Effect of Recombinant Human Erythropoietin and Intravenous Iron on Anemia and Disease Activity in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate whether treatment of anemia of chronic disease (ACD) in patients with rheumatoid arthritis (RA) with recombinant human erythropoietin (rHu-Epo) in combination with intravenous (IV) iron influences health related quality of life (HRQoL) and clinical outcome including disease activity.

Methods. Thirty patients with ACD and RA were treated with 150 IU/kg rHu-Epo twice weekly for 12 weeks. As well, in case of functional iron deficiency 200 mg of iron-sucrose per week was given intravenously. Vitality and fatigue as dimensions of HRQoL were evaluated by the vitality subscale of the Short Form-36 (SF-36-VT) and the Multidimensional Assessment of Fatigue (MAF). Muscle strength was measured by the Muscle Strength Index.

Results. All 28 patients completing the study responded to treatment; 23/28 patients developed functional iron deficiency and received IV iron (mean absolute dose 710 ± 560 mg). Average hemoglobin concentration increased from 10.7 ± 1.1 to 13.2 ± 1.0 g/dl after a mean treatment period of 8.7 ± 2.3 weeks. Muscle strength increased from 43.5 ± 11.2 to 49.1 ± 12.9 and SF-36-VT from 28.2% ± 14.3% to 47.1% ± 20.8%, while fatigue decreased (MAF from 34.7 ± 9.3 to 25.0 ± 11.3). Among the disease activity variables the number of swollen/tender joints, erythrocyte sedimentation rate, Disease Activity Score, and RA Disease Activity Index improved significantly during treatment.

Conclusion. Treatment of ACD in RA patients with rHu-Epo and IV iron is safe and effective in correction of anemia, increases muscle strength, improves vitality, and lowers fatigue. In addition we observed a reduction of disease activity. (J Rheumatol 2001;28:2430–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANEMIA RECOMBINANT ERYTHROPOIETIN IRON HEALTH RELATED QUALITY OF LIFE DISEASE ACTIVITY

The anemia of chronic disease (ACD) occurs in association with chronic inflammatory, neoplastic, or infectious processes. ACD is the most frequent extraarticular manifestation of rheumatoid arthritis (RA). Excluding other causes of anemia such as iron deficiency, ACD occurs in 20 to 50% of patients with RA[1-4]. Typically, ACD is mild to moderate[1-4]. In studies conducted since the first successful treatment of 2 RA patients with human recombinant erythropoietin (rHu-Epo) in 1989[5], rHu-Epo has proved successful in improving anemia in patients with RA and ACD. However, in nearly every study nonresponders to treatment have been observed, ranging from 6 to 80% of the patients receiving rHu-Epo, although even higher doses of rHu-Epo were used in RA anemia compared to renal anemia[5-14]. Limited responsiveness to rHu-Epo in renal anemia in the majority of patients is caused by functional iron deficiency. It has been shown that adequate iron supply can reduce the mean rHu-Epo requirement by up to 70%, for example in patients undergoing dialysis[15,16]. While oral iron administration frequently has not been sufficient, supplementation with intravenous (IV) iron saccharate in addition to rHu-Epo has proven to be effective, economical, and safe in patients with renal anemia[17]. Since IV iron dextran treatment resulted in flares of RA in some studies[18,19], iron was regarded as a potential proinflammatory agent. Thus iron chelators such as desferrioxamine and L1 have been tested as potential antiinflammatory drugs in RA[20-22]. IV iron supplementation during treatment with rHu-Epo in patients with RA has not been investigated, to our knowledge. In only a single small study of 11 patients with RA undergoing major orthopedic surgery, IV iron saccharate was given in addition to rHu-Epo to assist autologous blood donation[23]. No adverse effects on the activity of the rheumatic disease were reported.

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In many chronic disease states, including RA, health related quality of life (HRQoL) has become a major goal of treatment, and correction of anemia may be an important issue for that purpose. Although improvement in general well being has been observed in studies with rHu-Epo in RA[8-10,12,13], the clinical usefulness of this cost intensive treatment remains a matter of debate. Presently there are few clinical data concerning HRQoL in patients with RA undergoing treatment with rHu-Epo.

