FRI0002 IL-1 RECEPTOR ANTAGONIST (IL-1RA) TREATMENT IS ASSOCIATED WITH IMPROVEMENT OF ANAEMIA IN RHEUMATOID ARTHRITIS

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Background Anaemia occurs frequently as an extraarticular complication of rheumatoid arthritis (RA) and usually correlates with markers of disease activity. Interleukin (IL)-1, levels of which are elevated in serum and synovial tissue of patients with RA, inhibits erythropoiesis *in vitro*. Serum IL-1 levels are higher in anaemic patients with RA than in those without anaemia.¹

Objectives To determine if IL-1 receptor antagonist (IL-1ra) is associated with improvement of anaemia in patients with rheumatoid arthritis.

Methods We observed the effect of daily IL-1ra treatment in anaemic patients with active, severe RA who were enrolled in a 24-week, double-blind, randomised, placebo-controlled multicenter study of IL-1ra therapy. Fifty (14.2%) of the IL-1ra-treated patients and 13 (10.7%) of the placebo-treated patients were anaemic, defined as HCT < = 34%,² upon initiation of drug therapy.

Results Improvement in anaemia was stratified according to the increase after 24 weeks of treatment. Although the number of anaemic patients enrolled in this trial was small, more patients treated with IL-1ra exhibited improvement in HCT after 24 weeks of drug than did patients receiving placebo:

Abstract FRI0002 Table 1

	Placebo (N = 13)	IL-1ra 30 mg (N = 17)	IL-1ra 75 mg (N = 17)	IL-1ra 150 mg (N = 16)	Total IL-1ra (N = 50)
> = 3 vol-%	2 (15.4%)	10 (58.8%)	6 (35.3%)	5 (31.3%)	21 (42.0%)
> = 5 vol-%	1 (7.7%)	3 (17.6%)	4 (23.5%)	2 (12.5%)	9 (18.0%)
> = 6 vol-%	1 (7.7%)	2 (11.8%)	4 (23.5%)	1 (6.3%)	7 (14.0%)

Conclusion Anaemia improved in patients taking each of the 3 doses of IL-1ra. Interestingly, 3 of the 7 IL-1ra-treated patients with > = 6 vol-% improvement in their HCT did not meet ACR20 response criteria. Thus, IL-1ra therapy may improve anaemia in RA patients independently of its effect on articular disease activity. Further study of IL-1ra therapy in anaemic patients with RA is warranted to clarify its effects on erythropoiesis and the impact of these changes in Hct on clinical status.

REFERENCES

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FRI0003 HIGH DOSE CHEMOTHERAPY WITHOUT AUTOLOGOUS STEM CELL REINFUSION IN THE TREATMENT OF RA

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Background With increasing use of high dose cytotoxic chemotherapy with autologous peripheral blood stem cell (APBSC) rescue for the treatment of severe autoimmune diseases, including

RA, there is concern that the reinfusion of auto-aggressive T cells may reactivate the autoimmune process. High dose chemotherapy without the reinfusion of autologous stem cells permits a form of *in vivo* T cell depletion and stem cell selection that obviates the reinfusion of auto-aggressive T cells.

Objectives Evaluation of medium term outcome in patients undergoing high dose chemotherapy without autologous stem cell reinfusion in patients with severe RA.

Methods Three patients with RA and one with JRA, which was progressive and severe despite multiple DMARDs, were treated with Cyclophosphamide 50 mg/kg for four consecutive days, with G-CSF 300 mcg bd commencing from day five. Prior to this, APBSC were collected following priming with Cyclophosphamide and G-CSF. The APBSC were not intended for reinfusion unless prolonged cytopenias or severe infection occurred. DMARDs were discontinued at the time of high dose chemotherapy and low to moderate dose prednisolone was commenced in all patients. Immunophenotyping of lymphocyte subsets was performed to monitor immune regeneration.

Results High dose cyclophosphamide was well tolerated and all patients achieved haematological recovery without the need for APBSC reinfusion. Median time to neutrophil recovery (ANC >500/L) and platelet transfusion independence was 17 and 16 days, respectively. All patients required antibiotics for neutropenic fever for between 2 – 8 days.

Absolute change and% change from baseline at 6 and 12 months is shown in the Table 1. All subjects have required recommencement of a DMARD between 6 and 12 months post therapy. One patient, who had been taking long term oral steroids, developed bilateral avascular necrosis of the femoral heads.

Abstract FRI0003 Table 1

	Patient 1	Patient 2	Patient 3	Patient 4
ESR mm/hr	80, 80%: 70, 70%	10, 150%: 5, 25%	80, 66%: 15, 12%	0, 0%: 40, 44%
mHAQ	N/A: 4, 100%	+1: 0, 0%	2, 13%: 1, 6%	N/A: 0, 0%
VAS pain – mm	N/A: 74, 97%	51, 221%: 21, 50%	51, 94%: 12, 122%	N/A: 69, 97%
VAS quality of life – mm	N/A: 53, 96%	0, 0%: 2, 4%	47, 52%: 43, 47%	N/A: 27, 90%

Absolute and% change from baseline at 6 and 12 months post therapy (< 100% equals% improvement).

Conclusion Whilst high dose chemotherapy without stem cell reinfusion may be considered as a therapeutic option in cases of severe progressive rheumatoid arthritis, further research in maintaining the initial benefit is required.

FRI0004 VITAMIN D3 ANALOGUE – ALPHACALCIDIOL DECREASES IL1, TNF AND ANTIOXYDANT ENZYMES ACTIVITY IN RA AND JRA PATIENTS

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Background In recent years immunomodulatory action of vitamin D3 was clearly confirmed, when its used in high doses. 1-

alpha (OH) vitamin D3 (alphacalcidol) analogue was shown to induce less hypercalcemic side effects.

