The future of TNF-α antagonism

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'Other approaches to inhibition of TNF include oral inhibitors of TNF-α-converting enzyme ... and the use of phosphodiesterase-4 inhibitors'.

Although the cause of rheumatoid arthritis (RA) remains unknown, advances in molecular technology have facilitated identification of novel therapeutic targets including cell subsets, cytokines and other molecules contributing to the inflammatory and destructive aspects of this syndrome. Concurrent advances in biotechnology have permitted production of high-quality engineered proteins with specificity for relevant disease molecules. Of these, biologics targeting tumor necrosis factor (TNF)-α, particularly when used in combination with oral methotrexate, have enjoyed notable success in suppressing inflammation and markedly inhibiting the progression of structural damage, previously thought to be an unavoidable characteristic [1,2]. Despite the unprecedented clinical successes of TNF inhibitors, their availability is restricted by high costs, and a substantial proportion of RA patients fail to demonstrate clinical responses. Surprisingly, inhibition of radiographic damage has been reported even in patients failing to achieve a clinical response at the ACR 20 level [3].

At present, three biologic anti-TNF agents are licenced for treatment of RA. These are the antibodies infliximab (Remicade™) and adalimumab (Humira™), as well as etanercept (Enbrel™), a fusion protein comprising one of the naturally occurring TNF receptors linked to the Fc portion of human immunoglobulin G1. In the near future, another biologic TNF antagonist will be available, certolizumab pegol (Cimzia™), a pegylated Fab fragment which can be produced in the bacterium *Escherichia coli* [4].

New, achievable treatment goals

As a result of recent clinical advances, the goals of therapy for RA have evolved from simply ameliorating symptoms of the disease. Several key studies in early RA demonstrate improved outcomes with optimal use of oral disease-modifying antirheumatic drugs (DMARDs), either singly or in combination, with a clear demonstration that improved efficacy need not be at the expense of unacceptably high toxicity [5–10]. Studies with TNF-α antagonists have further improved the expectation for the magnitude of clinical improvement. When used in combination with methotrexate, a majority of patients treated with TNF-α antagonists benefit from significant inhibition of structural damage to joints of a magnitude not seen with traditional DMARDs [11–13]. Furthermore, using strategies designed to intensively suppress synovitis, remission has become an achievable goal for a proportion of patients [10–12].

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In a small randomized study of 24 early, poor prognosis RA patients on background methotrexate therapy, two treatment strategies were compared [14,15]. These comprised 2 years of infliximab, at a dose of 5 mg/kg, and 1 year of optimally-prescribed methotrexate monotherapy followed by the addition of infliximab in year 2. Synovial inflammation was suppressed more rapidly with early combined infliximab and methotrexate therapy, whereas for patients receiving methotrexate alone through the first year, persisting synovial inflammation was subsequently suppressed following addition of infliximab. Once added to background methotrexate, both early and delayed introduction of infliximab effectively inhibited radiographic progression. However, the difference in structural damage between the two treatment groups at the end of 2 years was of the same magnitude as the difference observed after 1 year, emphasizing the impact of delaying the introduction of anti-TNF treatment in patients with active early RA with a high likelihood of rapidly progressing joint damage [15].

In another, small, double-blind study, 20 very early RA, poor-prognosis patients with no previous DMARD therapy were randomized to

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receive infliximab 3 mg/kg or placebo in combination with methotrexate [16]. After 46 weeks, infliximab was withdrawn. Remarkably, during the second year of the study, in six of ten patients initially assigned to infliximab treatment, the benefits of therapy were largely sustained despite biologic withdrawal. Similar findings have been reported in a much larger single-blind, multicenter, randomized trial comparing four different treatment strategies at the first presentation of RA [17]. Three of these strategies involved initial intervention with conventional DMARDs and the fourth comprised initial treatment with infliximab together with once weekly methotrexate. Of 120 patients initially assigned to infliximab plus methotrexate, 77 achieved very low disease activity and 67 were able to discontinue infliximab after 9 months with a sustained low disease activity. After 3 years, a median of 26 months after infliximab discontinuation, 61 out of these 67 patients still had a persistent low disease activity. Of these, 45 were on methotrexate monotherapy and 16 in drug-free clinical remission [18]. This further suggests that very early treatment intervention with infliximab and methotrexate may beneficially alter the course of RA in a proportion of patients.