We evaluated HRQoL measures during rHu-Epo treatment of patients with RA and ACD. The frequency of functional iron deficiency induced by rHu-Epo treatment was recorded, as well as the effect of IV iron substitution on correction of anemia and RA disease activity. Finally, followup of HRQoL and disease activity indicators after discontinuation of rHu-EPO treatment was carried out for 3 months to monitor the duration of the observed clinical effects.

MATERIALS AND METHODS

Study design and patients. The investigation was carried out as an open 24 week single center study with a maximum treatment period of 12 weeks. Thirty consecutive patients with RA (revised American College of Rheumatology criteria[24]) fulfilling the inclusion criteria were enrolled (Table 1). All patients gave informed consent for participation in this trial, which was approved by the local institutional ethics committee.

ACD with hemoglobin concentrations < 12.0 g/dl for women and < 13.0 g/dl for men had to be present for at least 2 months. Other causes of anemia such as blood loss and iron, folate and vitamin B12 deficiency or hemolysis were excluded. Continuation of current treatment with disease modifying antirheumatic drugs (DMARD) was allowed if the dosage was stable for at least 3 months before the study. Baseline characteristics of patients are presented in Table 1.

Treatment. Patients were treated with 150 IU/kg rHu-Epo (Recormon®, Boehringer Mannheim, Mannheim, Germany) subcutaneously twice weekly for a maximum of 12 weeks. Treatment with rHu-Epo was stopped when hemoglobin concentrations increased above 13 g/dl for female and 14 g/dl for male patients. In case of functional iron deficiency patients additionally received 200 mg iron-sucrose (Ferrum Vitis®, Aschau, Germany) IV per week. Functional iron deficiency was defined by at least 2 out of 3 of the following measures: serum ferritin < 50 μg/l, saturation of total iron binding capacity (TIBC) < 15%, hypochromic red cells > 10%. Treatment with disease modifying drugs and steroids was continued at a stable dose during the study (Table 1). Intraarticular injections of steroids were not allowed 3 months before, during, and 3 months after the end of rHu-EPO treatment.

Data collection. Patients were evaluated every 2 weeks during treatment period and monthly for 3 months after the end of rHu-Epo treatment. A blood sample was taken at every visit. Blood pressure was measured every 2 weeks, a complete physical examination was carried out at monthly intervals. Muscle strength and vitality/fatigue as primary assessments of the study were measured monthly. All other measures of clinical outcome, disease activity, and HRQoL were evaluated before and at the end of the treatment period, and at the end of the study.

Laboratory assessments. Laboratory evaluation included complete blood cell counts and additionally counts of hypochromic red cells and reticulocyte count, serum iron, serum ferritin, and saturation of TIBC every 2 weeks, and monthly measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum erythropoietin level, rheumatoid factor (RF), and routine serum chemistry.

Clinical measures. Muscle strength was measured monthly by the Muscle Strength Index (MSI). The MSI is a disease-specific instrument developed in 1993 for patients with RA. Isometric measurement of flexion and extension of knee and elbow obtained with a hand-held pull gauge is aggregated into the MSI as percentage of a reference population of RA patients[25-27]. Disease activity was monitored by the Disease Activity Score (DAS) and the RA Disease Activity Index (RADAI). We used the DAS calculated by the number of swollen (SJC) and tender joints (TJC) of 28 joints and ESR[28]. The RADAI is a patient derived self-administered questionnaire. Patients rate the activity of their arthritis in general, their joint tenderness and swelling, their arthritis pain in general and in different joint areas, and the duration of morning stiffness[29,30].

Measurement of HRQoL. Short Form-36-Vitality Subscale (SF-36-VT): The SF-36 is a generic instrument widely used to measure aspects of HRQoL by a self-administered questionnaire[31]. The SF-36 is validated for many different disease states including RA[32,33]. It consists of 8 subscales that can be aggregated in 2 summary scales (physical component and mental component) or evaluated separately. SF-36-VT was chosen as the primary assessment for monthly evaluation of energy/fatigue.

