Effect of recombinant human erythropoietin on anaemia and disease activity in patients with rheumatoid arthritis and anaemia of chronic disease: a randomised placebo controlled double blind 52 weeks clinical trial

H R M Peeters, M Jongen-Lavrencic, G Vreugdenhil, A J G Swaak

Abstract

Objective—To study whether recombinant human erythropoietin (r-hu-Epo) improves anaemia and reduces disease activity in patients with rheumatoid arthritis and anaemia of chronic disease (ACD).

Methods—A 52 week placebo controlled randomised double blind trial with r-hu-Epo was performed in 70 patients with active rheumatoid arthritis and ACD. Thirty four patients were treated with 240 U kg⁻¹ r-hu-Epo subcutaneously, initially three doses weekly, while 36 patients received placebo.

Results—A significant increase of haemoglobin from a median of 112 to 135 g litre⁻¹ occurred in the Epo group within six weeks and could be sustained with reduced doses (median 240 U kg⁻¹ once weekly). Sustained benefit compared to placebo was also apparent by six weeks for disease activity, as indicated by the Paulus 20% response rate. Of patients in the Epo group, 32% eventually showed a Paulus 20% response, compared to 8% of the placebo group (P = 0.016). Significant differences in favour of the Epo group were also observed in the secondary disease activity measures Ritchie index, number of swollen joints, pain score, ESR, and patients’ global assessment of disease activity. C reactive protein concentrations did not change significantly.

Conclusions—Treatment of ACD in rheumatoid arthritis with r-hu-Epo is effective in restoring normal haemoglobin levels and also exerts a beneficial effect on disease activity.


Anaemia often occurs in patients with rheumatoid arthritis.¹ Anaemia of chronic disease (ACD) is the most important cause of anaemia in this condition.² It is characterised by low serum iron concentrations despite normal or increased body iron stores.³–⁵ The pathogenesis of ACD in rheumatoid arthritis is multifactorial.⁶ Iron retention by the mononuclear phagocyte system (MPS) and impaired iron transport to the erythroid blast have been described.⁷ Suppression of erythropoiesis by inflammatory cytokines, such as interleukin-1 (IL-1), tumour necrosis factor α (TNF-α), and γ interferon, has been shown in vitro.⁸ In addition, evidence has been provided for a relatively impaired production of erythropoietin in response to anaemia. Serum erythropoietin concentrations in ACD are lower than in other anaemic conditions⁹–¹⁰ and IL-1 and TNF-α have been shown to suppress hypoxia related erythropoietin production by HepG2 and Hep3b cell line in vitro.¹¹–¹²

In a number of studies treatment with r-hu-Epo resulted in improvement of ACD in rheumatoid arthritis patients.¹³–²⁰ However, higher doses of human recombinant erythropoietin (r-hu-Epo) were required to maintain the haematological response than in renal disease.²¹ In one open pilot study with r-hu-Epo, a decrease in both pain score and swollen and painful joint count was observed, indicating possible beneficial effects on disease activity as well.²² In the five other open and two controlled clinical studies only slight, or no, effects on disease activity were observed, although an improvement in general wellbeing was reported in several instances.²³–²⁶ These studies were of short duration (2–24 weeks) and involved only a limited number of patients (2–20). We conducted a 52 week placebo controlled randomised double blind trial with r-hu-Epo as adjuvant treatment in patients with active rheumatoid arthritis and ACD to investigate the effects of long term treatment with r-hu-Epo on haematological indices as well as on clinical and serological measures of disease activity.

Methods

Patients

Patients aged 18 years or older were eligible if they met the revised American College of Rheumatology (ACR) criteria for rheumatoid arthritis²⁸ and were classified in functional class I, II, or III.²⁹ Active disease was required, defined as a minimum of nine swollen joints and a Ritchie score of 9. Treatment with the following disease modifying antirheumatic drugs was allowed, provided the dose was stable for three months before the start of the trial: oral gold, hydroxychloroquine, D-penicillamine, sulphasalazine, and methotrexate. Parenteral gold salts were allowed if the dose was stable for at least six months. Patients receiving azathioprine, cyclophosphamide, or cyclosporin were excluded. Treatment with corticosteroids, equivalent to an average

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maximum daily dosage of 10 mg prednisone, was allowed if dosage had not been changed the last month before entry to the trial.

