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EDITORIAL

Risk of infectious complications during anti-TNFα therapy

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Tumour necrosis factor α (TNFα) is one of the cytokines that play an active role in inflammatory processes. The observation that TNFα was of major importance for the continued synovial inflammation in patients with rheumatoid arthritis (RA) and that blockade of TNFα decreased arthritis activity in animal models has stimulated the development of TNFα inhibitors for human use. The introduction of these agents has benefited many patients with rheumatoid arthritis. Meanwhile, TNFα inhibitors have also been licensed for the treatment of patients with Crohn's disease, psoriasis, psoriatic arthritis, and ankylosing spondylitis. In the near future the list of indications for this therapy may grow since promising therapeutic effects have been described in patients with sarcoidosis and uveitis.[1,2]

At present three TNFα inhibitors are available for use in daily clinical practice: infliximab, adalimumab, and etanercept. These agents differ in pharmacokinetics and mechanism of action. Infliximab is a chimeric (human-murine) monoclonal anti-TNFα antibody. It is administered intravenously in a dose of 3 to 5 mg/kg bodyweight once every six to eight weeks. Adalimumab is a recombinant fully humanised monoclonal anti-TNFα antibody, which is given subcutaneously in a dose of 40 mg every two weeks. Etanercept is a recombinant soluble p75 TNF-receptor:Fc fusion protein which is administered subcutaneously in a dose of 50 mg once weekly. These differences reflect the differences in duration of action. The half-lives of infliximab and adalimumab are 8 to 10 days and 10 to 20 days, respectively, whereas etanercept has a shorter half-life of four days.[3]

There are subtle differences in the mechanism of action. The TNFα antibodies (infliximab and adalimumab) are more effective in lowering TNF activity, in eliminating macrophages and monocytes, and in reducing γ-interferon production than etanercept.[3] As such, granuloma formation is inhibited to the largest extent by infliximab and adalimumab.

All three TNFα inhibitors have been licensed for the treatment of patients with RA, who have active disease despite treatment with conventional disease modifying antirheumatic drugs such as methotrexate or sulfasalazine. Although head-to-head comparisons are lacking, the agents seem to have similar efficacy for the treatment of patients with RA. In contrast, both monoclonal antibodies are effective in patients with Crohn's disease whereas etanercept, the recombinant soluble receptor, is not. It is tempting to attribute these differences to the abovementioned differences in effect on granuloma formation.

The cytokine TNFα plays an important role in the body's defence against the invasion of micro-organisms by stimulating the recruitment of macrophages and leucocytes to the site of inflammation. As discussed, TNFα also plays a role in the formation of granulomas, a host defence mechanism against intracellular micro-organisms such as *Mycobacterium tuberculosis*. These actions of TNFα suggested that its blockade may lead to a higher incidence of (serious) infections including predominantly those with intracellular micro-organisms. Indeed, the use of TNFα blockers has been associated with the development of granulomatous infections.

Of these, infections caused by *Mycobacterium tuberculosis* are reported most frequently. There is a special predominance of extrapulmonary forms of tuberculosis, as highlighted by the two cases in the report by Verhave *et al.* in this issue of the Netherlands Journal of Medicine.[4] The authors describe two patients with RA who both developed tuberculous peritonitis after starting treatment with the TNFα inhibitor infliximab. These cases underline the difficulties related to the screening of patients for latent tuberculosis, the importance of preventive measures, and the problems in the diagnosis of extrapulmonary tuberculosis. It is well advised to consider

tuberculosis as diagnosis in anti-TNFα treated patients with unexplained symptoms, and in individual cases a blind start of tuberculostatic treatment may be warranted. As pointed out by the authors, the incidence of tuberculous infections is higher during treatment with infliximab (or adalimumab) than with etanercept. This also holds for other granulomatous infections as shown in *table 1*.

