Study of erythropoietin in treatment of anaemia in patients with rheumatoid arthritis

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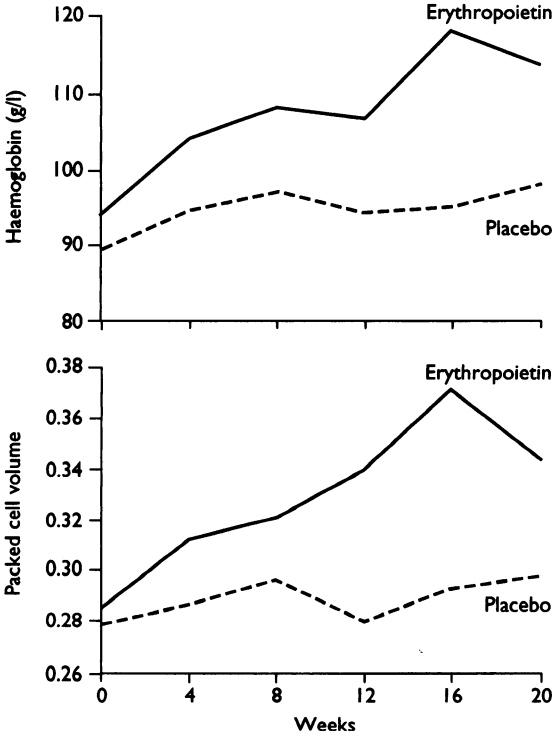
Anaemia often occurs in patients with rheumatoid arthritis, and its cause is often multifactorial. The effect of erythropoietin on such anaemia is controversial, and evidence exists that cytokines may affect haemopoiesis, possibly by affecting sensitivity to erythropoietin.[1-3] We assessed the therapeutic efficacy of human recombinant erythropoietin in the anaemia of chronic disease in rheumatoid arthritis in a randomised, double blind, placebo controlled study over 20 weeks.

Patients and methods

Twenty patients with definite rheumatoid arthritis and aged 42-75 were enrolled in the study; they were randomly allocated to erythropoietin (10) and placebo (10). Patients had been receiving a stable dose of second line drug treatment for at least 12 weeks. No patients were taking cytotoxic drugs or steroids. Entry into the study required a baseline haemoglobin concentration of <100 g/l (mean of three readings in the month before entry). Iron deficiency was excluded and all patients were given oral iron supplements. One patient with iron deficiency was enrolled in error and was withdrawn. Human recombinant erythropoietin and matching placebo (saline) were supplied in blinded phials. The drug or placebo was injected subcutaneously twice a week for 20 weeks, starting at 40 U/kg (patients 1-10) and 100 U/kg (patients 11-20). The dosage was reviewed every four weeks and increased if the rise in haemoglobin concentration was <10 g/l per four weeks.



Top: Median haemoglobin concentrations for each group in study. The difference in concentration between the groups was significant at 20 weeks (P=0·02 (95% confidence interval 0·1 to 3·5); Mann-Whitney U test). Bottom: Median packed cell volume values for each group in study. The difference between the groups was significant at 20 weeks (P=0·001 (0·005 to 0·108); Mann-Whitney U test)

Results

No significant difference existed between the group receiving erythropoietin and the group receiving placebo in terms of age (median 59 (range 42-75) and 61·5 (44-69) respectively). Two patients withdrew from the group receiving erythropoietin. The doses of drug varied from 40 U/kg to 300 U/kg; no patients needed a reduction. One patient developed an occlusion of the retinal vein (in week 11, when his haemoglobin concentration was 115 g/l and packed cell volume 0·352 and he was receiving 40 U/kg erythropoietin).

No significant change occurred in either group in white cell count, platelet count, C reactive protein concentration, rheumatoid factor, blood pressure, visual analogue pain score, Ritchie articular index, duration of morning stiffness, or Stanford health assessment questionnaire score during the study; no differences occurred between the groups for these variables except systolic blood pressure at week 0 ($P=0·04$, Mann-Whitney U test). A significant fall in the erythrocyte sedimentation rate occurred only in the group receiving erythropoietin ($P=0·008$, Wilcoxon's matched pairs test). A significant negative correlation existed between haemoglobin concentration and erythrocyte sedimentation rate ($r=-0·49$, $P=0·0031$, Spearman's rank coefficient). The Nottingham health profile score for energy improved significantly in the group receiving erythropoietin between weeks 0 and 20 ($P=0·028$, Wilcoxon's test). Haemoglobin concentration and packed cell volume increased only in patients receiving erythropoietin (figure).

