Editorial

Macromolecule Tumor Necrosis Factor Inhibitors: Are More Better?

You take Sally, and I'll take Sue,
There ain't no difference, between the two...
— Rev. Gary Davis (1896-1972), from "Cocaine Blues"

In this issue of *The Journal*, Furst and colleagues report results from a clinical trial of a novel macromolecule tumor necrosis factor (TNF) inhibitor, pegsunercept, in patients with rheumatoid arthritis (RA)[1]. Treatment with this molecule, a pegylated, truncated soluble form of the type I TNF receptor (p55; CD120a), resulted in significant, dose-dependent, clinical improvements as compared to placebo over 12 weeks of treatment. Further study is needed to define the extent to which the clinical efficacy and tolerability of this agent may compare to that of the 3 presently available TNF inhibitors etanercept, infliximab, and adalimumab. Another macromolecule TNF inhibitor, certolizumab pegol, a pegylated Fab fragment derived from an anti-TNF monoclonal antibody (Mab), is currently being assessed in randomized placebo-controlled clinical trials. Additional TNF inhibitors are in earlier phases of development. It is conceivable that these agents may join the therapeutic armamentarium for RA and other systemic inflammatory diseases. With a selection of TNF inhibitors available, the question naturally arises: what are the pertinent differences, if any, between the agents?

By now, most clinicians have become well aware, both from published literature as well as personal experience, that each of the currently available TNF inhibitors is highly effective[2]. In RA, ankylosing spondylitis, and psoriatic arthritis, the extent of clinical responses is remarkably consistent across trials of the 3 drugs. This is notable, given that the trials were done in different centers and at different times. In other conditions, differential clinical activity among the TNF inhibitors has been suggested. Thus, the Mab appear to be more effective in skin psoriasis and in inflammatory bowel disease (e.g., Crohn's disease). On the other hand, it has been suggested that certain adverse events, e.g., granulomatous infections, may also occur relatively more frequently with the Mab. Although it is possible that dose considerations, study designs, populations studied, and other factors may have contributed to these differences, mechanistic distinctions may also be involved.

There are certain differences in the constructs that could be hypothesized to result in clinical differences among the macromolecule TNF inhibitors. The monoclonal antibodies infliximab and adalimumab are specific for TNF-α, whereas the soluble TNF-receptor construct etanercept binds to TNF-α as well as lymphotoxin-α. Although all bind soluble TNF-α with high affinity, there may be variable avidity. Also, related to distinct binding requirements, the Mab may bind more readily to membrane-bound forms of TNF-α than do soluble receptor constructs. All have an IgG1 Fc piece that appears to be functional. How or whether any of these distinctions might affect the mechanisms of action of these agents in the clinic remains unclear.

Regarding their mechanisms of action, a progressively increasing body of data has addressed potential mechanisms of these potent immunomodulatory agents. The dramatic clinical efficacy of these drugs has made this question all the more intriguing. Given the myriad components of the immune response, the tendency for redundancy and pleiotropy of function of its consitutents, and the complex nature of stimulatory and inhibitory cascades in which they function, how can inhibition of a single cytokine be so effective?

From the earliest times, it was appreciated that TNF played a central role in inflammation insofar as it was able to stimulate numerous other mediators of the inflammatory response[3]. While inhibition of other proinflammatory factors may not be the entire explanation for the efficacy of TNF inhibitors, it appears to be a key mechanism of action. With further investigation in patients receiving treatment, it became appreciated that alteration of vascular function may be another important mechanism for these agents[4]. In addi-

See A phase 2 dose-finding study of PEGylated recombinant methionyl human soluble tumor necrosis factor type I in patients with RA, *page 2303*

tion to these presumably pivotal mechanisms, a variety of other interesting effects of TNF inhibition have been noted, including activation of T cells and macrophages, stimulation of T regulatory cell function, and attenuation of innate immune responses (Table 1)[5-8]. Although fascinating, some of these other putative mechanisms have been controversial, as discordant results have been reported in different studies. For example, in a study of T cells from patients with Crohn's disease and healthy controls, both etanercept and infliximab downregulated interferon-γ production and TNF-α expression[9]. In another study of T cells from patients with ankylosing spondylitis, these cytokines were decreased by infliximab, but increased by etanercept[10].

