lowered the risk of RA. The estimated odds ratio associated with alcohol consumption was about the same regardless of the presence of anti-CCP positive RA or anti-CCP negative RA. Furthermore, the association between alcohol consumption and RA was modified by both smoking and HLA-DRB1 SE alleles.

The results from the present study thus indicate that alcohol consumption is associated with a protective effect in relation to risk of developing RA, and that this effect is independent of anti-CCP status. The study points to the need to investigate mechanisms behind the protective effect of alcohol in both man and mice in order to understand the effect of life style on RA, and to identify new targets for therapy.

Induction of Remission in Early Rheumatoid Arthritis with Infliximab and Methotrexate Therapy

Early treatment with a combination of methotrexate (MTX) and infliximab (IFX) may be effective in inducing remission and altering the course of early rheumatoid arthritis (RA), according to the results of a study presented by Cornelia F. Allaart, MD, Leiden University Medical Center, Leiden, The Netherlands.

The BeSt study was a randomized trial comparing 4-year clinical and radiological outcomes using 4 different treatment strategies (groups) in patients with early and active RA [Goekoop-Ruiterman YP et al. *Ann Intern Med* 2007]. Patients in Group 4 (n=120) started treatment with IFX 3 mg/kg + MTX 25 mg/week. IFX treatment was adjusted every 8 weeks (ie, prior to each IFX infusion; if IFX was stopped the DAS was calculated every 3 months) throughout the study period based on Disease Activity Scores (DAS). In case of a continued DAS ≤2.4, IFX was discontinued and MTX was tapered to 10 mg/week. Beginning in year 3, MTX 10 mg/week was tapered to zero if the DAS remained <1.6.

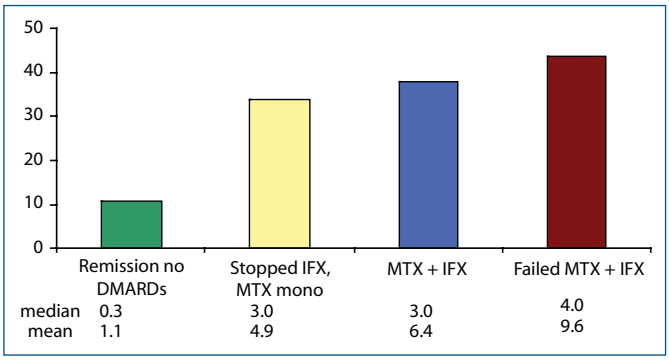
Disease progression over the course of the trial was determined by the Health Assessment Questionnaire (HAQ) and the van der Heijde modification of the Sharp score (SHS) to assess damage on hand and foot x-rays at initiation of the trial and at 4 years.

After 4 years, 113 patients remained in the study; 61 had successfully discontinued IFX after a mean of 13 months. At year 4 all of these patients had maintained a DAS ≤2.4, indicating a mean IFX-free period of 35 months. Twenty (20) of these patients had stopped all anti-rheumatic therapy and maintained a DAS <1.6 (mean 12 months without DMARDs).

During the 4th year, 4 patients who had previously discontinued all anti-rheumatic drugs were restarted on MTX (due to a DAS ≥1.6); 6 others who were on MTX monotherapy stopped using this medication. Four (4) patients who had previously discontinued IFX were required to restart, resulting in 22 patients on MTX+IFX combination therapy after 4 years. Thirty (30) patients failed on MTX+IFX and proceeded as per the protocol to the next pre-specified treatment steps.

SHS progression (>SDC, smallest detectable change) after 4 years was highest in patients who had failed MTX+IFX and minimal in the 20 patients who discontinued all anti-rheumatic therapy (Figure 1).

Figure 1. Percent of Patients with Progression SHS.



Four (4) years after receiving IFX and MTX as initial treatment for RA, 17% of patients have discontinued all anti-rheumatic medications and remain in clinical remission with minimal joint damage progression. Study leader Dr. Allaart commented, "Our findings indicate that clinical remission from RA is achievable, provided effective treatment is administered early in the course of the disease."

The RANKL Inhibitor Denosumab Reduces Progression of the Total Sharp Score and Bone Erosions in Patients with Rheumatoid Arthritis

Denosumab is a fully human monoclonal antibody that binds to and inhibits RANK Ligand (RANKL), a key mediator of osteoclast formation, function, and survival. There is no detectable binding to TNFα, TNFβ, TRAIL, or CD40L. RANKL-driven osteoclast activity has been

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.