Efficacy and Safety of Tocilizumab in Monotherapy, an Anti-Il-6 Receptor Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis: Results from a 24 Week Double-Blind Phase III Study

The efficacy and safety of tocilizumab, an anti-IL-6 receptor monoclonal antibody, was examined as a monotherapy in patients with active RA who had inadequate responses to MTX. In this Japanese study, RA patients previously treated with MTX received either tocilizumab 8 mg/kg every 4 weeks + a MTX placebo (tocilizumab group) or a tocilizumab placebo + MTX 8 mg/week (MTX group) for 24 weeks. Study endpoints included ACR20, 50, and 70 improvement rates, DAS28, EULAR response, and the numeric index of ACR response (ACR-N) area under the curve (AUC) at 24 weeks.

There were 61 patients in the tocilizumab group and 64 patients in the MTX group. After 24 weeks of treatment, ACR20 (80.3% vs 25.0%, $p<0.001$), ACR50 (49.2% vs 10.9%, $p<0.001$), and ACR70 (29.5% vs 6.3%, $p<0.001$) response rates were significantly higher in the tocilizumab group than in the MTX group. Consistent improvements were observed in the EULAR response criteria as well as ACR-N AUC index.

Fewer patients withdrew from the tocilizumab group (n = 7) compared with the MTX group (n = 31) indicating a greater tolerance for tocilizumab. The safety profiles of the two groups were similar. The most common adverse event was nasopharyngitis in both groups (tocilizumab 18.0% and MTX 10.9%).

This study indicates that tocilizumab is an efficacious and safe treatment in RA patients with inadequate response to MTX.

Concomitant Aspirin Use Reduces the Risk of Acute Myocardial Infarction in Users of Cyclooxygenase-2 Selective and Some Non-Selective Non-Steroidal Anti-Inflammatory Drugs

This study examined the ability of concomitant use of aspirin to off-set the risk of acute myocardial infarction (MI) in patients being treated with cyclooxygenase-2 (COX-2) selective and non-selective NSAIDs. The protocol was based on the increased risk of MI reported with the use of these agents. The hypothesis was based on studies that suggest that inhibition of thromboxane by aspirin may reverse the imbalance resulting from selective inhibition of COX-2-mediated prostacyclin formation.

Data was derived from a California Medicaid database of patients diagnosed with OA or RA. Patients were matched as to age, gender, and length of drug exposure. From this database, 15,343 cases of acute MI (8% fatal) were identified. Adjusted risk ratios (95% CI) of acute MI were 1.31 (1.20 - 1.43) with rofecoxib, 1.13 (1.04 – 1.19) with celecoxib, 1.08 (0.97 – 1.19) with ibuprofen, 1.65 (1.27 – 2.15) with indomethacin, 1.52 (1.14 – 2.03) with meloxicam, and 1.47 (1.03 – 2.11) with sulindac. Concomitant use of aspirin reversed MI risk with rofecoxib to 1.03, with celecoxib to 0.88, with meloxicam to 0.53, and with sulindac to 0.77. The risk was partially reversed with indomethacin to 1.21, but unchanged with ibuprofen (1.20).

The authors concluded that COX-2 selective and NSAIDS contribute to an increased risk of MI probably due to the inhibition of prostacyclin formation. This risk can be reduced by concomitant aspirin use. It was suggested that the incomplete reversal of risk with NSAIDS may be due to the pharmacodynamic interference of these NSAIDS with the binding of aspirin to platelet COX-1. It

was also suggested that further evaluation of the potentially-increased GI toxicity of aspirin-NSAID therapy was needed.

54 Week Results from IMPACT 2: Infliximab Inhibits Progression of Radiographic Damage in Patients with Active Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy condition characterized by an association of arthritis and psoriasis that can lead to progressive joint damage, disability, and reduced life expectancy *(Rheumatol* 2003;42:1460–8). A substantial proportion of patients have persistent inflammation. The extent of radiographic progression in patients with established PsA is comparable with that of RA patients when matched for age, sex, and disease duration (*Rheumatol* 2001;28:1041–4).

Historically, the decision to use a particular treatment modality for PsA has been mainly derived from the extrapolation of data from patients with RA. Results from the recent Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT), indicated that therapy with infliximab (IFX) 5 mg/kg significantly improved the signs and symptoms of arthritis, as well as reduced skin psoriasis, in patients with active PsA resistant to prior DMARD therapy (*Arthritis Rheum* 2005;52:1227–36).

Using data from the 54 week IMPACT 2 trial data, the authors assessed the effect of IFX 5mg/kg compared with a placebo on structural damage in 200 PsA patients. Radiographic data was obtained from hand and feet measurements at weeks 0, 24, and 54. Erosions and joint space narrowing were evaluated by the van der Heijde-Sharp method modified for PsA.

Radiographic data indicated that IFX was an effective inhibitor of radiographically documented progression of joint structural damage. At week 24, IFX-treated patients had significantly less radiographic damage than placebo patients (mean change in total van der Heijde-Sharp score = -0.70 ± 2.53 vs 0.82 ± 2.62, p<0.001). Twelve placebo-treated patients vs 3 patients in the IFX group had changes in the total van der Heijde-Sharp scores exceeding the the smallest detectable change at week 24 (p = 0.017). In patients continued on IFX through week 46, mean change was –0.94 vs 0.53 in patients who crossed over from placebo to IFX (p=0.001). These results indicate that IFX provides effective inhibition of radiographic progression in PsA patients as early as 24 weeks and continues to provide protection after 1 year of treatment.

The ATLAS Trial: Long-Term Adalimumab Treatment Reduces Signs and Symptoms in Ankylosing Spondylitis Patients

The Adalimumab Trial Evaluating Long-Term Efficacy and Safety in Ankylosing Spondylitis (AS) or ATLAS trial was a double-blind, phase III, placebo-controlled study to evaluate the ability of adalimumab to reduce signs and symptoms of AS over a one-year period. Patients with active AS refractory to at least one NSAID were given 40 mg adalimumab bi-weekly or placebo for 24 weeks.

Adalimumab efficacy was evaluated by ASsessment in AS (ASAS) 20 Criteria (inflammation, total back pain, function, and patient's global assessment of disease activity). The primary endpoint (ASAS20) was at Week 12, at which point patients had the option to switch to early escape therapy (EET) of open-label 40 mg adalimumab. One-year efficacy of ADA was assessed using the following analyses: 1) a non-responder imputation to Week 52 for