Objectives We organised open-label therapeutic trial in 20 RA and 15 JRA patients who have had three months active disease on basic therapy. Therapy regime remained unchanged but alphacalcidol in high oral dose was added during next three months (2µgr/day in RA or 0,05µgr/kg/day in JRA pts.).

Methods Spontaneous and PMA stimulated IL1 and TNF production was measured in all patients before and after the trial by ELISA method in PB mononuclear cells after 24 h cultures. GSH-Px (glutathione-peroxidase) and SOD (superoxide-dismutase) activity was measured by RANDOX kits.

Results Three months high oral dose therapy significantly improved clinical signs of disease activity in correlation with parameters we evaluated. Increased IL1 and TNF production was significantly lowered after the trial and riched values in healthy controls. GSH-Px and SOD activity were lowered in all patients before entering into the study. Alphacalcidol therapy induced significant increase of GSH-Px and, on contrary, decrease of SOD activity. Positive correlation trends among this enzymes during disease activity were turned into negative according to disease improvement after the trial finished.

Conclusion High dose alphacalcidol is powerful immunomodulatory agent as it is shown for other vitamin D3 analogues. Its main function seem to be stabilisation of impaired immunoregulation in RA and JRA which could be of benefit as possible therapeutic agent.

FRI0005 SAFETY OF NEW COX-2 INHIBITORS IN NSAID-INTOLERANT PATIENTS

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Background Non-steroidal anti-inflammatory drug (NSAID)-triggered urticaria and angioedema occurs in up to 3% of the population. The tolerance to new COX-2 selective inhibitors in intolerant patients has not been determined.

Objectives To study the clinical tolerance to Rofecoxib and Celecoxib in patients sensitive to conventional NSAIDs who develop urticaria and/or angioedema when exposed to these drugs.

Methods Sixty three subjects (female 44, male 19, mean age 33.0 ± 16.7 years, range 11 – 74 years) with challenge-proved urticaria/angioedema were studied. These patients were challenged by means of the single-blinded oral method, controlled with placebo.

Results Positive challenges were observed in 4 out of 53 subjects challenged with Rofecoxib (7.5%) and in 13 out of 47 individuals submitted to oral provocation with Celecoxib (27.6%) ($p = 0.01$).

Conclusion We conclude that: 1) The clinical tolerance to selective COX-2 inhibitors in NSAID-sensitive patients with skin manifestations differs between new drugs, which may be due to different degrees of enzyme selectivity or to other, not yet determined reasons. 2) COX-1 inhibition would be involved in the production of cutaneous adverse reactions to NSAIDs. 3) Controlled oral challenges are indicated especially for the management of sensitive individuals with chronic inflammatory and/or painful diseases.

FRI0006 DOUBLE-BLIND CLINICAL, LABORATORY AND ULTRASOUND ASSESSMENT OF THE EFFICACY OF ANTIBODIES TO INTERFERON-G (ANTI-IFN-G) IN RHEUMATOID ARTHRITIS (RA)

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Background

Objectives To objectively assess the efficacy and tolerability of anti-IFN-g in treating patients with active RA.

Methods Thirty patients with active RA were randomly assigned to receive intramuscularly injections of anti-IFN-g, antibodies to tumour necrosis factor a (anti-TNF) or placebo for 5 consecutive days (10 patients on each treatment regimen). The patients were clinically assessed daily for 7 days, then weekly up to the 28-th day. Clinical, laboratory and ultrasound indices were used for the evaluation of the treatment efficacy.

Results Both anti-cytokines were equally effective and significantly superior to placebo. Twelve patients stopped treatment due to the lack of efficacy: 1 on anti-TNF, 2 on anti-IFN-g and 9 on placebo. According to the physician's assessment improvement was achieved by the 7-th day on anti-TNF in 9 patients, on anti-IFN-g in 7, and on placebo in 2. At the 28-th day the corresponding figures were 8, 8, and 0, respectively. By the 28-th day each of the anti-cytokine groups showed significant improvement in 5 clinical measures including numbers of swollen and painful joints, pain and fatigue. The single patient in the placebo group who completed the trial had no positive changes in the disease activity. The thickness of the inflamed synovial membrane assessed by the ultrasound method decreased significantly only on anti-IFN-g (both by the 7-th and by the 28-th days).

Conclusion The results obtained suggest that IFN-g plays an important role in the pathogenesis of RA. The use of antibodies to this cytokine can be considered as a promising approach to the therapy of RA, especially its treatment-resistant forms.

FRI0007 PREFERENCES OF RHEUMATOLOGISTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS FLARE: IS THERE A STANDARD OF CARE?

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Background Differences in physician evaluations, heterogeneity of disease and within patient variability contribute to the lack of a uniform definition of RA flare. As a result, a standardised approach to treatment of RA flare is not likely to exist. However, when presented with the same case scenario, rheumatologists' choice of treatment should establish a standard of care.

Objectives To identify physician medication preferences and the role of steroids in the treatment of rheumatoid arthritis (RA) flare.

Methods A questionnaire describing two versions of the same case of a previously stable RA patient maintained on 17.5 mg/week of methotrexate (MTX), hydroxychloroquine and NSAIDs, and presenting with signs and symptoms suggesting an increase in disease activity was developed; the second version included the addition of a standing dose of 5 mg of prednisone. Rheumatologists were asked to identify their choice (s) of first-line therapy for each version of the case. The questionnaire was