Response of anaemia in rheumatoid arthritis to treatment with subcutaneous recombinant human erythropoietin

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Abstract

Eleven patients with chronic inflammatory arthritides and haemoglobin concentrations less than 105 g/l with symptoms from their anaemia were treated with a dose of 250 IU/kg/week of recombinant human erythropoietin for six weeks. The treatment was given as subcutaneous injections five days a week. All patients had active inflammatory disease. Nine patients responded to treatment with an increase in haemoglobin of more than 15 g/l. The mean (SD) haemoglobin concentration increased from 93.0 (8.0) g/l before treatment to 115.0 (12.0) g/l after six weeks. There was no correlation between the initial serum concentration of erythropoietin and the response. It was concluded that anaemia in chronic inflammatory arthritides responds to treatment with subcutaneous injections of recombinant human erythropoietin.

Chronic inflammatory disease is often associated with a relatively moderate degree of anaemia.¹⁻³ The aetiology of this anaemia in chronic inflammation appears to be multifactorial and is a matter of controversy. A shortened erythrocyte lifespan is accepted by most workers, but seems to be of quantitatively minor importance.⁴⁻⁵ A blockage in the release of iron from the reticulo-endothelial cells to the erythron has been advocated by some workers⁶⁻⁷ but studies have not been able to support this.⁸ A reduction in erythrocyte production is thought to be the most important cause.

Some studies of patients with rheumatoid arthritis (RA) and anaemia have shown a blunted erythropoietin response,⁹⁻¹¹ whereas we and others have shown appropriate serum concentrations of erythropoietin.¹²⁻¹⁴ Although patients with RA and anaemia have increased concentrations of serum erythropoietin, the anaemia is not corrected. Erythropoiesis must therefore be inhibited in some way. Patients with renal insufficiency as a group have a markedly blunted erythropoietin response to anaemia. Most, however, have serum erythropoietin concentrations above the reference range. They are not able to correct their anaemia, however, unlike the situation if uraemia is corrected after renal transplantation, when the haemoglobin levels are corrected even if the serum erythropoietin level is the same as before the transplantation. Anaemia of renal insufficiency must therefore be caused by some kind of inhibition of erythropoiesis and maintained by uraemia and a relative lack of erythropoietin. As these patients respond to treatment

with erythropoietin¹⁵ it seemed logical to try to overcome the inhibition of erythropoiesis in chronic inflammation by treatment with exogenous recombinant erythropoietin. The clinical use of recombinant human erythropoietin for anaemic patients with RA has been reported.¹⁶⁻¹⁹ The aim of this study was to evaluate the effect of subcutaneously administered recombinant human erythropoietin in patients with chronic inflammatory arthritides who were anaemic despite treatment with disease modifying drugs.

Patients and methods

PATIENTS

Eleven patients, eight women and three men, with stable inflammatory arthritides and with subjective symptoms of anaemia (haemoglobin <105 g/l) were included in the study. Ten patients, eight women and two men, fulfilled the criteria of the American Rheumatism Association²⁰ for classical RA and one 47 year old man had ankylosing spondylitis according to the New York criteria of the American Rheumatism Association.²¹ The mean age of the patients was 57 years (range 21-79) and the mean disease duration was 18 years (range 3-33).

Seven patients were treated with disease modifying drugs, seven with low dose corticosteroids, and nine patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) (table 1). Two patients had secondary amyloidosis with renal insufficiency (serum creatinine 350 and 280 µmol/l respectively; normal range 64-106 µmol/l). Table 1 gives the clinical data.

Tables 2 and 3 show that all patients had signs of active inflammatory disease with increased erythrocyte sedimentation rate, C reactive protein, and a high Ritchie index.

TREATMENT SCHEDULE

All patients were studied as outpatients at the department of medicine, University Hospital, Uppsala. Only patients with relatively stable, though in some instances high, inflammatory activity were accepted for the study. The drug regimens were not changed during the treatment period. Informed consent was obtained and the study was approved by the Uppsala University committee of medical ethics.

