication. In this respect, certain common features in our case series indicate how to identify infections early. First and most prominent is a rise in the CRP level, in which case an infection must be ruled out immediately, even if this involves extensive diagnostic procedures. Secondly, positive blood cultures or synovial fluid cultures with pathogens of low pathogenicity (e.g. coagulase-negative staphylococci) must be taken seriously even though the patient's well-being is not or only slightly affected and laboratory results are normal. Thirdly, once symptoms become clinically overt, severe sepsis must be anticipated and rapid deterioration averted.

Patients with RA, especially RA of long duration, have a record of fatigue and recurrent episodes of reduced well-being. They are used to managing these conditions without seeking medical attention. Likewise, physicians may be desensitized to potential warning signs. Considering the total number of treatments currently applied and the potential for a widening of indications for the use of anti-TNF-α agents, we strongly recommend that institutions using these therapies provide safeguards 24 h a day 7 days a week. Patient education is essential and may benefit from a structured programme. Finally, the question of immunization before the initiation of anti-TNF-α therapy must be considered. At present there are no data from controlled trials allowing specific recommendations. However, a well-informed patient, a physician highly suspicious of infectious complications, and rapid access to health-care will make it possible to take advantage of this new treatment option while minimizing potentially life-threatening complications.

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