The effects of recombinant human erythropoietin on autologous blood donation in rheumatoid arthritis patients with anaemia

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Abstract

Objectives

The effect of recombinant human erythropoietin (rHuEPO) treatment on autologous blood donation was evaluated in anaemic patients with rheumatoid arthritis (RA) undergoing total joint replacement surgery.

Methods

A total of 56 total knee or hip joint replacement operations were performed in the knee or hip joint in 36 anaemic RA patients (hemoglobin (Hb) concentration < 11.0 g/dl]. All of the patients received intravenous rHuEPO at a dose of 100 - 200 units/kg body weight three times a week for 3 weeks. An autologous blood donation of 800 - 1200 g was the goal for each patient. A refractory case was defined as a patient whose Hb level did not increase to 10.0 g/dl after 3 weeks of treatment with rHuEPO. The objective signs of arthritis were assessed by the Lansbury activity index (AI). During the treatment period, the patients underwent weekly hematological analyses, including routine hematology, serum iron, serum ferritin, C-reactive protein (CRP), and serum erythropoietin levels.

Results

The response to rHuEPO treatment was determined, and blood donation was possible in 47 of 56 joint replacements. In the other 9 operations, donation was not possible due to a poor response to rHuEPO. The mean Hb level before treatment in the refractory group (8.3 g/dl) was significantly lower than that in the responsive group (10.4 g/dl, p = 0.0002). During the treatment period, the mean erythropoietin level was above the normal limit in the refractory group. The mean AI for the refractory group tended to be lower than that in the responsive group. The mean pre-treatment CRP (6.4 mg/dl) and erythrocyte sedimentation rate (ESR) (87.1 mm/h) levels in the refractory group were significantly higher than those in the responsive group (CRP: 3.2 mg/dl, p = 0.008, ESR: 52.6 mm/h, p = 0.01).

Conclusions

The control of disease activity prior to rHuEPO treatment is considered to a prerequisite for autologous blood donation. In addition, severe anaemia (Hb concentration < 8.0 g/dl) appears to be another risk factor for refractoriness to rHuEPO treatment with the present protocol. A higher rHuEPO dose (> 200 units/kg/3 times a week for three weeks) was considered to be necessary in the refractory group.

Key words

Erythropoietin, autologous blood storage, rheumatoid arthritis, artificial arthroplasty.

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Introduction

Autologous blood transfusion has been widely utilized in patients who undergo elective orthopaedic surgery in order to avoid the side effects of allogeneic blood transfusion (such as viral infection and graft versus host disease) (1-3). Due to the existence of pre-operative anaemia, however, a considerable percentage of patients with rheumatoid arthritis (RA) require allogeneic blood transfusion when they undergo joint replacement surgery. Autologous blood donation using recombinant human erythropoietin (rHuEPO) has recently been reported to be effective in patients who have anaemia together with the characteristics of chronic inflammatory disease (4). A preliminary evaluation of the effectiveness of rHuEPO on autologous blood donation in RA patients scheduled to undergo surgery revealed that those with severe anaemia were likely to show a poor response to rHuEPO treatment (5).

The aim of the present study was to evaluate clinical factors correlating to the effectiveness of rHuEPO on autologous blood donation in RA patients in order to identify an efficient protocol for the administration of rHuEPO to RA patients with anaemia.

Patients and methods

Patients

This series consisted of 36 patients with RA, 32 women and 4 men, who underwent 56 total joint replacements for the knee or hip joint between September 1992 and August 1996 at Toyama University Hospital. The RA symptoms of all the patients were compatible with the revised criteria of the American Rheumatism Association (6). Their blood hemoglobin (Hb) concentrations were less than 11.0 g/dl on the day of admission, and no renal impairment or indications of gastrointestinal blood loss were noted in any of them. Informed consent for this study was obtained from all patients.