All patients received 50 IU of recombinant human erythropoietin (Recormon, Boehringer Mannheim, Mannheim, Germany) for each kilogram body weight subcutaneously five days

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Table 1 Clinical features of ten patients with rheumatoid arthritis and one patient (patient 11) with ankylosing spondylitis undergoing six weeks' treatment with recombinant human erythropoietin

Patient No	Sex/age (years)	Disease duration (years)	Serology*	Radiological examination†	Extra-articular symptoms	Functional class	Ritchie index	Disease modifying drugs
1	F/69	31	RF+	Y	None	II	12	Sulphasalazine‡, §
2	F/35	10	RF+	Y	None	II	16	Auranofin
3	F/76	29	RF+, ANA+	Y	Amyloidosis, renal insufficiency	III	11	‡, §
4	F/70	17	RF+, ANA+	Y	Secondary Sjögren's syndrome	II	20	Azathioprine‡, §
5	F/56	22	RF+, ANA+	Y	Rheumatoid nodules Cutaneous vasculitis	II	11	Sodium aurothiomalate‡, §
6	M/42	10	Negative	Y	None	III	14	Sodium aurothiomalate‡, §
7	F/21	15	Negative	Y	None	II	19	
8	M/79	3	RF+	Y	None	II	3	‡, §
9	F/77	28	RF+	Y	Secondary Sjögren's syndrome	II	13	Azathioprine‡, §
10	F/56	11	RF+	Y	Rheumatoid nodules	II	14	Sulphasalazine§
11	M/47	18	Negative	AS	Amyloidosis Renal insufficiency	III	—	

*(RF+) positive rheumatoid factor; (ANA+) positive antinuclear antibody (titre >1/25).

†Radiological erosions yes (Y) or no (N); ankylosing spondylitis (AS).

‡Patients receiving corticosteroids.

§Patients receiving non-steroidal anti-inflammatory drugs.

Table 2 Laboratory features of ten patients with rheumatoid arthritis and one patient with ankylosing spondylitis before undergoing a six week treatment period with recombinant human erythropoietin

	Mean (SD) (range) for patients	Reference values
Haemoglobin (g/l)		
Women (n=8)	95 (6.8) (81–103)	113–134
Men (n=3)	88 (11) (75–97)	134–166
Packed cell volume		
Women (n=8)	0.30 (0.03) (0.24–0.34)	0.35–0.44
Men (n=3)	0.28 (0.004) (0.27–0.28)	0.40–0.49
MCV* (fl)	89 (11) (72–109)	70–98
MCH* (pg)	29 (5) (20–37)	28–35
MCHC* (g/l)	315 (19) (281–339)	320–360
Reticulocytes (%)	1.9 (0.8) (0.2–3.4)	0.2–2.0
White blood cells (10 ⁹ /l)	7.7 (2.7) (4.3–13.1)	4–9
Platelets (10 ⁹ /l)	394 (181) (227–841)	150–400
Erythrocyte sedimentation rate (mm/h)	76 (42) (23–145)	2–15
Haptoglobin (g/l)	3.8 (2.3) (1.9–10.0)	0.2–1.4
Serum iron (µmol/l)	6.3 (3.8) (2.0–12.8)	11–35
Serum transferrin (µmol/l)	44.1 (18.5) (29–85)	45–72
Serum ferritin (µg/l)	334 (445) (10–1353)	10–240
Serum erythropoietin (IU/l)	19.5 (11.6) (6.1–43.0)	3.3–13.5

*(MCV) mean corpuscular volume; (MCH) mean corpuscular haemoglobin; and (MCHC) mean corpuscular haemoglobin concentration.

a week—that is, a weekly dose of 250 IU/kg. A maximum dose of 4000 IU/day was not exceeded and patients who required doses higher than 2000 IU were given injections at two sites. The treatment goal was an increase in haemoglobin of more than 15 g/l. When this goal was achieved, the recombinant human erythropoietin dose was reduced by 50% to 25 IU/kg five days a week.

