Enbrel's phase III reinforces prospects in RA

In mid-September, Immunex (Seattle, WA) announced positive data from the phase III trial of its rheumatoid arthritis drug, a recombinant soluble form of the receptor for tumor necrosis factor alpha (TNFα). This came less than two months after positive results from the phase II study. Immunex's stock price soared 28%, and the company declared it would be filing in the first half of 1998 for approval of the drug.

In this study, 234 patients with advanced disease were given the soluble receptor, (tradename Enbrel), twice a week for six months at one of three doses. Each dose produced statistically significant improvements in joint swelling and tenderness compared with placebo, duplicating its phase II results. This efficacy was shown at both three and six months, the company reported. It also said that it had not seen antibodies to the fusion protein. It may be important that patients in the latest trial were those in whom "disease-modifying drug therapies" such as methotrexate had failed—a difficult population to treat. Immunex will release the full details of the study at the American College of Rheumatology meeting in November.

These positive results, and the advanced stage of Immunex's trials, gives Enbrel a definite edge over other drugs that also target TNFα. One of them is Centocor's (Malvern, PA) humanized monoclonal antibody, cA2, which is beginning a phase III trial; it seems to work well with methotrexate, but loses efficacy when given more than once, suggesting an immune reaction to the initial dose.

Immunex is running three additional Enbrel trials. One is a long-term, open-label safety trial with 100 patients who are being treated for 12–24 months. The second is a trial involving patients who have not been given earlier drug treatments; they will receive either Enbrel or methotrexate. The third trial involves children and teenagers. The company says it plans to complete one more phase III trial before a second filing for use in disease-modifying drug naive patients, hopefully in 1999.

One direct result of the trial results is that the pharmaceutical company that owns most of Immunex, American Home Products (Madison, NJ), will pay $100 million to copromote Enbrel in North America. The agreement applies to all disease areas outside oncology.

Numerous companies are pursuing targets other than TNFα in autoimmune conditions such as rheumatoid arthritis and Crohn's disease. The Immune Response Corporation (Carlsbad, CA) and Anergen (Redwood City, CA) are attempting to downregulate autoreactive T cells by using peptides. AutoImmune (Lexington, MA) is attempting to suppress the abnormal immune response by using orally administered chicken collagen extract to control the systemic release of IL-4 and IL-10. Isis (Carlsbad, CA) is using antisense molecules to downregulate yet another inflammatory target—cell adhesion ICAM-1 molecules. All these drugs are in phase II testing.

Other drugs in very early-stage developments aim to reset the cytokine "rheostat" by intervening in signal pathways from TNF or interleukin-1 receptors. Cadus (Tarrytown, NY) is working on the TNF receptors pathway, while Tularik (S. San Francisco, CA) is focusing on orally available drugs that regulate pathways leading from IL-1 and TNF receptors.

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