Anaemia of chronic disease for a minimum duration of three months had to be present in all patients. Haemoglobin concentrations below 117 g litre\(^{-1}\) (for both males and females) were required without signs of vitamin and iron deficiency, blood loss, haemolysis, or other haematological disorder. Body iron stores were assessed preferably by iron staining of bone marrow smears. A semiquantitative scale was used: 0 = no stainable iron; 0 - 1 = minimal to very small amount; 2 = slight small and patchy content; 3 or more = increased stainable iron. Patients with a stainable iron content of 2 or more were considered not to be iron deficient.\(^{16}\) When patients did not agree with bone marrow aspiration, serum ferritin levels should be above 50 mg litre\(^{-1}\) and serum transferrin levels below 50 mmol litre\(^{-1}\).\(^{13}\)

Further exclusion criteria were: history of thromboembolic events or epileptic fits, uncontrolled hypertension, and clinically relevant impairment of kidney or liver function.

All patients gave their informed consent for the trial, which was approved by the institutional ethics committee.

**TREATMENT**

The study was a 52 week randomised double blinded placebo controlled parallel clinical study. Disease activity measures were assessed by the first observer (RP), who remained blinded for treatment schedules and laboratory results. Randomisation of the patients, control of adverse events and laboratory results, and administration of the study medication was done by a second independent observer (MJ).

The treatment group received r-hu-Epo (Recormon, Boehringer Mannheim) at a dose of 240 U kg\(^{-1}\) subcutaneously (sc), initially three times a week. The aim of the treatment was a normal Hb level (female > 117; male > 136 g litre\(^{-1}\)) and the dose was adjusted accordingly by changing the frequency of administration. The placebo group received a visually similar placebo. After randomisation, patients in the placebo group were matched with patients in the treatment group and followed their treatment regime with respect to frequency of administration. Oral iron supplementation was given if serum ferritin fell below 50 mg litre\(^{-1}\), and was discontinued upon iron repletion. Adjustment of the dose of disease modifying antirheumatic drugs or prednisone, as well as local measures, particularly intra-articular corticosteroid injections, was not allowed during the study.

**ASSESSMENTS**

Patients were evaluated every two weeks for three months and monthly afterwards until week 52.

**Primary assessments**

Effects of treatment of anaemia were evaluated using haemoglobin (Hb). As primary disease activity measure the clinical response in individual patients was analysed using a modified Paulus index.\(^{18}\) According to this composite index, patients are considered to show a significant clinical response if at least four out of six variables (Ritchie index, number of swollen joints, duration of morning stiffness, both patients’ and observers’ assessment of disease activity, and erythrocyte sedimentation rate (ESR)) improve. As our secondary disease activity measures did not include an observer’s global assessment of disease activity, the Paulus response was evaluated using the other five variables. Patients had to show simultaneous improvement of these five variables in order to fulfil the criteria for a 20% Paulus response. Improvement was defined by a 20% decrease in the continuous variables and a 40% decrease in the patients global assessment of disease activity (1-10 scale) (or 20% in case of baseline value below 4.0).

**Secondary assessments**

As secondary evaluation criteria a core set of single measures of disease activity endorsed by the ACR\(^{17}\) was used. Besides the Ritchie index, the number of swollen joints, patients’ global assessment, and Westergen ESR, this includes a pain score (1-10) and C reactive protein concentrations. Serum ferritin was assessed on every visit as the primary marker for iron status and as a guideline for iron suppletion.

**STATISTICAL PROCEDURES**

Data from the patient files were transferred to software packages (SPSS 5.01 and Egret) for statistical analysis. All variables were checked for their suitability for standard statistical analysis. In case of non-parametric distribution a transformation towards normality was tried.

