with LEF from February 2000 to January 2001. From patient records data were collected, like patient characteristics, medication data and Disease Activity Scores (DAS28). Analysis was performed on intention to treat basis. Primary endpoints are occurrence of adverse events possibly related to LEF use, incidence and reasons for LEF withdrawal and change in DAS28.

Results 110 patients (n = 38 men and n = 72 women), mean age (SD) 65 (13) years and a median disease duration of 5.5 years were included; mean follow up (SD) was 170 (91) days. Last DMARD prescribed prior to LEF was methotrexate (MTX) 28%, sulfasalazine (SASP) 25%, hydroxychloroquine (HCQ) 18% and others 10%; 19% of the patients used LEF as first DMARD. Mean number of DMARDs prescribed before starting LEF was 1.8 ± 1.4 . In 9% of the patients LEF was given in combination with another DMARD [MTX (6%), HCQ (2%) or SASP (1%)]. Adverse events (AE) possibly related to LEF use occurred in 56% of patients during follow up, most frequently involving the gastrointestinal tract (62 AE) and skin (21 AE). During follow up 27% discontinued LEF, 16% due to side effects, 5.5% due to inadequate response, 4.5% due to a combination of both. For 1% an undefined cause for withdrawal was recorded. The incidence density for withdrawal of LEF treatment is 56.6 per 100 patient years. Using the change in DAS28 as an efficacy parameter, at the first follow up visit (mean two months) after starting LEF, 22% were categorised good, 48% moderate and 30% non responder. At the second visit (mean six months) 26%, 42% and 31% were categorised good, moderate or non responder.

Conclusion In an outpatient rheumatology practice the incidence density per patient year for withdrawal of LEF treatment is high. Adverse events were the most frequent reasons for withdrawal; gastro-intestinal tract and skin being the organ (systems) most frequently involved. Using the change in DAS28 as efficacy parameter at the sixth month 68% were categorised as good and moderate responders to LEF.

FRI0013 OPEN-LABEL EVALUATION OF THE EFFICACY AND SAFETY OF ETANERCEPT IN COMMON RHEUMATOLOGY USAGE (ECRU)

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Background Tumour Necrosis Factor-alpha (TNF α) plays an important role in the inflammatory processes of RA and the resulting joint pathology. Etanercept is a dimeric fusion protein consisting of two p75 TNF α receptors linked to the Fc portion of the human IgG1. This protein can bind and inactivate up to two free molecules of TNF α . The safety and efficacy of etanercept has been demonstrated in human clinical trials of early RA and active RA.

Objectives The Primary efficacy variable was the proportion of patients achieving 20% improvement in symptoms according to American College of Rheumatology (ACR) response criteria at Week 16. Patients were evaluated clinically for adverse events at each visit.

Methods This study was conducted in 55 Austrian outpatients with active RA who have failed at least one disease-modifying anti-rheumatic drug (DMARD). Each patient received twice-weekly subcutaneous injections of etanercept 25 mg administered over a treatment period of 16 weeks. Stable doses of methotrexate (MTX) and steroids were permitted. A clinical

assessment of the patient's response to therapy and safety assessments were performed at each regular visit.

Results Efficacy: At week 16, 80% of the patients achieved an ACR 20 response (primary outcome measure). Moreover, 45,5% of patients achieved an ACR 50 response and 10,9% patients achieved an ACR 70 response at week 16.

The mean number of swollen joints fell from 17 at baseline to 6,7 at week 16. The mean number of tender joints fell from 18,9 at baseline to 7,1 at week 16.

The mean score of Patient's Global assessment fell from 6,6 at baseline to 2,9 at week 16. The mean score of Physician's Global Assessment score fell from 6,5 at baseline to 2,7 at week 16.

Safety: Etanercept 25 mg twice weekly was well tolerated. Adverse Events were primarily mild injection site reactions.

