LETTERS

New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis

A P Cairns, M K J Duncan, A E Hinder, A J Taggart

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The management of severe rheumatoid arthritis (RA) has been revolutionised by the introduction of the biological agents infliximab (Remicade—a chimeric anti-tumour necrosis factor (TNF) α antibody), and etanercept (Enbrel—a soluble TNF α receptor). Both these agents lower the effective level of TNF α , and have been shown to be effective in the management of active RA, either alone (etanercept) or in combination with methotrexate (infliximab).^{1,2} Full blown drug-induced systemic lupus erythematosus (SLE) has been reported with infliximab,³ but not (until very recently) with etanercept,⁴ although antinuclear antibodies and autoimmune skin rashes have been reported with etanercept.^{5,6} We report a case of new onset SLE in a patient receiving etanercept.

CASE REPORT

Treatment of a 51 year old woman with severe seropositive erosive RA with methotrexate, sulfasalazine, Myocrisin (sodium aurothiomalate), D-penicillamine, hydroxychloroquine, and leflunomide had previously failed and she continued to require repeated courses of systemic corticosteroids to control her disease. She started etanercept, receiving twice weekly doses of 25 mg subcutaneously, and achieved a good clinical response, with a significant reduction in disease activity scores. Other drugs taken were meloxicam and co-codamol. The etanercept was withheld for a total of four weeks during an intercurrent chest infection, but no other side effects were noted until after seven months of etanercept treatment.

At this stage the patient developed a photosensitive “burning” rash on the exposed areas of her face, neck, and arms. She felt generally lethargic, and described Raynaud’s phenomenon. She had clinically active synovitis. There was no evidence of sepsis. An antinuclear antibody test, which had previously been negative, was now strongly positive (titre 1 in 320 by indirect immunofluorescence on rat liver sections), and dsDNA antibodies were present (9.2 mg/l by the Farr assay) (normal range 0–8). Antinucleosome antibodies were strongly positive by enzyme linked immunosorbent assay (ELISA; Organtec) at 180 U/ml (normal range 0–20 U/ml). Total white cell count had fallen to $1.62 \times 10^9/l$ (neutrophils 0.58, lymphocytes 0.88). Haemoglobin and platelet counts were normal. Vasculitic screen was negative, while rheumatoid factor remained positive. There was a polyclonal rise in immunoglobulins, and erythrocyte sedimentation rate was raised (46 mm/1st h). Renal and liver function tests were normal.

A diagnosis of SLE was made and her etanercept was discontinued. She received three intramuscular injections of triamcinolone 40 mg over three weeks, and treatment with prednisolone 10 mg/day and alendronate 70 mg/week was started. Three weeks after stopping etanercept and starting corticosteroids the rash had completely disappeared, the patient was feeling generally better. The synovitis had also improved. After three months the total white cell count had

increased to $3.63 \times 10^9/l$ (neutrophils 2.21, lymphocytes 1.07). A yellow card reporting this probable drug reaction was completed.

DISCUSSION

We have described the new onset of SLE in a patient receiving etanercept for RA. Before receiving etanercept the patient had, on a number of occasions, had a total white cell count between 2.5 and $4 \times 10^9/l$ (normal range 4–11). An ultrasound scan of the abdomen had shown a mild degree of splenomegaly of normal consistency in keeping with Felty’s syndrome. There were no other prior features of SLE. In particular, antinuclear antibody and anti-double stranded DNA antibody tests were negative (on two separate occasions), there was no history of rash or photosensitivity, and no history of renal or neurological disease. The improvement in symptoms, signs, and white cell count on stopping the etanercept would be in keeping with a case of drug-induced SLE. The alternative explanation is that the pre-existing leucopenia was a manifestation of a pre-existing lupus-like disease which was unmasked by the etanercept. This would be supported by occasional pre-etanercept episodes of lymphopenia, which is less common in Felty’s syndrome.