At baseline, groups were compared using Student’s t test, the Mann-Whitney test, and the \(\chi^2\) test where appropriate. The repeated measurements of continuous outcome variables in the two groups were analysed by analysis of variance for repeated measurements (MANOVA) using weeks 0 (baseline), 6, 12, 24,36, and 52 as time points. The overall effect of treatment was tested for significance using the F test on the interaction between the two patient groups and the repeated measurements factor time. In case of significance, differences between the groups at individual time points were investigated with Bonferroni correction for multiple testing. Overall treatment effects on the Paulus 20% response rate were evaluated using logistic regression with random effects. Groups were compared at individual points of follow up using Fischer’s exact tests.

Analysis was done on the basis of intention to treat as well as on completers. Both methods led to the same results except for slight differences in the Paulus 20% response rate. Results of the intention to treat analysis are shown and end point differences in Paulus response described separately.

**Results**

**PATIENTS**

Seventy patients were enrolled in the study, 34 receiving r-hu-Epo (Epo group) and 36 receiv-
Recombinant human erythropoietin in rheumatoid arthritis

No significant differences in demographic and disease characteristics between the treatment groups were found (Table 1). Baseline haemoglobin concentrations were the same in the two groups (Table 1). In 51 patients the diagnosis of anaemia of chronic disease was made by iron staining of bone marrow smears, while in the remaining 19 patients iron deficiency was ruled out using serum ferritin and transferrin levels. Fifty patients completed the study. Five patients withdrew from the Epo group (after a median period of 24 weeks) because of high disease activity and in two because of poor compliance. Seven patients withdrew from the placebo group (after a median of 16 weeks), five for reasons of high disease activity and two because of poor compliance. Injections of r-hu-Epo were tolerated well. No local reactions or other serious side effects were observed. None of the patients, including those patients already being treated with antihypertensive drugs before the start of the trial, showed a significant rise in blood pressure. No thromboembolic complications were observed.

### PRIMARY ASSESSMENTS

The Epo group showed significantly higher haemoglobin concentrations during treatment (Figure 1, panel A). A statistically significant increase in Hb occurred within six weeks and could be sustained during entire follow up period. At the end of follow up the Epo group showed a median Hb of 134 (range 110 to 158 g litre⁻¹), compared to 112 (86-128 g litre⁻¹) in the placebo group. After a median of six weeks (range 2 to 24) the dose of r-hu-Epo could be decreased in 90% of responders to an eventual median of one injection (range 0.5 to 2) of 240 U kg⁻¹ weekly at the end of follow up. Of 34 patients in the Epo group, 32 (94%) achieved a normal Hb during follow up, compared to eight out of 36 (22%) of placebo treated patients. The first of the two non-responders initially showed a rise in Hb from 98 g litre⁻¹ at baseline to 118 g litre⁻¹ at week 8, but consequently fell back to 98 g litre⁻¹ again without responding to an increase of the weekly dosage to four times 240 U kg⁻¹. The other non-responder showed no response of Hb at all, despite increasing dosages of rh-h-Epo. In both patients no other causes of anaemia besides ACD were diagnosed. The first patient used sulphasalazine, while the second patient was treated with hydroxychloroquine.

A Paulus 20% response was observed significantly more often in patients of the Epo group, compared to patients of the placebo group (Figure 1, panel B). This effect occurred within six weeks of treatment and could be sustained throughout follow up. Of all patients treated with rh-h-Epo 22% achieved a Paulus 20% response at the end of their follow up compared to 8% in placebo group. For those patients completing 52 weeks these percentages were respectively 38% and 8%.

### SECONDARY ASSESSMENTS

Compared to the placebo group, significant improvements were observed in Ritchie articular index, the number of swollen joints, patients' global assessment of disease activity, and pain score in the Epo group (Table 2). The changes within time in these variables were similar to those in the primary outcome measures, with sustained improvement in the Epo group reached within six weeks (Ritchie index and swollen joint count) or 12 weeks (patient assessment and pain). ESR showed a rapid decline in the Epo group, reaching its lowest level during weeks 6-12, and then increased again but remained significantly lower than in the placebo group (Table 2). C reactive protein concentrations levels did not change significantly in either of the treatment groups (Table 2).