Table 1. *Number and incidence of granulomatous infections in patients with rheumatoid arthritis treated with TNFα blockade*[3]

Infection	Infliximab	Etanercept
	n (n/100,000 treated patients)	
Tuberculosis	106 (54)	32 (28)
Histoplasmosis	37 (19)	3 (2.7)
Atypical mycobacteriosis	22 (11)	7 (6.2)
Candidiasis	20 (10)	6 (5.3)
Aspergillosis	17 (8.6)	7 (6.2)
Listeriosis	17 (8.6)	1 (0.88)
Cryptococcosis	10 (5.1)	8 (7.1)
Coccidioidomycosis	11 (5.6)	1 (0.88)
Nocardiosis	7 (3.6)	1 (0.88)
Toxoplasmosis	4 (2.0)	(0)
Total	*255 (130)*	*68 (60)*

The recognition of an increased risk of tuberculosis during anti-TNFα therapy has resulted in the development of a guideline by the Dutch Society for Rheumatology concerning the necessary screening procedures to detect active or latent tuberculosis in these patients before starting therapy.[5] As reflected by the two patients in the case report, foreign-born migrants may be at particular risk. The prevalence of active tuberculosis in immigrants from countries with a high incidence of tuberculosis is <1%. However, the prevalence of latent tuberculosis, defined as a positive tuberculin skin test without chest radiographic abnormalities, may be as high as 35 to 42%.[6] Travel to areas with a high incidence of tuberculosis poses a risk. This has been addressed in a study from the Netherlands which documented that the risk of developing a positive tuberculin skin test was related to the total time spent in the high incidence area. Increased risk was limited to persons who had been travelling for longer than three months.[7]

What about other infectious complications? The early controlled clinical trials with infliximab, adalimumab or etanercept could not document a significantly increased risk of infectious complications.[8-10] However, these clinical trials primarily addressed the efficacy of TNFα inhibitors in RA, and were certainly not powered to detect an increased risk of infection. Studies that are used for the registration of new drugs have important weaknesses with respect to the detection of infrequent, late occurring severe side effects.[11]

The interpretation of the early controlled studies that incorporated evaluation of infectious complications in patients with RA is further complicated by the presence of confounding factors that influence the risk of development of infections such as disease activity, comorbidity, and use of concomitant immunosuppressive drugs. It is well-known that treatment with steroids is an important risk factor for development of infectious complications, a relation which is dose-dependent. Furthermore, Doran *et al.* showed that RA patients not treated with biologicals (and after adjustment for steroid use) were at increased risk to develop infections compared with matched non-RA controls.[12] This means that the disease itself and/or the use of other drugs with immunosuppressive effects could explain the higher infection rate.

Although the abovementioned clinical trials could not document a relation between infections and TNFα inhibition, there are data to support an association between anti-TNFα therapy and the development of serious infections, defined as infections that require antimicrobial therapy or hospitalisation. The most important evidence comes from a large meta-analysis of randomised placebo-controlled trials that included RA patients receiving treatment with infliximab or adalimumab.[13] This meta-analysis compared 3493 RA patients treated with a TNFα inhibitor and 1512 control patients. The relative risk for a serious infection was 2.0 in the patients treated with infliximab or adalimumab.

Data from national registries in which patient cohorts with and without anti-TNFα therapy were compared also suggest an increased risk of infections. An overview of the German registry, including 512 patients treated with etanercept and 346 patients treated with infliximab, showed that the risk of serious infections was significantly elevated during treatment with a TNFα inhibitor.[14] Although the British registry, with data on 7664 anti-TNF treated RA patients, could not document an overall increased risk of infections, there was a relative risk of 4.3 for the development of serious skin and soft tissue infections.[15] The data from the British registry confirmed the particular risk of infections with intracellular bacteria. Infections caused by *Mycobacterium tuberculosis, Legionella pneumophilia, Listeria monocytogenes* and *Salmonella* were exclusively observed in anti-TNF treated patients.

In view of an expected increased risk of postoperative wound infections in patients treated with TNFα inhibitors it is recommended to discontinue these agents temporarily in the perioperative period. The guideline of the Dutch Society for Rheumatology advises withholding TNFα inhibitors preoperatively. The agents should be stopped

to allow disappearance of the drug before the operation, i.e. the time period should be approximately four times the half-life of the particular agent.[16] However, this policy is under debate since there are discussions on the risk of anti-TNF related postoperative infections. In a retrospective study, den Broeder *et al.* concluded that perioperative continuation of anti-TNFα was not an important risk factor for surgical wound infections.[17] In contrast, Giles *et al.* demonstrated a significant association between infectious complications following orthopaedic surgery and treatment with TNFα inhibitors.[18]

In conclusion, patients who are treated with TNFα inhibitors are at risk for infections. Tuberculosis is the major problem; however, other infections may also occur more frequently. The infection risk is no reason to withhold therapy with TNFα inhibitors; however, the agents should be stopped in case of a suspected serious infection. The perioperative use of these agents is under discussion.

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