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Problems encountered during anti-tumour necrosis factor therapy

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Worldwide, over 400 000 patients have been treated with tumour necrosis factor (TNF)-α antagonists for indications that include rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis and ankylosing spondylitis. Since their approval, concerns regarding safety have been raised. There is a risk of re-activation of granulomatous diseases, especially tuberculosis, and measures should be taken for detection and treatment of latent tuberculosis infections. Preliminary data suggest that anti-TNF therapy may be safe in chronic hepatitis C. However, TNF-α antagonists have resulted in re-activation of chronic hepatitis B if not given concurrently with antiviral therapy. Solid tumours do not appear to be increased with anti-TNF therapy. Variable rates of increased lymphoma risk have been described with anti-TNF therapy compared with the general population, although no increased risk was found compared with a rheumatoid arthritis population. Large phase II and III trials with TNF-α antagonists in advanced heart failure have shown trends towards a worse prognosis, and should therefore be avoided in this population. Both etanercept and infliximab are associated with the formation of autoantibodies, and these autoantibodies are rarely associated with any specific clinical syndrome. Rare cases of aplastic anaemia, pancytopenia, vasculitis and demyelination have been described with anti-TNF therapy. This chapter will discuss the safety profile and adverse events of the three commercially available TNF-α antagonists: etanercept, infliximab and adalimumab. The data presented in this review have been collected from published data, individual case reports or series, package inserts,

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the Food and Drug Administration postmarketing adverse events surveillance system, and abstracts from the American College of Rheumatology and European Congress of Rheumatology meetings for 2005.

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SAFETY OF TNF-α ANTAGONISTS AND INFECTIONS

General infections

Bacterial and viral infections following use of tumour necrosis factor (TNF) antagonists continue to be a source of concern. In this examination of such infections, several caveats have to be considered. Firstly, although preregistration studies can be used, postmarketing studies, which are longer, are examined more frequently. Unfortunately, postmarketing studies are not well controlled for selection bias and bias by indication, and follow-up is often not as close as in premarketing studies. Secondly, significant infections and serious infections are often poorly defined and definitions differ between studies. This section will review studies of infections in general separately from serious infections. The data reviewed comes from preregistration studies, retrospective studies, observational studies, and registry data.

Infections

Data regarding infections in general come from epidemiological studies. The CORRONA database examined 5596 rheumatoid arthritis (RA) patients, followed for 6817 patient-years, and compared patients on TNF inhibitors (3012 patients over 2722 patient-years; 48% on infliximab, 40% on etanercept and 12% on adalimumab) with patients not using TNF inhibitors. Infections were physician estimated and no specific definitions were given. Thirty-seven infections occurred per 100 patient-years in the anti-TNF group, compared with 29 infections per 100 patient-years in patients not using TNF inhibitors. After adjusting for age, sex, disease duration, disease activity, comorbid conditions, previous disease-modifying antirheumatic drugs (DMARDs) and prednisone, there was a small increase in these infections in patients using TNF inhibitors; the incident rate ratio was 1.16 [95% confidence interval (CI) 1.06–1.28, $P = 0.002$].[1] Data from the German Biologics Registry gave fairly similar results.[2] Although fewer patients were included, the analysis in the German study was well conducted. A 1-year follow-up was performed and 512 etanercept-treated patients, 346 infliximab-treated patients and 601 patients on DMARDs were examined. In this study, the definition of serious adverse events was similar to that used by the Food and Drug Administration (FDA) (i.e. requiring hospitalization, prolonging hospitalization, associated with death or felt to be potentially life-threatening), but the definition of a serious infection was not clear. Other infections were also studied, although their definitions were also unclear. Between 22.6% and 28.3% of patients on TNF blockers had some type of infection, compared with 6.8% of the DMARD controls. The controls had less severe disease than the anti-TNF-treated patients and, after propensity scoring was used for adjustment, the authors pointed out that the relative risk for comparable patients should probably be decreased by approximately one-third. Thus, for all infections, the relative risk of 3.3–4.14 (95% CI > 1) was decreased to 2.13–2.16 (95% CI > 1) after adjusting for propensity scoring. This article pointed out that

pulmonary, skin, and herpes infections, in particular, occurred more frequently in patients using etanercept or infliximab, while infections of the gastrointestinal tract, bones and joints did not appear to be increased in these patients.

Serious infections

Of a total of seven studies, three indicated that serious infections occurred more frequently in association with TNF-blocking agents, and four studies showed no differences compared with other DMARDs.