The mean age of the patients was 57.7 years (range: 42-71), and the mean disease duration was 14.3 years (range: 5-34). According to Steinblocker's classification (7), functional impairment was class II in 7 patients, class III in 22, and class IV in 7. The plain radiographic stage assessed by the most severely damaged joint was stage 4 in all patients. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) were performed in 21 and 35 joints, respectively. Twelve patients underwent the Harris non-cement THA procedure in 15 joints, and 3 underwent the Harris pre-coat hip procedure in 6 joints. Twenty-one patients underwent the non-cement Miller-Galante TKA procedure in 35 joints. In all patients undergoing the TKA procedure, a tourniquet was used throughout the operation. The whole donated blood was re-infused to each patient either during the operation or within 24 hours post-operatively.

Administration of recombinant human erythropoietin and iron sulfate

All of the patients received rHuEPO (Chugai Pharmaceutical Co., Tokyo, Japan) intravenously at a dose of 100 - 200 units/kg body weight three times a week for 3 weeks as in-patients at the University Hospital (Fig. 1). The mean total dose of rHuEPO per week was 398.5 units/kg (range: 285 - 642). All patients were administered ferrous sulfate orally 200 mg per day throughout the 3-week treatment period (Fig. 1).

Autologous blood donation

The Hb concentration was measured just before each blood donation. If a patient had a pre-treatment Hb concentration of 10.0 g/dl or more, 200 - 400 g of blood was collected. If the Hb concentration increased to ≈ 10.0 g/dl after the administration of rHuEPO, 200 - 400 g of blood was collected per week. A refractory case was defined as a patient whose Hb concentration was not increased to 10.0 g/dl after the 3-week administration of rHuEPO. The target amounts for blood donation were 800 g and 1200 g for the TKA and THA procedures, respectively. Red blood cells were stored in a mannitol-adenine-phosphate solution (Japanese Red Cross Institute, Tokyo, Japan) at 4˚C for 4 weeks at most. Fresh-frozen plasma was made from whole blood units within 1 hour after collection.

Assessment of the Hb response ratio to rHuEPO

In patients who showed a response to

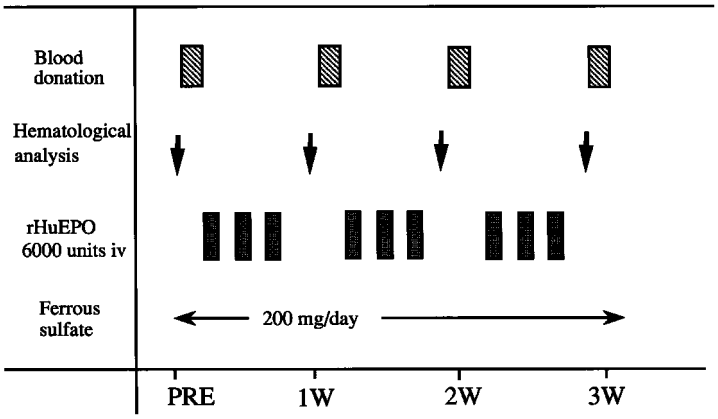

Fig. 1. Protocol for recombinant human erythropoietin administration and blood donation. Recombinant human erythropoietin (rHuEPO) was intravenously administered at a dose of 6,000 units three times a week for three weeks. If the patient's hemoglobin concentration was 10.0 g/dl or more at the pre-treatment examination or during the treatment period, 200 - 400 g of blood per week was collected.

rHuEPO and were able to donate blood, the Hb recovery rate was calculated, as shown below. In the patients who were refractory to rHuEPO, the anaemia recovery rate was calculated as shown in the second formula below:

Hb recovery rate = (post-treatment Hb concentration - estimated Hb concentration) x 100 / estimated Hb concentration

Anaemia recovery rate = (post-treatment Hb concentration - initial Hb concentration) x 100 / initial Hb concentration

Estimated Hb = the pre-treatment Hb concentration - the initial Hb concentration x donated blood volume / 0.06 x body weight (The blood volume was assumed to be 6% of the body weight in this assessment.)

