FRI0069 EFFICACY AND SAFETY OF REMICADE (INFLIXIMAB) PLUS ARAVA (LEFLUNOMIDE) IN RHEUMATOID ARTHRITIS (RA)

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Background Leflunomide is a new disease-modifying antirheumatic drug (DMARD) approved for the treatment of active RA as an alternative to methotrexate (MTX) therapy. Infliximab is approved for the treatment of RA when used in combination with MTX. However, in patients either intolerant of or refractory to MTX therapy, combination therapy with leflunomide is sometimes utilised.

Objectives To assess the efficacy and safety of infliximab plus leflunomide in patients with RA.

Methods Select community practices were surveyed about the use of infliximab in combination with leflunomide for the treatment of RA. Demographic data and information on prior and concomitant medications were documented. Further data regarding efficacy (numbers of swollen and tender joints, functional class, ESR/CRP) and safety (occurrence of nausea, vomiting, alopecia, or any other symptoms) are being collected at baseline (prior to start of the combination) and after 4 to 5 doses of the combination.

Results Twenty-one community practices were included in the survey; 31 patients were identified who recently started on the combination of infliximab plus leflunomide. The patient population consisted of 20 (65%) women and 11 (35%) men. Patients ranged in age from 29 to 80 yrs (mean of 56.3 yrs). The duration of RA ranged from 2 to 50 yrs (mean of 10.6 yrs). Twenty-six (84%) patients had received MTX at a mean dose of 18.2 mg/wk. 42% of the population developed intolerance to MTX. MTX was ineffective in 45% of patients and contraindicated in 16% of patients. Patients were generally started on leflunomide at 20 mg QD. Rheumatologists added infliximab (3 mg/kg q 8 wks after loading doses at Weeks 0, 2, and 6 in the majority of patients) due to an incomplete response achieved with leflunomide. 71% of these patients also continued to receive concomitant prednisone at 2.5 to 20 mg/day. While patients had only received a few doses each, no serious adverse experiences were reported. This population will continue to be followed over time for both safety and efficacy of the infliximab/leflunomide combination.

Conclusion Infliximab has been used in combination with leflunomide in select RA patients in whom MTX has not been tolerated, is ineffective, or is contraindicated. The ongoing clinical experience of these and similar patients will be monitored.

FRI0070 SAFETY AND TOLERABILITY OF A RAPID INFUSION OF REMICADE (INFLIXIMAB) IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Background The safety of infliximab has been established in both open-label and randomised controlled clinical trials in which patients received infliximab over 2 hrs. In clinical trials,

no difference was observed in the incidence of infusion reactions at any infliximab dose between 3 and 10 mg/kg given over 2 h. This clinical experience supported the safety of administering infliximab 3 mg/kg over 1 hr (Maini, 1999). Current guidelines advise infusing infliximab over at least 2 h.

Objectives To determine if infliximab given at 3 mg/kg over 1 hr is safe and well tolerated in the clinic setting.

Methods Patients with active RA enrolled at selected sites in an ongoing open-label clinical trial of infliximab were eligible to receive two open-label 1-hr infusions of infliximab 3 mg/kg if they had previously tolerated four 2-hr infusions (at Weeks 0, 2, 6, and 14) without any moderate to severe infusion related reactions or hypersensitivity reactions and had no significant history of cardiac or renal impairment. Safety evaluations included measurements of vital signs during and immediately after the infusions of infliximab and assessment for adverse events.

Results One hundred ninety patients (76% women and 24% men) received infliximab 3 mg/kg given over 1 hr. Patients ranged in age from 26 to 82 yrs (mean of 59.4 yrs). Twelve (6%) patients reported adverse events associated with the first or second 1-hr infusion of infliximab. Headache, hypersensitivity, and hypertension were each reported by two (1%) patients. The following adverse reactions were reported by one (0.5%) patient each: anaphylactic reaction, blood pressure decreased, chest tightness, dizziness, itching, maculopapular rash, and somnolence. Only 3 patients discontinued infliximab therapy as a result of an infusion-related reaction (1 with anaphylactic reaction and 2 with allergic reaction). All reactions, which were generally mild or moderate in nature, resolved within 1 day of onset.

Conclusion Infliximab 3 mg/kg administered over 1 hr was well tolerated by these patients with active RA.

REFERENCE

- 1 Maini RN, St. Clair EW, Maini RN, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999;**354**:1032-1039

FRI0071 RESPONSES TO INFLIXIMAB THERAPY IN THE ATTRACT TRIAL ASSESSED WITH THE DISEASE ACTIVITY SCORE (DAS): CLINICAL RESPONSE MEASURED BY DAS AT 102 WEEKS CORRELATES WITH ARREST OF RADIOLOGIC PROGRESSION AND SHOWS HIGHER RESPONSE RATE THAN ACR20 CRITERIA

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Background In the ATTRACT trial, the anti-TNF-monoclonal antibody infliximab showed significant improvement in disease activity score (DAS), reduction in signs and symptoms, inhibition of progression of structural damage and improved quality of life in rheumatoid arthritis (RA) patients, at 54 weeks. Inhibition of radiologic progression by infliximab occurred in both ACR20 responders and non-responders. This suggests that the ACR20 criteria might underestimate clinical responses to therapeutic agents.

Objectives To examine effect of infliximab on DAS RA patients after two years of treatment.

Methods DAS was calculated as follows:

$0.56 \times \text{SQRT}(\text{TJC}) + 0.28 \times \text{SQRT}(\text{SJC}) + 0.7 \ln(\text{ESR}) + 0.014 \times (\text{pt global (VAS)})$.