Two retrospective reviews indicated some propensity for increased serious infections among patients using TNF-blocking agents. Salliot et al examined 707 patients and compared infections occurring in the period before starting TNF-α inhibitors with infections occurring during TNF-α-blocker therapy.[3] Among the 275 infections that were noted after anti-TNF therapy was initiated, 5% were serious (14 infections). Of the 14 serious infections, 10 were bacterial infections and four were either mycobacterial or viral. The authors calculated that the serious infection rate was 2.9 ± 35 per 100 patient-years in the period prior to anti-TNF therapy, compared with 8.8 ± 78 per 100 patient-years during anti-TNF therapy ($P = 0.02$). However, given the very high standard deviations, the inference that there was a difference cannot be drawn with any confidence. The second retrospective study examined 60 patients from a single centre and did not define serious infections.[4] Eleven infections were reported; six in patients using infliximab and five in patients using etanercept. Methotrexate and prednisone were used by most patients. The infection rate before using TNF blockers was 0.08 infections/year compared with 0.181 infections/year after starting TNF blockers.

A retrospective analysis of clinical trials using adalimumab was carried out by Kent et al.[5] In these phase I-III trials, with a long-term open-label extension in 2504 patients over 7591 patient-years, infections were defined primarily as those requiring hospitalization. There were 257 serious infections. The serious infection rate was between 0.042 and 0.049/patient-year. This was compared with historical DMARD controls of 0.03—0.10/patient-year, and was not found to be different. Without concomitant controls, these data need to be viewed with some scepticism. Another study had concomitant controls.[6] On a methotrexate background, patients were given adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo. There were approximately 200 patients/group. Although infections were not defined, the infection rate/year was 0.06 in the placebo group, 0.08 in the alternate-week adalimumab group and 0.18 in the weekly adalimumab group (no statistics were given but these do not appear to be markedly different in this 1-year study).

The results of three studies of infections with TNF-α antagonists came from registries. The UK nationwide registry compared patients on TNF-α antagonists (2247 etanercept patients, 2398 infliximab patients and 659 adalimumab patients) with 648 patients on DMARDs.[7] Serious infections were defined as those requiring hospitalization, intravenous antibiotics or resulting in death. After adjusting for age, sex, disease duration, disease severity (not defined), steroids, comorbidities and smoking, there were no differences between the serious infection rates in those using etanercept, infliximab or adalimumab compared with the DMARD controls (0.97 vs 0.98 vs 1.27, respectively; P = not significant). The same conclusion was made by the Swedish Arthritis Treatment Group, which followed anti-TNF therapy in 412 RA patients between 1999 and 2001.[8] These patients represented more than 90% of all RA patients given TNF blockers in eight hospitals in Sweden. Severe infections such as sepsis, septic arthritis, meningitis, peritonitis or death occurred in eight patients during 778 patient-years in patients using TNF blockers compared with 28 in 2538 patient-years in those

not using TNF blockers. A clear weakness in this study was that the RA patients on TNF blockers were from hospitals and the control patients were from the community. After adjusting for numerous other variables, including disease severity, steroids and other DMARDs, the relative risk ratio for these severe infections was between 0.89 and 1.15 (not significant). The German Biologics Registry, mentioned previously, also examined serious infections (see above for definition).[2] In this case, in a registry that appeared to be somewhat larger than the other two registries, the relative risk ratio of serious infection was approximately 2.1.

Summary

There is some evidence that non-serious infections are increased slightly (relative risk of approximately 2) when patients use TNF blockers. While the data regarding serious infections are somewhat inconsistent, it is probable that there is no increase in these infections compared with RA patients using DMARDs.

Tuberculosis

In animal models, TNF-α plays an essential role in host defence against tuberculosis (TB), including granuloma formation and containment of disease.[9–12] In a mouse model of latent TB, antibodies to TNF-α caused re-activation of TB, suggesting that TNF-α antagonists may increase susceptibility to TB.[13] Although preregistration studies with TNF-α antagonists revealed 15 cases of TB among approximately 8000 treated RA patients, passive surveillance studies have indicated a higher incidence of TB in association with TNF-α antagonists, and a possible higher incidence associated with infliximab over etanercept.[14] The data available to date are briefly reviewed below.