Clinical and laboratory evaluation

The objective signs of active arthritis were assessed by the Lansbury activity index (AI) (8). This evaluation of disease activity was made at the time of admission. During the 3-week rHuEPO treatment period, the patients underwent weekly blood pressure measurements and hematological evaluation before blood donation, including routine hematology, serum iron, serum ferritin, and C-reactive protein (CRP). The serum erythropoietin levels were also measured in several patients before the day of the first rHuEPO administration and then weekly. Hemolytic parameters and the reticulocyte count were not assessed before giving rHuEPO nor during the study. Drugs for the treatment of RA were checked from the charts. Clinical and laboratory data were compared between the group in which blood donation was possible and the group who proved to be refractory to rHuEPO even after 3 weeks of administration.

Statistical analysis

The differences between means were analyzed for significance by Student's t-test with Welch's correction. The significance level was set at $p < 0.05$.

Results

Effectiveness of rHuEPO on autologous blood donation

Of the 56 total joint replacements carried out in 36 patients, a response to the therapy was observed in 47 joint replacements. The average amount of donated blood was 783 g. Among these 47 joint replacement operations, allogeneic blood transfusion could be completely avoided in 42 (89.4%).

In the other 9/56 joint replacements, autologous blood donation was not possible due to a poor response to rHuEPO, and an average of 590 g of allogeneic blood transfusion was required during surgery or post-operatively.

The average dose of rHuEPO given to the responsive group was 359.7 units/kg/week (n = 47), which was not significantly different from that administered to the refractory group (413.5 units/kg/week, n = 9). There was no correlation between the rHuEPO dosage administered and the response to rHuEPO. The clinical characteristics of the two groups were compared as follows.

Age, gender and clinical stage of RA patients

The average age of the refractory group (62.4 years) tended to be older than that of the responsive group (57.0 years, p = 0.10). All of the patients in the refractory group were female. There was no significant relationship between the Steinbrocker class and the response to rHuEPO.

Serial changes of hemoglobin concentration

Before rHuEPO treatment, the mean Hb concentration in the refractory group (8.3 g/dl) was significantly lower than that in the responsive group (10.4 g/dl, p = 0.0002, Fig. 2). Although the mean Hb concentration showed a gradual decrease after autologous blood donation in the responsive group, the concentration remained over 10.0 g/dl. In contrast, in the refractory group the mean Hb concentration showed no significant increase even through no blood was collected. The Hb recovery rate in the responsive group was 41.3 ± 22.6%, while the anaemia recovery rate in the refractory group was -0.04 ± 11.0%. Thus, from the viewpoint of Hb recovery and anaemia recovery, there was a significant difference in the response to rHuEPO between the two groups ($p < 0.00001$).

Serial changes of erythropoietin concentration

The mean baseline erythropoietin level was within the normal range (8 - 30 mU/ml) in both groups. In the responsive group (n = 11), the mean erythropoietin level throughout the treatment was also within the normal range. In contrast, in the refractory group (n = 3), the mean erythropoietin level was above the normal limit during the treatment period (Fig. 3).

Lansbury activity index, CRP, and ESR

Before the treatment, the mean Lansbury Activity Index (AI) for the refractory group (68.0) tended to be lower than that in the responsive group (79.0, p = 0.20). With respect to the relationship between the effectiveness of rHuEPO and the CRP or the erythrocyte sedimentation rate (ESR), the mean pre-treatment CRP (6.4 mg/dl) and ESR (87.1 mm/h) val-