Conclusion

- This was an open-label, uncontrolled, 16 week study conducted in 55 Austrian RA patients for whom DMARD therapy was inappropriate or ineffective. Stable doses of MTX and steroids were allowed.
- The percentage of patients with an ACR 20 response in the present study (80%) is slightly greater than that reported in prior large multicentre studies (range 70-75%).
- No unusual patterns of AEs were identified.
- The safety and efficacy of etanercept 25 mg s.c. twice weekly in a single European country in a naturalistic, "common usage" setting were similar to that observed in controlled clinical trials in the US and EU.

FRI0014 FACTORS PREDICTING METHOTREXATE TOXICITY

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Background Methotrexate is the most effective treatment in rheumatoid arthritis. The treatment is limited by adverse events. Gastro-intestinal toxicity and hepatotoxicity occur the most. Various different factors have been reported to contribute to methotrexate toxicity.

Objectives To determine predictive factors for developing methotrexate toxicity, and methotrexate withdrawal because of toxicity.

Methods Data from a double-blind placebo controlled multicenter study on patients with active rheumatoid arthritis were used. In this trial the effect of folic acid (1-2 mg/day), folinic acid (2.5 mg/week) and placebo along methotrexate therapy (7.5-maximum 25 mg/week) was compared. The patients never had methotrexate before, had active disease and a creatinine clearance >50 ml/min. The three groups contained 133, 141 and 137 patients respectively. The follow-up was 48 weeks.

By means of multiple stepwise regression analysis we studied the relation between baseline variables and the following: hepatotoxicity (ALAT >3xULN), the ten most frequent subjective adverse events, and methotrexate withdrawal because of toxicity.

With the different toxicities we studied specific independent factors, for example NSAID's and alcohol use in hepatotoxicity.

Results Hepatotoxicity:

We found a significant association between folate supplementation and lack of hepatotoxicity (p < 0.0001). Smoking was negatively associated with hepatotoxicity, with less hepatotoxicity when the patient smoked (p = 0.003).

($P = 0.06 + 0.237$ no folate $- 0.023$ smoking)

The ten most subjective adverse events:

- Upper abdominal pain was significantly related to corticosteroid use ($p = 0.047$) ($P = 0.183 + 0.109$ corticosteroid)
- Fatigue/malaise was significantly associated with smoking ($p = 0.049$) ($P = 0.231 - 0.021$ smoking)
- Diarrhoea was significantly associated with age and a positive gastro-intestinal history, e.g. peptic ulcers and abdominal surgery ($p = 0.003$ and $p = 0.012$) ($P = 0.291 - 0.0037$ age $+ 0.087$ GI-history)

There were no significant associations between the other subjective adverse events (nausea, dizziness, headache, rash, stomatitis, cough and alopecia) and baseline characteristics.

Methotrexate withdrawal:

Significant factors predicting methotrexate withdrawal are folate suppletion, smoking and gastro-intestinal history. ($p = 0.000$, 0.009 and 0.019 respectively).

($P = 0.124 + 0.236$ no folate $- 0.027$ smoking $+ 0.103$ GI-history)

Conclusion Folates strongly protect against hepatotoxicity and methotrexate withdrawal, but not against subjective adverse events. An interesting finding is the relation between smoking and hepatotoxicity and fatigue/malaise. In smokers the methotrexate withdrawal was significantly less. A positive gastro-intestinal history and age were predictive factors for the occurrence of diarrhoea. In this study a declining creatinine clearance was no risk factor.

FRI0015 AZATHIOPRINE WITHDRAWAL IN RHEUMATOID ARTHRITIS PATIENTS. ROLE OF TPMT GENETIC POLYMORPHISMS

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Background Dose-dependent Azathioprine's bone marrow toxicity is widely accepted, although identification of the genetic polymorphism of the Thiopurine methyltransferase (TPMT) is being recently recognised.

Objectives The aim of the study was to investigate, if the appearance of drug related side effects, such as haematologic toxicity was due to the presence of allelic variants of the TPMT gene.