Multidimensional Assessment of Fatigue (MAF): The MAF is a disease-specific self-administered questionnaire of 16 items concerning 4 dimensions of fatigue (severity, distress, timing, degree of interference in activities of daily living) and is scored from 0 (no fatigue) to 50 points (very severe fatigue)[34]. We used a recently developed German version of the MAF.

For measurement of physical function we used the Health Assessment Questionnaire (HAQ), which evaluates functional disability concerning activities of daily living[35,36].

Data analysis and statistics. We used SPSS for Windows v. 5.0 statistical software. Changes in variables were examined with the nonparametric Wilcoxon matched-pairs signed rank test. All results are given as mean ± standard deviation.

RESULTS

Thirty patients (27 women, 3 men; age range 22–77 yrs) were enrolled in the study. Baseline characteristics of patients are shown in Table 1.

The median hemoglobin (Hb) concentration at baseline was 10.7 g/dl (range 7.2–12.4). Twenty-two patients received DMARD, 8 patients were DMARD–naive during the study. Twenty-seven patients were treated with low dose steroids (range 5–20 mg/day prednisolone). Twenty-eight of 30 patients completed the treatment and followup period. Two patients withdrew from the trial due to vitritis in Week 4 (Patient 1) and rupture of a Baker's cyst in Week 5 (Patient 16) requiring surgical treatment.

Laboratory assessments. All 28 patients completing the study responded to treatment. Hb concentration increased to normal values (> 13 g/dl women, > 14 g/dl men) or showed an increase of ≥ 2 g/dl during the treatment period. In 22 of the 28 patients treatment with rHu-Epo could be terminated prior to Week 12 due to faster normalization of Hb concentration. The mean treatment period was 8.7 ± 2.3 weeks. Hb increased from 10.7 ± 1.1 to 13.2 ± 1.0 g/dl during treatment with rHu-Epo. During the first month of treatment the mean increase of Hb was 1.35 ± 0.8 g/dl. There were no significant differences concerning response to treatment for different subsets of patients in comparison with the whole study population. The subgroup of patients with initial Hb ≤

Table 1. Baseline characteristics of patient population.

Patient	Age, yrs	Sex	Disease Duration, yrs	DMARD	Steroids, mg PDN	RF	Hb, g/dl	IV Iron, g
1	60	F	27	MTX	15	–	7.4	–
2	60	F	2	—	5	–	9.7	0.8
3	60	F	13	—	15	+	10.7	–
4	38	F	23	—	6	–	10.1	1.6
5	73	F	4	—	7.5	+	12.1	–
6	61	F	9	MTX	20	+	7.2	2.4
7	66	F	16	MTX	15	+	10.6	1.4
8	55	F	7	MTX	5	–	11.8	0.8
9	68	F	4	MTX	7.5	–	12.1	0.2
10	58	M	16	MTX	7.5	+	11.5	0.4
11	62	M	9	MTX	10	+	12.2	1.2
12	56	F	3	MTX/SSZ	10	+	10.9	0.8
13	60	M	19	CSA	6	+	12.4	–
14	40	F	10	SSZ	5	–	9.7	1.2
15	65	F	7	—	5	+	9.8	0.4
16	45	F	1	MTX	10	+	11.2	1.0
17	35	F	14	MTX	10	+	10.2	0.6
18	38	F	1	AZA/SSZ	–	–	11.5	0.8
19	77	F	4	SSZ	5	+	10.8	–
20	58	F	50	MTX	10	–	10.1	1.2
21	65	F	2	SSZ	12.5	+	10.5	1.0
22	36	F	12	MTX	–	+	10.1	1.0
23	31	F	1	AZA	10	–	11.2	0.4
24	25	F	2	HCQ	5	–	11.2	1.0
25	74	F	4	MTX	5	–	10.8	0.8
26	28	F	4	SSZ	2.5	–	11.9	0.4
27	48	F	13	MTX/SSZ	5	+	11.4	0.4
28	55	F	6	—	12.5	+	10.1	–
29	72	F	24	—	10	–	9.6	0.6
30	22	F	1	SSZ	–	–	10.5	0.4
Mean	53		10		9		10.6	0.7
Range	22–77		1–50		0–20		7.2–12.4	0–2.4

MTX: methotrexate, SSZ: sulfasalazine, CSA: cyclosporine A, AZA: azathioprine, HCQ: hydroxychloroquine.

