implicated in the bone erosions that are characteristic of rheumatoid arthritis (RA).

This ongoing, double-blind, placebo-controlled, phase 2 study was conducted to determine if denosumab treatment could reduce the progression of bone erosions in patients with RA who were on background methotrexate (MTX). Based on previous pharmacokinetic studies of denosumab in postmenopausal women, a 6 month dosing schedule was selected for this initial trial [Bekker PJ et al. *J Bone Miner Res* 2004; Peterson M et al. *J Bone Miner Res* 2003].

A total of 227 patients (9 patients never received test article) were randomly assigned to receive subcutaneous injections of denosumab 60 mg (n=71) or 180 mg (n=72) or placebo (n=75) every 6 months. Of this group, 2 patients discontinued from the 60 mg group, 6 discontinued from the 180 mg group, and 6 discontinued from the placebo group. Radiographs of the hands and feet were taken at baseline, 6, and 12 months. Randomization was stratified for prior use of biologics and current steroid use. Change from baseline in MRI erosion scores at 6 months was the primary endpoint. Key secondary endpoints included changes in the modified Sharp erosion score (ES), modified Sharp joint space narrowing score (JSN), and modified total Sharp score (TSS) from baseline and at months 6 and 12. Radiographs of the hands/wrist and feet were analyzed using the van der Heijde-modified Sharp method. Increasing scores reflected increased damage. Safety was monitored throughout the study.

The mean change in ES at 6 months was significantly (p=0.02) less for patients treated with 180 mg of denosumab vs placebo. Data for 209 patients are included in the 12 month analysis. At 12 months, the change was significantly (p≤0.01) less for both doses of denosumab.

No significant differences were noted for any treatment group for ACR response. Modeling of data for collagen C-telopeptide Type II (CTX-II, a biomarker of cartilage turnover) suggests that the dose/frequency used in this study may not have been sufficient to preserve cartilage. The radiographic erosion scores were consistent with MRI erosion scores analyzed at the primary endpoint of the study.

Adverse events were similar across the 3 treatment groups. The most frequent, occurring at ≥10%, were flare, upper respiratory infection, sinusitis, nasopharyngitis, and influenza.

Denosumab treatment (60 mg and 180 mg) every 6 months reduced progression of TSS and ES, but not JSN vs placebo. No change in ACR response was noted. The incidence of adverse events was similar among the placebo and denosumbab 60 mg and 180 mg treatment groups.

Change in Score at 12 Months

Measurement, Mean (SD)	Placebo n=71	Denosumab 60 mg n=69	Denosumab 180 mg n=69
Total Sharp Score	1.87 (5.06)	0.85 (2.52)*	0.97 (2.70)†
Erosion Score	1.34 (4.40)	0.33 (1.22)#	0.19 (1.61)#
Joint Space Narrowing	0.53 (1.49)	0.51 (1.63)	0.78 (1.72)

*p=0.03 vs placebo, †p=0.18 vs placebo #p<0.05 vs placebo.

Professor Désirée van der Heijde, MD, Leiden University Medical Center and lead author of the study commented, "These data show the significant potential of denosumab, revealing that patients receiving denosumab experienced a reduced progression of erosions compared to control…"

Combination TNF-Inhibitor-MTX Therapy is Superior to MTX Monotherapy in Reducing the Risk of Acute Myocardial Infarction in Patients with Rheumatoid Arthritis

It is well known that patients with rheumatoid arthritis (RA) have an increased risk of fatal and non-fatal acute myocardial infarction (AMI). Endothelial dysfunction is part of the RA disease process and is mediated by TNF-alpha [Hurlimann D et al. *Circulation* 2002]. Localized inflammatory responses in the intimal layer of the arterial wall have been shown to be responsible for many aspects of intimal thickening and plaque disruption, leading to acute cardiovascular events. TNF inhibitors may reduce the risk of AMI in RA patients because their strong anti-inflammatory effect improves endothelial function [Bacon PA et al. *Int Rev Immunol* 2002].

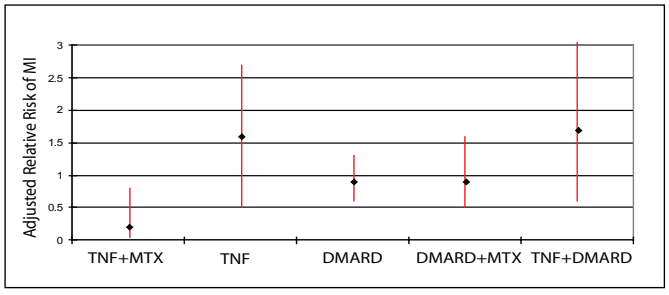
The risk of AMI with TNF-inhibitor therapy, methotrexate (MTX), and other DMARDs was studied by Gurkirpal Singh, MD, Standford University School of Medicine, in a large population (MediCal, the Medicaid program for California) of patients with RA, many of whom were on concomitant aspirin therapy.