There have been several reviews of the FDA's Adverse Events Reporting System (AERS) examining reports of TB associated with TNF-α antagonists. Keane et al published the first review of the AERS database, conducted from 1998 to May 2001.[15] Seventy cases of TB were reported with infliximab, occurring at a median interval of 12 weeks after initiation of infliximab therapy. Forty of the 70 patients (56%) had extrapulmonary disease and 24% had disseminated disease. The estimated rate of TB among RA patients treated with infliximab in the USA was 24.4 cases/100 000/year, compared with a background rate of TB in patients with RA in the USA of 6.2 cases/100 000/year.[16] Although no statistical parameters were provided, the authors suggested that there was a higher risk of TB in patients with RA treated with infliximab, that this risk was highest soon after initiation of treatment, and that the pattern of TB disease was unusual with a greater percentage of extrapulmonary and disseminated disease.[15] Mohan et al reviewed the AERS database from November 1998 to March 2002 and described 25 cases of TB occurring in association with etanercept, with a median interval of 11.5 months.[13] Thirteen of the 25 patients (52%) had extrapulmonary disease. The estimated reporting rate of TB in patients with RA treated with etanercept was approximately 10 per 100 000 patient-years of exposure, yet no statistical parameters were provided. The authors alerted clinicians of the unusual extrapulmonary presentations of TB that can be seen with etanercept. Wallis et al recently published a review of granulomatous infections with TNF-α antagonists that were reported to the AERS database from January 1998 to September 2002.[17,18] TB was the most frequently reported disease, with 144 cases per 100 000 patients reported with infliximab and 35 per 100 000 patients reported with etanercept. The authors

concluded that the risk of granulomatous infection was 3.25-fold greater among patients who received infliximab than in patients who received etanercept (no statistical analysis was given), and that the clustering of reports shortly after initiation of infliximab treatment likely represented re-activation of latent infection.

Recently, Abbott Pharmaceuticals released data regarding adalimumab and the risk of TB.[19,20] In global clinical trials with 10 050 patients with longstanding RA (defined as disease duration $\geq$3 years), all of whom were screened for latent TB before entering the trials, the event rate of TB per 100 patient-years was 0.24. For 542 patients with early RA (defined as disease duration $<$3 years), again prescreened for TB, the event rate of TB was 0.11 per 100 patient-years.[19] In an analysis of the US postmarketing safety of adalimumab from Abbott-supported trials from 2002 to 2004, with prescreened patients with an estimated 55 384 patient-years of exposure, 11 patients were reported to have TB, yielding a rate of 0.02 per 100 patient-years.[20] Only three of the 11 (27%) patients had extrapulmonary TB.

Several studies have been performed to evaluate the risk of TB in patients treated with TNF-α antagonists. Gomez-Reino et al analysed the BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products) database established in February 2000 for patients with rheumatic diseases treated with biologic therapy.[21] As of February 2002, there were 17 reported cases of TB in the 1540 patients registered, and all were associated with infliximab. Compared with a background rate of TB of 21 cases per 100 000 inhabitants in Spain in 2000, the relative risk ratio of TB in patients treated with infliximab compared with the general population was 90.1 (95% CI 58.8–146.0). Compared with an RA cohort from a similar patient population not treated with anti-TNF therapy, where the incidence of TB was estimated to be 95 cases per 100 000 patients, the estimated relative risk of TB in infliximab-treated patients compared with RA patients not treated with TNF-α antagonists was 19.9 (95% CI 16.2–24.8) in 2000 and 11.7 (95% CI 9.5–14.6) in 2001. The authors concluded that therapy with infliximab was associated with an increased risk of TB compared with the general population and the RA controls. It should be remembered, however, that this data arose in an era when prescreening for TB was just beginning and it would be difficult to extrapolate the data to the present day.

Two recent studies were performed in an era when prescreening for TB is standard of care. Thus, these studies are more appropriate for today's practice. Wolfe et al published a study that evaluated the rate of TB in RA patients treated with anti-TNF therapy in the USA.[16] The risk of TB in RA patients treated with infliximab and etanercept was evaluated and compared with 10 782 RA patients treated in the era prior to biologics. Evaluating the 10 782 patients from June 1998 to December 1999 who were not treated with biologics, the baseline rate of TB was calculated to be 6.2 cases per 100 000 patients (95% CI 1.6–34.4). This was compared with the Centers for Disease Control and Prevention's reported rate of TB in the general US population of 6.4 per 100 000 people in 1999 and 5.8 per 100 000 people in 2000. Thus, the authors concluded that the rate of TB in patients with RA compared with the general population was not increased. When they evaluated the patients treated with infliximab (6460 patients) and etanercept (2327 patients), a total of four cases of TB were reported, all occurring in the infliximab-treated group. Seventy-five percent of the TB cases were extrapulmonary and generally occurred shortly after infliximab treatment was started. The calculated rate of TB in RA patients treated with infliximab was 61.9 cases per 100 000 patients; a figure much higher than the rate for the general population (5.8–6.4 per 100 000 people) and control RA group (6.2 cases per 100 000 patients).

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