Why should TNF α blocking therapy cause or unmask SLE? One possible explanation is that TNF α may up regulate the cellular expression of the adhesion molecule CD44, which has a role in the clearance of apoptotic neutrophils by phagocytes.^{7,8} Impaired clearance of apoptotic cells, and reduced leucocyte CD44 expression, have been described in SLE.^{9,10} This is, however, a complex area which requires clarification by further study. There is no doubt that etanercept and infliximab represent great advances in the treatment of RA. This case serves to illustrate that patients receiving these drugs should be closely monitored, and caution exercised in any patient with lupus-like or leucopenic disease features.

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Biochemical and morphological study of human articular chondrocytes cultivated in the presence of pulsed signal therapy

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Pulsed signal therapy (PST) is an extension of pulsed electromagnetic fields (PEMF) therapy. PEMF have been used widely to treat non-healing fractures and related problems in bone healing since approval by the Food and Drug Administration in 1979.^{1,2} Recently, PEMF therapy has been used to treat patients with osteoarthritis (OA) of the knee and cervical spine, with encouraging results.^{3,4} In vitro studies have also shown a stimulating activity of PEMF on cartilaginous metabolism.⁵

PST, in contrast with PEMF, uses specific physiological changing rectangular pulses as stimuli, which are transmitted in a programmed alternating fashion that mimics the body's natural streaming potentials for one hour of treatment.

We studied the effects of PST on human OA chondrocytes cultivated in the presence and absence of a negative stimulus represented by interleukin 1 β (IL1 β) and we evaluated the concentration of proteoglycans (PGs) in the culture medium and the morphology of the chondrocytes after exposure to PST.

Human OA chondrocytes were cultivated in alginate gel on Petri dishes for 72 hours with and without IL1 β (5 ng/ml). Some dishes were exposed to PST for three hours a day.⁵ The PST stimulation was administered by a device constructed for in vitro study. This apparatus has suitable dimensions for insertion in a CO₂ incubator. The device produces extremely low frequency (less than 30 Hz) varying pulsed electromagnetic fields averaging 10–20 G of magnetic energy at a coil current of up to 2 A drawn from a power source of 120 V AC. The pulse phase duration was 67 ms, including 15 micropulses with a pause duration of 0.1 s.

Control cultures were maintained under identical conditions but in the absence of PST. After the culture period the medium was removed and collected for determination of the PGs by an immunoenzymatic method on microplates for the quantitative measurement of human PGs.⁶ Cells in alginate gel were immediately fixed for transmission electron microscopy (TEM) and for scanning electron microscopy (SEM). For each different experimental condition we observed 50 cells for TEM and 100 cells for SEM.

Table 1 shows the PG concentration in the culture medium at baseline, in the presence of IL1 β , and with and without PST stimulation. The presence of IL1 β produced a significant decrease ($p < 0.05$) in PG levels, but when the cells were cultured in the presence of IL1 β and given PST stimulation, PG

Table 1 PG concentration (ng/ μ g DNA) in culture medium in various experimental conditions. The data are expressed as the mean (SD) of PG release into the culture medium per microgram of DNA in the eight tested cultures.

Basal	IL1	Basal PST	IL1 PST
435.9 (282.7)	208.9 (93.8)*	458.4 (259.3)	365 (210.7)*

Student's *t* test was used for statistical analysis.

* $p < 0.05$, IL1 v basal and IL1 PST v IL1.

production was significantly restored ($p < 0.05$). The results for metabolic production are further confirmed by the morphological findings obtained by TEM (fig 1) and SEM analysis (data not shown). TEM analysis showed that IL1 β causes marked cellular damage, confirmed by the presence of several vacuoles in the cytoplasm, which is devoid of typical structures (fig 1B). When the cells were cultured in the presence of IL1 β and given PST stimulation, the cell structures were clearly restored (fig 1D).

These experiments confirm the negative effect of IL1 β on PG production.^{6–8} Exposure of the chondrocytes to PST significantly restored the PG concentration in the culture medium. Such a resumption of anabolic activity was confirmed by morphological observations obtained by TEM and SEM analyses. The PST signals create a “streaming potential” of ionic flow similar to that generated in a moving joint, and thus they stimulate the anabolic activity of chondrocytes.