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The promising results of these studies suggest a rationale for the future treatment of many more patients with anti-TNF agents at the earliest stages of RA, particularly if there is stratification for accompanying poor prognostic features. However, a pressing need for the future is to develop means of identifying which patients will respond to particular therapies.

Difficulties in the use of anti-TNF agents in combination with other biologics

The widespread use of conventional DMARDs in combination with an apparent increase in efficacy without significant accompanying safety concerns [19], has prompted the investigation of combination anticytokine therapy. Potential attractions of this approach include superior immunomodulation and, hence, enhanced efficacy. However, in a 24-week, randomized, controlled trial, conducted in 242 patients with RA not previously treated with biologic agents but taking background methotrexate, the combination of etanercept 25 mg twice weekly together with anakinra 100 mg once daily resulted in an increased incidence of both infection and neutropenia in the combination group without any therapeutic benefit of the combination treatment over etanercept alone [20].

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Whether the same principles apply to the combined use of TNF antagonists and abatacept was addressed in the adjuvant sorafenib or sunitinib in unfavorable renal-cell carcinoma (ASSURE) trial, in which safety was compared for the addition of abatacept, at a fixed dose approximating 10 mg/kg by weight range, or placebo infusions to a background treatment regime of at least one nonbiologic or biologic DMARD taken for at least 3 months [21]. In the group of 1456 patients as a whole, the proportion of serious adverse events occurring in each treatment arm was similar at 13% for abatacept and 12% for placebo. In the subgroup of patients receiving abatacept and background biologic therapy, mostly anti-TNF agents, serious adverse events occurred almost twice as frequently (22.3%) as in the other subgroups (12.5%). In particular, significantly more serious infections were observed when abatacept was combined with other biologic therapies (5.8 vs 1.6% for the subgroup on background biologic therapy plus placebo infusions). Furthermore, the clinical benefits of abatacept tended to be less in these patients. These findings were mirrored in a smaller, recently-reported, randomized, placebo-controlled, double-blind Phase II pilot study. This Phase IIb trial investigated the efficacy and safety of the addition of abatacept infusions at 2 mg/kg over 1 year in patients with active RA despite at least 3 months treatment with etanercept [22]. The biologic combination had limited clinical benefit over etanercept and placebo infusions but was associated with an increased incidence of serious adverse events (16.5 vs 2.8%) and serious infections (3.5 vs 0%).

On the basis of these observations, the concomitant use of TNF inhibitors and either interleukin-1 blockade or costimulatory molecule blockade is not recommended. This does not

exclude the possibility that future improvements in the proportion of RA patients responding, and the magnitude of response to TNF antagonists, can be enhanced by appropriate combination therapy. There are animal model data to support the case for combination therapy to certain molecular targets [23], but the clinical trial data from combining anti-TNF with abatacept or anakinra make it more difficult to further test such hypotheses in man.

Future perspective

The expense and inconvenience of parenteral administration of biologic TNF antagonists is such that development of less expensive, orally active, synthetic agents that inhibit bioactivity of TNF-α is an attractive future goal.

> 'Owing to toxicity concerns, there is interest in more selective targets for inhibition of inflammatory-gene expression'.

One approach is to use inhibitors of p38 mitogen-activated protein (MAP) kinase to block signaling in the p38 pathway, and thus the post-transcriptional stabilization of mRNA for the proinflammatory cytokines TNF-α and interleukin-1, as well as other proteins such as cyclo-oxygenase-2. A number of p38 MAP-kinase inhibitors have been developed, and there are encouraging preliminary preclinical data demonstrating amelioration of disease in the established phase of collagen-induced arthritis [24]. The full results of clinical trials in man are awaited, although there have been preliminary reports of hepatic and other toxicities with some compounds [25]. Owing to toxicity concerns, there is interest in more selective targets for inhibition of inflammatory-gene expression, for example, MAP-kinase-activated protein kinase II, a major substrate of p38-α and -β, and downstream post-transcriptional events. Other approaches to inhibition of TNF include oral inhibitors of TNF-α-converting enzyme, which cleaves membrane-bound TNF from the surface of producer cells to yield the soluble form of the cytokine [26], and the use of phosphodiesterase-4 inhibitors [27]. However, it is important to bear in mind that many of the reported adverse events associated with biologic agents targeting TNF-α, particularly infective complications, were anticipated given the specificity of the drug for a single target with well-defined biological activities. By contrast, owing to their multiple intracellular actions, it may prove much harder to predict the spectrum of toxicities that could arise from administration of small molecules, currently under development, that indirectly target TNF-α or other cytokine pathways.

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