Cases of acute myocardial infarction (AMI) were risk-set matched with 4 controls for age, gender, and date of AMI. All analyses were adjusted for 38 confounding risk factors (including surrogate variables for smoking and dyslipidemias) as well as concomitant aspirin and NSAID treatment (prescription or over-the-counter use).

A total of 19,233 RA patients (mean age 54.7 years, 79.4% women) were identified. Of these, 13,383 patients took MTX, 14,958 took other DMARDs, and 4,943 took TNF inhibitors. Treatment groups included TNF inhibitors (monotherapy), TNF inhibitors plus MTX, TNF inhibitors plus non-MTX DMARDS, non-MTX DMARDs alone, and MTX plus non-TNF DMARDs.

During 74,006 person-years of follow-up, 441 cases of AMI were identified, of which 8% were fatal. Treatment with TNF inhibitors plus MTX significantly reduced the risk of AMI vs MTX monotherapy (multivariate-adjusted relative risk 0.20 (95% CI 0.05 – 0.88, p<0.03; Figure 1). No statistical difference was seen with TNF-inhibitor monotherapy (RR 1.17, 95% CI 0.50–2.75), TNF-inhibitor with other DMARDs (RR 1.78, 95% CI 0.60–5.27), other DMARD therapies without MTX (RR 0.88, 95% CI 0.60–1.31) or a combination of DMARDs and MTX (RR 0.93, 95% CI 0.54–1.62) vs MTX monotherapy. Systemic corticosteroid use was an independent risk factor which significantly increased the risk of AMI (adjusted RR 1.37, 95% CI 1.07–1.75, p<0.01).

Figure 1. Adjusted Relative Risk of AMI, Compared to MTX Monotherapy.



These results indicate that combination therapy using a TNF-inhibitor plus MTX is associated with a reduction in the risk of acute myocardial infarction by 80% vs MTX monotherapy in patients with RA. Such a dramatic effect enhances the therapeutic gains of TNF-inhibitor therapy in patients with RA and should be seriously considered, particularly in high-risk patients.

Non-Vertebral Fracture Reduction with High- vs Low-Dose Ibandronate

Results from the Oral IBandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) study showed a significant (p=0.0001) 62% reduction in the risk of vertebral fractures in women with postmenopausal osteoporosis treated with oral ibandronate, either as 2.5 mg daily or as 20 mg every other day for 12 doses every 3 months [Chesnut CH et al. *Bone Miner Res* 2004]. Although the study was not powered to evaluate the outcome in non-vertebral fractures, a significant (p=0.013) relative risk reduction for non-vertebral fractures of 69% was seen in a subgroup of high risk patients (mean femoral neck bone mineral density (BMD) T-score ≤3).

This meta-analysis was conducted to assess the efficacy of high vs low doses of ibandronate on non-vertebral factures. All randomized-controlled trials of ibandronate were reviewed and variable definitions of high vs low doses were explored. A time to event analysis was conducted comparing high annual cumulative exposure (ACE) with low ACE with 2-year data taken from two equivalent non-inferiority trials [Reginster JY et al. *Ann Rheum Dis* 2006; Emkey R et al. *Arthritis Rheum* 2005]. Hazard ratios, derived from a Cox model, were adjusted for clinical fracture, age, BMD, and study. ACE was based on an oral bioavailability of 0.6% and IV bioavailability of 100%.

A reduced non-vertebral fracture rate was seen when comparing combined high doses equivalent to an ACE of ≥10.8 mg with a low ACE of 5.5 mg (HR 0.620; relative risk reduction: 38%; 95% CI 0.40-0.97; p=0.04). Similar treatment effects were seen when high doses (ACE ≥10.8 mg) were compared with medium doses equivalent to an ACE of 5.5-7.2 mg. There was a dose-response effect with increasing ACE (7.2-12 mg) compared with ACE 5.5 mg. Adjustment for covariates in the analysis had a minimal effect.

A significant effect on non-vertebral fracture risk reduction was seen when combining trials using high ibandronate doses equivalent to an ACE of ≥10.8 mg versus a low ACE of 5.5 mg, and also with ACE ≥10.8 mg versus ACE ≤7.2 mg.

The treatment effect was dose-dependent. Higher doses of ibandronate significantly increase bone mineral density at the spine and hip, and reduce the risk of non-vertebral fractures more effectively than lower doses.