Immunoregulatory therapies targeting inflammatory cytokines against inflammatory bowel disease

Department of Internal Medicine, Keio University School of Medicine
Toshifumi HIBI, MD

Although the pathogenesis of inflammatory bowel disease (IBD) remains elusive, it appears that there is chronic activation of the immune and inflammatory cascade in genetically susceptible individuals. The conventional therapies by anti-inflammatory agents, aminosalicylates and corticosteroids continue to be a first choice in the management of IBD. Immunomodulators, such as azathioprine, 6-mercaptopurine, methotrexate or cyclosporin, are demonstrating increasing importance against steroid-dependent or -resistant patients. However, some patients are still refractory to these therapies. Recent advances in the understanding of the pathophysiological conditions of IBD have provided us with new immune system modulators by focusing on the inflammatory cytokines. Studies with chimeric monoclonal anti-TNF-α antibody (Infliximab/Remicade) treatment have been reported with dramatic successes. Observations in larger numbers of treated patients has already been made in U.S. to explicate fully the safety of or risks posed by this agent, and there has been no evidence of an increased risk of malignancy in Infliximab-treated patients, but longer follow-up is necessary. Another anti-cytokine therapy includes anti anti-IL-6R, anti-IL-12 or anti-IFN-γ. IL-6 plays an important role in the physiopathology of Crohn’s disease, and animal studies have demonstrated that blocking IL-6 signaling with monoclonal antibody to IL-6 receptor abrogated “apoptosis resistance” of lamina propria T cells, and suppressed the expression of vascular adhesion molecules such as ICAM-1 and VCAM-1. Based on these results, a randomized, double-blind, placebo-controlled trial was carried out in Japan to evaluate the safety and efficacy of humanized monoclonal antibody to IL-6 receptor in patients with Crohn’s disease, and this preliminary study showed that this antibody treatment was safe, well tolerated by the patients with Crohn’s disease, and suggested a beneficial clinical effect. Furthermore, adhesion molecules expressed by circulating leukocytes, such as α4 integrin, mediate their attachment to vascular endothelial cells lining blood vessels within the intestine and facilitate their migration into the tissue. Thus a clinical study using a humanized monoclonal antibody against α4 integrin was performed and this agent that interfere with these adhesive interactions hold great potential for suppressing the cycle of leukocyte infiltration and activation, and thereby, for ameliorating chronic inflammation. Although some of them still need more confirmatory studies, those immune therapies will provide new insights into cell-based and gene-based treatment against IBD in near future.