explanation for the anti-inflammatory effect of rHu-Epo in patients with RA.

FRI0034 DOES HEAVY CAFFEINE INGESTION AFFECT THE EFFICACY OF METHOTREXATE

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Background In a proportion of patients methotrexate (MTX) has to be withdrawn because of lack of efficacy or side effects. MTX results indirectly in increased adenosine release. Adenosine, acting at the A2 receptor, mediates the anti-inflammatory effects of MTX. Caffeine is a non selective adenosine receptor antagonist and reverses the anti-inflammatory effects of MTX in the rat adjuvant arthritis model.

Objectives To see if there was any correlation between withdrawal of MTX due to treatment failure and caffeine ingestion.

Methods Over a 10 month period 91 sequential patients in 2 centres who had ever been on MTX were interviewed. They were classified as either minimal or regular coffee drinkers dependant on whether they drank more or less than 7 cups of coffee per week. Concomitant theophylline medication and tea and cola ingestion were also documented. Doses used varied from 5 to 15 mg weekly (mean = 10.3 ± 2.75).

Results The proportion of people who have to discontinue MTX is higher in those who are regular coffee drinkers (P value = 0.02). In this group the reason for discontinuing was due to treatment failure in 80% of cases. 90% of those still on MTX and 74% of those who discontinued MTX were minimal coffee drinkers.

Conclusion Patients who are on MTX should decrease their caffeine intake as there is a statistically significant increase in treatment failure in those who drink coffee regularly. This may account for the reason that much higher doses of MTX are used in countries with a heavier caffeine consumption.

FRI0035 RISK FACTORS FOR CLINICALLY IMPORTANT UPPER GI EVENTS: THE VIGOUR STUDY

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Background The VIGOUR (VIOXX GI Outcomes Research) study was a prospective, randomised, double-blind comparison of rofecoxib (a COX-2 inhibitor) vs. naproxen (a dual COX-1/COX-2 inhibitor) in > 8000 patients with rheumatoid arthritis (RA). The study showed that rofecoxib was associated with significantly fewer clinically important upper gastrointestinal (GI) events (perforation, obstruction, bleeding, symptomatic gastric and duodenal ulcers) than naproxen.

Objectives To assess whether the risk reduction in clinically important upper GI events seen with rofecoxib was similar in "high risk" and "low risk" sub-populations; and, to predict the risk of these events based on baseline characteristics.

Methods In the VIGOUR trial, 8076 RA patients expected to require NSAIDs for > 1 yr were randomly assigned rofecoxib 50 mg qd or naproxen 500 mg bid for minimum of 6-month

follow-up. Patients were classified as "low risk" or "high risk" for clinically important upper GI events based on recognised risk factors – age, steroid use, previous history of clinical GI events, and H. pylori sero-status. Relative risk analyses were conducted in both low- and high-risk subgroups. A multifactorial model to predict clinically important upper GI events was developed. Multiple steps in the analysis included: 1. Covariates were examined in a univariate Cox model; 2. Factors that trended (p < 0.20) plus treatment were put into Cox model and backwards stepwise regression chose significant (p = 0.05) predictors; and, 3. Interactions between each covariate with treatment were tested one at a time in Cox models.

Results The % risk reduction (rofecoxib relative to naproxen) of clinically important upper GI events was 88% in the low-risk subgroup, 51% in the high-risk subgroup and 54% in the overall population.

Abstract FRI0035 Table 1

	Relative risk (95% CI)	p-value
65–74 vs	2.37 (1.70, 3.30)	<0.001
Uncomplicated vs No Hx of PUBs	3.08 (1.98, 4.77)	<0.001
Complicated vs No Hx of PUBs	3.73 (2.25, 6.17)	<0.001
ARA Class IV vs I/II/III	2.27 (1.10, 4.69)	0.027
Prior Hx GI symptoms vs none	1.81 (1.28, 2.56)	<0.001
Prior H2 blocker use vs none	1.62 (1.09, 2.43)	0.018
Prior steroid use vs none	1.59 (1.15, 2.18)	0.005
Prior NSAID use vs none	0.57 (0.40, 0.79)	<0.001

Risk Factors for Clinically Important Upper GI Events based on Multifactorial Model.

Conclusion (1) The relative risk reduction of GI events in the rofecoxib group was maintained in both the high and low risk subgroups. (2) Multivariate analyses found the risk factors significantly associated with GI events to include age, prior history or clinical GI events (complicated and uncomplicated), disease severity, duration of disease, prior history of GI symptoms, prior use of low dose H2 blockers, steroids, and NSAIDs.

FRI0036 POPULATION PHARMACOKINETICS (PK) OF ANAKINRA IN SUBJECTS WITH RHEUMATOID ARTHRITIS (RA)

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Background Anakinra is a recombinant interleukin-1 receptor antagonist that reduces signs and symptoms and slows joint destruction in RA patients in clinical trials. Population PK analysis was conducted on data from RA patients treated with anakinra.

Objectives The objective was to investigate the effect of covariates such as creatinine clearance (CLcr), body weight (WT), age, and sex, on anakinra PK.

Methods Subjects (n = 341) received daily SC injections of anakinra at 30, 75, or 150 mg for 6 months; one plasma sample for anakinra measurement was collected from each subject at baseline, and at weeks 1, 4, 12, 20, and 24 before anakinra administration for that day. Plasma samples were analysed for anakinra levels by an ELISA method. Plasma anakinra data were analysed by nonlinear mixed-effects modelling using NONMEM.