

Short-term adalimumab therapy improves endothelial function in patients with rheumatoid arthritis refractory to infliximab

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Key words

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ABSTRACT

Objective. Endothelial dysfunction has been found in patients with rheumatoid arthritis (RA). In this study we aimed to assess whether adalimumab, a fully human monoclonal antibody directed against TNF- α , was able to improve endothelial function in RA patients with long-standing disease refractory to infliximab.

Methods. Eight RA patients (7 women; range: 24- 74 years) were studied. They had been treated with the chimeric monoclonal anti-TNF- α antibody-infliximab for at least 1 year and were switched to adalimumab therapy because of loss of efficacy following periodical treatment with infliximab. Endothelial dependent (EDV) and independent vasodilatation (EIV) were measured by brachial ultrasonography. Patients were assessed prior to (day 0) and at day 2, and weeks 2 and 12 after the onset of adalimumab therapy.

Results.

Following adalimumab administration a rapid increase in the percentage (%) of EDV was found in all patients (mean \pm SD: $10.1 \pm 5.1\%$ at day 2 compared to $5.8 \pm 4.1\%$ at day 0). At weeks 2 and 12 the %EDV was also significantly increased compared to day 0. All patients showed decrease in the disease activity score 28 and C-reactive protein levels ($P = 0.012$). Moreover, at week 12 the atherogenic index was reduced in all patients ($P = 0.012$).

Conclusion. Our study confirms that short-term adalimumab therapy yields an active and positive effect on endothelial function in long-standing RA patients with severe disease. This observation emphasizes the potential role of the TNF- α blockade in the mechanisms implicated in the development of atherogenesis in RA.

Introduction

Rheumatoid arthritis (RA) patients have increased mortality due to cardiovascular (CV) events (1, 2). This is a consequence of accelerated atherosclerosis (3). RA and atherosclerosis share pathogenetic mechanisms including the involvement of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) (4).

Endothelial dysfunction is the key event in early atherogenesis and also contributes to the development of clinical features in the later stages of the vascular disease including progression of the atherosclerotic plaque. This may be determined as an impaired ability of the arteries to dilate in response to physical and chemical stimuli due to a decreased release or increased breakdown of nitric oxide (NO) (4).

Endothelial function can be non-invasively determined by post-occlusion flow-mediated vasodilatation of the brachial artery using high-sensitivity brachial ultrasonography (4). By this technique endothelial dysfunction has been observed in RA patients with early and long-standing actively treated disease (5, 6).

Targeted TNF- α antagonists have yielded a significant impact on the treatment of patients with RA (7). Hürlimann *et al* shown that TNF- α blockade improved endothelial function in RA patients after a 12-week treatment with the chimeric anti-TNF- α monoclonal antibody-infliximab (8). We observed that anti-TNF- α infliximab therapy also actively modulated the endothelial function in long-term infliximab treated RA patients (9). However, this effect was transient and values of endothelial dependent vasodilatation (EDV) returned to baseline by 4 weeks after infusion of the drug (9). Adalimumab is a fully human monoclonal antibody directed against TNF- α . This drug is also effective in patients with active RA who have an inadequate response to standard antirheumatic therapy, including one or more traditional disease modifying antirheumatic drugs (DMARDs) (10).

In the present study we have sought to assess whether patients with RA refractory to infliximab have improvement of endothelial function following short-term adalimumab therapy.

Methods

Patients

This study comprised 8 consecutive patients (7 women and 1 man; range: 24- 74, median 51 years; 6 of them rheumatoid factor positive) that fulfilled the 1987 American College clas-

sification criteria for RA (11). They were patients with long-standing disease (range disease duration: 7-29, median 20 years) recruited from the outpatient rheumatology clinic of the Hospital Xeral-Calde, Lugo, Northwest Spain, between May and September 2004.

Following a treatment protocol previously established in the Rheumatology Division from this hospital either infliximab or etanercept are used in RA patients with active disease refractory to at least two DMARDs, including methotrexate (MTX) at a dose of at least 15 mg/week. Infliximab treated patients who experience bad response or exhibit loss of efficacy following periodical treatment with this drug, manifested by worsening of the disease and a disease activity score (DAS) 28 > 3.2, are switched to adalimumab therapy.

Since the purpose of this study was to assess endothelial function following short-term adalimumab treatment in RA patients previously treated with infliximab, subjects included in this study were required 1) to have been treated with infliximab for at least 1 year, and 2) to have active disease despite MTX treatment along with infliximab therapy at a dose of 5 mg/Kg/8week. Moreover, for the pur-

pose of inclusion in the present study, patients seen during the period of recruitment required to have normal blood pressure. Patients seen during the period of recruitment with diabetes mellitus, plasma glucose levels greater than 110 mg/dl, body mass index (BMI) less than 20 or greater than 30 or who had suffered cardiovascular or cerebrovascular events were excluded. Patients also had to be non-smokers or had stopped smoking at least 5 years previously.

For ethical reasons, patients were not randomized to a placebo group. The same procedure has been found acceptable and followed in previous studies on anti-TNF- α therapy and endothelial function in RA (8, 9).