10 g/dl (n = 5) showed a rapid increase of Hb of 1.96 ± 0.6 g/dl after 4 weeks of treatment. Those without DMARD treatment (n = 7) responded to rHu-Epo with a Hb increase of 1.8 ± 0.8 g/dl after 4 weeks.

Twenty-three of 28 patients (82%) developed functional iron deficiency after 4.5 ± 2.7 weeks and therefore received IV iron at a mean absolute dose of 710 ± 560 mg of ferric iron (Table 1). After termination of rHu-Epo treatment, Hb decreased in the followup period to 12.6 ± 0.9 g/dl after one month and 11.6 ± 1.1 g/dl three months after the end of treatment (Figure 1). ESR decreased from 35.1 ± 20.1 to 19.3 ± 17.3 mm/h during treatment ($p < 0.001$), whereas CRP was only slightly reduced from 2.70 ± 2.5 to 2.55 ± 2.3 mg/dl (Table 2).

Clinical assessments. As shown in Figure 2 muscle strength improved by an increase of MSI from 43.5 ± 11.2% to 49.1 ± 12.9% ($p < 0.001$). After termination of treatment it decreased again towards baseline.

Disease activity variables are summarized in Table 2. The DAS, as well as the swollen and tender joint count in particular, showed a highly significant reduction during treatment with rHu-EPO ± parenteral iron. The patient derived RADAI also decreased significantly during treatment.

Health related quality of life. The improvement of the primary HRQoL assessments, the MAF and SF-36-VT, are illustrated in Figures 3 and 4. The increase of vitality during rHu-Epo treatment is shown by a change of SF-36-VT from 28.2 ± 14.3% to 47.1 ± 20.8% ($p < 0.001$). Three months after the end of the treatment period it decreased again to 36.0 ± 18.9%. MAF decreased from 34.7 ± 9.3 to 25.0 ± 11.3 ($p < 0.001$) at the end of treatment and increased again towards baseline during followup (Figure 4).

In addition we observed a statistically nonsignificant increase of physical function evaluated by the HAQ, which was reduced from 1.85 ± 0.97 at baseline to 1.71 ± 1.03 at the end of treatment with rHu-Epo ($p = 0.051$).

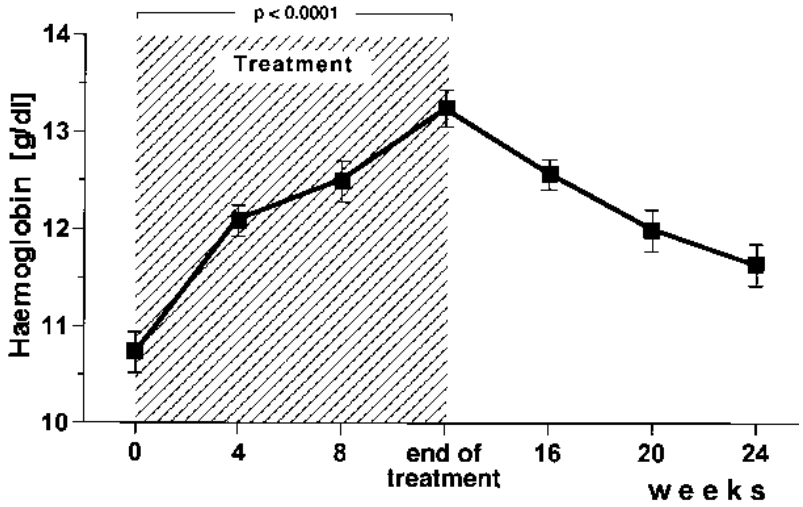

Figure 1. Erythropoietic response indicated by increase of Hb during administration of rHu-Epo with iron (shaded area). Data are mean ± SEM in 28 patients with RA. Weeks 12–24 are posttreatment surveillance.