Our results are supported by numerous in vitro and in vivo observations, such as electric stimuli and PEMF enhanced cartilage repair processes. External oscillating electric fields increased the incorporation of [³H]thymidine into the DNA of chondrocytes isolated from embryonic chick epiphyses, and capacitatively coupled electric fields stimulated cell proliferation ([³H]thymidine incorporation) and glycosaminoglycan synthesis (³⁵SO₄ uptake) by isolated bovine growth plate chondrocytes.^{9,10} One mechanism suggested for the actions of these electric and magnetic stimuli is an effect on charged transmembrane molecules, such as receptors.^{9,10} Furthermore, electromagnetic fields cause a movement of calcium and other ions across cell membranes and stimulate DNA transcription, resulting in increased protein synthesis.^{9,10}

Figure 1 Transmission electron micrographs of chondrocytes cultured in vitro for 72 hours. (A) Basal conditions: the nucleus (N) appears euchromatic, the cytoplasm contains abundant rough endoplasmic reticulum (RER) and lipid droplets (arrows). $\times 9000$. (B) IL1 β present: the cell shows a vacuolate cytoplasm devoid of the typical structure. N, nucleus; V, vacuole. $\times 9000$. (C) Basal conditions and given PST stimulation: the cell shows an euchromatic nucleus (N) and a cytoplasm rich in rough endoplasmic reticulum (RER) and lipid droplets (arrows). $\times 10\,000$. (D) IL1 β present and given PST stimulation: the cell clearly recovers its good state of health. Rough endoplasmic reticulum (RER) is present and vacuoles are almost absent. N, nucleus. $\times 9000$.

Our study has confirmed, for the first time, the effect of PST on human chondrocytes cultured in alginate gel. The observed increased concentration of PGs in the culture medium, supported by ultrastructural and morphological analyses by TEM and SEM, confirmed the stimulating activity of this “non-pharmacological treatment” on chondrocytes. Further in vitro and in vivo studies are necessary to verify the effects and the mechanism of action of PST.

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Ultrasonographic diagnosis of de Quervain's tenosynovitis

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de Quervain's disease is a stenosing tenosynovitis. There is inflammation of the cellular lining membrane of fibrous tube through which the tendons of abductor pollicis longus and extensor pollicis brevis move, at the radial styloid process beneath the flexor retinaculum. The disease may occur in rheumatoid arthritis, other inflammatory synovitides, and pregnancy. Patients have considerable pain and a weak hand grip.

PATIENTS AND METHODS

We investigated the value of ultrasonography in the diagnosis of de Quervain's tenosynovitis and monitored the changes in tendon sheath after ultrasound guided local steroid injection. Twenty one patients with a clinical diagnosis of de Quervain's

tenosynovitis and 10 healthy subjects were studied prospectively. We used a visual analogue scale (VAS) 0–10 and grip strength to measure pain.

The ultrasound examination was performed using an HDI 3000 from ATL (USA) with an 11 MHz linear array transducer. The marginal appearance of the tendon sheath in the transverse and longitudinal scans was examined and measured.

RESULTS AND DISCUSSION

The ultrasound longitudinal scan of the symptomatic tendon showed distension in the tendon sheath with a surrounding fluid film giving the appearance of diffuse circumferential hypoechogenicity. The transverse scan of the tendon showed a double target pattern (fig 1A).

Several studies have shown that ultrasound is a reliable and sensitive method for detecting tenosynovitis.^{1–5} This study on de Quervain's tenosynovitis clearly detected structural changes, even minimal tendon abnormalities, tendon inner structure, tendon thickening, effusion, and paratendinitis. The affected tendons were inflamed and thickened and showed a significantly increased thickness compared with normal subjects (fig 1A).

