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ORIGINAL ARTICLE

Etanercept in the treatment of rheumatoid arthritis: clinical follow-up over one year by ultrasonography

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Abstract We evaluated clinically and sonographically the effects of etanercept therapy in patients with rheumatoid arthritis (RA) over 12 months of treatment. Eighteen patients affected by RA who were non-responders or partial responders to disease modifying therapy were commenced on Etanercept treatment. Before starting therapy (T0) and at 12 months (T1), the following parameters were evaluated: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analogue scale (VAS) for pain, number of painful and swollen joints, health assessment questionnaire (HAQ) and disease activity score in 28 joints (DAS 28). Musculoskeletal ultrasound (US) was performed in the following joints: second and fifth metacarpophalangeal, third interphalangeal, wrist and knee joints and a semiquantitative score (0–3) calculated and used to indicate the presence of a localised inflammatory process (synovitis, tenosynovitis, bursitis) and/or structural damage (bone erosion and cartilaginous change). An overall score was calculated based on the sum of the single scores to obtain a comprehensive score indicative of the global pathological change. The US global scores significantly reduced between T0 and T1 ($p<0.0001$). The following laboratory and clinical parameters also significantly reduced: ESR ($p<0.0001$), CRP ($p<0.02$), VAS ($p<0.001$), number of total swollen joints ($p<0.001$), number of total painful joints ($p<0.01$), HAQ scores ($p<0.05$) and DAS 28 ($p<0.0001$). A positive response to treatment with Etanercept was demonstrated both by US examination of several joints and by clinical evaluation of several parameters. US is a useful tool in the monitoring of biologic therapy in RA, assessing both inflammatory and destructive changes.

Keywords Etanercept · Follow-up · Rheumatoid arthritis · Ultrasonography

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with systemic features in which the principal targets of the inflammatory process are articular and peri-articular tissues [1]. In recent years, rheumatological research has witnessed a revolution related to the study of molecules involved in the inflammatory process and primarily the identification of the key role of tumour necrosis factor alpha (TNFα) [2]. Its capacity to stimulate the production and secretion of pro-inflammatory cytokines, regulate the expression of adhesion molecules on endothelial cells, control the migration of leucocytes to sites of inflammation, increase the production of metalloproteinases from synovial macrophages and inhibit the production of proteoglycans has been well demonstrated to date [3]. Moreover, TNFα stimulates neovascularisation of synovial

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Table 1 US, clinical and laboratory parameters

Joints and parameters studied with US	
Joints studied (bilaterally)	II MCP/V MCP/III PIP/wrist/knee
US parameters evaluated	Synovial membrane: proliferation/ thickness/hyper-perfusion (power Doppler) Synovial fluid: effusion Tendons and bursae: tenosynovitis and bursitis Bone: erosions Cartilage: cartilagenous change
Score	0–3
Clinical and laboratory parameters	ESR/CRP/patient VAS/HAQ/number of tender joints/number of swollen joints/DAS 28

tissue, a phenomenon which correlates with the level of local inflammatory activity [4]. In essence, TNFα represents a key molecule in the activation and perpetuation of the inflammatory process within joints and systemically in RA, leading subsequently to joint erosion and permanent structural damage [5].

In light of the fundamental role played by such cytokine in the pathogenesis of the inflammation seen in RA, research has concentrated on implementing new pharmacological strategies to directly antagonise TNFα, with the aim of blocking or slowing down its molecular impact [6–9]. Enbrel is one agent which inhibits the soluble TNFα receptor. Randomised double-blind control trials have demonstrated the safety, tolerability and the reduction in disease activity of anti-TNFα therapy [10]. In RA, TNFα blockade results in an improvement in the number and severity of joints involved, the indices of inflammation and the parameters of disease activity both compared to placebo and compared with other disease-modifying drugs particularly methotrexate [11].