DAS responses were characterised as ?None?, ?Moderate? or ?Good? using DAS scores at 102 week and change in DAS from baseline to 102 week. Patients with ?Good? or ?Moderate? response were considered DAS responders. Fisher's exact test was used to compare proportion of patients with DAS response by treatment group.

Results Clinical responses as measured by ACR20 and DAS correlated with each other; however, overall the response rate was higher with the DAS. At week 102, 84% of patients achieving ACR20 response were also responders using DAS; 45% of ACR20 non-responders were DAS responders. The DAS showed a statistically significant difference for each infliximab treatment group vs placebo ($p < 0.001$). ACR20 and DAS response rate at Wk 102 are presented below, by treatment group.

Abstract FRI0071 Table 1

	MTX Alone	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	Total Infliximab
N	88	86	86	87	81	340
ACR20	16%	42%	40%	48%	40%	42%
DAS	21%	54%	54%	68%	53%	57%

Conclusion Responses assessed with ACR20 and DAS have previously been shown to correlate. Analysis of data from the ATTRACT trial suggests that the DAS may be more sensitive to clinical improvement. The improved sensitivity of DAS, and the fact that it evaluates both change in response to therapy and also extent of residual disease activity, support its routine use as an endpoint in clinical trials.

FRI0072 METHOTREXATE IN RHEUMATOID ARTHRITIS: A 5 YEAR PROSPECTIVE STUDY

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Background

Objectives The aim was to evaluate the efficacy and tolerability of low dose of longterm Methotrexate (MTX) treatment of rheumatoid arthritis (RA).

Methods This study examines prospectively the response to oral MTX (5 ? 12,5 mg) over a 5 year period of 70 patients (pts) with active RA. 54 pts were female, mean age $53,61 \pm 12,8$ years range (27 ? 76) and mean diseases duration $9,76 \pm 7,58$ years (range 0,6 ? 35). Patients who were receiving Prednizone at entry to the trial, were maintained by the same dose, not exceeding 10 mg/day. Clinical evaluation were performed by the same physician ? investigator every 3 months for the first year of the study and every 6 months thereafter. Every 4 weeks complete blood count and every 12 weeks thereafter complete erythrocyte sedimentation (ERS), blood count, serum creatinine and liver blood tests were obtained. Patients were assessed at 0 stage (beginning) with 70 pts, after 3 months (mts) (with 62), 6 mts (with 52), 12 mts (with 49), 24 mts (with 36), 36 mts (with 26), 48 mts (with 13), and after 60 mts (with 11) patients.

Results 11 (15,7%) pts completed the 5 year study, 14 (20%) dropped out because of an adverse event or due to inefficacy.

After 3, 6, 12, 24, 36 mts of treatment a good clinical response was shown by significant clinical improvement in the joint swelling ($p < 0, 001$), morning stiffness ($p < 0, 001$), as well as in both physicians and patients assessment of the disease activity ($p < 0, 001$) compared to pretreatment values. The clinical improvement was also associated with a decrease of ESR after 3, 6, 12 mts ($p < 0, 001$), after 24 and 36 mts ($p < 0, 05$). Although a sustained clinical response was noted in the diseases variables during the 5 year study, there was no significant difference noted in the improvement in the joint swelling after 48 and 60 mts, in duration of morning stiffness and in decrease of ESR after 60 mts of treatment.

Conclusion Methotrexate therapy appears to be effective and safe in the treatment of RA in this 5 year prospective study

REFERENCE

- Weinblatt ME, Maier AL, Fraser PA, Coblyn S. Longterm prospective study of methotrexate in rheumatoid arthritis. Conclusion after 132 months of therapy. *J Rheum.* 1998;**25**(2):239-42

FRI0073 TOPICAL NERVE GROWTH FACTOR FOR THE TREATMENT OF CHRONIC LEG ULCERS IN RHEUMATOID ARTHRITIS

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Background Connective tissue diseases and, in particular, rheumatoid arthritis (RA), may provoke a cutaneous vasculitis leading to skin ulceration very difficult to heal. A depletion of neuropeptides from the nerve endings may contribute to the retardation of wound contraction and healing.¹ Nerve Growth Factor (NGF) is a neurotrophic and immunomodulatory factor that, in the skin, contributes to the control of cutaneous morphogenesis, wound healing and inflammation.²

Objectives Evaluate the efficacy of topical NGF administration in the treatment of vasculitic ulcers in course of RA and systemic sclerosis (SSc).

Methods Four long lasting RA patients (3 F, 1 M, age 73 ± 8.7 ; disease duration 17 ± 6.2 yrs) and 4 SSc patients (4 F, age 58.25 ± 5.5 ; disease duration 12 ± 4.3), were selected. All patients presented vasculitic chronic leg ulcers showing very poor or absent response to systemic and local treatments. Ulcers were treated daily with 50 µg of NGF (0.01% dissolved in saline solution) for 4 weeks and twice a week in the following month. Before the application of NGF, fibrin or scab were mechanically removed. Eventually the lesion was dressed with a hydrocolloid patch (Duoderm, Convatec, England). Size and characteristics of the ulcers were recorded twice a week.

Results During the first 2 weeks of treatment, the 4 patients with RA showed a rapid improvement of leg ulcers (both in size and descriptive parameters such as pain, presence of granulation, absence of inflammation), followed by a slower but progressive reduction of size which lead, in all cases, to healing within 5/8 weeks. In SSc patients, the ulcers showed an amelioration in size and characteristics during the first 2 weeks but, in the following weeks, the healing stopped and went back to the torpid course that characterised the ulcers before the treatment. None of them achieved the healing after 8 weeks.

Conclusion In RA patients treated with NGF, despite the chronicity of the disease and of the ulcers, a rapid healing was achieved. In these cases, NGF was able to restore the progressive