If the serum ferritin value before the start of the treatment with recombinant human erythropoietin was less than 250 µg/l (eight patients), treatment by mouth with iron (100 mg/day) was started simultaneously with the recombinant human erythropoietin treatment to prevent the iron deficiency that accompanies increased erythrocyte production after treatment with recombinant human erythropoietin.²²

CLINICAL AND LABORATORY EVALUATION

Subjective symptoms (morning stiffness and joint pain during movement and at rest) were evaluated by interviews and graded using a 10 grade visual analogue scale. Objective signs of active arthritis were estimated by the Ritchie

Table 3 Laboratory features of ten patients with rheumatoid arthritis and one patient with ankylosing spondylitis before and six weeks after treatment with recombinant human erythropoietin

Patient No	Haemoglobin (g/l)	Packed cell volume	Reticulocytes (%)	WBC* (10 ⁹ /l)	Platelets (10 ⁹ /l)	Serum erythropoietin (IU/l)	Erythrocyte sedimentation rate (mm/h)	C reactive protein (mg/l)	Ritchie index
1 Baseline	81	0.24	2.8	5.7	306	11.9	28	19	12
Follow up	108 (111)†	0.34	0.5 (3.0)	5.8	196	—	12	48	8
2 Baseline	98	0.32	2.2	7.8	289	12.5	40	36	16
Follow up	110 (120)	0.34	2.2 (5.6)	8.9	375	12.6	40	57	11
3 Baseline	98	0.29	1.4	11.9	318	8.1	120	62	11
Follow up	130 (130)	0.40	1.4 (6.6)	10.3	334	17.9	60	25	8
4 Baseline	98	0.34	1.4	13.1	519	37.9	62	111	20
Follow up	98 (103)	0.32	4.2 (8.0)	10.0	565	47.0	19	122	11
5 Baseline	89	0.29	1.4	8.3	559	14.2	90	97	10
Follow up	100 (108)	0.34	2.8 (3.6)	8.9	448	16.2	42	56	8
6 Baseline	97	0.28	1.8	8.4	841	17.3	94	174	14
Follow up	105 (105)	0.35	2.0 (2.0)	8.5	718	33.3	73	198	14
7 Baseline	95	0.30	1.2	7.0	392	21.3	47	32	19
Follow up	114 (115)	0.35	2.2 (2.6)	4.5	364	12.3	29	29	17
8 Baseline	91	0.27	3.0	5.9	326	21.3	145	108	3
Follow up	131 (131)	0.41	2.2 (5.6)	6.9	262	13.7	37	11	2
9 Baseline	102	0.31	0.2	4.3	262	20.6	60	18	12
Follow up	130 (132)	0.35	1.2 (3.0)	5.6	425	14.3	46	40	15
10 Baseline	98	0.32	2.2	7.2	291	43.0	23	51	14
Follow up	119 (119)	0.38	2.6 (9.0)	7.4	330	13.0	14	54	16
11 Baseline	75	0.27	3.4	4.9	227	6.1	71	<0	—
Follow up	117 (117)	0.35	1.0 (1.8)	8.1	258	33.4	117	13	—
p Value	0.001	0.001	NS	NS	NS	NS	0.01	NS	NS

*(WBC) white blood cells.

†Maximum levels observed during treatment are given in parentheses.

index²³ and functional capacity was estimated according to Steinbrocker *et al.*²⁴ This evaluation of disease activity was made before and after six weeks of treatment with recombinant human erythropoietin and at six weeks follow up after the discontinuation of recombinant human erythropoietin treatment. During the treatment period, the patients were interviewed and examined weekly. Blood pressure was also monitored before each injection of erythropoietin.

Each patient underwent haematological evaluation before treatment, including serum iron, serum transferrin, serum ferritin, tests for haemolysis, and bone marrow aspiration with staining for iron to exclude causes of anaemia other than chronic inflammation (table 2). Patients with laboratory signs of increased haemolysis or without stainable bone marrow haemosiderin were not accepted for the study.

The following measurements were performed weekly: haemoglobin, packed cell volume, reticulocyte and white blood cell counts, platelets, serum creatinine, serum potassium, C reactive protein, erythrocyte sedimentation rate, and haptoglobin, all measured according to standard clinical laboratory procedures. The

same evaluation was carried out every other week during the six weeks after treatment with recombinant human erythropoietin was discontinued.