Besides non-steroidal anti-inflammatory drugs, all were in treatment with low dosage of prednisone (range 5-10 mg/day, median 7.5 mg/day) and MTX (median 15 mg/week) when adalimumab therapy was started. A patient was receiving angiotensin-converting-enzyme inhibitor therapy because of hypertension but remained normotensive throughout the period of study. None of them was on treatment with statin lipid-lowering drugs. In all cases concomitant medications remained unchanged throughout the study

course. The local institutional committee approved anti-TNF- α therapy and ultrasonography studies. Patients gave informed consent to participate in this study. Neither this study nor the former one (9) were supported by any pharmaceutical drug company.

Study protocol

Patients were required to initiate adalimumab therapy 40 mg every other week by subcutaneous injection 10 weeks after the last infliximab infusion. Endothelial function was determined by standard techniques using high-sensitivity brachial ultrasonography (6, 9). In all cases a cardiologist (CG-J) blind to the clinical information analyzed all the ultrasound data offline. Based on 12 controls the intra-observer variability showed the following coefficients of variation: baseline diameter (1.1%); EDV (1.3%); EIV (1.9%).

EDV and EIV were evaluated prior to the first adalimumab administration (day 0) and then at day 2 after adalimumab administration and at weeks 2 and 12 after the onset of this treatment. In all cases brachial artery reactivity was measured at day 0 at week 2 and at week 12 two hours before the subcutaneous administration of adalimumab.

In each patient a DAS 28 (determined by the same rheumatologist- MAG-G) was assessed at day 0 and at weeks 2 and 12 prior to adalimumab administration. Also, C-reactive protein (CRP-immunoturbidity method), erythrocyte sedimentation rate (ESR-Westergren), glucose, total cholesterol, HDL cholesterol (fasting overnight determinations), and the total cholesterol/HDL ratio (the atherogenic index) were determined at day 0, and at weeks 2 and 12 two hours before adalimumab administration.

Statistical analysis

Measurements of EDV and EIV represented the maximal increase in brachial diastolic artery diameter and were expressed as percentage (%) of change from baseline. Continuous variables were compared using the Wilcoxon signed-rank test for matched observations. Values of %EDV and %EIV at day 0 (prior to the onset of adalimumab

Table 1. CRP, ESR, DAS28, total cholesterol, HDL cholesterol, and atherogenic index before the first adalimumab administration (day 0) and at weeks 2 and 12 after the onset of this therapy *.

Baseline values		Values after the onset of adalimumab therapy		<i>P</i>
	Mean ± SD		Mean ± SD	
CRP day 0	25.7 ± 19.5 mg/L	CRP week +2	15.7 ± 14.9 mg/L	0.012
		CRP week +12	14.0 ± 12.4 mg/L	0.012
ESR day 0	39.4 ± 21.7 mm/h	ESR week +2	31.4 ± 21.3 mm/h	0.058
		ESR week +12	25.3 ± 15.5 mm/h	0.012
DAS 28 day 0	5.5 ± 1.3	DAS 28 week +2	3.7 ± 0.9	0.012
		DAS 28 week +12	3.6 ± 0.7	0.012
Total cholesterol day 0	193.6 ± 21.8 mg/dl	Total cholesterol week +2	188.9 ± 25.4 mg/dl	0.833
		Total cholesterol week +12	200.5 ± 16.5 mg/dl	0.183
HDL cholesterol day 0	55.5 ± 9.2 mg/dl	HDL cholesterol week +2	58.1 ± 13.7mg/dl	0.292
		HDL cholesterol week +12	62.1 ± 11.5mg/dl	0.012
Atherogenic index day 0	3.52 ± 0.50	Atherogenic index week +2	3.30 ± 0.55	0.012
		Atherogenic index week +12	3.28 ± 0.48	0.012

* Continuous variables were compared using the Wilcoxon signed-rank test for matched observations. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; DAS 28: Disease activity score 28.

therapy) were compared by Mann Whitney test with those observed in a group of controls (2 controls for each individual patient) matched by age \pm 3 years, sex, BMI, and cardiovascular risk factors. All tests were two tailed. Statistical significance at $P \leq 0.05$.

Results

Short-term adalimumab therapy was associated with clinical improvement in all 8 patients manifested by significant decrease of DAS 28 at weeks 2 and 12 compared to baseline results ($P = 0.012$) (Table I). Laboratory markers of inflammatory response, in particular CRP, showed significant reduction following this therapy (Table I). The atherogenic index was significantly reduced at week 12 ($P = 0.012$) (Table I). At that time all patients showed reduction in this index compared to baseline results.

Values of %EDV prior to the onset of adalimumab therapy in the group of 8 RA patients ($5.8 \pm 4.1\%$) were reduced compared with the 16 matched controls ($9.6 \pm 4.4\%$; $P = 0.05$). No differences of %EIV between patients ($20.1 \pm 6.9\%$) and controls ($17.8 \pm 7.0\%$) were observed at that time ($P = 0.46$).

