Use of Targeted Anticytokine Treatments in Heart Failure

To the Editor:

As we explore the utility of cytokine modulation in heart failure (HF), it is imperative that the biological rationale of potential therapeutic agents be fully understood. A recent editorial \(^1\) questioned the rationale for the use of Enbrel (etanercept) as an effective tumor necrosis factor (TNF) antagonist as described in a recent study by Deswal et al in patients with heart failure.\(^2\) The following comments will attempt to clarify the mechanism and the rationale for etanercept therapy in this population of patients.

Construction of an effective TNF inhibitor should be based on the known biological properties of TNF and TNF receptors. There are 2 distinct types of cell surface TNF receptors (TNFRs), the p55 TNFR (TNFR1) and the p75 TNFR (TNFR2). To exert its biological activity, TNF (a homotrimeric molecule) must bind to at least 2 cell surface receptors, causing cross-linking and cell signaling. Thus, a dimeric soluble receptor that binds to 2 sites on the TNF molecule provides greater competitive inhibition of TNF than monomeric soluble receptors. Etanercept is a recombinant dimer consisting of 2 p75 sTNFR molecules fused to the Fc fragment of human IgG1. Use of an immunoglobulin Fc region as a fusion element in this construction also imparts an extended serum half-life compared with monomeric soluble receptors. Thus, the design of etanercept incorporates several properties that enhance its biological potency and were based on our current understanding of TNF.\(^3,4\)

The editorial\(^1\) questioned the use of an antagonist that employed sTNFR2 (p75 TNFR) to block the effects of TNF, as opposed to an antagonist that employed sTNFR1 (p55 TNFR), since as noted in the editorial, most of the deleterious effects of TNF in cardiac myocytes are thought to be mediated by TNFR1 (p55 TNFR). However, as noted above, etanercept effectively binds to and inhibits the biological activity of TNF. Thus, etanercept is a potent inhibitor of TNF-dependent responses regardless of whether the biological response is initiated via TNFR1 or TNFR2 signaling. Accordingly, etanercept provides a logical approach for studying cytokine modulation in heart failure.

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