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Intravenous Iron and Erythropoietin for Anemia Associated with Crohn Disease

A Randomized, Controlled Trial

Christoph Gasché, MD; Clemens Dejaco, MD; Thomas Waldhoer, PhD; Wolfgang Tillinger, MD; Walter Reinisch, MD; Gerhard F. Fueger, MD; Alfred Gangl, MD; and Herbert Lochs, MD

Background: Anemia often complicates Crohn disease and affects quality of life.

Objective: To evaluate the efficacy of intravenous iron alone and in combination with erythropoietin for the treatment of anemia associated with Crohn disease.

Design: Double-blind, randomized, placebo-controlled trial with a subsequent open-label phase.

Setting: University-based gastroenterology outpatient clinic.

Patients: 40 patients with Crohn disease and a hemoglobin concentration of 10.5 g/dL or less.

Intervention: All patients received intravenous iron saccharate for 16 weeks. During the blinded phase of the trial, they received either erythropoietin or placebo. During the open phase, the erythropoietin dose was increased in nonresponders who had received erythropoietin and erythropoietin therapy was initiated in nonresponders who had received placebo.

Measurements: Response was defined as an increase in hemoglobin concentration of 2 g/dL or more.

Results: 15 of 20 patients in the placebo group (75% [95% CI, 51% to 91%]) and 18 of 19 patients in the erythropoietin group (95% [CI, 74% to 100%]) responded to intravenous iron ($P = 0.20$). The erythropoietin group had a higher cumulative response rate ($P = 0.036$) and a more pronounced mean increase in hemoglobin concentration (4.9 g/dL in the erythropoietin group compared with 3.3 g/dL in the placebo group, a difference of 1.6 g/dL [CI, 0.6 g/dL to 2.5 g/dL]; $P = 0.004$). In the open phase, all 6 previous nonresponders had a response. Hematologic response was associated with improved quality of life ($P = 0.03$).

Conclusions: Most patients who have anemia associated with Crohn disease respond to intravenous iron alone. Erythropoietin has additional effects on hemoglobin concentrations.

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From the University of Vienna, Vienna, Austria; and the University Hospital Graz, Graz, Austria. For current author addresses, see end of text.

The cause of Crohn disease is still unclear, and therapeutic interventions for this condition are therefore designed to alleviate symptoms and improve quality of life (1). Along with diarrhea and abdominal pain, anemia is an important symptom of Crohn disease. It occurs in about one third of patients; in approximately 15% of patients, it is severe (hemoglobin concentration ≤ 10.5 g/dL [to convert g/dL to g/L, multiply by 10]). It is associated with a decrease in quality of life and an increase in rates of hospitalization and death (2, 3), which suggests that it should be effectively treated. Anemia in patients with Crohn disease results primarily from iron deficiency due to chronic intestinal blood loss (4). Furthermore, intestinal inflammation is mediated by overproduction of cytokines (including interferon-γ, interleukin-1, or tumor necrosis factor-α) (5, 6), which may contribute to the generation of the anemia of chronic disease (7), accompanied by inadequate erythropoietin production (4).

Since it was first used in chronic renal failure (8), recombinant human erythropoietin has been shown to be effective for treating the anemia that accompanies several chronic diseases (9). After it was used successfully in three selected cases of anemia associated with inflammatory bowel disease (10), recombinant human erythropoietin was studied in a controlled trial of patients with anemia refractory to oral iron treatment (11). The therapeutic effectiveness of erythropoietin, however, was limited by concomitant iron deficiency. Because erythropoietin therapy is costly, its therapeutic potency should be maximized. Our primary objective was to test the efficacy of intravenous iron alone and supplemented with erythropoietin for the treatment of anemia associated with Crohn disease. A second objective was to investigate the effect of the treatment of anemia on quality of life.

Methods

Patients

Forty patients with Crohn disease and severe anemia (hemoglobin concentration ≤ 10.5 g/dL) were randomly assigned to receive erythropoietin or placebo after giving informed consent. All patients had been unresponsive to oral iron therapy (100 mg/d) for at least 2 months ($n = 14$) or had been unable

to tolerate oral iron therapy because of gastrointestinal side effects (n = 26). Patients who were younger than 18 years of age; who were unable to comply with the protocol; who needed surgery; or who had recently had myelosuppressive or immunosuppressive therapy, cancer, hemolysis, deficiencies in folic acid or cobalamin, creatinine concentrations greater than 2 mg/dL (152 μmol/L), hypertension, thrombosis, or iron overload were excluded. The protocol was approved by the local ethics committee of our faculty.