Following adalimumab therapy patients experienced a significant and rapid increase in the %EDV (Fig. 1). In all patients %EDV values at day 2 after subcutaneous administration of this drug (mean SD: $10.1 \pm 5.1\%$; range 1.3 to 17.2%; median 10.4%) were greater than at day 0 (mean SD: $5.8 \pm 4.1\%$; range: -2.3 to 9.9%; median 6.9%). Also, at weeks 2 and 12 %EDV values in all these patients were greater than at day 0 (median at week 2: 9.5% and at week 12: 10.4%; $P = 0.012$) (Table II). No differences in %EIV values (Table II) or baseline arterial diameter (day 0: median 0.36; range 0.26 to 0.42 cm; day 2: median 0.35; range 0.27 to 0.42 cm; week 2: median 0.34; range 0.27 to 0.43 cm; week 12: median 0.36; range 0.27 to 0.41 cm) before and after the onset of adalimumab therapy were observed.

Changes between day 0 and week 12 in CRP and EDV were negatively correlated, although without reaching statistical signification (Spearman rho = -

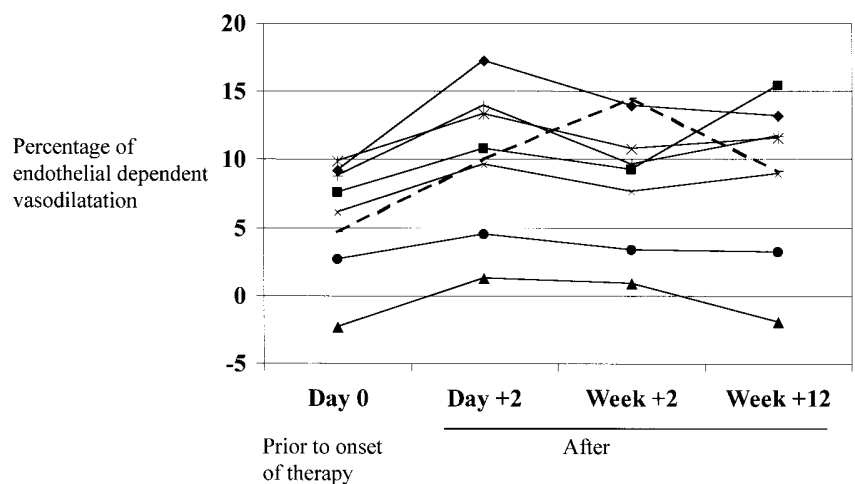


Fig. 1. Percentage of endothelial dependent vasodilation before (day 0) and after the onset of adalimumab therapy (day 2, week 2, and week 12) in 8 rheumatoid arthritis patients refractory to infliximab therapy.

Table II. Percentage of endothelial dependent and independent vasodilation, before the first adalimumab administration (day 0) and at day 2 and weeks 2 and 12 after the onset of this therapy *.

Baseline values		Values after the onset of adalimumab therapy		<i>P</i>
	Mean \pm SD		Mean \pm SD	
%EDV day 0	$5.8 \pm 4.1\%$	EDV day +2	$10.1 \pm 5.1\%$	0.012
		EDV week +2	$8.8 \pm 4.7\%$	0.012
		EDV week +12	$8.9 \pm 5.7\%$	0.012
%EIV day 0	$20.1 \pm 6.9\%$	EIV day +2	$21.5 \pm 7.4\%$	0.093
		EIV week +2	$22.1 \pm 6.3\%$	0.263
		EIV week +12	$20.6 \pm 8.0\%$	0.484

* Continuous variables were compared using the Wilcoxon signed-rank test for matched observations. EDV = endothelial dependent vasodilation; EIV = endothelial independent vasodilation.

0.691, $p = 0.102$), while CRP and EIV were uncorrelated (Spearman rho = -0.191, $p = 0.651$).

No significant changes in BMI, blood pressure and glucose levels throughout the course of the study were found (data not shown).

Discussion

The present study constitutes the first attempt to assess the potential effect of short-term adalimumab therapy on endothelial function in RA patients with long-standing disease refractory to infliximab. Following adalimumab therapy significant clinical improvement and rapid positive effect of this drug on endothelial function were achieved. Decrease of inflammation and improvement of atherogenic index at week 12 after the onset of adalimumab were also found.

Impaired NO bioavailability mediated by TNF- α is a primary manifestation of endothelial dysfunction (12). TNF- α also modulates hepatic synthesis of CRP (12). High CRP serum levels have also been found associated with endothelial dysfunction, (13). In RA increased subclinical atherosclerosis has been correlated with CRP values (14). Dyslipidemia is also closely linked to the development of endothelial dysfunction and atherosclerosis (12). Short-term infliximab therapy was associated with a significant increase of both total cholesterol and HDL-cholesterol levels, which correlated with decreasing disease activity (15). In the present study we also found a significant reduction in the atherogenic index following short-term adalimumab therapy.

In conclusion, our results emphasize

the potential role of the TNF- α blockade in the mechanisms implicated in the development of atherogenesis in RA.

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