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.

"This study specifically highlights the potential of naturally–induced hormones in protecting individuals from developing rheumatoid arthritis in the future. Furthermore, it adds to the growing body of evidence in favor of breast feeding and its positive health implications," said Dr. Keshavarz.

Rheumatoid Arthritis Disease Activity is Significantly Reduced During Pregnancy

Results of a prospective nationwide study (the PARA-study) presented by Yaël de Man, MD, Erasmus MC University Medical Center, Rotterdam, the Netherlands, demonstrated that rheumatoid arthritis (RA) disease activity is significantly reduced during pregnancy.

In the first prospective study conducted among women with RA, patients were monitored for disease activity scores (DAS) throughout their pregnancy and for 6, 12, and 26 weeks postpartum. DAS were calculated using the DAS28 and the level of C-reactive protein (CRP) with 3 variables (DAS28-CRP-3). Remission was defined as DAS28 <2.6.

The change in DAS28 between the 1st and 3rd trimester was used to categorize response using the EULAR response criteria. The change between the DAS28 at 6 weeks and 12 or 26 weeks postpartum was used to determine if a severe or moderate flare was present using inverted EULAR response criteria. The changes in DAS28 were tested for significance by a linear mixed model.

The study population was comprised of 124 women (mean age 31.6 years; median disease duration 5.2 years). Seventy-one percent (71%) of patients were RF positive, 61% were anti-CCP positive, and 72% were erosive. The mean pregnancy duration was 38 weeks and 6 days.

During pregnancy 11% of patients were considered good responders, 40% were at least moderate responders, and 60% were non-responders as indicated by the change in DAS28 between the 1st and 3rd trimesters.

The mean DAS28 decreased significantly by the 3rd trimester (vs prior to conception or to the 1st trimester (p=0.003), indicating an improvement of RA during pregnancy. Remission was seen in 17% of patients as early as the 1st trimester; 26% of patients were in remission by the 3rd trimester.

The DAS28 increased significantly by 12 weeks postpartum (vs 6 weeks postpartum) indicating a relapse of disease activity. Postpartum, 64% of patients remained relatively stable or improved. Only 36% of patients experienced at least moderate flare and only 5% a severe flare. Postpartum, the number of patients in remission decreased to 17% at 12 weeks. With medication, however, the number of patients in remission at 26 weeks postpartum increased to 20%.

DMARD use was lowered before pregnancy, remained stable during pregnancy (52% of patients), but increased postpartum (82% of patients), mainly due to methotrexate and biologics use.

Dr. de Man noted, "…the existence of a complex interaction between female hormones during pregnancy and the epidemiology of RA may contribute to the development of new prevention and treatment approaches in the future".

Strontium Ranelate Reduces the Risk of Vertebral Fracture in Postmenopausal Women with Severe Osteoporosis

Vertebral fractures in postmenopausal women (<65 years of age) with osteoporosis can lead to acute and chronic back pain, loss of weight, reduced pulmonary function, back related disability, depression, and a sustained decrease in quality of life. Early fractures occurring within the first 10 years after menopause are especially troublesome since they are a major risk factor for further additional fractures.

Strontium ranelate is an anti-osteoporotic treatment with a unique mode of action which reduces bone resorption while promoting continued bone formation [Marie PJ et al. *Calcif Tissue Int* 2001]. It has been shown to be effective in reducing the risk of vertebral fractures in two phase 3 studies. In the Spinal Osteoporosis Therapeutic Intervention (SPOTI) study of 1,649 postmenopausal women (mean age 69.4±7.2) with osteoporosis, strontium ranelate 2g/day produced a risk reduction for vertebral fracture of 49% in the first year and 41% over 3 years [Meunier PJ et al. *N Engl J Med* 2004]. The Treatment of Peripheral Osteoporosis (TROPOS) study was designed to examine the effect of strontium ranelate on non-vertebral fractures in postmenopausal women with osteoporosis (mean age 76.7±8). Three thousand six hundred and forty (3,640)