change from baseline of the modified Sharp scores and proportion of patients in whom joint destruction was arrested after 24 weeks of treatment.

Abstract FRI0061 Table 1

	Placebo	30 mg	75 mg	150 mg
Mod. Sharp Score: mean	4.33	2.36 p =	2.25 p =	1.72 p =
change		0.005	0.003	0.0004
Mod. Sharp Score:% pt w/no	16.7%	31% p =	24% p =	31% p =
change		0.026	0.234	0.022

Conclusion In patients with erosive disease, the rate of deterioration was significantly less in those who received anakinra. Significantly more patients with erosive RA who received anakinra for 24 weeks demonstrated an arrest of progressive joint damage. Moreover, an increasing benefit was associated with increasing dosages.

FRI0062 EFFECTS OF METHOTREXATE AND LONG TERM LOW PREDNISONE DOSES ON BONE MINERAL DENSITY IN PATIENTS WITH EARLY SEVERE RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.1191

Background Patients suffering from rheumatoid arthritis (RA) may feature significant loss of bone mineral density (BMD). early aggressive treatment and sometimes low corticosteroids doses are required; however, long term effects on bone are not extensively characterised.

Objectives To assess the effects of 10 mg prednisone daily + 7.5 mg methotrexate (MTX) on BMD in patients with early active and severe RA.

Methods 32 patients with active RA, with a disease duration less than 2 years, without prior treatment with any disease modifying antirheumatic drugs were randomised to receive either MTX and prednisone or sulphasalazine alone. Osteoporosis treatment was not permitted. Disease activity and BMD were monitored at baseline, 6, 12 and 24 months; BMD was determined by quantitative ultrasound at the calcis bone and was appreciated as broadband ultrasound attenuation (BUA) and quantitative ultrasound index (QUI). BMD loss was calculated in% of baseline. Subgroup analysis (high and low disease activity) was performed upon ESR and CRP values.

Results After 6 and 12 months of treatment mean% BUA has decreased significantly ($p < 0.05$) compared to baseline in both study groups, but greater in patients with high disease activity; after 24 months BMD has fallen significantly more in the combination group in patients with severe RA (-3.5%) compared to monotherapy group in patients with mild disease ($+0.07\%$, $p < 0.05$). Change in BMD correlates more closely with measure of inflammation than with administration of prednisone and MTX.

Conclusion High disease activity is closely associated with bone loss in early active severe RA compared to bone loss due to aggressive therapy including MTX and low doses prednisone.

FRI0063 ANAKINRA REDUCES THE RATE OF JOINT DESTRUCTION AFTER 1 YEAR OF TREATMENT IN A RANDOMISED CONTROLLED COHORT OF PATIENTS WITH RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.1192

Background

Objectives To assess the effect of anakinra on progressive joint damage in patients with rheumatoid arthritis after 12 months of treatment.

Methods 472 patients were randomised to a 24 week study. On completing the 24 week, placebo-controlled, randomised clinical trial, patients receiving anakinra 30, 75 or 150 mg daily continued blinded treatment for a further 24 weeks. Patients originally randomised to placebo were re-randomised to blinded treatment with one of the 3 anakinra doses for an additional 24 weeks resulting in a blinded cohort of patients ($N = 309$) followed for up to 1 year by radiographic assessments, using a modified Sharp method (Genant A&R, 41:1583, 98).

Results Treatment with 75 or 150 mg anakinra was significantly superior in terms of reducing joint destruction after 1 year, when compared to the group of patients originally randomised to placebo. This analysis demonstrated a dose proportional relationship with increasing doses of anakinra providing superior reduction of joint destruction when measured by a modified Sharp score.

Abstract FRI0063 Table 1 p-values for pairwise comparisons vs placebo are the result of an analysis using a repeated measures mixed model.

	Placebo n =	30 mg n	75 mg n	150 mg n
	59	= 66	= 64	= 48
Mean change in mod. Sharp score after 1 year	3.81	2.43 p = 0.099	1.91 p = 0.025	1.90 p = 0.025

Conclusion Anakinra provides a statistically significant reduction in joint destruction, compared with patients originally randomised to placebo after 1 year of treatment. The reduction in joint destruction was dose proportional.

FRI0064 PENTOXIFYLLINE THERAPY FOR REMISSION MAINTENANCE IN RHEUMATOID VASCULITIS

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10.1136/annrheumdis-2001.1193

Background Pentoxifylline (PTX), a phosphodiesterase inhibitor, is a vasodilator and antiplatelet drug credited with TNF α transcription inhibition as well. PTX was successfully used in refractory cases of rheumatoid arthritis and in some vasculitides, mainly cutaneous.

Objectives The study aim was to evaluate the efficacy of PTX given as monotherapy after induction of remission in systemic rheumatoid vasculitis (RV).

