Tocilizumab, a Novel Monoclonal Antibody Targeting IL-6 Signaling, Significantly Reduces Disease Activity in Patients with Rheumatoid Arthritis

The cytokine IL-6 plays a central role in maintaining chronic inflammation in rheumatoid arthritis (RA). Among other phase 2 trials, a previous European study indicated that targeted blockade of IL-6 signaling promises to be a highly efficacious means of decreasing disease activity in RA [Maini RN et al. *Arthritis Rheum* 2006]. Tocilizumab is the first humanized interleukin-6 (IL-6) receptor inhibiting monoclonal antibody and represents a novel mechanism of action to treat RA.

This report presents data from the phase 3 OPTION (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders) international study, involving 623 patients with moderate to severe RA. In this 3-arm, randomized, double-blind study, patients received tocilizumab 4mg/kg, tocilizumab 8mg/kg, or placebo intravenously every 4 weeks for a period of 6 months. All three groups continued to receive methotrexate (oral or parenteral) at their pre-study dose (10-25 mg weekly). All other DMARDs were discontinued at study entry.

After 24 weeks of treatment, a significantly ($p<0.0001$) higher proportion of patients receiving tocilizumab 8 mg/kg (58.5%) and tocilizumab 4 mg/kg (47.9%) achieved the ACR20 endpoint vs placebo (26.5%). In the tocilizumab 8 mg/kg group, significantly more patients achieved ACR50 (43.9%) and ACR70 (22.0%) responses vs placebo (10.8% and 2.0% respectively, $p<0.0001$). In addition, 28% of patients in the 8mg/kg tocilizumab group and 14% of patients in the 4mg/kg tocilizumab group achieved DAS28-remission (DAS 28 ≤2.6) vs 1% of patients receiving methotrexate alone.

A reduction in Disease Activity Score (DAS28) was observed from week 2 onwards in both tocilizumab groups, with significant change from baseline to week 24 for both tocilizumab 8 mg/kg (-3.43) and 4 mg/kg (-2.68) vs placebo (-1.55, $p<0.0001$). A significantly higher proportion of patients achieved a good/moderate EULAR response at 24 weeks in both tocilizumab groups, compared with placebo ($p<0.0001$). Good/moderate response was seen in 79.5% of patients receiving tocilizumab 8 mg/kg, 61.9% receiving tocilizumab 4 mg/kg and 34.8% on placebo. The overall frequency of adverse events was similar in all 3 groups, with serious infections reported by 6 patients in the 8 mg/kg tocilizumab group, 3 patients in the 4 mg/kg tocilizumab group and 2 patients in the placebo group.

Patients treated with tocilizumab in combination with methotrexate achieved rapid and significant improvement in their signs and symptoms of RA when compared to patients continuing methotrexate alone.

"The efficacy of IL-6 receptor inhibition in this study confirms the critical role of IL-6 in the causal pathways of rheumatoid arthritis. On this basis, the profound clinical success observed with tocilizumab by targeting a novel pathway is extremely encouraging, as is the opportunity for rheumatoid arthritis patients to benefit from a potential new treatment option," commented lead investigator, Professor Josef S. Smolen, MD, Medical University of Vienna.

Breast Feeding Reduces the Risk of Rheumatoid Arthritis

Results of an observational study presented by lead researcher Mitra Keshavarz, MD, Malmö Hospital University, Sweden, indicated that breast feeding for a period of 13 months or more reduced a woman's risk of developing rheumatoid arthritis (RA).

Data for this study was derived from a community-based health study incorporating information from the Swedish National Hospital Discharge and the National Cause of Death Register. Health information from 136 women who later developed RA was compared with that of 544 controls. Information on the use of oral contraceptives, hormone replacement therapy, and other lifestyle factors was derived from a self-administered questionnaire.

The mean age of onset of RA was 63.3, years with a median duration of 5.5 years from enrolment in the health study to RA onset. Longer history of breast-feeding was associated with a reduced risk of RA (OR: 0.46; 95% CI 0.24-0.91 for women with ≥13 months of breast-feeding, and OR 0.74; 95% CI 0.45-1.20 for those with 1-12 months, vs those who never breast-fed).

The protective effect of longer breast-feeding remained significant when adjusted for parity and either smoking or level of education in multivariate models. Parity, oral contraceptive use, or hormonal replacement therapy, were not significantly associated with future development of RA.