CONCISE REPORT

High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor α receptor (etanercept)

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Objective: High resolution ultrasound (HRUS) was used to investigate the effects of tumour necrosis factor α (TNFα) blockade on pannus formation and vascularisation of small finger joints in patients with active rheumatoid arthritis (RA).

Methods: Five patients with active RA were treated with etanercept, a soluble TNFα receptor protein, for one month. Before, during, and after treatment the patients were followed up by clinical rheumatological examination, determination of their subjective pain score, blood chemistry, and by HRUS of the second metacarpophalangeal (MCP) joint of the right hand.

Results: One month after treatment with etanercept, rheumatological examination showed a significant decrease in a modified single joint rheumatic disease activity index (from 2.9 (SD 0.2) to 1.2 (0.7); p<0.05) in all patients. Moreover, a significant decrease in the general pain score (from 4.7 (0.4) to 1.8 (0.6); p<0.05) and in C reactive protein (CRP) levels was seen (from 3.02 (0.9) to 0.24 (0.1); p<0.05). Concordantly, HRUS showed a significant reduction in pannus vascularisation of the MCPII joints (from 23 602 (5339) to 2907 (1609) colour signals/region of interest, CS/ROI; p<0.001). Pearson's correlation coefficient between the results obtained by HRUS and the clinical response was 0.85.

Conclusion: HRUS is promising as an additional useful method in the assessment of RA activity, and probably also in monitoring therapeutic responses.

Rheumatoid arthritis (RA) is a chronic inflammatory disease which often results in progressive joint destruction. This derives from chronic inflammation of synovial membranes, which is the result of a concerted action of different cell types and finally leads to the development of pannus.[1 2] Neovascularisation of pannus appears to be crucial for its invasive and destructive behaviour.[2 3] Reduction of neovascularisation by treatment with tumour necrosis α (TNFα) blockers was shown first in synovial biopsies from an animal model,[4] and later also in patients with RA.[5] It has been claimed that TNFα participates in several mechanisms of pannus formation. It increases synoviocyte proliferation and triggers a cascade of secondary mediators which play a part in the recruitment of inflammatory cells and in the process of joint destruction,[6] including angiogenesis, by directly affecting endothelial cells and by promoting the production of pro-angiogenetic factors.[7 8]

Recently, we have shown that high resolution ultrasound (HRUS) is a useful method of determining pannus vascularisation in inflamed finger joints of patients with RA.[9] Because TNFα blockade has been shown to reduce vascularisation of inflamed joints,[10] here we investigated whether changes in pannus vascularisation of inflamed finger joints from patients with RA by treatment with etanercept (a soluble TNFα receptor protein) could be quantitatively assessed by HRUS.

PATIENTS AND METHODS

Patients

Over a period of one month we examined patients with RA with active disease before and during treatment with etanercept. Five patients (four female, one male) were recruited from the medical outpatient department and gave informed consent before inclusion in our study.

All patients fulfilled the classification criteria of the American College of Rheumatology for RA and had active erosive disease at the wrist and at multiple metacarpophalangeal (MCP) and proximal interphalangeal joints of both hands.

In patients with active disease, despite combination treatment with at least two disease modifying antirheumatic drugs (DMARDs) (one of which was methotrexate) in appropriate doses and low dose corticosteroids, treatment was started with etanercept (2×25 mg/week subcutaneously). Methotrexate was continued except in one patient because of side effects. Other DMARDs were stopped at least four weeks before study entry. During the study the dose of oral corticosteroids was stable in two of the patients and could be reduced in three of the five patients (for patient data see also table 1). Application of intra-articular corticosteroids was not allowed. Table 1 shows the clinical data of the patients.