Serum erythropoietin was measured before the start of treatment, weekly during the treatment period, and every other week during the following six weeks after discontinuing treatment with recombinant human erythropoietin. Serum erythropoietin was measured using a previously reported radioimmunoassay method.²⁵ The detection limit is 0.5 IU/l, and the mean erythropoietin level in normal subjects is 6.7 IU/l (reference range 3.3–13.5 IU/l).

Statistics

Student's *t* test was used for statistical evaluation of the arithmetic data and the one factorial ANOVA repeated measures test was used to evaluate repeated measurements. Linear correlation analysis of data was used as indicated.

Results

The mean (SD) haemoglobin concentration for the whole group was 93.1 (8.4) g/l before treatment and 116.3 (10.1) g/l after five weeks of treatment with recombinant human erythropoietin ($p < 0.001$). The mean (SD) packed cell volume increased during this period from 0.29 (0.028) to 0.36 (0.021) ($p < 0.001$), and the reticulocyte count increased significantly ($p < 0.05$) (fig 1). Nine of the 11 patients responded to treatment with an increase in haemoglobin of more than 15 g/l, and in four patients the recombinant human erythropoietin dose was reduced according to the treatment schedule. The reduction in the recombinant human erythropoietin dose was associated with a minor decrease of the haemoglobin concentration and reticulocyte count (fig 1). The two patients with renal insufficiency due to secondary amyloidosis responded, despite active inflammation; haemoglobin increased from 98 to 130 and from 75 to 117 g/l respectively (fig 2). Figure 3 shows the individual haemoglobin curves of the nine patients with normal kidney function. Seven of these patients responded

Figure 1 Haemoglobin, packed cell volume, and reticulocyte counts in 11 patients with inflammatory arthritides during and after treatment with recombinant human erythropoietin. The data are presented as mean (SD) values. The *p* values were calculated by one factorial ANOVA. The treatment period with recombinant human erythropoietin is indicated.

Figure 2 Individual haemoglobin curves for two patients with anaemia of mixed aetiology due to chronic inflammatory arthritides and renal insufficiency (amyloidosis) during and after treatment with recombinant human erythropoietin. The treatment period with recombinant human erythropoietin is indicated.

Figure 3 Individual haemoglobin curves for nine patients with anaemia due to rheumatoid arthritis during and six weeks after treatment with recombinant human erythropoietin. The treatment period with recombinant human erythropoietin is indicated. The non-responders are indicated by broken lines.

with an increase in haemoglobin concentration of more than 15 g/l, whereas two showed no response. One of the non-responders had an increase in the reticulocyte count to 8% during the fifth week of treatment.

The two non-responders (patients 4 and 6) had high inflammatory activity with a high erythrocyte sedimentation rate (62 and 94 mm/hour) and a high C reactive protein concentration (111 and 170 mg/l). Both patients had clinically active polyarthritis with Ritchie index scores of 20 and 14 respectively.

All patients were monitored every other week for six weeks after discontinuing treatment with recombinant human erythropoietin. Six weeks after the end of treatment, the mean haemoglobin and packed cell volumes were still significantly higher than before treatment ($p < 0.001$ and $p < 0.01$ respectively). There were significant reductions in the reticulocyte counts and packed cell volumes, however, but no significant decrease in the haemoglobin levels (fig 1). The haemoglobin level fell to the pretreatment level in only one patient (fig 3). No significant difference was observed in the mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, serum iron, serum ferritin, nor serum transferrin before and after the recombinant human erythropoietin treatment period in responders and non-responders.

The mean (SD) serum concentration of erythropoietin before treatment was 19.5 (11.6) IU/l (range 6.1–43). Four patients had a serum erythropoietin concentration within the reference range for normal subjects, two just above this range, and five patients had serum erythropoietin concentrations greater than 20 IU/l (table 3). One of the patients with the highest serum erythropoietin concentration (37.9 IU/l) did not respond to treatment with recombinant human erythropoietin, and the other non-responder had a serum erythropoietin

concentration of 17.3 IU/l. There was no significant correlation between the initial serum erythropoietin concentrations and the response of haemoglobin ($r = 0.5$; $p < 0.11$) or packed cell volume ($r = 0.4$; $p < 0.19$).