Ultrasound (US) of joints and tendons is a useful imaging method in the diagnosis and follow-up of rheumatic disorders [12]. It can demonstrate changes in the soft tissues particularly hypertrophy of the synovial membrane, joint inflammation, tenosynovitis and bursitis [13]. Moreover, with the advent of power Doppler, US is capable of revealing the extent of synovial flow in presence of neovascularisation and therefore the increase in perfusion of the synovial membrane in cases of synovitis [14]. As a result, it is now possible to demonstrate the level of inflammatory activity present within synovial tissue, differentiating between acute and chronic inflammation [15]. US is of particular benefit when searching for bone erosion and cartilaginous change in early phases of the disease process, thereby allowing a diagnosis to be confirmed and the progression of the disease to be followed [16]. Furthermore, multiplanar scanning permits examination of superficial areas which cannot be studied satisfactorily with conventional X-ray [17, 18].

Only a few studies have been published to date in which the response to biologic therapy has been followed. The results obtained have, however, underlined the potential role for US in the monitoring treatment response [19–21]. Unfortunately, the small number of patients and the brevity of follow-up make further studies necessary.

The object of this study was to evaluate, by means of US, the effects of etanercept therapy in RA after 1 year and correlate these findings with clinical and laboratory indices.

Materials and methods

Eighteen consecutive patients, 4 men and 14 women, receiving etanercept (25 mg subcutaneously twice weekly) plus methotrexate (10–15 mg weekly) and/or hydroxychloroquine (400 mg daily) and/or salazopyrin (2 g daily) and non-steroid anti-inflammatories (diclofenac 50–100 mg daily or indomethacin 50–100 mg daily or nimesulide 100–200 mg daily) and steroids (methylprednisolone 4–8 mg daily) for RA and fulfilling the American Rheumatology Association diagnostic criteria were studied. All patients were non-responders or partial responders to disease-modifying therapy. The mean age was 50.8 (range 31–69) with mean disease duration of 13.05 years (range 3–31). This study was conducted only in one center, the Rheumatology Unit of "Sapienza" University of Rome, in compliance with the protocol and good clinical practices, following the routinely monitoring procedures performed in our unit for patients with arthritis.

Table 2 Subdivision of all US, clinical and laboratory parameters into four classes of severity

Class	US	ESR	VAS	HAQ	No pain joints	No swollen joints	DAS 28
I	<10	≤10	≤30	<0.5	≤6	≤3	<2.6
II	≥10<20	>10<25	>30<55	≥0.5<1	>6≤15	>3≤7	≥2.6<3.2
III	≥20<30	≥25<40	≥55<80	≥1<1.5	>15≤24	>7≤10	≥3.2<5.1
IV	≥30	≥40	≥80	≥1.5	>24	>10	≥5.1

Table 3 Results for all patients at T0 and T1

Patients	US T0	US T1	ESR T0	ESR T1	CRP T0	CRP T1	VAS T0	VAS T1	HAQ T0	HAQ T1	Pain T0	Pain T1	Swel T0	Swel T1	DAS 28 T0	DAS 28 T1
BC	34	26	16	19	neg	neg	75	68	1.25	2	13	15	4	3	5.57	5.67
BL	18	8	30	27	pos	neg	67	21	2	1	21	1	8	3	6.75	3.77
BN	21	13	43	5	pos	pos	40	30	1.38	0.75	8	10	7	4	4.62	4.43
CP	27	13	22	11	pos	pos	95	53	1.625	1	25	6	16	6	6.92	4.15
CF	18	12	42	19	pos	neg	55	40	0.5	0.5	16	10	5	5	6.25	5.02
CP	17	6	40	18	neg	neg	20	10	0.125	0.125	1	1	1	0	3.7	2.72
CA	27	16	45	15	pos	neg	81	36	1.125	0.625	14	9	6	0	6.58	4.08
DE	21	8	10	8	neg	neg	70	35	1.875	0.25	20	14	6	0	5.78	4.04
DM	31	7	30	17	pos	neg	70	0	1.5	0.625	15	0	4	0	5.32	1.98
LR	21	4	62	18	pos	pos	73	40	2	2	27	11	11	8	7.88	5.23
MS	20	12	28	22	neg	neg	40	33	1	1	22	10	12	8	6.42	5.34
PP	17	8	40	33	pos	neg	100	50	1.5	1.125	2	4	2	1	5.17	4.55
PA	25	8	21	11	neg	neg	48	20	1	0	1	0	2	0	3.61	1.92
PL	21	16	76	50	pos	neg	70	67	1.375	1	6	1	4	0	5.94	4.24
PS	15	5	32	10	neg	neg	50	0	1.25	0	19	3	11	1	6.92	2.86
SM	30	13	40	22	pos	neg	90	27	2	5	29	4	12	1	7.79	5.1