Clinical examination

Clinical activity of single finger joints was determined by an independent joint assessor who was not directly involved in the treatment of the patients. The degree of swelling and tenderness was assessed according to a modified index of synovitis activity in a single joint.[10] The rheumatic disease activity index (RDAI) represents the mean value of the parameters swelling and tenderness on a scale from 0 to 3 (where 0 = no, 1 = moderate, 2 = strong, 3 = very strong), determined separately for each patient and each finger joint. Because the ultrasound examination focused only on the MCPII joint of the right hands, besides the total RDAI (referred to as $RDAI_{total}$, corresponding to the score of all small finger joints together)

Abbreviations: CRP, C reactive protein; CS/ROI, colour signals/region of interest; DMARDs, disease modifying antirheumatic drugs; HRUS, high resolution ultrasound; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; RDAI, rheumatic disease activity index; SPS, subjective pain score; TNF α, tumour necrosis factor α

Table 1 Baseline characteristics of the study group

Patient	Age (years)	Sex	Duration of disease (years)	Treatment during study period
1	64	F	6	Methotrexate 25 mg IV/week; prednisolone 5 mg/day
2	49	F	15	Methotrexate 25 mg IV/week; prednisolone, reduced from 15 to 7.5 mg/day (days 16–29)
3	65	F	36	Methotrexate 20 mg IV/week; prednisolone 7.5 mg/day
4	61	M	7	Methotrexate 15 mg IV/week; prednisolone, reduced from 20 to 15 mg/day (days 15–29)
5	47	F	27	Prednisolone, reduced from 12.5 to 7.5 mg/day (days 1–16: 10 mg, days 17– 29: 7.5 mg)

we also determined a single joint RDAI for the respective right MCPII joints, referred to as $RDAI_{II}$. In addition, a general subjective pain score was determined according to a standard visual analogue scale ranging from 0 (no pain) to 10 (very strong pain) referred to as "subjective pain score" (SPS_{total}).

Blood chemistry

During the study venous blood samples were drawn from each patient at several defined times (days 0, 8, 16, and 28) to determine the corresponding CRP values, blood sedimentation rates, and other routine parameters (with the exception of CRP values data not shown).

Ultrasound examination

Immediately after clinical examination, US was performed by an experienced radiologist who was not aware of the results of the clinical parameters obtained by the rheumatologists (that is, RDAI, SPS, and serum parameters). Each MCP joint was scanned longitudinally and transversely from the dorsal view, with the joint in 20° of palmar flexion and was documented in the longitudinal and transverse view in B mode and colour mode, as previously described.[10] All data were saved in a digital archiving computer system (ALI UltraPACS; SEPP, Röttenbach, Germany).

In this study we used a Sonoline Elegra Advanced equipped with a multi-D linear array transducer (VFX 13–5, Siemens Medical Systems, Ultrasound Group, Issaquah, WA). For adjustment, we chose constant parameters—that is, a pulse repetition frequency of 551 Hz, a B mode frequency of 12.0 MHz, a colour mode frequency of 9.0 MHz, a gain of 70 dB, and a low filter. Stored images were evaluated on a 21 inch screen.

Intra-articular colour density was quantified in the longitudinal and transverse views within a user defined region of interest (CS/ROI) by computer aided image analysis (Echotech, Hallbergmoos, Germany). On longitudinal and transverse scans, the border of the respective ROIs was defined as previously described (longitudinal scans: tendon of the muscle extensors (top), the joint cavity (base), and the convex articular surfaces of corresponding bones (lateral border); transverse scans: tendons of the muscles extensors (top), the joint cavity (base), and the skin surface (lateral border)[9]). A pannus vessel index was calculated as the sum of all colour