An overall difference in ferritin concentrations between the two treatment groups was observed (Table 2). Ferritin showed a fast and steep decline in the Epo group during the first phase of the trial. Iron supplementation proved necessary in 88% of Epo treated patients, predominantly in the first period of r-hu-Epo treatment (after a median of four weeks). In 77% of these patients it was later possible to discontinue iron supplementation. The duration of treatment with iron supplements was a median of eight weeks. During the later stage of the trial, serum ferritin concentrations remained significantly lower in the Epo group compared to baseline or to the placebo group.

### Discussion

Our results suggest that in patients with active rheumatoid arthritis and well classified ACD, r-hu-Epo is effective in restoring normal Hb concentrations as well as reducing rheumatic disease activity. Sustained benefit compared to placebo was apparent by six weeks for both Hb concentrations and the primary measures of disease activity. Normalisation of Hb was achieved in 94% of treated patients. At the end of follow up 32% of the patients in the Epo group fulfilled the criteria for a Paulus 20% response, compared to 8% of the placebo treated patients. Significant differences in favour of the treatment group were also observed in the secondary outcome measures: Ritchie index, number of swollen joints, pain

### Table 1 Baseline characteristics of the two treatment groups. Data are presented as median (5th to 95th centile) or number (percentage).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Female (%)</td>
<td>27 (79%)</td>
<td>31 (86%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (23/79)</td>
<td>58 (39/75)</td>
</tr>
<tr>
<td>Haemoglobin (g litre⁻¹): All</td>
<td>111 (93-116)</td>
<td>113 (101-106)</td>
</tr>
<tr>
<td>Female</td>
<td>109 (93-116)</td>
<td>113 (101-106)</td>
</tr>
<tr>
<td>Male</td>
<td>114 (107-116)</td>
<td>114 (113-116)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3.5 (0.3/21)</td>
<td>4.7 (0.3/32)</td>
</tr>
<tr>
<td>Positive rheumatoid factor (%)</td>
<td>18 (53%)</td>
<td>21 (58%)</td>
</tr>
<tr>
<td>Erode joint damage (%)</td>
<td>29 (85%)</td>
<td>28 (78%)</td>
</tr>
<tr>
<td>No of patients using DMARD (%)</td>
<td>23 (68%)</td>
<td>27 (75%)</td>
</tr>
<tr>
<td>% of patients using methotrexate</td>
<td>3 (9%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>No of patients using prednisone (%)</td>
<td>3 (9%)</td>
<td>6 (17%)</td>
</tr>
</tbody>
</table>

Epo, erythropoietin; DMARD, disease modifying antirheumatic drugs
score, ESR, and patients' global assessment of disease activity. C reactive protein concentrations did not change significantly. Normal levels of Hb could be sustained with reduced dosage of r-hu-Epo in most patients, and concomitant iron suppletion proved only temporarily necessary during the induction of the haematological response.

The observed response of Hb during r-hu-Epo treatment was comparable with previous clinical studies with r-hu-Epo in rheumatoid arthritis and ACD. As in the present study, dosage of r-hu-Epo could be reduced in responders, although the maintenance dosage of r-hu-Epo varied considerably between patients. Although an initially higher dosage of r-hu-Epo was used in the present study than in previous clinical trials, the eventual maintenance dosage did not differ significantly.