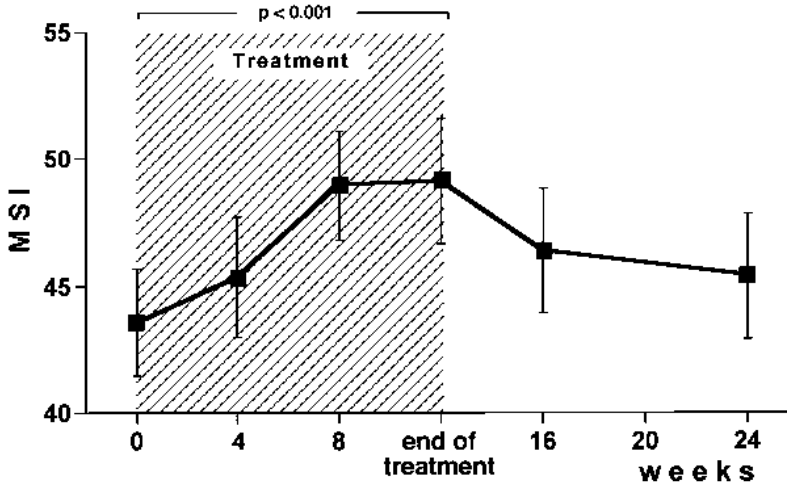

Figure 2. Muscle Strength Index data (percentages, mean ± SEM) of 28 patients with RA who completed the study. Shaded area: treatment with rHu-Epo plus iron. Note the decrease of MSI after termination of treatment.

Table 2. Disease activity variables.

	Baseline	p	End of Treatment	3 Months After Treatment
Disease activity score	5.8 ± 1.2	< 0.001	4.3 ± 1.8	5.3 ± 1.6
Swollen joint count	4.5 ± 3.6	< 0.001	2.4 ± 2.4	3.2 ± 2.9
Tender joint count	8.6 ± 7.8	< 0.001	5.4 ± 7.2	7.4 ± 8.5
ESR, mm/h	35.1 ± 20.1	< 0.001	19.3 ± 17.3	33.3 ± 20.1
RADAI score	5.4 ± 1.9	< 0.01	4.6 ± 2.4	4.9 ± 2.1
CRP, mg/dl	2.70 ± 2.5	0.706	2.55 ± 2.3	2.60 ± 2.3

RADAI: Rheumatoid Arthritis Disease Activity Index.

DISCUSSION

Our data show that recombinant human erythropoietin plus intravenous iron is effective in correcting ACD in patients with inflammatory active RA, and improves various clinical outcome and health related quality of life variables.

In comparison to earlier clinical trials[6-14], nonresponse to treatment was not observed in this study. Analysis of different subsets of patients showed that treatment with DMARD or the grade of anemia had no influence on the response to treatment with rHu-Epo. The reason for the rapid increase of hemoglobin in our study and the lack of nonresponders may be that the development of functional

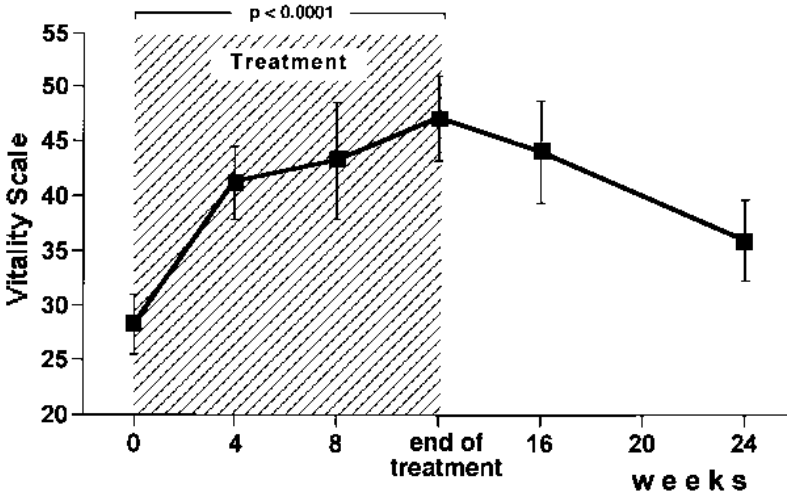

Figure 3. Vitality data from the SF-36 (mean ± SEM) for 28 patients with RA during and after treatment with rHu-Epo plus iron (shaded area).