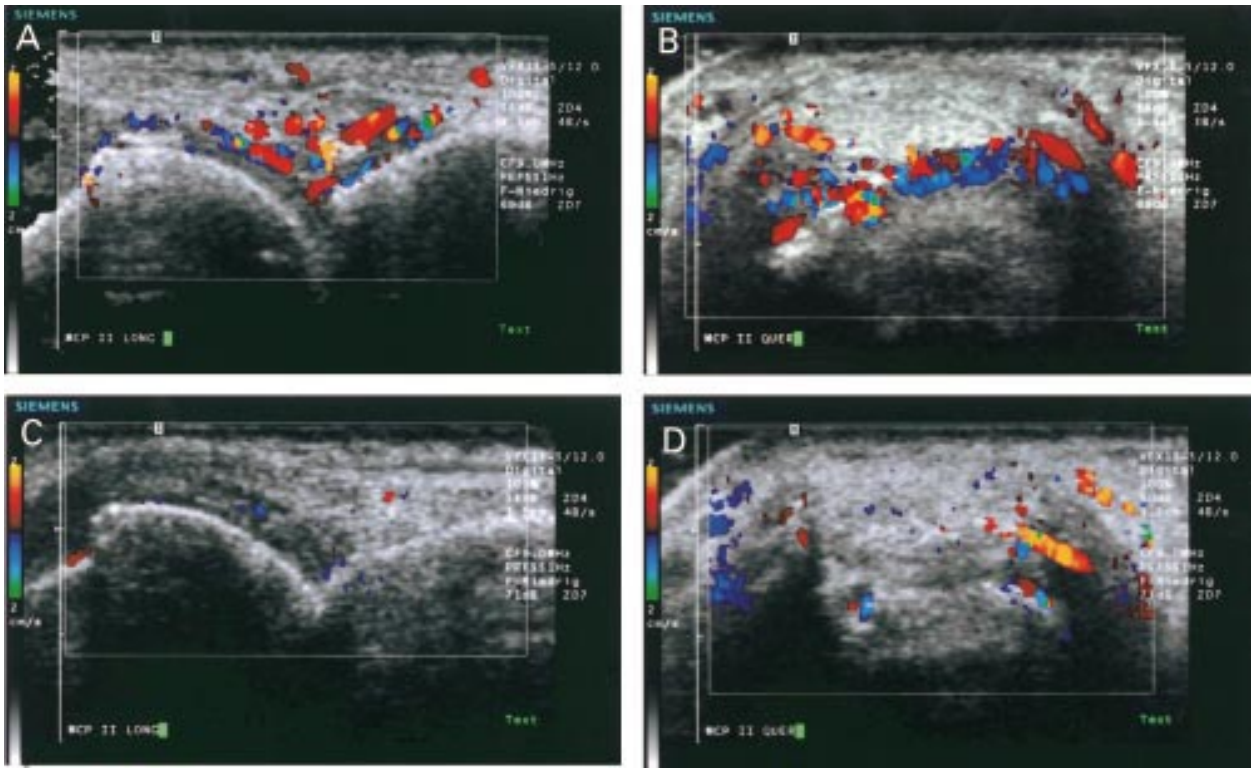

Figure 1 Longitudinal (A) and transverse (B) scan of an MCPII joint of the right hand before treatment with etanercept, showing hypoechogenic pannus and a high degree of intra-articular vascularisation. Longitudinal (C) and transverse (D) scan of the same joint as shown in (A) and (B) during treatment with etanercept for 29 days. A significant decrease of intra-articular vascularisation can be seen.