Methods 111 RA patients DNA's from WBC were amplified by PCR. Digestion with enzymes (MwoI and Acc) were performed, to identify the different allelic variants of the TPMT gene. MwoI digestion of the 284 bp PCR product resulted in fragments that either remained intact (mutant allele A460) or were cut in two segments of 267 bp and 17 bp (wild type allele G460A). AccI restriction site was present when the G719 mutation existed, the PCR products containing this mutation were cleaved (207 bp and 86 bp fragments) when digested with AccI, while the wild type fragments (A719) were not digested. Results were compared with 105 DNA samples from healthy donors. X2 tests on genotype frequencies and $p < 0.05$ was statistically significant.

Results 9.5% of healthy controls and 7.2% RA patients were heterozygous for a mutant allele of the TPMT gene. The most frequent variant in both groups was the TPMT 3A (G460A, A719G). Within the 111 RA, 40 of them had followed Aza

therapy. 8 of them were still following this therapy, and 32 had to withdrawal Azathioprine therapy due to non response ($n = 27$) or adverse side effects ($n = 5$): These last 5 patients were homozygous for the Wild type TPMT allele.

Conclusion TPMT genotype is to identify patients at risk of severe bone marrow toxicity if treated with Aza. Our study reveals that, severe side effects due to Azathioprine cannot be explained by the presence of these two mutant alleles.

REFERENCES

- 1 Kerstens PJ, Stolk JN, De Abreu RA, Lambooy LHJ, van de Putte LBA, Boeremooms A. Azathioprine-related bone marrow toxicity and low activities of purine enzymes in patients with rheumatoid arthritis. *Arthritis Rheum.* 1995;**38**:142-5
- 2 Yates CR, Krynetski EY, Loennechen T, Fessing MY, Tai HL, Pui CH, Relling MV, Evans WE. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med.* 1997;**126**:608-14

FRI0016 FACTORS PREDICTING METHOTREXATE DOSE AND EFFECTIVITY

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Background Methotrexate is the most effective treatment in rheumatoid arthritis. Dose and clinical effect are related.

Objectives To determine predictive factors for reaching a dose of > 12.5 mg/week and effectivity.

Methods Data from a double-blind placebo controlled multicenter study on patients with active rheumatoid arthritis were used. In this trial the effect of folic acid ($1 \square$ mg/day), folinic acid (2.5 mg/week) and placebo along methotrexate therapy (7.5 -maximum 25 mg/week) was compared. The patients never had methotrexate before, had active disease and a creatinine clearance > 50 ml/min. The three groups contained 133, 141 and 137 patients respectively. The follow-up was 48 weeks.

By means of multiple stepwise regression analysis we studied the relation between baseline variables and the following: methotrexate dose > 12.5 mg/week and effectivity (lowest DAS1.08).

Results Effectivity:

We found no significant relation between baseline characteristics and effectivity.

When we only look at a change in DAS > 1.08 the disease duration (months) is significantly associated ($p = 0.035$)

($P = 0.678 + 0.0015$ disease duration)

Methotrexate dose > 12.5 mg/week:

Reaching a dose > 12.5 mg/week is significantly associated with folate suppletion ($p < 0.0001$) and negatively with gastro-intestinal history, e.g. peptic ulcers and abdominal surgery ($p = 0.037$).

($P = 0.678 - 0.292$ no folate $- 0.013$ GI-history)

Conclusion Baseline characteristics do not predict effectivity. A positive gastro-intestinal history had a small negative effect on methotrexate dose. Reaching a high dose methotrexate is mainly predicted by folate suppletion. This is most likely explained by a reduction of toxicity. Our results suggest that when using folate adjuvant therapy, a weekly methotrexate dose of > 12.5 mg/week will be reached in 68%. Thus, with adjuvant folate, starting methotrexate therapy at a weekly dose of 15 mg seems justified.