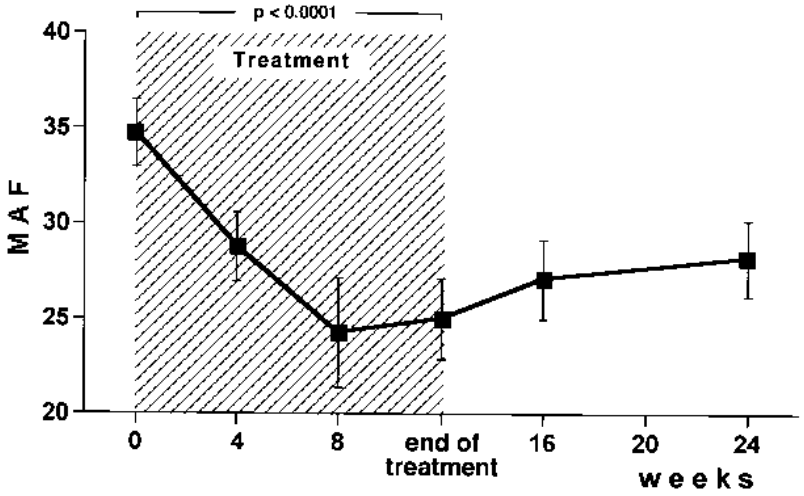

Figure 4. Multidimensional Assessment of Fatigue (MAF) data (mean ± SEM) for 28 patients with RA during and after treatment with rHu-Epo plus iron (shaded area). Note significant decrease of fatigue during treatment.

iron deficiency induced by treatment with rHu-Epo was carefully observed and appropriately corrected by IV iron administration. Functional iron deficiency can be easily detected by measuring serum ferritin in combination with saturation of TIBC and percentage of hypochromic red cells in the peripheral blood. In our study 82% of patients developed functional iron deficiency and therefore received IV iron in a mean cumulative dose of 710 ± 560 mg iron-sucrose. The high incidence of functional iron deficiency in our study seems to be an important feature regarding the effectiveness of rHu-Epo. As in renal anemia[15,16], IV iron supplementation in case of functional iron deficiency obviously is also a prerequisite for an optimal effect of rHu-Epo in ACD, and seems to be the major reason for best suitable hematological response in our study.

Of particular interest is the finding that IV iron, which may be regarded as a potentially proinflammatory agent due to generation of toxic oxygen species, had no proinflammatory effects. Richmond and colleagues described in 1958 a beneficial effect of IV iron saccharate on hemoglobin concentration, functional capacity, and disease activity in anemic patients with RA[37]. In accord with that finding, other authors[38,39] have shown that iron supplementation in anemic RA patients with ACD in combination with frank iron deficiency had no deleterious effects on RA disease activity, while small studies with IV iron dextran resulted in flares of RA after iron administration[18,19]. In the circumstance of functional iron deficiency, supplemented IV iron may be bound in the erythropoietic compartment, thus neutralizing its proinflammatory properties.

As noted, IV iron did not induce flares of RA in this study. In contrast, a significant decrease of several clinical disease activity variables was observed, as shown in Table 2. The observed effects on Hb as well as on disease activity, including failure of CRP normalization, are in close correlation with the data of Peeters and colleagues[13]. In a 52 week placebo controlled, double blind trial a stable correction of the anemia and a significant decrease in disease activity were observed. A modified Paulus index showed a 20% decrease in 8% of the placebo group compared to 32% in the rHu-Epo treated group. Peeters and colleagues explained the observed decrease of disease activity during treatment with rHu-Epo by an equally rapid decrease in body iron stores (serum-ferritin). Thus, reduction of iron availability in inflamed synovial tissue is believed to account for the physical improvement. In contradiction to this assumption, our patients had the same reduction of inflammatory activity, although mean serum-ferritin increased throughout treatment due to IV iron supplementation. We therefore assume an antiinflammatory effect of erythropoietin that could be mediated by the increased number of erythrocytes or an iron independent effect of rHu-Epo on the inflammation.