Methods 12 systemic RV patients (diagnosed according to the Scott&Bacon criteria) were taken into study after the induction of clinical remission (irrespective of the remissive therapy). Each patient received a daily dose of 600 mg PTX. The following were evaluated upon enrollment and after 3 months: clinical signs of vasculitis (on a modified BVAS log), morning stiffness, ESR, CRP and C4 (Mancini), TNF α (ELISA- R&D). The data were compared using the Student's t test for paired variables.

Results A relapse presenting with constitutional signs appeared only in one of the 12 patients; however, new ocular signs (?red eye?) appeared in 2 patients. Minor cutaneous vasculitis resolved in 1 patient and appeared newly in 3 patients on PTX. Morning stiffness reduced from 107 ± 79 to 75 ± 44 min ($p = 0.01$). ESR decreased (50.4 ± 21.3 to 42.9 ± 13.8 mm/h, $p = 0.02$), but CRP and C4 did not vary significantly. TNF α decreased from 4.2 ± 2.5 to 3.8 ± 1.8 ng/ml ($p = 0.05$).

Conclusion PTX seems to be useful in maintaining the remission of systemic RV and possibly for the prophylaxis of occlusive vasculopathy in these patients. Moreover, PTX is useful also for managing the arthritis of these patients. Its effects in the long-term prevention of relapse of RV have to be evaluated.

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FRI0065 ANTI-TNF ALPHA MONOCLONAL ANTIBODIES ALTER THE ACTIVATION AND DIFFERENTIATION PATTERN OF MONOCYTES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.1194

Background Anti-TNF α monoclonal antibodies (mAbs) have recently been introduced as a treatment for rheumatoid arthritis (RA). Whereas anti-TNF α mAbs are potent inhibitors of inflammation, their effect on the activation and differentiation of myeloid cells has not been elucidated.

Objectives To investigate the function and the phenotype of monocytes from RA patients during their differentiation to macrophages *in vitro* before and 4 weeks after a single administration of mAbs to TNF α .

Methods Patients with highly active disease who were resistant to treatment with disease modifying antirheumatic drugs and corticosteroids were included into the study. Monocytes were isolated from the peripheral blood by negative selection, and their phenotype was analysed directly after isolation and during differentiation to macrophages.

Results Treatment was effective as 4 weeks after mAb application the inflammatory activity, as assessed by DAS 28, and the sedimentation rate were significantly reduced. Whereas the

expression of HLA-DR, CD40, CD25, CD80, CD86, CD14 and CD68 in freshly isolated monocytes was similar before and after treatment with anti-TNF α , marked differences were found during maturation. After treatment, upregulation of HLA-DR and CD80 was markedly enhanced during macrophage differentiation. In contrast, the expression of CD40 was decreased after treatment.

Conclusion The results demonstrate that a single therapy with anti-TNF α mAbs alters the ability of macrophages to upregulate molecules involved in cellular inflammation even 4 weeks after treatment. However, as those changes were associated with clinical benefit, the data suggest that the clinical effect of anti-TNF α mAbs treatment is not restricted to neutralising TNF α but may be due to long lasting anti-inflammatory alterations that remain active even after the mAb has been cleared from the circulation.

FRI0066 LEFLUNOMIDE INHIBITS PROLIFERATION AND DIFFERENTIATION OF PRO-INFLAMMATORY TH1 CELLS

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10.1136/annrheumdis-2001.1195

Background Leflunomide has been recently introduced as a new treatment for rheumatoid arthritis. It has been shown that this immunomodulatory drug blocks the *de novo* pyrimidine synthesis by inhibiting the enzyme dihydroorotate dehydrogenase. However, the functional consequences of this action for T cells are still unclear.

Objectives To evaluate the effect of leflunomide on the proliferation and differentiation of human naive CD4^{pos} T cells isolated from cord blood and of memory CD4^{pos} T cells isolated from peripheral blood of healthy individuals.

Methods The proliferative response of naive and memory T cells activated with anti-CD3 and anti-CD28 was determined by incorporation of ³H-thymidine into newly synthesised DNA. The impact of leflunomide on T cell differentiation was assessed in an *in vitro* system in which effector cells were generated after short term priming. T cell differentiation was induced by priming with anti-CD3 and anti-CD28 in the presence or absence of leflunomide. The phenotype of freshly isolated and primed T cells was determined by cytometric analysis of intracellular cytokines.

Results Leflunomide inhibited T cell proliferation induced by stimulation with anti-CD3 and anti-CD28 in a dose-dependent manner in naive and memory CD4^{pos} T cells. Moreover, the expression of the activation markers CD25, CD69 and CD40L was markedly suppressed. Leflunomide significantly decreased the frequencies of T cells capable of producing IFN- γ . Most interestingly, the generation of Th2 effectors was enhanced by leflunomide in some donors.

Conclusion Leflunomide may exert its anti-inflammatory effect by preventing the proliferation of pro-inflammatory Th1 effectors and by switching the T cell differentiation from the Th1 to the Th2 direction.