Are their differences among TNF blocking agents?

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TNF alpha is released by macrophages, causes endothelial and fibroblast up-regulation to express cell adhesion molecules, stimulates WBC chemotaxis, and, secondarily, results in the release of elastins, proteases, and matrix metalloproteinases. In addition TNF alpha promotes activation of osteoclasts and contributes to angiogenesis. Finally, it may have an effect on the bone marrow, resulting in the anemia of chronic disease which is seen in rheumatoid arthritis. In this context, the development of TNF blocking agents has been a significant boon to patients with rheumatoid arthritis and they are used in 10 to 20% or more of RA patients in the United States.

It is tempting to use the three TNF-blocking agents available in the United States interchangeably, but there are differences among them. This review will examine some of the differences and similarities among TNF blocking agents.

Pharmacological comparisons among TNF blocking agents

Etanercept is a recombinant fusion protein composed of two soluble 75 receptors attached to the Fc portion of human IgG1 (1). Etanercept binds equally well to TNF alpha and lymphotoxin alpha. It binds in a one-to-one complex with the TNF trimer, occupying two of the three receptor sites on the TNF molecule. Etanercept has peak absorption at 51 hours and a mean serum half-life of 4.3 days. It forms a relatively unstable complex with TNF alpha, with a fast rate of association and dissociation (2). It is administered subcutaneously, with the usual dosage regimen being 25 mg twice weekly.

Infliximab is a chimeric monoclonal antibody with a murine variable and human IgG1 and K constant regions. Each molecule of infliximab is able to bind 2 molecules of TNF alpha in a relatively stable complex. Its biological half-life is 8 to 9.5 days and it is administered intravenously at doses between 3 and 10 mg per kg, given every 6 to 8 weeks (3).

Infliximab is highly effective in Crohn's disease while etanercept is not, pointing to some differences in their mechanisms of action. Infliximab induces monocyte apoptosis in patients with Crohn's disease. In in vitro experiments, it appears that infliximab binds with higher affinity and more infliximab molecules bind to transmembrane TNF than does etanercept. In ankylosing spondylitis, infliximab was associated with down regulation of the Th1 cytokines interferon-gamma and TNF alpha while etanercept triggered up-regulation of Th1 cytokines, although both were equally effective in this disease (4). Thus, there are inconsistencies in the apparent mechanisms of action of these two compounds, leaving open the question of how, and whether, these differences in mechanism results in differential efficacy.

Adalimumab is the newest TNF blocking agent to be registered in the United States. It is a fully human monoclonal antibody, constructed using phage technology. It also forms a relatively stable complex with the TNF molecule and it has a serum half-life of 10 to 13.5 days It binds both soluble and membrane-bound TNF and is usually given using a dosing regimen of 40 mg subcutaneously every other week.

Efficacy

Although it is very tempting to directly compare studies of these compounds for efficacy, subtle differences in study populations, study design and analysis make cross trial comparisons inappropriate.

Monotherapy trials

In an early RA trial comparing methotrexate and etanercept over twelve months, etanercept had a much more rapid response than methotrexate but there were no differences in the ACR 20, 50 to 70 responses at six or twelve months (5). In the adalimumab monotherapy trial, done in patients with particularly active disease and versus placebo (not versus methotrexate), the ACR20 responses were 46% in the adalimumab

group and 19% in the placebo group (6). An early infliximab trial showed that infliximab was superior to placebo but that human anti-chimeric antibodies developed. Higher doses of infliximab and concomitant treatment with even low-dose methotrexate (7.5 mg per week) substantially decreased the human anti-chimeric antibody response to 7% and 0% respectively (7). This finding has led to the routine use of methotrexate in patients given infliximab.