No adverse events could be attributed directly to the treatment with recombinant human erythropoietin. One patient (patient 2) had increased shoulder pain but did not require increased doses of analgesics. Three patients (patients 3, 4, and 8) were receiving antihypertensive drugs when the study began. None of these patients required additional antihypertensive treatment during the study. Furthermore, blood pressure did not increase in any of the normotensive patients during the study. The recombinant human erythropoietin injections were well tolerated and six of the patients gave the subcutaneous injections themselves after instructions from a nurse.

Neither the inflammatory activity, as measured by C reactive protein and haptoglobin levels or the Ritchie index, nor functional capacity according to Steinbrocker changed significantly during the study. Subjective symptoms in the form of morning stiffness and degree of joint pain during movements or at rest or night were not influenced by the treatment with recombinant human erythropoietin. C reactive protein increased in six patients, decreased in four and was unchanged in one patient (table 3). There was a significant difference in the erythrocyte sedimentation rate before and after six weeks of treatment with recombinant human erythropoietin ($p < 0.01$). The erythrocyte sedimentation rate decreased in ten patients and remained unchanged in one patient. This effect on the erythrocyte sedimentation rate did not correlate to other laboratory variables of inflammation or disease activity, nor to the increase in haemoglobin or packed cell volume.

The patients' need of daily rest decreased slightly ($p < 0.05$) during treatment with recombinant human erythropoietin by an average of 42 minutes or from 1.8 (1.0) (range 0–3) hours to 1.1 (0.9) (0–3) hours. Furthermore, there was a significant improvement in the patients' subjective general condition ($p < 0.01$), graded on a five grade visual analogue scale from 3.0 (1.3) (range 2–5) to 2.0 (1.5) (1–5).

Eight patients had initial serum ferritin concentrations of less than 250 µg/l and were treated by mouth with iron (100 mg/day). Two of these eight patients were non-responders.

Discussion

Anaemia in chronic inflammation is generally moderate. It is often difficult to evaluate the role of anaemia with respect to the well being of the patient. The inflammatory disease itself entails general fatigue and, as many patients with inflammatory arthritides have a limited functional capacity due to joint pain and disfigurement, the cardiovascular system is not tested by physical activities. Many doctors, however, have noticed an improvement in general well being when successful treatment of anaemia has been provided, even when there

has been no change in the activity of the inflammatory disease. It therefore seems worthwhile to test the possibility of increasing the haemoglobin level in patients with anaemia in chronic inflammation. In this study we have shown that recombinant human erythropoietin induced a haematological response with an increase in haemoglobin of more than 15 g/l in nine of 11 arthritic patients receiving various disease modifying drugs.

Human recombinant erythropoietin has proved effective in treating anaemia in patients with renal insufficiency and reports of responses in patients with anaemia due to RA have been published. Means *et al* reported two patients who responded to recombinant human erythropoietin.¹⁷ One of the patients had an iron deficiency before the start of the study and the other became iron depleted after eight weeks of treatment with recombinant human erythropoietin, despite treatment with iron (II) sulphate. After discontinuing the recombinant human erythropoietin treatment, the patients' packed cell volume decreased. Tauchi *et al* also reported a successful response to recombinant human erythropoietin treatment in two patients who had not previously been treated with cytotoxic drugs.¹⁶ Pincus *et al* reported the treatment with recombinant human erythropoietin of 17 patients with active RA receiving NSAIDs. All patients were also treated with iron by mouth. In the blind part of the study (eight weeks) four of the patients (4/13) reached the treatment goal (increase in packed cell volume >0.06) and, in the open part of the study, all patients (11/11) achieved this definition of response. Pincus *et al* did not report the laboratory disease activity of their patients.¹⁸ Takashina *et al* reported that four of six patients with active RA responded to treatment with recombinant human erythropoietin.¹⁹ In two of the four responders, the haemoglobin concentrations decreased after treatment with recombinant human erythropoietin was discontinued.¹⁹ Whether Takashina *et al* treated the patients with iron by mouth is not mentioned. In all these studies, recombinant human erythropoietin was given intravenously three times a week. Our patients were treated with subcutaneous injections five times a week. Six of the patients were able to give the injections themselves. The five patients who did not inject themselves had practical obstacles due to poor manual function and one patient had poor vision due to cataracts. Self treatment reduces health care costs and inconvenience to the patients.