The affected tendon sheath was infiltrated with a combination of 15 mg triamcinolone diacetate and 2 ml of 2% lidocaine. After carefully identifying the area of the diseased tendon, the ultrasound guided 23 gauge needle was inserted through the sterile skin at the radial styloid process and advanced anteriorly and slightly downwards in a direction parallel to the tendon. The insertion of the needle into the tendon sheath and delivery of the therapeutic agents were done under direct sonographic visualisation. An ultrasound examination was performed after clinical evaluation and repeated immediately after infiltration of the therapeutic agents, then 1, 6 and 12 weeks later.

A significant decrease in the thickness of the tendon sheath was seen one week after the local corticosteroid injection. Complete relief of symptoms and signs was further observed at 6 and 12 weeks (fig 1B). No complications after injection were reported. The VAS 0–10 scale and hand grip strength were significantly improved after the local injection ($p < 0.001$).

Recently, ultrasound has been used to direct the needle in delivering therapeutic agents into joints and enthesial sites with more accuracy.^{6–8} Ultrasonography allows safe and correct placement of needles and injection of drugs into the tendon sheath. Ultrasonography helps to establish the exact location of the inflammation and directs delivery of the drug into the correct target by direct sonographic visualisation.^{6–9} Therefore, this technique is cost effective in daily rheumatology practice. It also minimises the risk of iatrogenic damage and prevents intra-tendinous injection of the therapeutic materials.^{7–10}

Our ultrasonographic study showed that the local steroid treatment was significantly effective in reducing pain and the amount of increased thickness and swelling of the tendons of the abductor pollicis longus and extensor pollicis brevis within a week after the injection. It was shown clinically to produce longlasting reversal of inflammation in the patients, as was demonstrated by the ultrasound examination follow up at weeks 1, 6, and 12.

Figure 1 (A) Ultrasonographic transverse image of the symptomatic tendons of the abductor pollicis longus and the extensor pollicis brevis, showing a diffuse circumferential hypoechoic thickening of the synovial sheath (0.27 cm), giving a characteristic double target pattern, denoting de Quervain's tenosynovitis; (B) ultrasound transverse scans of the same patient. After one week of injection, note the decrease in thickening of the synovial sheath (0.17 cm). T, tendon; RSP, radial styloid process. 11 MHz.

We believe that ultrasound has both diagnostic and therapeutic value in the daily practice of rheumatology. The ultrasound technique is readily reproducible and helps to confirm the clinical diagnosis and treatment of de Quervain's tenosynovitis.

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Diagnosis of Takayasu's arteritis by unexpected findings on abdominal CT scan

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We report the case of a 30 year old woman with atypical presentation of Takayasu's disease in whom the diagnosis was first made by an abdominal computed tomography (CT) scan.

CASE REPORT

A 30 year old woman was admitted for investigation of an eight month history of lower abdominal pain. The pain was cramping in character, preceded bowel motions, and radiated to the back. She also had a four year history of general malaise with fleeting arthralgias and myalgias, and persistently raised inflammatory markers had been noted. Past medical history included alopecia, occasional mouth ulcers, and pulmonary embolism two years previously. Both her father and paternal

grandfather had died of "ruptured aortic aneurysms". Previous investigation of her abdominal pain at another hospital with an ultrasound scan had shown a small scarred right kidney.

On examination she was afebrile, with a regular radial pulse of 84 beats/min and blood pressure of 120/70 mm Hg in both arms. There was a soft ejection systolic murmur which radiated to the neck. All peripheral pulses were palpable. Abdominal examination showed mild right iliac fossa tenderness with no guarding. Examination of the respiratory and nervous systems (including fundoscopy) were unremarkable. Investigations showed a raised erythrocyte sedimentation rate (ESR) of 88 mm/1st h and raised C reactive protein (CRP) of 77 mg/l. Perinuclear antineutrophil cytoplasmic antibodies

Figure 1 Abdominal CT scan without (A) and with (B) contrast medium. Note the thickening of the aortic wall on both images, with evidence of intimal calcification (A) and the encasement of the origin of the coeliac axis (B).

were demonstrated by immunofluorescence, but enzyme linked immunosorbent assay (ELISA) measurements of antibodies to myeloperoxidase and proteinase 3 were normal. Serum angiotensin converting enzyme and complement levels were normal; rheumatoid factor and antinuclear antibodies were negative. An echocardiogram showed mild aortic regurgitation and a slightly dilated ascending aorta, but normal cardiac function.