A modified Paulus index was used as a primary measure of disease activity. The observed frequency of a Paulus 20% response in 8% of all controls is comparable with the observed responses in 3-12% of control patients in previous trials. Significant bias due to the modification of the Paulus criterion seems unlikely. The occurrence of a Paulus 20% response in 32% of all r-hu-Epo treated patients is comparable with results of controlled studies with several of the now widely used disease modifying antirheumatic drugs. The fall of ESR in the Epo treated patients may reflect correction of anaemia. However, one cannot exclude the possibility that the changes in ESR are partially related to changes in disease activity as well. In the later stage of the trial a rise in ESR was observed without significant concomitant changes in Hb levels, suggesting the possible role of other factors involved in the ESR. The other secondary disease activity measures used in the Paulus index are not clearly influenced by correction of anaemia and all show significant improvement in the Epo treated patients. Therefore the differences in 20% Paulus response between the two treatment groups should be considered to reflect the

### Table 2 Course of secondary disease activity measures and serum ferritin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Follow up</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Week 6</td>
</tr>
<tr>
<td>Ritchie articular index (0-81)</td>
<td>Epo</td>
<td>26 (10 to 43)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>31 (17 to 44)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>30 (10 to 43)</td>
<td>0.002</td>
</tr>
<tr>
<td>Swollen joints (number 0-52)</td>
<td>Epo</td>
<td>28 (13 to 34)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>29 (17 to 37)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>18 (7 to 31)</td>
<td>0.003</td>
</tr>
<tr>
<td>Patients' global assessment (VAS score 0-10)</td>
<td>Epo</td>
<td>4.4 (2.5 to 6.0)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4.3 (2.0 to 7.0)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>3.8 (1.0 to 6.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Pain (VAS score 0-10)</td>
<td>Epo</td>
<td>5.0 (2.0 to 8.0)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>5.0 (2.0 to 8.0)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>4.5 (1.0 to 7.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>ESR (mm h⁻¹)</td>
<td>Epo</td>
<td>56 (25 to 110)</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>44 (15 to 110)</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>45 (17 to 110)</td>
<td>0.035</td>
</tr>
<tr>
<td>CRP (mg l⁻¹)</td>
<td>Epo</td>
<td>28 (2 to 101)</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>19 (2 to 66)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>23 (2 to 84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum ferritin (µg l⁻¹)</td>
<td>Epo</td>
<td>93 (28 to 402)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>79 (25 to 241)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>27 (23 to 200)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (25th to 75th centile). No significant differences between groups were found at baseline. CI, confidence interval. Statistics: Overall effect of treatment (P value on the interaction between groups and time) and between-group comparison at individual time points (95% CI and P values: *P < 0.05, **P < 0.01, ***P < 0.001) calculated with analysis of variance for repeated measurements (MANOVA).
improvement of disease activity in Epo treated patients. It is not clear why C reactive protein concentrations did not change despite the observed clinical response. However, the relation between disease activity and the acute phase response is not fully understood yet. A subset of rheumatoid arthritis patients has been described in whom disease progresses clinically without an increase in C reactive protein and ESR. Non-steroidal antiinflammatory drugs fail to lower C reactive protein, although they reduce inflammatory activity. Recently oral corticosteroids were reported to decrease rheumatoid disease activity and the progression of joint destruction without effect on acute phase response. Independent development of erosions, clinical symptoms, and the acute phase response was observed, though the separate control mechanisms have not yet been identified. One should consider the possibility that r-hu-Epo may exert beneficial effects on disease activity without decreasing C reactive protein levels. However, the mechanisms for this action still remain unclear.

Comparison of the observed clinical effects with previous trials with r-hu-Epo in rheumatoid arthritis is made difficult, since a similar measure of disease activity was not used. Two studies were placebo controlled double blind studies, but comprised considerably fewer patients (17 and 20 respectively). Pincus and coworkers measured pain score and a health assessment questionnaire (HAQ) and found no differences between r-hu-Epo treated patients and controls. Patients receiving disease modifying antirheumatic drugs were excluded and r-hu-Epo was given intravenously (three times a week at 50-150 U kg⁻¹). Murphy et al evaluated pain score, Ritchie index, duration of morning stiffness, HAQ score, and C reactive protein and observed a trend towards improvement in pain score and C reactive protein but not the other variables.