Perhaps nowhere has the discussion of mechanism of action of TNF inhibitors been more perplexing than that surrounding induction of apoptosis. In the gastroenterology literature, the efficacy of TNF inhibitors in Crohn's disease is felt to correlate directly with their ability to induce apoptosis[11]. However, there are data that belie such a straightforward explanation. Thus, it has been suggested that etanercept is capable of inducing apoptosis, but at the doses studied in Crohn's disease was ineffective, whereas certolizumab pegol does not effect apoptosis, yet has clinical efficacy in Crohn's patients with elevated C-reactive protein (data presented at an oral session at Digestive Disease Week, June 2005; Dr. Andrew Nesbitt, personal communication). In rheumatology the situation is even more confusing. In one study of patients with RA, using synovial biopsies at 48 hours and again at 28 days, decreased synovial cellularity but no indication of apoptosis after TNF inhibitor therapy was observed[12]. In another study looking at the peripheral blood and synovial tissue of patients with RA treated with both infliximab and etanercept, it was found that both agents induced apoptosis of macrophages but not lymphocytes, in both the synovium and the peripheral blood[13]. Although there were some differences in techniques used in these 2 studies, the reasons for the discrepancies are not clear.

Interestingly, it is possible that distinct effects may be observed in different diseases, for example between RA and Crohn's disease. Might these differences relate to distinct aspects of the inflammatory milieu in these disparate conditions? For the clinician, however, the results of esoteric assays may not be relevant, particularly if they are not associated with clinical efficacy or toxicity. As Albert Einstein said, "Not everything that is important can be measured, and not everything that can be measured is important." If any mechanistic factors were shown to be useful in optimizing treatments for individual patients, that would be of great relevance. For example, preliminary work has suggested that allelic polymorphisms in FcγR IIIA receptors may correlate with treatment response to TNF inhibitors[14].

The most tangible advantages of the introduction of additional TNF inhibitors may be economic. The relatively high acquisition costs of these agents, which exceed those of the traditional disease modifying antirheumatic drugs, has affected their utilization in the clinic. Even though the currently available TNF inhibitors have been shown to have an incremental cost efficacy within the range of accepted medical interventions[15], lower costs would be welcomed. As more TNF inhibitors are brought to the clinic, will market forces cause their price to decline, as has been the case with other classes of medication, such as proton pump inhibitors? Similarly, will there ever be cheaper generic versions of biologic agents? The situation regarding generic versions is more complex for biologics than it is for smaller, more easily synthesized chemicals[16]. Factors such as variable glycosylation have been shown to affect both the efficacy and toxicity of biologic agents; these considerations will certainly influence regulatory approval and, ultimately, cost.

It seems inevitable that additional TNF inhbitors will be brought to the clinic. For macromolecule inhibitors, such as Mab and soluble receptor constructs, it would seem that clinicians should pretty well know what to expect as regards efficacy and toxicity. Whether future agents will have any distinct properties, and whether any of these differences will result in clinically relevant outcomes remain to be seen.

Table 1. TNF inhibitors: potential mechanisms of action.

Downregulate other inflammatory mediators
Other cytokines, e.g., IL-1, IL-6, GM-CSF
Chemokines, e.g., IL-8, RANTES
Other mediators, e.g., metalloproteinases, PGE_2
Alter vascular function/leukocyte traffic/cellular activation
Adhesion molecule expression/function
Angiogenesis
Downregulate innate immune system interactions, e.g., decreased TLR2/4 expression
Modulate the function of immunocompetent cells
T cells
Increase regulatory T cell number/function
Normalize the activation threshold for CD3/TCR signalling
Alter Th1/Th2 phenotype/cytokine secretion (?)
Induce apoptosis (?)
Monocytes/macrophages
Increase MHC Class II expression/stimulation of T cells
Induce apoptosis (?)

IL: interleukin; GM-CSF: granulocyte macrophage-colony stimulating factor; RANTES: regulated on activation, normal T cell expressed and secreted; PGE_2: prostaglandin E_2; TLR: Toll-like receptor; TCR: T cell receptor.

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