Inflammatory Cytokines as a Molecular Target in the Treatment of Inflammatory Disorders of Unknown Etiology

Department of Medicine and Rheumatology, Tokyo Medical & Dental University

Nobuyuki MIYASAKA, MD

Recent advances in molecular biology and immunology made us possible to identify molecules or genes involved in the pathogenesis of inflammatory disorders of unknown etiology. Rheumatoid arthritis is a typical inflammatory condition characterized by synovial proliferation in the joints leading to destruction of both cartilage and bone. Tumor necrosis factor $\alpha$ was identified as one of the most important cytokines that cause synovial proliferation and joint destruction, and strategies to block TNF$\alpha$ activity have been successfully introduced in the treatment of rheumatoid arthritis. To date, three different types of TNF$\alpha$ blockers, chimeric anti-human TNF$\alpha$ monoclonal antibody (Infliximab), fully-human anti-TNF$\alpha$ monoclonal antibody (Adalimumab) and soluble TNF$\alpha$ receptor (Etanercept) have been used in the United States and Europe. In Japan, only Infliximab has been approved for the treatment of rheumatoid arthritis by the Ministry of Health, Welfare and Labor (MHWL) in July 2003. MHWL imposed to conduct a special postmarketing survey for the initial 5,000 cases on the pharmaceutical company because of its possible serious adverse effects including tuberculosis. We have therefore made the guideline for the use of infliximab to safely treat rheumatoid arthritis patients in Japan. Inclusion criteria is active rheumatoid arthritis having more than six swollen and tender joints with concomitant use of methotrexate of over 6 mg/week. Patients are mandatory to have either CRP $>$ 2.0 mg/dl or ESR $>$ 28 mm/hr. Patients are also required to have more than 4,000/cmm of WBC, and more than 1,000 of peripheral blood lymphocytes in addition to negative $\beta$-glucan in sera. PPD skin test was performed in all patients. Prophylactic use of isoniazid is recommended to the patients showing chest X-ray findings suggestive of old pulmonary tuberculosis. Patients having concurrent infecton or histories of serious infection for the last six months are excluded from the study. Safety and efficacy data of Infliximab will be presented in this symposium. Cytokine antagonists are also applied to treat other inflammatory disorders. Infliximab is indicated for Crohn’s disease and Etanercept for juvenile rheumatoid arthritis, ankylosing spondylitis and psoriasis in certain countries. Anti-human IL-6 receptor antibody has been on clinical trial for rheumatoid arthritis and Castleman’s disease in Japan and Europe showing promising results. These findings definitely indicate that inflammatory cytokines can be a good therapeutic target in inflammatory disorders.