Patients with anaemia due to RA may have a blunted or adequate serum erythropoietin response.⁹⁻¹⁴ Even if serum erythropoietin levels are adequate as regards the degree of anaemia, however, further increases in the erythropoietin concentration may be necessary to overcome the inhibition of erythropoiesis induced by inflammatory mediators such as interleukin 1 and tumour necrosis factor α .²⁶⁻²⁷ Our patient group is too limited to evaluate whether or not the initial serum erythropoietin level has any effect on the response to recombinant human erythropoietin. We found no

correlation between the initial serum erythropoietin levels and the relative increase in haemoglobin during recombinant human erythropoietin treatment. The two patients with renal and inflammatory anaemia showed the most dramatic response, indicating that recombinant human erythropoietin treatment is effective in this mixed type of anaemia despite active inflammation.

The fact that serum ferritin did not change significantly during the study indicates that the amount of iron that was absorbed was used for haemoglobin production.

In previous reports, no follow up periods have been included, but Means *et al*¹⁷ and Takashina *et al*¹⁹ reported a decrease in haemoglobin or packed cell volume after discontinuing recombinant human erythropoietin treatment. In our study, the haemoglobin response lasted several weeks after stopping recombinant human erythropoietin treatment, though the reticulocyte count decreased significantly (fig 1). This finding indicates a normal erythrocyte lifespan despite inflammation; increased haemolysis seems to be of minor importance in the aetiology of anaemia in chronic inflammation. At the end of the treatment period, the mean (SD) haemoglobin level was 114.7 (11.9) g/l, and at the six week follow up the mean (SD) haemoglobin was 106.6 (13.2), still significantly higher ($p < 0.01$) than before treatment. Thus anaemia in RA may be treated with intermittent periods of recombinant human erythropoietin injections.

No significant difference was observed in disease activity or functional capacity before and after recombinant human erythropoietin treatment, but the need for daily rest decreased and the patients' subjective estimation of their general condition improved significantly during the study. Four of the responders have chosen to restart treatment with recombinant human erythropoietin.

In conclusion, we have found that patients with anaemia due to chronic inflammatory arthritides respond to treatment with moderate doses of subcutaneous recombinant human erythropoietin and that the treatment is safe. Many patients are capable of giving the subcutaneous injections themselves.

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- 1 Strandberg O. Anaemia in rheumatoid arthritis. *Acta Med Scand* 1966; 180 (suppl 454): 7-153.
- 2 Miller R K, Altz-Smith M. Usefulness of serum ferritin in detecting iron deficiency in rheumatoid arthritis. *Arthritis Rheum* 1982; 25 (suppl): 114.
- 3 Mowat A G. Hematologic abnormalities in rheumatoid arthritis. *Semin Arthritis Rheum* 1971; 1: 195-219.
- 4 Cavill I, Bentley D P. Erythropoiesis in the anemia of rheumatoid arthritis. *Br J Haematol* 1982; 50: 583-90.
- 5 Bentley D P, Cavill I, Ricketts C, *et al*. A method for the investigation of reticuloendothelial iron kinetics in man. *Br J Haematol* 1979; 43: 619-24.
- 6 Cartwright G E. The anaemia of chronic disorders. *Semin Hematol* 1966; 3: 351-75.
- 7 Konijn A M, Hershko C. Ferritin synthesis in inflammation I. Mechanism of impaired iron release. *Br J Haematol* 1977; 37: 7-15.
- 8 Bentley D P, Williams P. Serum ferritin concentrations as an index of iron stores in rheumatoid arthritis. *J Clin Pathol* 1974; 27: 786-90.

