LETTERS

Secondary addition of methotrexate to partial responders to etanercept alone is effective in severe rheumatoid arthritis

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Etanercept, a soluble tumour necrosis factor α (TNFα) receptor fusion protein, may be combined with methotrexate (MTX) in severe rheumatoid arthritis (RA).[1] Etanercept is generally given to patients treated with MTX who have an inadequate response. However, MTX could be introduced to patients who have already been treated with etanercept and who initially had a good response but subsequently a secondary failure. It was decided to evaluate, in an open prospective study, the clinical, biological, and functional benefit of the secondary addition of MTX in patients with RA with an inadequate response to etanercept alone.

PATIENTS, METHODS, AND RESULTS

A cohort of 93 patients with active and severe RA was observed for a mean duration of 8 months (range 1–20). The group comprised 75 women, 18 men, with an average age of 49.5 years (range 17–75), and positive rheumatoid factor in 67 (72%). All had been previously treated with a median of four disease modifying antirheumatic drugs (DMARDs). The mean disease duration was 12.4 years (range 3–42). Patients were treated with subcutaneous injections of etanercept alone, 25 mg twice weekly. Eighteen of the 93 patients had an inadequate response (did not reach the American College of Rheumatology (ACR) 20 criteria, prerequisite for inclusion in this cohort) with etanercept alone; we therefore added MTX to the treatment, no other DMARDs being allowed. The mean dose of added MTX was 15.5 mg a week. The dosage was given orally to 12 patients and intramuscularly to the remaining six. All 18 patients (16 female, two male, average age 51 years, mean disease duration 13.3 years, with a positive rheumatoid factor in 14 (78%) patients) had previously received MTX before etanercept alone, but it had produced an insufficient result. This failure with MTX was a requirement before starting etanercept. A prospective follow up of these patients took place every month for 3 months and from then on every 3 months during a 12 month period, with recording of the usual clinical and biological measures in order to obtain the ACR20, 50, and 70 and the Disease Activity Score 28 (DAS28). This enabled us to assess the efficacy of this addition. The Health Assessment Questionnaire (HAQ) was also used in this study.

Table 1 summarises the results obtained. The data show an improvement in disease activity, which was sustained through the 12 month follow up. A favourable response was obtained at 3 months with 10 (56%) achieving the ACR20, 5 (28%) the ACR50, and 2 (11%) the ACR70. At 12 months of this combination therapy, 12 (67%) had achieved the ACR20, 9 (50%) the ACR50, and 3 (17%) the ACR70. DAS28 decreased from 4.9 to 3.0 at 3 months and to 2.4 at 1 year, suggesting a significant clinical improvement in disability. The HAQ score changed from 1.7 to 1.1 at 1 year.

There was also a rapid therapeutic biological response, with a decrease in the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) of 50% after 3 months. No serious adverse events were reported and only two patients required antibiotics (bronchitis, urinary infection).

DISCUSSION

In summary, this open study suggests that the secondary addition of MTX to etanercept produced a marked improvement among patients who had had an inadequate response to etanercept alone after a first inadequate response to MTX given alone. To our knowledge, this is the first open study to evaluate the efficacy of MTX in addition to etanercept in a two step strategy. Previous studies have demonstrated the efficacy of etanercept alone compared with MTX,[2] its efficacy in early RA[3] or in addition to methotrexate,[1] and, in particular, in juvenile idiopathic arthritis.[4] This suggests that when MTX is added to the etanercept regimen patients with RA improve both clinically and biologically without any increase in side effects. The addition of MTX to the treatment of patients who respond incompletely to etanercept alone may be useful in the management of RA. It will be interesting to evaluate this strategy in further studies. Therefore, the preferred treatment

Table 1 Results of secondary addition of MTX to etanercept

	MTX duration (months)					
	0	3	6	9	12	Friedman; p value
ACR20 (%)		56	61	67	67	
ACR50 (%)		28	28	39	50	
ACR70 (%)		11	6		17	
DAS28, mean	4.9	3.0	2.9	2.8	2.4	0.0017
Score HAQ, mean	1.7	1.3	1.2	1.2	1.1	0.0081
ESR (mm/1st h), mean	49.1	33.2	30.6	33.8	27.2	0.1266
CRP (mg/l), mean	56.6	24.0	13.8	17.1	12.3	0.0001

for RA may very well be the combination of MTX plus a TNF antagonist.