To investigate the abdominal pain further abdominal CT scanning was performed. This showed a normal gastrointestinal tract, but was remarkable for diffuse thickening of the abdominal aortic wall and narrowing of the aortic lumen (fig 1). Image A also shows some evidence of calcification of the intima. Administration of intravenous contrast showed that the aortic wall was ~1 cm thick. Image B shows encasement of the origin of the coeliac axis. As well as aortitis, this thickening might possibly represent periaortitis.

On re-examination of the patient bilateral renal bruits were noted. In view of the history of prominent inflammatory symptoms—malaise, arthralgias, myalgias; symptoms suggestive of vessel involvement—abdominal aortic narrowing causing ischaemic pain; and the physical examination, a diagnosis of Takayasu's arteritis was considered. This was confirmed by aortography which, as well as showing the dilated ascending aorta and the narrowed abdominal aorta, also demonstrated stenoses of both subclavian and proximal renal arteries. Small aneurysms of the third and fourth order branches of the right renal artery were seen.

She was treated with pulsed intravenous methylprednisolone and discharged on oral prednisolone. After two weeks the patient reported that her pain had resolved completely and she was considerably less fatigued. At this time the ESR was 6 mm/1st h and CRP 2 mg/l.

DISCUSSION

Although a thorough history and examination can allow the diagnosis of Takayasu's arteritis to be made, confirmation and assessment of the extent of the disease depends on arteriography. Classically, the aortogram shows both dilatation and stenosis of large arteries, but this is not always the case. However, unusually in this patient the diagnosis was suggested by CT scanning demonstrating aortitis. Recent published reports have shown that CT can be very useful in detecting Takayasu's arteritis because it shows such details as wall thickening and perivascular oedema, which cannot be detected by arteriography.¹⁻³ CT is also useful as a non-invasive means of monitoring patients with Takayasu's arteritis who are undergoing treatment, to examine disease resolution or progression.

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Is soluble CD44 variant isoform 5 useful as a predicting factor and a parameter for long term observation in rheumatoid arthritis?

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In addition to its widespread expression, CD44 is a homing receptor for human T cells and an adhesion molecule in cell-cell and cell-matrix interaction.^{1 2} CD44 is a receptor for hyaluronan and other extracellular matrix and cell surface proteins. CD44 has been characterised in detail on lymphocytes, macrophages, fibroblasts, epithelial cells, and keratinocytes. It is part of the regulation of immune mediated inflammation. The binding of CD44 leads to lymphocyte homing, lymphocyte binding to high endothelial venules, myelopoiesis, lymphocyte activation, natural killer target lysis, B cell lymphopoiesis, cell adhesion, inflammation, and tumour dissemination.³ Binding of CD44 monoclonal antibodies or hyaluronan induces intracellular signals that enhance T lymphocyte mitogenesis and releases cytokines (interleukin 1, tumour necrosis factor α) from macrophages. Furthermore, it has been suggested that extravasation of T lymphocytes is mediated by CD44.

The soluble CD44 isoform variant 5 (sCD44v5) was found to be increased in the serum of patients with active rheumatoid arthritis (RA).^{4 5} So far no longitudinal studies have been carried out.

We examined whether sCD44v5 correlates with inflammation or joint destruction, or both, in the long term treatment of patients with RA.