US examination

In all patients, the following joints were studied bilaterally: second and fifth metacarpophalangeal (MCPs), third interphalangeal (PIP), wrist and knee. The joints evaluated were chosen because they are commonly involved in RA, and they can be reliably assessed by US. The US examination was performed using a Philips/HP Image Point HX machine with a 10-MHz linear probe for knee joints and a 14-MHz probe for the hands and wrists. In addition, power Doppler was used with the following settings: PRF varying from 700–1,000 Hz (according to the joint studied) gain 18–30 dB, low filter. The examination was performed before the initiation of etanercept (T0) and after 52 weeks (T1). The US study was performed by an experienced rheumatologist sonographer (AI) who was blinded to the clinical and laboratory findings in each patient.

In every joint, a multiplanar scanning technique [17, 18] was used and the presence of inflammation documented in joints and or peri-articular tissues (joint effusion, synovial proliferation, hyperaemia in the synovial tissue, tenosynovitis and bursitis) together with the presence of permanent damage (bone erosions and cartilaginous abnormalities). The changes within each articular and peri-articular structure were recorded as being present in accordance with the reported definitions in the literature [22, 23]. For all the changes, a semiquantitative score (0–3) was used for each structure examined indicating the degree of inflammatory activity and structural damage (0 = normal; 1 = mild change; 2 = moderate change; 3 = severe change) and the subsequent summed total used as an indicator of global change at each time point. An increase in score from T0 to T1 was considered indicative of global deterioration in the pathological process, whilst a reduction was indicative of an overall improvement.

Clinical evaluation

The clinical and laboratory parameters measured at T0 and T1 are listed in Table 1.

Table 4 Results (mean and median) at T0 and T1

Variable	T0 (n=18)	p	T1 (n=18)
Age (years)	50.8(31–69)	>0.05	51.8 (32–70)
US[a]	21 (18–27)	<0.0001	11.2 (8–13)
CRP>0.5 mg/dl n (%)[b]	8 (44)	<0.02	3 (17)
ESR	35±17	<0.0001	19±12
VAS[a]	70.0 (50–70)	<0.001	33.5 (21–50)
HAQ[a]	1.38 (1,12–1,87)	<0.05	1.03(0.37–1.12)
Painful joints[a]	14.5 (8–21)	<0.01	6.5 (1–10)
Swollen joints[a]	6 (4–11)	<0.001	1 (0–5)
DAS 28	5.9±1.2	<0.0001	4.1±1.4

t Test for dependent samples. Data are presented as mean± SD or median (25th–75th percentile)

[a] Wilcoxon signed rank test

[b] Chi-square test

For each US, clinical and laboratory parameter 4 degrees of severity were assigned to the changes to grade the effects of therapy (Table 2).

Statistical analysis

Data were reported as mean values±standard deviations or as median values with the inter-quartile ranges in cases of variables with non-standard distribution. Appropriate statistical tests were used to analyse the data. In particular, normally distributed variables were analysed using the Student's *t* test for unpaired data and Pearson correlation. For all other nonparametric data, the following tests were used (Mann–Whitney *U* test, Kruskal–Wallis, analysis of variance and Spearman correlation test). The differences in percentages were analysed using the chi-squared test. Statistical significance was taken at a p value<0.05. All calculations were made using IBM 'Statistica' (StatSoft, Tulsa, OK, USA) software.

Results

The results of this study are summarised in Tables 3 and 4 and Fig. 1.