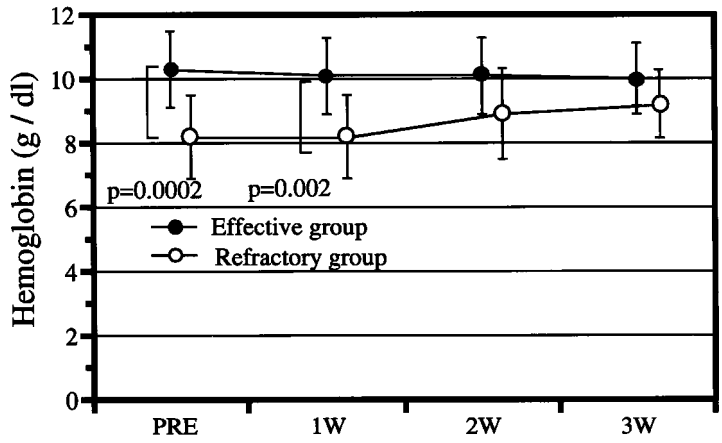

Fig. 2. Serial changes in hemoglobin (Hb) concentration in the responsive group compared with the refractory group. The mean Hb concentration of the responsive group (n = 47) was over 10.0 g/dl during the 3-week treatment period in spite of the blood donation. In the refractory group (n = 9), the mean Hb concentration was significantly lower than that of the responsive group both before treatment and one week after the beginning of treatment. The data represent the mean ± standard deviation.

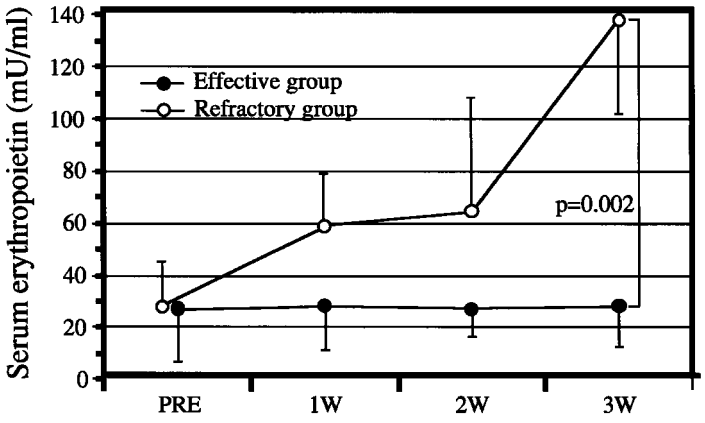

Fig. 3. Serial changes in the serum erythropoietin level in the responsive and refractory groups. The mean erythropoietin level in the responsive group (n = 11) was within the normal range before and during rHuEPO treatment. In the refractory group (n = 3), the mean erythropoietin level was over the upper limit during the treatment. After 3 weeks of treatment, the mean erythropoietin level in the refractory group was significantly higher than that in the responsive group (p = 0.002).

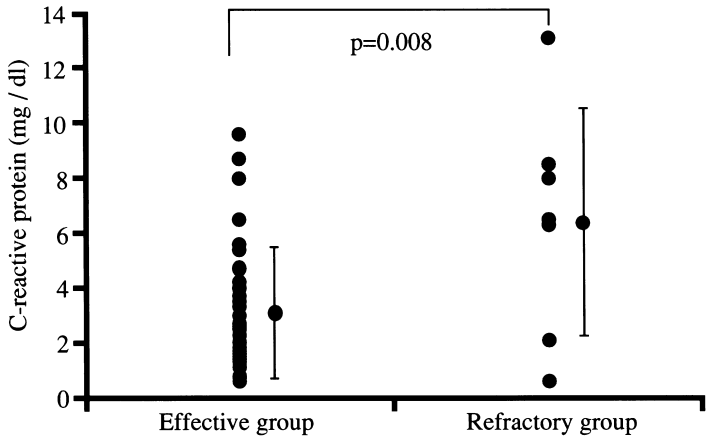

Fig. 4. Comparison of pre-treatment C-reactive protein (CRP) in the responsive group (n = 47) and the refractory group (n = 9). The mean pre-treatment CRP value in the refractory group (6.4 mg/dl) was significantly higher than that in the responsive group (3.2 mg/dl).

ues in the refractory group were significantly higher than those (CRP: 3.2 mg/dl, p = 0.008, ESR: 52.6 mm/h, p = 0.01, Figs. 4 and 5) in the responsive group.