Comment

This study shows that human recombinant erythropoietin corrects secondary anaemia and results in a clinical improvement in patients with rheumatoid arthritis. In contrast with previous studies of erythropoietin in patients with rheumatoid arthritis,[4,5] this study included patients with active disease and receiving modifying treatment—that is, patients in whom persistent anaemia is most difficult to treat. Erythropoietin given twice a week was sufficient for an adequate therapeutic response, giving an increase in haemoglobin by week 4. The fall in erythrocyte sedimentation rate in the group receiving erythropoietin may reflect correction of anaemia as a significant negative correlation existed between the haemoglobin concentration and the erythrocyte sedimentation rate. It is difficult, however, to exclude a modifying effect on the disease of erythropoietin as a trend also existed towards improvement in the group receiving erythropoietin in the values for C reactive protein concentration, visual analogue pain score, and platelet count, although this was not significant. While the expense of human recombinant erythropoietin may limit its clinical use, it may be useful in patients with rheumatoid arthritis undergoing elective surgery or in

patients starting second line drug treatment who require faster correction of their anaemia than would be achieved by the modifying effect on the disease of such drugs.

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Simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in patients with normal lungs

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Two clinical trials in the 1960s led to opposing recommendations for initial management of spontaneous pneumothorax,[1,2] and the debate has continued since. Recently, simple aspiration has gained favour as a more acceptable procedure for patients and doctors.[3,4] We conducted a randomised comparison of simple aspiration with intercostal drainage to assess acceptability and outcome at one year.

Subjects, methods, and results

Patients who presented with spontaneous pneumothorax and whom the admitting team thought required a drainage procedure were randomly allocated to either simple aspiration or intercostal drainage. Patients with signs of a tension pneumothorax or with lung disease other than previous pneumothorax were excluded.

Simple aspiration was undertaken by inserting a 16-18 gauge catheter under local anaesthetic and aspirating air through a three way tap with the exit tube under water. The procedure was continued until no more air could be aspirated, the patient became uncomfortable, or a maximum of three litres had been removed. Intercostal drainage was managed according to the participating physician's usual practice. No sclerosing drugs were allowed with either technique.

Patients completed symptom score charts indicating the degree of pain experienced during drainage and throughout their hospital admission. Patients were reviewed at one and 12 months, and recurrence of pneumothorax or referral for thoracic surgery was recorded. The size of pneumothorax in presenting radiographs was graded (see table).

Both groups were similar with respect to age, sex, height, weight, smoking history, lung function, and history of pneumothorax (table). There were no significant differences between the two groups in either the size or side of pneumothorax. No difference was reported in pain experienced while undergoing drainage, but those treated by intercostal drainage experienced significantly more pain during their hospital admission and spent an average of two days longer in hospital (table).

In all 28 out of 35 aspirations were successful, although five patients required two aspirations. The remaining seven patients were subsequently treated by intercostal drainage. None of them had a recurrence or required pleurectomy within one year. The amount of air aspirated during the first aspiration was significantly different in successful and unsuccessful aspirations (successful 1·59 (SD 0·72) *v* unsuccessful 2·52 (0·91) l; $P<0·01$). A logistic regression model found no significant associations with failed aspiration. In particular, there was no association with a history of pneumothorax or initial radiographic appearances. No significant differences were found in the recurrence rate at one year, but more patients who had intercostal drainage required pleurectomy than those patients who had had aspiration ($P=0·02$).

Comment

Simple aspiration is a simple and safe procedure and should be the initial treatment of choice for patients with normal lungs who present with a spontaneous pneumothorax, irrespective of its size. This study has shown that aspiration is less painful than intercostal drainage, leads to a shorter admission, and reduces the need for pleurectomy with no increase in recurrence rate at one year.

As a result of this study, and after consultation with over 150 British respiratory physicians and thoracic

Characteristics and clinical details of patients having aspiration or intercostal drainage for pneumothorax. Values are means (SD) unless stated otherwise

	Aspiration (n=35)	Intercostal drain (n=38)	P value
Age (years)	34·6 (15·0)	34·6 (13·1)	0·8
Sex (M/F)	28/7	29/9	0·92
Height (m)	1·79 (0·11) (n=32)	1·76 (0·09) (n=31)	0·81
Weight (kg)	64·8 (9·2) (n=31)	63·6 (11·0) (n=37)	0·65
Smoking history (pack years)	8·09 (9·32) (n=34)	7·94 (9·16) (n=38)	0·95
Previous pneumothorax	6	8	0·90
% Of predicted FEV_1 after one month	94·5 (25·7) (n=16)	97·3 (17·1) (n=20)	0·70
Radiographic appearances:			
Left side pneumothorax	13 (n=30)	12 (n=32)	0·83
Size of pneumothorax:			
Small rim	3	1	0·054
Partial collapse	16	12	
Complete collapse	10 (n=29)	18 (n=31)	
Clinical details:			
Pain score during procedure	0·9 (0·9)	1·1 (0·9)	0·33
Average daily pain score	0·7 (0·7)	1·5 (0·6)	<0·001
Total pain score	2·7 (3·3)	6·7 (3·6)	<0·001
Hospital stay (days):			
Mean (SD)	3·2 (2·9)	5·3 (3·6)	0·005
Median	2	4·5	
No having pleurectomy within 1 year	0	7	0·02
No of recurrences	5 (n=30)	10 (n=35)	0·40

FEV_1=Forced expiratory volume in one second.