TNF blockers plus methotrexate

In a comparison between methotrexate plus etanercept versus methotrexate plus placebo in patients with longer duration disease and who were on 18 and 19 milligrams methotrexate weekly, etanercept was significantly better than methotrexate using the ACR20 response (71% versus 27%) (8). A well done, large trial of etanercept versus methotrexate versus their combination, in patients with approximately 6 to 7 years of disease, showed that the combination had an impressive 85 percent response compared to the 75 percent response to methotrexate and a 48 percent response to etanercept. Here, methotrexate alone looked better than etanercept alone, while the combination was clearly quite effective. In a large, dose-response trial of infliximab plus methotrexate, 20 percent of methotrexate plus placebo patients achieved in ACR20 response compared to approximately a 50 to 52% response in the infliximab plus MTX treated patients (9). A recent trial comparing methotrexate and methotrexate plus 6 mg per kg infliximab in early rheumatoid arthritis patients (mean disease duration: 0.6 yrs.) showed that the infliximab patients had a statistically significant better response than the methotrexate patients (66% versus 54%) but also showed that methotrexate was quite effective in this group of patients. A dose-response trial of adalimumab in patients with long duration disease, using approximately 16.5 mg weekly methotrexate, demonstrated that ACR20 responses were 15% (methotrexate group) versus 67% (adalimumab group). Given different trial durations and somewhat different patient populations, the results of all these trials show that all TNF blockers are effective but cannot allow a direct comparison.

Radiographic comparisons

All three TNF blockers are effective in slowing or, possibly, even preventing further radiographic disease progression over 6 to 24 months. Etanercept appeared to require more time for full radiological response, however (10).

Safety

TNF blocking agents are quite effective in modifying macrophage function. Consequently, infections which are controlled by macrophages are of particular interest when considering the safety of TNF blocking agents. As TNF blocking agents also have effects on T cells, their safety with respect to cancers, and particularly with respect to lymphomas, needs to be carefully considered. These areas will be covered in some detail.

On the other hand, potential for demyelinization, seizure disorders, congestive heart failure, leukocytoclastic vasculitis, autoantibody formation/ drug-induced lupus and hematologic abnormalities --- all of which occur rarely --- will not be addressed in this article.

Infections

All three TNF alpha antagonists have been associated with an increased risk of infections in general (defined as infections requiring treatment). For example, in the infliximab studies, 36% of patients on infliximab compared to 26% in placebo treated groups required such treatment. In trials using methotrexate as the comparison group, 64 percent of the etanercept treated patients developed infections compared to 72 percent in the methotrexate group. For adalimumab, the percents were 53% on adalimumab vs. 47% in those treated with placebo.

With respect to serious infections (those requiring hospitalization or prolonging hospitalization), there appeared to be some difference between patients with Crohn's disease and those with rheumatoid arthritis. Among Crohn's patients treated with infliximab, 5.2% develop serious infections compared to 1.8% in the placebo group; in contrast, 8.1% of the RA patients in the infliximab plus MTX group versus 9.0% of the RA patients in the placebo plus MTX group developed serious infections (11). For adalimumab in rheumatoid arthritis, the percentages were 1.7% for adalimumab treated patients versus 1.4% in the placebo group. In the pre-TNF alpha antagonist era, serious infections in RA patients occurred at the rate of approximately 0.03-0.09 cases per patient year (12). In patient years, the rate for etanercept was 0.04 per patient year; for infliximab, it was 0.06 per patient year and for adalimumab it was 0.04 per patient year. Thus, there was an increased incidence of infections in RA patients, per se, but there did not appear to be an increased incidence of serious infections in the RA patients secondary to TNF blockers. On the other hand, there might be an increased incidence of serious infections in the Crohn's disease patients treated with TNF blocking agents compared to Crohn's patients not given this compound.

Bacterial infections

Tuberculosis

TNF alpha plays an important role in maintaining granuloma formation and in containment of latent

granulomatous disease. It is not surprising, therefore, that activation of latent tuberculosis has been reported when TNF blocking agents are used. There have been 277 cases of infliximab associated tuberculosis reported to the FDA Medwatch program (37 cases per 100,000 patients exposed) (14). As of one year earlier, there were 38 cases of tuberculosis reported with the use of etanercept. There were 13 cases of tuberculosis using adalimumab during clinical trials, but the institution of tuberculosis prophylaxis for latent tuberculosis in the phase three trials and since registration has resulted in only two to three more cases.The background rate of tuberculosis in rheumatoid arthritis patients is between 6.2 and 20 cases per 100,000 patients (in the U.S. and in Europe, respectively). From this data, it may appear that there is an increased incidence of activation of latent tuberculosis among patients given infliximab compared to etanercept... there needs to be significant caution about such an interpretation, however. Some of the differences in reported cases, for example, might have been due to the fact that more infliximab was used in Europe (where latent TB is fairly prevalent) and more etanercept was being used in the U.S. (where latent TB is less common).