Other laboratory findings

There were no significant differences between the two groups in terms of the red blood cell count, serum iron, or total and unsaturated iron binding capacity before and during treatment. Serum ferritin in the refractory group showed lower values, especially at the first week of treatment ($p < 0.05$), compared with that in the responsive group.

Drugs for the treatment of RA

Thirty-four patients were treated with disease-modifying anti-rheumatic drugs (bucillamine [150-300 mg/day] in 30 patients, auranofin [6 mg/day] in 1, salazosulfapyridine [2-4 g/day] in 1, and actarit [300 mg/day] in 3). Methotrexate (2.5 mg/week) was given orally in one patient and mizoribin (150 mg/day) was given orally in two patients. Patients in the refractory group were not given any specific drugs.

Prednisolone was administered to 2 refractory and 8 responsive patients. The average prednisolone dose was 15,300 mg (n = 2) and 10,485 mg (n = 8) in the refractory and responsive groups, respectively. There were no significant differences in the average dosage between the two groups.

Discussion

The results of the present study indicate that RA patients with anaemia who are refractory to rHuEPO treatment may show elevated pre-treatment CRP and ESR values. The effectiveness of rHuEPO treatment seen with the present protocol was expected to some degree, although the responses seemed to be adversely influenced by the inflammatory activity of the disease. Thus, the control of disease activity before rHuEPO treatment by the introduction or by increasing the dosage of steroids could be beneficial.

In addition, severe anaemia (Hb concentration < 8.0 g/dl) was considered to be another risk factor for refractoriness to rHuEPO treatment with the present protocol. Baer *et al*. (9) found an impaired

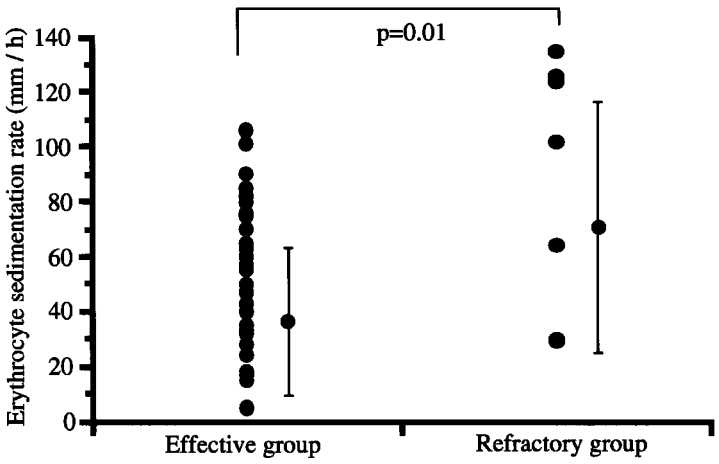

Fig. 5. Comparison of the pre-treatment erythrocyte sedimentation rate (ESR) in the responsive group (n = 47) and the refractory group (n = 9). The mean pre-treatment ESR value in the refractory group (87.1 mm/h) was significantly higher than that in the responsive group (52.6 mm/h).

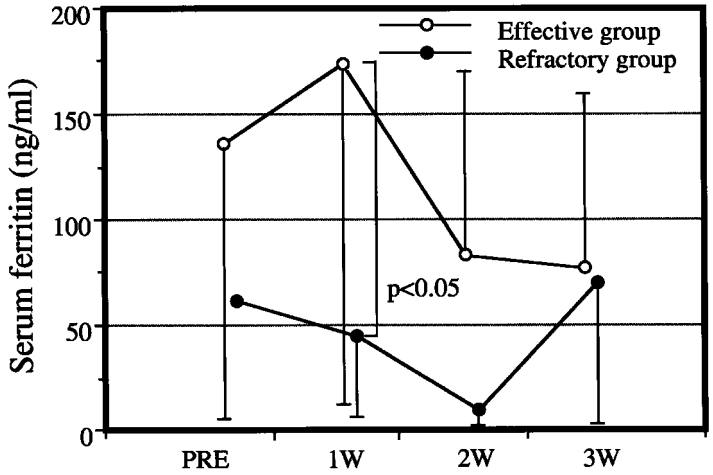

Fig. 6. Serial changes in the serum ferritin level in the responsive group and the refractory group. In the refractory group, the mean serum ferritin level was below the lower limit during the treatment. At the first week of the treatment, the mean ferritin level in the refractory group (n = 3) was significantly lower than that in the responsive group (n = 8, $p < 0.05$). In the responsive group, the mean serum ferritin level showed a decrease at the second and third weeks of treatment due to autologous blood donation.