Three of the open label studies examined more than 10 patients. Swaak et al described a statistically significant reduction in number of swollen joint, Ritchie index, pain score, and duration of morning stiffness in 10 patients treated for nine weeks. Güdbjörnsson et al required patients to have active disease and observed a reduction of the Ritchie index in seven of 10 patients within six weeks, although the mean Ritchie index of the entire group did not improve significantly. Functional capacity, duration of morning stiffness, and joint pain did not change. Pettersson et al evaluated joint pain, morning stiffness and a joint score in 11 patients without finding any effect. However, an improvement in general wellbeing was described by most workers even in the absence of clinical improvement. As in the present study, a decrease of ESR, but not of C reactive protein was observed in most studies.

Thus indications for a possible effect of r-hu-Epo on disease activity were found in previous studies. A similar improvement of disease activity—as observed in the present study—in patients with rheumatoid arthritis has not been described before. Considerable differences in number and selection of patients, dosage of r-hu-Epo, duration of treatment, and concomitant iron supplementation, as well as disease activity measures used, could perhaps account for these differences in observed clinical responses to r-hu-Epo.

Several mechanisms can explain the beneficial effects of r-hu-Epo. Treatment with r-hu-Epo increases iron turnover, which is mobilised from storage elsewhere in the body and transferred to the bone marrow to fulfil the enhanced requirements of stimulated erythropoiesis. Deposition of iron in synovial tissue was found to be increased in rheumatoid arthritis. This has been associated with persistent joint inflammation in rheumatoid arthritis, since iron catalyses the generation of toxic oxygen radicals, stimulates DNA synthesis in synovial cells, and has an additive effect on the activity of human cytokines for proliferation of synovial cells. Iron supplementation has been associated with exacerbation of synovial inflammation in rheumatoid arthritis patients, whereas iron chelators caused a rapid decrease in body iron storage and an improvement in clinical disease activity. In the present study an equally rapid decrease in body iron stores and rheumatic disease activity was observed, which is in agreement with the assumption that iron availability in synovial tissue could account for the observed improvement in disease activity during r-hu-Epo treatment.

In addition to effects on iron deposition, modulating effects of r-hu-Epo on the immune system cannot be ruled out entirely. Erythropoietin has been found to regulate IgE production in vitro by T cell and monocyte dependent mechanisms. In renal patients treated with r-hu-Epo, an improvement in T cell function has been described. To what extent these observations are associated with the beneficial clinical effects of r-hu-Epo in rheumatoid arthritis in the present study remains to be established. A randomised study of the effects of rhu-Epo and blood transfusion on both the immune system and clinical disease activity might be helpful in elucidating the way of action of r-hu-Epo.

The clinical use of r-hu-Epo may be limited by its expense. Furthermore, one can argue whether ACD should be treated in rheumatoid arthritis patients, as it is usually mild. However, ACD is a frequent manifestation in rheumatoid arthritis, and in our study treatment of this typically mild anaemia with r-hu-Epo had a beneficial effect. Furthermore, no side effect of r-hu-Epo was observed in the present study, which might result in an important improvement of the quality of life of rheumatoid arthritis patients, which is considered to be a major aim of treatment. Therefore further research on the effects of r-hu-Epo on quality of life in relation to its costs—as compared to standard regimens—is required to elucidate the value of r-hu-Epo in the treatment of rheumatoid arthritis and ACD. Other patient groups, like anaemic patients undergoing surgery or anaemic patients starting with slow acting second line drugs, still require further studies.

In summary, our study is the first randomised placebo controlled long term study with r-huEpo in which effects on
anemia as well as on disease activity were studied extensively and adequately in a large number of patients with active rheumatic disease and anemia of chronic disease. Rapid normalisation of HB occurred in the majority of patients. Parallel to the response of HB, a rapid and sustained improvement in disease activity was observed. The results of this trial suggest that r-hu-Epo might serve as a useful addition to the therapeutic armamentarium in rheumatoid arthritis patients with active disease and ACD.

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