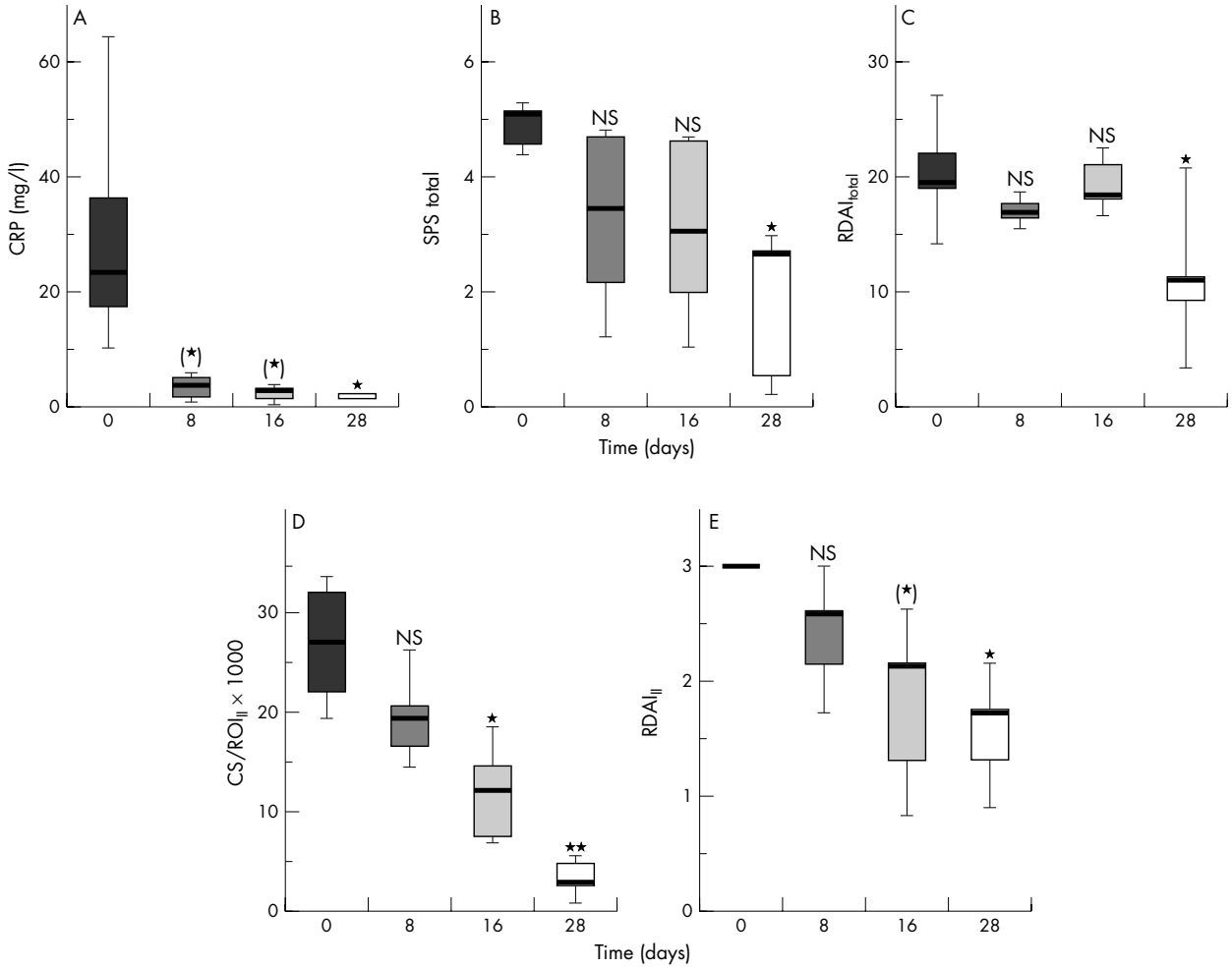

Figure 2 Box and whiskers graphs of clinical parameters obtained from five patients treated with etanercept for 28 days. (A) CRP; (B) total subjective pain score (SPS_{total}); (C) total rheumatic disease activity index ($RDAI_{total}$); (D) colour signals per region of interest (CS/ROI_{II}); (E) single joint disease activity index ($RDAI_{II}$) of the second MCP joints. Error bars correspond to the range of the respective values, boxes correspond to the 25% and 75% centiles and the bold horizontal bars to the median values. Individual variables were tested for significance by the Kruskal-Wallis test followed by Dunn's multiple comparison procedure. NS, not significant; (*)p<0.1; *p<0.05; **p<0.001

signals for each ROI (CS/ROI) from both longitudinal and transverse scans of the MCPII joints.

Baseline US examination was performed before treatment with etanercept. During a one month period the second MCPII joint of the right hand of every patient was examined on days 8, 16, and 28, directly after the rheumatological examination.

Statistics

All data are given as mean (SD). Because of the small number of patients we did not assume normal distribution of the data. Significance between the mean values obtained for $RDAI_{total}$, $RDAI_{II}$, subjective pain score, CRP, and CS/ROI in the course of our study (days 0, 8, 16, and 28 repeated measurements) was analysed by Kruskal-Wallis test followed by Dunn's multiple comparison test. A p value <0.05 was considered significant. Moreover, Pearson's correlation coefficient was calculated between the $RDAI_{II}$ and CS/ROI values obtained for each MCPII joint from every patient at defined time points (that is, on days 0, 8, 16, and 28).

RESULTS

Clinical parameters

All patients investigated had active RA lasting more than six months despite treatment with DMARDs in an appropriate dose (table 1). During treatment with etanercept the total disease activity index ($RDAI_{total}$) of the MCPII joints decreased significantly only after 28 days of treatment from 19.3 (3.3) to 11.2 (2.8) ($p<0.05$; fig 2), whereas the single joint $RDAI_{II}$ rapidly (within eight days of treatment) and constantly decreased from 2.9 (0.2) to 1.2 (0.7) ($p<0.05$). Similarly, the general subjective pain score improved (from 4.7 (0.4) to 1.8 (0.6); $p<0.05$) as did serum CRP (from 3.02 (0.9) to 0.24 ± (0.1); $p<0.05$; fig 2). Note, that parallel treatment with corticosteroids could be reduced in three of the five patients (table 1).

