Anti-IL-6 receptor antibody therapy for Crohn’s disease

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Introduction: Interleukin-6 (IL-6) is a pleiotropic cytokine with central roles in immune response and inflammation. In addition to the signal transduction pathway through the membrane-bound receptors, IL-6 can give its signal to the cells lacking IL-6 receptors (IL-6R) by forming a complex with soluble IL-6R (sIL-6R). Experimental animal studies have demonstrated that blocking IL-6 signaling with monoclonal antibody to IL-6R had both preventive and therapeutic efficacy against intestinal inflammation by abrogating apoptosis resistance of lamina propria T cells and by suppressing the expression of vascular endothelial adhesion molecules including ICAM-1 and VCAM-1. Aims & Methods: Based on the results of preclinical studies, we carried out a randomized, double-masked, placebo-controlled study to investigate the safety and efficacy of humanized monoclonal antibody MRA (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) to IL-6R in patients with Crohn’s disease. Thirty-six patients at 7 study centers in Japan with scores on Crohn’s Disease Activity Index (CDAI) above 150 were randomly allocated to receive every-2-week intravenous infusions of either placebo, MRA, or MRA/placebo alternately (every-4-week MRA) for 12 weeks at a dose of 8 mg/kg, while the baseline therapy was continued. The study’s primary end point was a clinical response rate that was defined as a reduction of 70 points and over in the CDAI score. The secondary end points were the remission rates, that was defined by the CDAI score less than 150, and the changes from baseline of the Inflammatory Bowel Disease Questionnaire (IBDQ), C-reactive protein (CRP), and erythrocyte sedimentation rates (ESR) at each assessment time. Results: The infusion was generally well tolerated. With respect to the primary endpoint, 80 percent of the patients given biweekly MRA had clinical response at the final evaluation, as compared to 31 percent of the placebo-treated patients (P=0.019). Twenty percent of the patients on this regimen went into remission, as compared to 0 percent of the placebo-treated patients. Serum CRP levels and ESRs were completely normalized within 2 weeks after a single dose of MRA. The quality of life measured by IBDQ showed a significant improvement from the baseline at 6 weeks and 12 weeks in MRA-treated patients, while no improvement was observed in the placebo-treated patients. The clinical response of the every-4-week MRA regimen was 42 percent. The incidence of adverse events was similar in all the groups. Notably, no serious infusion reaction was reported. No patient developed anti-nuclear antibody, anti-DNA antibody, or specific antibody to MRA. Conclusions: This is the first clinical study of humanized anti-IL-6R monoclonal antibody therapy for Crohn’s disease. Every-2-week infusions of 8 mg/kg MRA for 12 weeks were safe, well tolerated, and suggested a beneficial clinical effect in Crohn’s disease patients. Acknowledgement: This study was supported by Chugai Pharmaceutical Co., Ltd.