It is very difficult to compare the effects of rHu-Epo treatment on HRQoL and clinical outcome variables observed in our study with those of the published studies, because inclusion criteria as well as the chosen variables of HRQoL and clinical outcome do differ considerably. In particular, Hb concentration, disease activity, and the co-treatment (DMARD, steroids) at inclusion may influence the possibility of observing significant clinical effects.

Pincus and coworkers[6], for example, studied only RA patients (n = 35) taking no corticosteroid or DMARD treatment and observed no significant clinical effect (score for activities of daily living and VAS for pain) during 8 weeks of rHu-Epo treatment. Murphy, *et al*[12] included only patients with Hb concentrations < 10.0 g/dl, who were allowed to take DMARD, but corticosteroids were forbidden. The Nottingham health profile score for energy was used in this study as the indicator of changes in HRQoL, and significant improvement could be observed. Gudbjörnsson, *et al*[9] reported a therapeutic trial with 250 IU/kg rHu-Epo given subcutaneously per week in 10 patients with inflammatory active RA and one with active ankylosing spondylitis. A reduction of Ritchie index in 7 of 10 RA patients was observed within 6 weeks. In addition patients' need for daily rest decreased and patients' subjective general condition improved significantly. In another Swedish open label trial with 12 RA patients[10] most participants subjectively reported an increase in general well being. In addition to the above described clinical effects, Peeters, *et al*[13,40] observed a correlation between a rating scale measure of utility derived HRQoL and the disease activity.

While improvement of ACD with rHu-Epo treatment in RA patients taking appropriate iron supplement seems to be sufficiently proven, the effect of treatment of ACD on HRQoL and clinical outcome still requires more evidence. It was the major goal of our study to focus on this aspect of rHu-Epo treatment in ACD. As ACD in RA is mostly mild to moderate, we also included patients with only slightly reduced Hb concentration.

Muscle strength, measured by the MSI, has been shown to correlate with self-reported physical functional disability in RA, measured by HAQ. On the other hand muscle strength is associated with the Hb concentration[26]. We therefore chose the MSI to investigate the influence of rHu-Epo on this objective clinical outcome variable. However, the change in muscle strength we observed, did not translate into a significant increase of the HAQ, which was most probably due to the short mean treatment period of 8.7 weeks. Indeed, the HAQ showed a slight reduction, similar to the initial effects after start of a new DMARD therapy with MTX or SASP[41].

To measure HRQoL we selected the vitality subscale of SF-36 as a generic instrument and the Multidimensional Assessment of Fatigue for disease-specific primary assessment. Addressing the anemic state, fatigue is the most commonly reported symptom, which has an important effect on HRQoL[42]. As shown by the significant decrease of the MAF fatigue score and the concomitant increase in vitality in our study, correction of the anemia in RA obviously has a remarkable benefit on HRQoL in patients with mild anemia. We observed a rapid improvement of all measures of HRQoL and clinical outcome. After discontinuation of rHu-Epo all beneficial effects concerning HRQoL, clinical outcome, and disease activity declined rapidly. As shown by Peeters, *et al* maintenance therapy over 52 weeks can sustain the clinical and hematological response to treatment[13]. The optimal treatment schedule for effective and economical maintance therapy needs further investigation.

Anemia of chronic disease in RA can be successfully treated by recombinant human erythropoietin. The additional supplementation of IV iron in case of functional iron deficiency is safe and economical and ensures an optimal hematological response. Despite its cost rHu-Epo may find a place in the therapy of RA due to the increase of health related quality of life and the beneficial effects on disease activity.

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