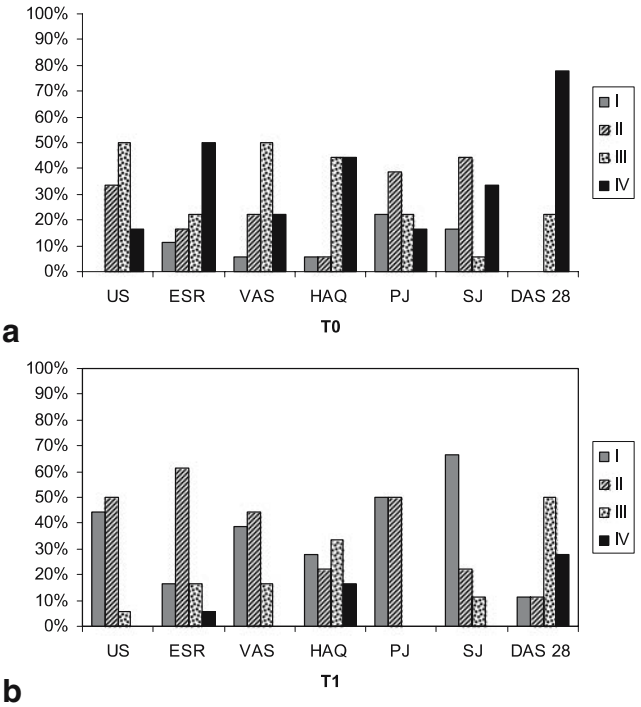

Fig. 1 Subdivision into classes of severity of the changes seen in all the parameters evaluated. A response to therapy was demonstrated in patients who had more severe changes (classes III and IV) at T0 and less severe changes (classes I and II) at T1. The p values were respectively: US global score, p<0.0001; CRP, p<0.02; ESR, p<0.0001; VAS, p<0.001; HAQ, p<0.05; number of total painful joints, p<0.01; number of total swollen joints, p<0.001; DAS 28, p<0.0001

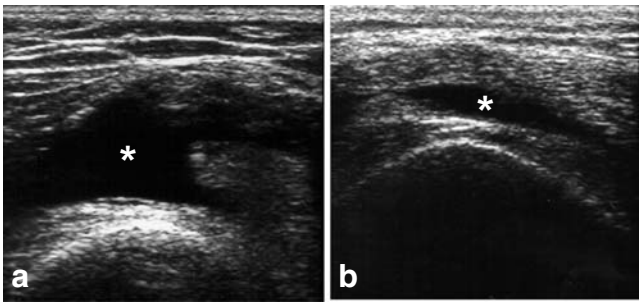

Fig. 2 Knee US. Supra-patellar transverse scan. **a** At T0, an effusion (*) and synovial proliferation were present in the supra-patellar bursa. **b** At T1, a reduction in the size of effusion (*) and synovial proliferation was seen

US evaluation demonstrated a significant reduction (median changes=−10; p<0.0001) in the US global score (sum of the semiquantitative score or each structure examined indicating the degree of inflammatory activity and structural damage) from T0 to T1. In particular, before starting therapy, the median US global score was 21 [inter-quartile ranges (IQR), 18–27] and after 1 year of etanercept therapy was reduced to 11.2 (IQR, 8–13). The evaluation of the knee joint is shown in Fig. 2 at T0 and T1.