Ultrasound findings

All MCP joints examined could be visualised by US allowing for a further detailed analysis of intra-articular pannus vascularisation. In all patients the MCPII of the right hand had detectable pannus with a high vascularisation as determined by longitudinal and transversal scans (figs 1A and B). Concordant with the clinical and serological findings a gradual decrease of pannus vascularisation of the MCPII joints was seen during treatment with etanercept (figs 1C and D and fig 2). After treatment for 28 days HRUS showed a significant reduction in pannus vascularisation of these joints in all five patients (from 23 602 (5339) to 2907 (1609) CS/ROI; $p<0.001$). There was quite a good correlation between HRUS and clinical parameters ($HRUS_{II}/RDAI_{II}$: $R=0.85$ (fig 3, insert); HRUS/SPS: $R=0.67$).

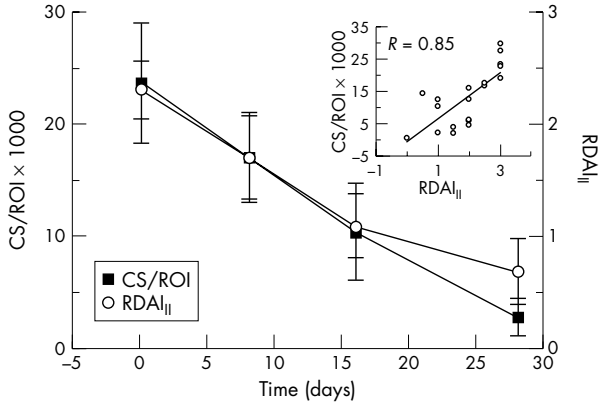

Figure 3 Decrease in intra-articular vascularisation and clinical symptoms of five patients with active RA receiving treatment with etanercept. Values given correspond to the respective mean values obtained before (t=0) and during the study (days 8, 16, and 28). Error bars indicate the standard deviation of the respective mean values. The insert shows the Spearman correlation between the data obtained by HRUS (CS/ROI) and the clinical examination of the second MCPII joints (RDAI$_{II}$).

DISCUSSION

Treatment decisions in RA are based on an estimation of disease progression and responsiveness to treatment.[9 11 12] So far, there is a diagnostic gap between the symptoms of inflammation as determined by clinical examination of the hands and those resulting from imaging methods such as scintigraphy and/or magnetic resonance imaging (MRI).[13] HRUS seems to be useful in helping to make therapeutic decisions; it allows for detection of pannus and its degree of vascularisation, which have been shown to be associated with the activity of RA.[9] Hypervascularisation and angiogenesis within the pannus are essential pathogenic mechanisms leading to joint destruction during the chronic phase of RA. Inhibition of vascularisation by drug treatment[14–16] improves symptoms in animal models of RA; in addition, synovial biopsy studies have shown that TNFα blockade improves disease activity[10] through reduction of pannus vascularisation.[4 5]

To investigate the effects of TNFα blockade on pannus formation and vascularisation we treated patients with active RA with the soluble TNFα receptor protein etanercept. In general, an ACR20 response was recorded in all five patients within one month of treatment. To compare the results obtained by US with clinically relevant parameters, in this preliminary study we focused on the evaluation of disease activity in the MCPII joint (referred to as RDAI$_{II}$), which was chosen as an "index joint". The clinical effect correlated well with the extent of pannus formation and vascularisation, as determined by HRUS (fig 3). Our observations are in line with a previous study using MRI to monitor patients with RA receiving a TNFα monoclonal antibody.[13] However, in contrast with MRI, HRUS imaging offers a routinely available, inexpensive bedside method that might enable the examiner to monitor therapeutic effects within a given time period. As a consequence, immunosuppressive treatment could be modified earlier, which might help to prevent further damage. In conclusion, the data from our pilot study are encouraging and show that imaging by HRUS may represent an additional helpful tool for the rheumatologist in the assessment of RA disease activity. The next step is for a larger number of patients to be investigated by HRUS in order to evaluate whether this method should be generally recommended for clinical routine.

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