- 9 Bear A N, Dessypris E N, Goldwasser E, Krantz S B. Blunted erythropoietin response to anaemia in rheumatoid arthritis. *Br J Haematol* 1987; **66**: 559–64.
- 10 Hochberg M C, Arnold C M, Hogans B B, Spivak J L. Serum immunoreactive erythropoietin in rheumatoid arthritis: impaired response to anemia. *Arthritis Rheum* 1988; **31**: 1318–21.
- 11 Vreugdenhil G, Löwenberg B, van Eijk H G, Swaak A J G. Anemia of chronic disease in rheumatoid arthritis. Raised serum interleukin-6 (IL-6) levels and effects of IL-6 and anti-IL-6 on in vitro erythropoiesis. *Rheumatol Int* 1990; **10**: 127–30.
- 12 Birgegård G, Hällgren R, Caro J. Serum erythropoietin in rheumatoid arthritis and other inflammatory arthritides: relationship to anaemia and the effect of anti-inflammatory treatment. *Br J Haematol* 1987; **65**: 479–83.
- 13 Erslev A J, Caro J, Miller O, Silver R. Plasma erythropoietin in health and disease. *Ann Clin Lab Sci* 1980; **10**: 250–9.
- 14 Nielsen O J, Andersen L S, Ludwigsen E, *et al*. Anemia of rheumatoid arthritis. *Ann Rheum Dis* 1990; **49**: 349–53.
- 15 Eschbach J W, Adamson J W. Anemia of end-stage renal disease (ESRD). *Kidney Int* 1985; **28**: 1–5.
- 16 Tauchi T, Ohyashiki J H, Fujieda H, Lin K-Y, Ohyashiki K, Toyama. Correction of anaemia in rheumatoid arthritis by recombinant human erythropoietin [letter]. *Br J Rheumatol* 1990; **29**: 235–6.
- 17 Means R T, Olsen N J, Krantz S B, *et al*. Treatment of anemia of rheumatoid arthritis with recombinant human erythropoietin: clinical and in vitro studies. *Arthritis Rheum* 1989; **32**: 638–42.
- 18 Pincus T, Olsen N J, Russell I J, *et al*. Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. *Am J Med* 1990; **89**: 161–8.
- 19 Takashina N, Kondo H, Kashiwazaki S. Suppressed serum erythropoietin response to anemia and the efficacy of recombinant erythropoietin in anemia of rheumatoid arthritis. *J Rheumatol* 1990; **17**: 885–7.
- 20 Arnett F C, Edworthy S M, Bloch D A, *et al*. The American Rheumatism Association 1987. Revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; **31**: 315–24.
- 21 Bennet P H, Wood P H N. In: Bennet P H, Wood P H N, eds. *Population studies of the rheumatic diseases*. Amsterdam: Excerpta Medica, 1968: 456–7.
- 22 Stone W J, Graber S E, Krantz S B, *et al*. Treatment of the anemia of pre-dialysis patients with recombinant human erythropoietin. *Am J Med Sci* 1988; **296**: 171–9.
- 23 Ritchie D M, Boyle J A, McInnes J M, *et al*. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; **37**: 393–406.
- 24 Steinbrocker O, Traeger C H, Batterman R C. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; **140**: 659–64.
- 25 Wide L, Bengtsson C, Birgegård G. Circadian rhythm of erythropoietin in human serum. *Br J Haematol* 1989; **72**: 85–90.
- 26 Maury C P J, Andersson L C, Teppo A M, Partanen S, Juvonen E. Mechanisms of anemia in rheumatoid arthritis: demonstration of raised interleukin-1 β concentrations in anemic patients and of interleukin-1 mediated suppression of normal erythropoiesis and proliferation of human erythroleukemia (HEL) cells in vitro. *Ann Rheum Dis* 1988; **47**: 972–87.
- 27 Roodman G D. Mechanisms of erythroid suppression in anemia of chronic disease. *Blood Cells* 1987; **13**: 171–84.