CRP values significantly decreased after 12 months. Of the 11 patients with an elevated CRP at baseline, eight had normal values at T1 and three remained high (p<0.02). Erythrocyte sedimentation rate (ESR) also fell significantly (p<0.0001) from a mean of 35(±17 mm/h) at T0 to 19 (+SD 12) at T1. The median VAS fell significantly (p< 0.001) from 70 (IQR, 50–70) at T0 to 33.5 (IQR, 21–50) at T1. Median Health assessment questionnaire (HAQ) values fell significantly (p<0.05) from 1.38 (IQR, 1.12–1.87) at baseline to 1.03 (IQR, 0.37–1.12) at 1 year. The number of painful total joints changed significantly (p<0.01) from a median of 14.5 (IQR, 8–21) at baseline to 6.5 (IQR, 1–10) at T1. Similarly, the median number of total swollen joints also fell significantly (p<0.001) from 6 (IQR, 4–11) at baseline to 1 (IQR, 0–5) at T1. The mean DAS 28 scores fell significantly (p<0.0001) from 5.9 (±1SD, 1.2) to 4.1 (±1SD, 1.4) at 1 year. The subclasses in the degree of change demonstrated in all the parameters evaluated more severe involvement (III, IV) at baseline and less severe degrees of involvement (I, II) at 1 year.

Discussion

In recent years, the role of US as a diagnostic tool and as a mode of monitoring therapy in rheumatic disease has been progressively confirmed. It has enabled the exploration of various articular and peri-articular structures [24] together with local neovascularisation, thanks to power Doppler. It is now possible to identify and monitor the progression of active inflammation.

To date, very few scientific papers have documented the use of US in the monitoring of biologic therapy. D'Agostino et al. [25] demonstrated a significant reduction in synovial perfusion within the Achilles insertion in two patients treated with infliximab (3 mg/kg at time 0, 2 and 6 weeks) after 14 weeks. Ribbens et al. [26] subsequently showed a clear reduction in synovitis and power Doppler signal in the small joints of the hand in 11 patients treated with infliximab for 6 weeks. Furthermore, in 2004, a randomised placebo-controlled trial compared radiographic methods in the evaluation of the joints of the hand and feet with US in patients with RA treated with methotrexate and infliximab or placebo [27]. This study showed a reduction in inflammation and retardation of joint destruction in patients who had been randomised to receive infliximab both in terms of radiographic and sonographic findings. At present the effects of etanercept in the treatment of patients with RA has not been extensively studied.

Hau et al. [28] studied the effects of etanercept (25 mg×2/week) in five patients after 1 month of therapy and showed a significant reduction in synovial perfusion with power Doppler at the level of the second MCP joint. A further study evaluated the changes in synovial perfusion in 11 patients with RA treated with etanercept (50 mg/week) at the level of the wrist and the MCP joints and documented an important initial reduction in perfusion after 1 week of treatment [29]. More recently, 12 patients with RA and eight with psoriatic arthritis and knee synovitis treated with etanercept had a significant reduction in power Doppler signal which correlated with reductions in indices of disease activity including ESR and CRP. This improvement in synovitis was maintained for 12 months of biologic therapy and was confirmed by the reduction in thickness of the synovial membrane sonographically [30].

The results of these studies underline the emerging role of greyscale US and power/color/contrast-enhanced Doppler in the evaluation of anti-inflammatory efficacy of biologic therapy with infliximab and etanercept in chronic arthritis, most notably RA [31–35]. Unfortunately, these studies have been limited by the number of patients evaluated together with the short period of follow-up. With this in mind, our study followed 18 patients with RA treated with etanercept and monitored sonographically, clinically and serologically over a 52-week period. We have clearly demonstrated a significant reduction in US score calculated on the joint examination. The importance of these data was confirmed by a parallel reduction in all the clinical and laboratory indices of disease activity. Furthermore, it seems that the response of US parameters is greater than DAS 28. The results of our study are supportive of those presented in other reports where US was used to monitor disease activity. We were able, however, to demonstrate this in a wider range of anatomical targets than in previous studies [28–30]. To our knowledge, this study represents the first attempt to investigate the effects of biologic therapy on multiple parameters in various joints affected by a chronic arthropathy. Then, US appears to be a valuable tool for the assessment of the response to treatment in RA, and it has many advantages over other diagnostic methods and clinical indices of disease activity such as the low cost, non-invasiveness and possibility of a contemporaneous assessment of inflammatory and structural changes. The close relationship between our US findings and the standardly used clinical and serological indices of disease activity strengthen further the case for using US as one of the investigations of choice in the monitoring of biologic therapy in RA [36–46].

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