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Background In a proportion of patients methotrexate (MTX) has to be withdrawn because of lack of efficacy or side effects.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.

"Population" mean PK parameters, intersubject variability in the PK parameters, and residual error were estimated.

Results Anakinra PK appeared to be dose independent and was adequately described by a one-compartment model with first-order absorption and elimination. Results showed that anakinra volume of distribution (Vd/F) increased linearly with increasing WT ($Vd/F = 0.142 * WT$, $p < 0.05$). Both CLcr and WT were significant predictors of anakinra plasma clearance (CL/F); clearance increased with increasing CLcr and WT ($CL/F = 23.0 + 0.343 * CLcr + 0.713 * WT$, $p < 0.05$). The plasma clearance of anakinra was higher in men (164 ± 25 mL/min, $n = 79$) than in women (144 ± 22 mL/min, $n = 262$) and higher in younger subjects (< 65 yr, 152 ± 24 mL/min, $n = 262$) than in older subjects (> 65 yr, 138 ± 23 mL/min, $n = 79$), these differences could be explained by differences in CLcr and WT.

Conclusion Results from population PK analyses confirmed non-clinical and clinical data, which showed the kidney to be a major clearance organ for anakinra.

FRI0037 RESULTS OF A PIVOTAL (PHASE III) PLACEBO AND ACTIVE COMPARATOR CONTROLLED EFFICACY TRIAL OF ROFECOXIB 25 AND 50 MG IN ADULT PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

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Background

Objectives To determine the efficacy and safety profile of rofecoxib 25 mg and 50 mg versus placebo and naproxen in patients with RA.

Methods 1058 RA patients were randomised in a double-blind fashion to: placebo ($n = 299$), rofecoxib 25 mg ($n = 315$), 50 mg ($n = 297$), or naproxen 1000 mg (given as 500 mg bid; $n = 147$). Eligible patients were chronic NSAID users and demonstrated a clinical worsening or flare upon withdrawal of prestudy NSAID(s). Efficacy assessments included all components of the ACR core set. Four endpoints were prespecified as primary: the patient and investigator global assessments of disease activity and counts of tender and swollen joints. The proportion of patients meeting the ACR20 criteria, patient assessment of pain, and a modified HAQ score were key secondary measurements. Safety was assessed based on adverse experience reporting by investigators (particularly discontinuations due to adverse experiences [AEs]) and routine laboratory and vital sign measurements.

Results After 12 weeks, patients receiving rofecoxib 25 mg, 50 mg, and naproxen showed similar improvements compared with placebo: a 3 to 4-joint reduction in the number of tender joints; a 1-joint reduction in the number of swollen joints; a 7 to 10 mm improvement on the patient global assessment (1 -100 mm VAS) and a 0.3 to 0.4-unit reduction on the investigator global assessment (0 to 4 Likert scale). All improvements were statistically significant ($p < 0.05$) versus placebo, except naproxen on swollen joint count. For key secondary measurements, all three active treatments showed a $>10\%$ difference ($p < 0.05$) versus placebo for the proportion of patients meeting the ACR20 criteria. All active treatments showed a significant difference from placebo, consistent with improvement, for the modified HAQ and the patient assessment of pain. No statistically significant differences were noted between 25 mg and 50 mg rofecoxib or between naproxen and either rofecoxib group for any efficacy

measurement. Fewer patients discontinued due to AEs in the rofecoxib 25 mg group (3.8%) compared with the other active treatment groups ($\sim 8\%$) and placebo (4.7%).

Conclusion Overall, improvements with 25 mg rofecoxib were similar to those with 50 mg rofecoxib and naproxen but with improved tolerability, supporting the use of 25 mg rofecoxib for treating the signs and symptoms of RA in adults.

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FRI0038 INTRAMUSCULAR METHOTREXATE (IM-MTX) IN INFLAMMATORY RHEUMATIC DISEASE ? CLINICAL AND PATIENT PERSPECTIVES

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Background Methotrexate is regarded as an effective and safe disease modifying drug (DMARD). The IM route of administration has been shown to have certain advantages over the oral route. There has been an increase use of IM-Mtx in our department in the last 2 years, leading to increased workload in the nurse-led monitoring clinics and cost.

Objectives To review both the clinical and patient experiences with IM-Mtx, focusing on efficacy and side-effects as well as patient satisfaction.

Methods Medical case-notes of 31 patients, identified from our database, were reviewed. The clinical diagnosis, previous drug therapies, reason for changing to IM-Mtx, efficacy and side-effects were noted. In addition, the patients were asked to complete a questionnaire, looking at patient satisfaction and preferred venue for injections (monitoring clinic or local doctor's surgery).

Results Our patient cohort was made up of 24 rheumatoid arthritis, 4 seronegative spondyloarthritis, 2 lupus and 1 undifferentiated connective tissue disease. The majority of patients has been on a previous DMARD, including 24 patients on oral Mtx. Reasons for changing to IM-Mtx therapy were as follows: side-effects in 11 patients, loss of efficacy in 12 patients and poor oral compliance in 8 patients. The median starting and maintenance doses were 10 mg weekly (range 5-17.5) and 15 mg weekly (range 10-17.5) respectively.

In the period of study, 5 patients discontinued IM-Mtx; 2 because of side-effects, 1 developed multiple nodulosis, 1 did not attend for follow-up and 1 died from an unrelated cause. Median duration of therapy in the remaining 26 patients was 10 months (range 1-20). Significant improvement in disease activity, as measured by ESR and CRP, was seen after 3 months ($p < 0.01$), with improvement maintained after 9 months ($p < 0.01$) of IM-Mtx therapy.

24 of the 26 current patients completed the questionnaire. On a satisfaction scale of 1 to 5, the average rating was 4.2, indicating patients were either very or extremely satisfied with their IM-Mtx therapy. 14 patients preferred their injections in the monitoring clinic, 5 patients preferred their local doctor's surgery and 5 patients expressed no preferences. Only 3 patients stated that weekly clinic visits were inconvenient.

Conclusion IM-Mtx was found to be effective and well tolerated. It should be considered as an alternative in patients intolerant to other DMARDs, including oral Mtx. Despite weekly clinic visits, patients were either very or extremely satisfied with