rHuEPO response in a group of anaemic patients with RA compared to those with various etiologies not associated with RA. It has been reported that iron deficiency-anaemia patients with RA had significantly lower erythropoietin levels than non-RA patients with comparable anaemia (9-11). Noé *et al.* (12) recently showed that the erythropoietin concentrations in RA patients are elevated above normal levels, but are nevertheless lower than expected. In the present study the erythropoietin concentrations before rHuEPO treatment in both groups were also lower than expected. During rHuEPO treatment, the erythropoietin concentrations in patients who showed an impaired response tended to be increased and were significantly higher at 3 weeks of treatment compared with those of patients who responded to rHuEPO treatment. The response of the serum erythropoietin to anaemia is known to vary in degree with the etiology of the anaemia (13, 14). However, the mechanism of an impaired response to rHuEPO in RA patients with severe anaemia consists of multi-factorial processes and still remains unclear.

Regarding the correlation between drugs for the treatment of RA and the response to rHuEPO, no noteworthy correlations emerged in the present study. However, the disease-modifying anti-rheumatic drugs methotrexate and mizoribin do have some myelosuppressive effects. In addition, it has been suggested that a reduced release of renal erythropoietin due to anti-rheumatic drugs may be involved in the underlying mechanism (9, 15). However, bucillamine administered to refractory and responsive patients has been confirmed to have no such adverse effects (16). On the other hand, exacerbation of rheumatoid synovitis by intravenous iron dextran has been reported (17, 18). Increased inflammation in RA patients may affect the response to rHuEPO. But in the present study, iron sulfate was orally administered in both the refractory and responsive groups, so that the effect of oral iron sulfate was considered to be negligible. Further study of the influence of the drugs used for the treatment of RA or anaemia on the response to rHuEPO is necessary, especially in RA patients with severe anaemia.

Smith *et al*. (19) recently reported that interleukin-1 (IL-1) or tumor necrosis factor-α (TNF−α) may be responsible for a blunted reaction of RA erythroblasts to erythropoietin at the colony-forming unit erythroid level. Stockenhuber *et al.* (20) indicated that an impaired response to endogenous erythropoietin showed a correlation with elevated serum TNF-α. These inflammatory cytokines are generated in the setting of an underlying inflammatory disease and might disturb hematopoietic cell proliferation.

Regarding the issue of costs versus benefit, in RA patients with severe anaemia whose Hb concentrations are less than 8.0 g/dl, removal of the inhibitory factor of erythropoiesis (i.e., inflammation) may be appropriate. If removal of this inhibitory factor is not possible, a prolongation of the treatment period, an increase in the rHuEPO dosage, or allogeneic blood transfusion should be considered.

In the present study, rHuHPO was intravenously applied in severely anaemic RA patients as hospital in-patients. Recently, we administered rHuEPO subcutaneously in out-patients with either osteoarthrosis or RA who were scheduled to undergo joint replacement surgery. Subcutaneous application is reported to decrease the total dose and administration time of rHuEPO and hence its cost (21, 22). With use of the subcutaneous route

of administration, pre-operative autologous donations may be performed over a short period of time in patients on an out-patient basis.

In conclusion, the results of this study indicate that RA patients with severe anaemia (Hb concentrations < 8.0 g/dl) have a blunted response to rHuEPO treatment. The control of disease activity prior to rHuEPO treatment must be considered a prerequisite to autologous blood donation in these patients. A higher dose of rHuEPO (> 200 units/kg/3 times a week for three weeks) was found to be necessary in the refractory group.

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