Furhter, because the FDA Medwatch program is a voluntary reporting system, the apparent differences in incidence among these TNF blocking agents cannot lead one to a statistically valid conclusion. Despite apparent differences (which may eventually be shown to be real), it is strongly advised that all patients be screened for latent tuberculosis before starting ANY TNF blocking agent. Assuming that tuberculosis is not resistant in the local area, one should institute isoniazid in these patients one to two weeks prior to starting anti-TNF medications. Isoniazid should be continued for 6 to 9 months, with appropriate laboratory follow-up.

Fungal infections

Histoplasmosis: There have been 22 cases of histoplasmosis reported to the FDA in the U.S. -- 19 on infliximab and 3 on etanercept. Cases of histoplasmosis were also seen in the adalimumab clinical trials.

Pneumocystis carinii pneumonia (PCP): As of June 2001, there were 10 cases of PCP in the U.S. on infliximab and five cases on etanercept.

Other fungal infections: There have been cases of Aspergillus and cryptococcosis as well as systemic candidiasis and coccidioidomycosis on these agents. The incidence is so rare, however, that no specific conclusions can be made.

Summary: Patients living in high-risk areas for granulomatous fungal infections and granulomatous diseases in general should be monitored closely. Screening for latent tuberculosis and treatment of patients with latent disease is appropriate prior to starting TNF blocking agents.

Viral infections:. As of June 2001, 94 cases of viral infections were reported to the FDA following the use of infliximab and 553 cases following etanercept. Overall, there is little evidence that TNF blocking agents predispose to an increased incidence of viral infections compared to a nontreated RA population.

Cancer

Lymphomas

RA patients have an increased risk of non-Hodgkin's lymphomas and that risk is markedly increased when the rheumatoid arthritis is particularly active (14). Depending on disease activity, geographic location and methodology used, the standardized incidence ratio (incident cases divided by the expected incidence in the general population for an age, gender and race matched cohort not having RA) varies between approximately 2 and 25 (the latter being RA patients with very active disease). For etanercept, the standardized incidence ratio is 6.98 (95 percent confidence interval: 0.85-5.03); for infliximab, it is 6.98 (2.56-15.19) and for adalimumab, it is 5.4 (2.6-10). Using the Medwatch system, an incidence rate of 0.03 per 100 patient-years for etanercept and 0.017 per 100 patient-years for infliximab were calculated, compared to an expected rate of 0.03 per 100 patients years in the general population.

Despite the lack of definitive evidence, the biologic plausibility of lymphomas associated with immunomodulators continues to raise concerns about potential causality and careful observation is warranted.

Solid tumors

Although malignancies such as breast cancer, colon cancer, cervical cancer, prostate cancer, squamous and basal cell carcinomas and melanomas have all been reported with the use of TNF alpha blocking agents, these do not exceed the age and sex matched incidence in the U.S. population. Solid tumors are not increased in patients using TNF blocking agents (55).

Conclusions

There are clear differences in the pharmacology and uses of the TNF blocking agents. Differences in modes of administration, frequency of administration and insurance coverage (in the U.S.) clearly differentiate these compounds. Further, there is a real possibility that monoclonal

antibodies have a different efficacy profile than receptors. The data above suggest that, for example, monoclonal antibodies are effective in Crohn's disease while the receptor (etanercept) is not.

Differences in the safety profiles also seem to hint that monoclonal antibodies will, eventually, be shown to be different from etanercept. While no statistical differences have been shown, and it is clear that one must treat all three compounds similarly with respect to tuberculosis and infections, the data is trending towards an increased incidence of granulomatous infections when one uses anti-TNF monoclonal antibodies.

Perhaps it is appropriate to say that, according to an American saying: "You never get something for nothing.". With potentially increased potency of the monoclonal antibodies, there will also be potentially increased toxicity. As usual, individualization of medications, taking into account to patient demographics and disease characteristics, will be the appropriate course.

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