METHODS AND RESULTS

Serum levels of sCD44v5 were measured in 81 patients with RA according to the criteria of the American College of Rheumatology, who were admitted at least three times during an observation period of 10 years (table 1). A commercially available enzyme linked immunosorbent assay (ELISA), developed by Bender-Med Systems, Vienna, was used to measure sCD44v5. The influence of rheumatoid factor (RF) on the measurements of sCD44v5 was ruled out by dilution experiments. The results of sCD44v5 at the first visit and the area under the curve as measure for the long term course were compared with the disease activity score, 28 joint count, 30 swollen joint count, Ritchie index, proximal interphalangeal score, Stoke index, Larsen score, Steinbrocker stage, C reactive protein, erythrocyte sedimentation rate, RF, and treatment with disease modifying antirheumatic drugs (DMARDs) as well.

Table 1 Clinical data of 81 patients (57 female, 24 male) at the first visit

	Mean	SD	Minimum	Maximum
Age at onset (years)	48.6		18.0	72.0
Disease duration (years)	11.6		0.9	58.0
Observation period (years)	6.7		2.7	10.0
ESR (mm/1st h)	35.2	22.3	4.0	108.0
sCD44v5 (ng/ml)	41.7	27.6	6.3	160.8
CRP (mg/l)	29.8	27.8	0.0	120.0
DAS	3.9	1.1	0.8	7.1
PIP	1.8	3.0	0.0	10.0
RF (U/ml)	272.8	764.6	0.0	6634.0
Ritchie index	14.1	10.2	0.0	41.0
Steinbrocker stage	2.3	0.8	1.0	4.0
Stoke	6.4	3.4	1.0	17.0
28JC	17.2	11.9	0.0	55.0
30SJC	8.4	6.6	0.0	28.0
Larsen score	50.8	43.9	0.0	178.0

ESR, erythrocyte sedimentation rate; sCD44v5, soluble CD44 variant isoform 5; CRP, C reactive protein; DAS, disease activity score; PIP, proximal interphalangeal score; RF, rheumatoid factor; 28JC, 28 joint count; 30SJC, 30 swollen joint count.

Table 2 Spearman correlation coefficient of sCD44v5 at visit 1 and AUC sCD44v5 compared with clinical and laboratory parameters

	RF	ESR	CRP	Stoke	28JC	30SJC	Δ Larsen
CC	0.6068	0.1201	0.0448	0.0010	-0.1123	-0.1238	-0.0470
Visit 1 CD44	0.0001	0.2883	0.6910	0.9929	0.3181	0.2706	0.6767
CC	0.2265	0.1118	0.2152	0.1229	-0.1101	-0.1653	-0.0013
AUC CD44	0.0419	0.3235	0.0537	0.2742	0.3278	0.1402	0.9906

CC, correlation coefficient; ESR, erythrocyte sedimentation rate; AUC, area under the curve; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; 28JC, 28 joint count; 30SJC, 30 swollen joint count.

When appropriate, results were analysed by repeated measures analysis of variance, general linear model, and Spearman's correlation coefficient.

We detected raised serum levels of sCD44v5 in 50/356 measurements, with a range from 58.4 to 312.9 ng/ml. The mean sCD44v5 was 42.3 ng/ml. We could not find a significant correlation between sCD44v5 and the clinical and laboratory data of visit 1, except for a correlation with RF (table 2). Increased Steinbrocker stages and Larsen scores did not show a correlation with sCD44v5. To demonstrate sCD44v5 as a predicting factor we therefore correlated the sCD44v5 values of the first visit with Δ Larsen, but the result was not significant.

DISCUSSION

SCD44v5 is described as a measure of inflammation and as an indicator for treatment response in RA.⁶

We aimed at examining whether sCD44v5 might be useful as a predicting factor and measure of treatment response to different DMARDs. Although sCD44v5 is known to be raised in patients with rheumatoid flare, such a correlation could not be shown in our study of patients with weakly to moderately inflamed disease. Soluble CD44 seems to be raised only in severe inflammation.⁷ We found no evidence that sCD44v5 might be a predicting factor. In particular, no significant difference was found between sCD44v5 and Steinbrocker stages or the Larsen score.

Earlier studies have shown that sCD44v5 has an important role as an indicator of inflammation in RA, but in our long term study sCD44v5 had no clinical relevance.

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