THU0192 COMBINATION THERAPY OF LEFLUNOMIDE (LEF) AND METHOTREXATE (MTX) IS EFFECTIVE AND WELL TOLERATED IN RHEUMATOID ARTHRITIS (RA) PATIENTS INADEQUATELY RESPONDING TO METHOTREXATE (MTX) ALONE

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Background Combination therapy for the treatment of patients with RA may improve response rate in those who have responded inadequately to MTX alone. As LEF is increasingly being used in RA management, it is relevant to determine the impact of adding LEF to MTX.

Objectives To investigate the benefits of adding LEF to an existing MTX regimen on efficacy, tolerability, physical function, and health-related quality of life (HRQOL) in patients with active RA in a 24-week multi-centre, randomised, double-blind placebo (PLC)-controlled trial.

Methods Subjects with active RA receiving MTX (15±20 mg/week) for ≥ 6 months and at a stable dose for ≥ 8 weeks were randomised to receive LEF 100 mg QD x 2 days followed by 10 mg QD thereafter (n = 130) or matching PLC (n = 133). Mean doses of MTX were 16.7 mg/week and 16.2 mg/week for LEF+MTX and PLC+MTX, respectively. The primary efficacy endpoint was ACR 20 responder rate at 24 weeks, with a secondary endpoint of ACR 20 response using LOCF, with both analysed in the ITT population. ACR 20, 50 and 70 response rates, as well as safety monitoring, were assessed every

2 weeks up to week 8, and every 4 weeks thereafter. The Health Assessment Questionnaire (HAQ) and Medical Outcomes Survey Short Form (SF-36) questionnaire were administered and the mean improvements from baseline were compared at week 24 for the LEF+MTX group and the PLC+MTX group.

Results Using the LOCF method, the ACR 20, 50 and 70 rates were LEF+MTX = 51.5%, 26.2% and 10.0% vs PLC+MTX = 23.3%, 6.0% and 2.3% (p < = 0.0001, p < = 0.0001, and p < = 0.02). At week 24, ACR 20 responder rates were LEF+MTX = 46.2% vs PLC+MTX = 19.5% (p < = 0.0001). Mean baseline values for the disability index (DI) derived from the HAQ were LEF+MTX = 1.6 vs PLC+MTX = 1.5 (NS). At 24 weeks, mean changes from baseline in HAQ DI were LEF+MTX = -0.42 vs PLC+MTX = -0.09 (p < = 0.0001); representing mean improvements of 29% and 5%, respectively, based on individual percent changes. Mean baseline values for the physical component summary scale (PCS) derived from the SF-36 were LEF+MTX = 28.4 vs PLC+MTX = 29 (NS). At 24 weeks, mean changes from baseline in the PC were LEF+MTX = 6.8 vs PLC+MTX = 0.3 (p < = 0.0001); representing mean improvements of 29% and 3%, respectively, based on individual percent changes. Reported AEs included diarrhoea (LEF+MTX = 25.4% vs PLC+MTX = 13.5%), upper respiratory infections (LEF+MTX = 22.3% vs PLC+MTX = 24.1%), nausea (LEF+MTX = 16.2% vs PLC+MTX = 11.3%) and dizziness (LEF+MTX = 7.7% vs PLC+MTX = 5.3%). Increases in LFTs of >3×ULN at any time during the 24-week treatment period for ALT and AST for LEF+MTX were 3.8% and 1.5%, respectively, compared to 0.8% on both for PLC+MTX.

Conclusion LEF combined with an existing MTX regimen in patients with active RA is well tolerated and confers significant therapeutic advantages in terms of both efficacy and quality of life.

THU0193 DETERMINATION OF THE POTENTIAL FOR AN *IN VITRO* PROTEIN BINDING INTERACTION BETWEEN THE LEFLUNOMIDE (LEF) METABOLITE, A77 1726 AND THE SULFASALAZINE (SSZ) METABOLITE, SULFAPYRIDINE (SP)

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Background LEF is a relatively new DMARD licensed for the treatment of rheumatoid arthritis (RA). When orally administered, it is rapidly and almost completely converted into its active metabolite, A77 1726, which is highly bound to plasma proteins (>99%). A77 1726 may therefore be subject to interactions with other highly bound drugs. SSZ is also a DMARD used in the treatment of RA. It is metabolised to 5-aminosalicylate (5-ASA) and SP with the latter thought to be responsible for the toxicity of SSZ. SP may also bind to plasma protein, thus there is a possibility of a protein binding interaction. Competitive displacement of bound drug molecules from the binding site may alter the pharmacokinetics of A77 1726 or SP and possibly alter the tolerance of a combined regimen.

Objectives This study investigated the potential for a protein binding interaction between the LEF metabolite, A77 1726 and the SSZ metabolite, SP.

Methods The free and bound fractions of 14C-labelled A77 1726 and 14C-labelled SP were determined by dialysis of drug fortified human plasma against phosphate buffer (pH 7.4) at 37 degrees celcius. The extent of equilibration was determined after 4, 6, 8, 10 and 12 h of dialysis and the time to equilibration was evaluated at concentrations of 10 and 50µg/ml for both A77 1726 and SP. The extent of binding of 14C-labelled A77 1726, alone, and in the presence of 10, 20 and 50µg/ml of non-labelled SP was determined at nominal A77 1726 concentrations of 10, 20 and 50µg/ml. Conversely the extent of 14C-labelled SP binding alone, or in the presence of 10, 20 and 50µg/ml of non-labelled A77 1726 was determined at nominal SP concentrations of 10, 20 and 50µg/ml.

Results No time-dependent changes in A77 1726 and SP free fractions were observed over the 4 to 12-hour sampling period so a dialysis time of six hours was chosen for the subsequent interaction experiments. Under study conditions, 14C-labelled A77 1726 was 99.2% to 99.3% protein-bound over the concentration range 10 to 50µg/ml. The free fractions of A77 1726 tended to be slightly greater at 50µg/ml (0.78%) than at 10 or 20µg/ml (0.73% and 0.74%, respectively). Addition of SP to the plasma had no effect on the observed binding of A77 1726. In contrast to A77 1726, 14C-labelled SP was only 24 to 28% bound over a concentration range of 10 to 50µg/ml. Free fractions of SP were relatively constant (73% to 76%) as the concentration was increased from 10 to 50µg/ml. Addition of A77 1726 to plasma to provide concentrations of 10, 20 and 50µg/ml had no effect on the observed binding of SP. In addition, the free fractions of SP did not change (72-76%) in the presence of 0, 10, 20 and 50µg/ml A77 1726.

Conclusion Free fractions of both A77 1726 and SP did not change when each underwent dialysis in the presence of the