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Blunted coronary flow reserve in systemic sclerosis: a sign of cardiac involvement in asymptomatic patients

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Cardiac disease is often present in systemic sclerosis (SSc), even if rarely of clinical significance.[1–3] Therefore, we investigated the coronary flow reserve (CFR), by transthoracic contrast enhanced second harmonic Doppler echocardiography, a non-invasive method that might detect early heart dysfunction in patients with SSc even in the absence of clinical signs or symptoms.

Twenty nine consecutive patients (2 male, 27 female, mean (SD) age 55 (14) years) affected by SSc,[4 5] not complaining of signs or symptoms of cardiovascular involvement, were recruited. No further serious disease other than SSc was present. Eleven healthy subjects matched for age and sex (mean (SD) age 53 (5) years) were also evaluated as controls. Echocardiography was performed with an ultrasound unit using a broadband transducer with second harmonic capability in both B mode and Doppler modality. Levovist was used as the ultrasound contrast agent.[6 7] The CFR, expressed as the ratio between hyperaemic (peak adenosine infusion) and resting, both peak, diastolic velocity (PdvCFR) and velocity time integral (VtiCFR), was non-invasively assessed in the distal left anterior descending coronary. Peripheral microangiopathy was assessed by nailfold video-capillaroscopy (NVC), as previously reported.[8]

All patients were found in sinus rhythm, without any significant ECG alteration. All ECG parameters were normal.

The study showed a reduced CFR in 14/29 patients with SSc, when compared with the normal range of healthy subjects matched for age and sex (CFR >2.00).[7] In particular, both PdvCFR and VtiCFR, were strongly reduced in patients with SSc (mean (SD) 1.93 (0.56) and 1.81 (0.56), respectively) in comparison with controls (3.11 (0.72) and 2.83 (0.51), respectively) ($p<0.0001$). Furthermore, both PdvCFR and VtiCFR were significantly lower in patients with diffuse SSc (1.74 (0.46) and 1.59 (0.38), respectively) than in patients with limited SSc (2.39 (0.52) and 2.35 (0.38), respectively) ($p<0.004$ and $p<0.001$, respectively) (fig 1).

Nineteen patients (mean (SD) age 52 (13) years) and 10 patients (mean (SD) age 63 (12) years) had diffuse SSc (dSSc) and limited SSc (lSSc), respectively; the patients with dSSc were younger than those with lSSc ($p<0.04$).

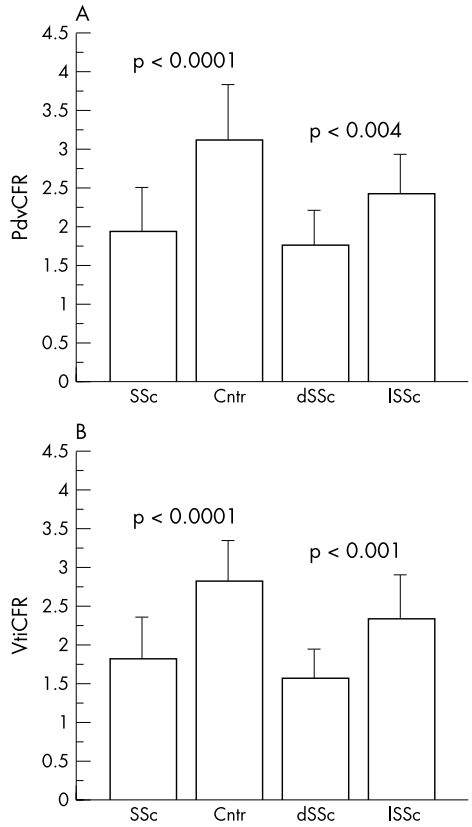

Figure 1 CFR in patients with SSc and controls (Cntr), assessed by transthoracic contrast enhanced second harmonic Doppler and expressed as the ratio between hyperaemic and resting, both peak, diastolic velocity (PdvCFR) (A) and velocity time integral (VtiCFR) (B). dSSc, patients with diffuse SSc; lSSc, patients with limited SSc.

Glucose serum levels were normal in all patients with SSc. No statistically significant correlation was found between CFR and history of smoking and cholesterol or triglyceride serum levels. Moreover, no statistically significant correlation was found between CFR and blood pressure values.