Study Design

Blinded Phase

Patients were randomly assigned to receive erythropoietin or placebo in a 1:1 ratio using the minimization method described by White and Freedman (12). This method was used to balance the two study groups for the following prognostic variables: hemoglobin concentration (group boundary, 9.0 g/dL), Crohn's disease activity index (group boundary, 200 points), and sex. Individual allocations to treatment group were done at a central location in a blinded manner. All patients received iron saccharate as an intravenous infusion for 16 weeks. During the first 8 weeks, all patients received either erythropoietin or placebo in a double-blind manner. A response was defined as an increase in hemoglobin concentration of 2 g/dL or more within 8 weeks. Treatment was stopped early in patients who reached a hemoglobin concentration greater than 14.0 g/dL before the end of the blinded phase.

Open Phase

During the second 8 weeks of the study (the open-label phase), the erythropoietin dose was increased in nonresponders in the erythropoietin group and erythropoietin therapy was started in nonresponders in the placebo group. All patients continued to receive intravenous iron saccharate.

Laboratory data on hemoglobin concentration (normal value, 14 to 18 g/dL for men, 12 to 16 g/dL for women), reticulocyte count (normal, 0.5% to 2.0%), transferrin level (normal, 2.00 to 3.80 g/L), transferrin saturation (normal, 16% to 45%), ferritin level (normal, 55 to 440 μg/L), and C-reactive protein level (normal, < 0.5 mg/dL) were obtained every second week. The Crohn's disease activity index (a composite of 8 items: number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestations, use of opiates, abdominal mass, hematocrit, and body weight [range, 0 to >500 points (no upper limit), with ≥200 points indicating active disease]) (13) was also assessed every second week. Serum concentrations of erythropoietin (normal value, 5 to 29 mU/mL) were analyzed at study entry by using radioimmunoassay (Incstar, Stillwater, Minnesota) (14). Quality of life was determined at study entry, after the blinded phase, and at the end of the open phase by using a previously validated questionnaire that contained nine items (feeling of well-being, mood, level of activity, pain, nausea, appetite, physical ability, social activities, and anxiety [range, 9 to 45 points, 45 indicating lowest quality of life]) (15).

Medication

Ten milliliters of iron saccharate, corresponding to 200 mg Fe^{3+} (Ferrum Hausmann, Vifor AG, St. Gallen, Switzerland), diluted in 250 mL of 0.9% sodium chloride solution, was given intravenously to all patients throughout the trial. Infusions were given twice weekly during the first 2 weeks and once weekly thereafter until the end of the trial. To avoid iron overload, iron supplementation was withheld when transferrin saturation exceeded 50% and was restarted when saturation decreased to less than 30%. In the blinded phase, 150 IU of erythropoietin per kg of body weight (Erypo, Janssen & Cilag Pharma, Vienna, Austria) or placebo were injected subcutaneously three times a week by each participant. The drug and the placebo were similar in appearance and were supplied in vials that contained a white sterile powder, which was clear and colorless when reconstituted with 1 mL sterile water. In the open phase, nonresponders in the erythropoietin group received erythropoietin, 300 IU/kg, and nonresponders in the placebo group received erythropoietin, 150 IU/kg.

Statistical Analysis

The sample size necessary to detect an increase from an assumed success rate of 60% in the placebo group to 95% in the erythropoietin group with a power of 80% and at a level of 5% was estimated as 20 for each group (two-sided). The Fisher exact test, paired and unpaired Wilcoxon tests, the Kaplan–Meier estimation, the Mantel–Cox test, and the Spearman rank correlation were used for statistical evaluation. Baseline values are expressed as the mean ± SD.

Results

Baseline Data

Forty patients receiving intravenous iron therapy were randomly assigned to receive either erythropoietin (n = 20) or placebo (n = 20). Four patients had isolated small bowel disease, 4 had colonic disease, 27 had ileocolonic disease, and 5 had additional stomach or esophageal disease. The patients

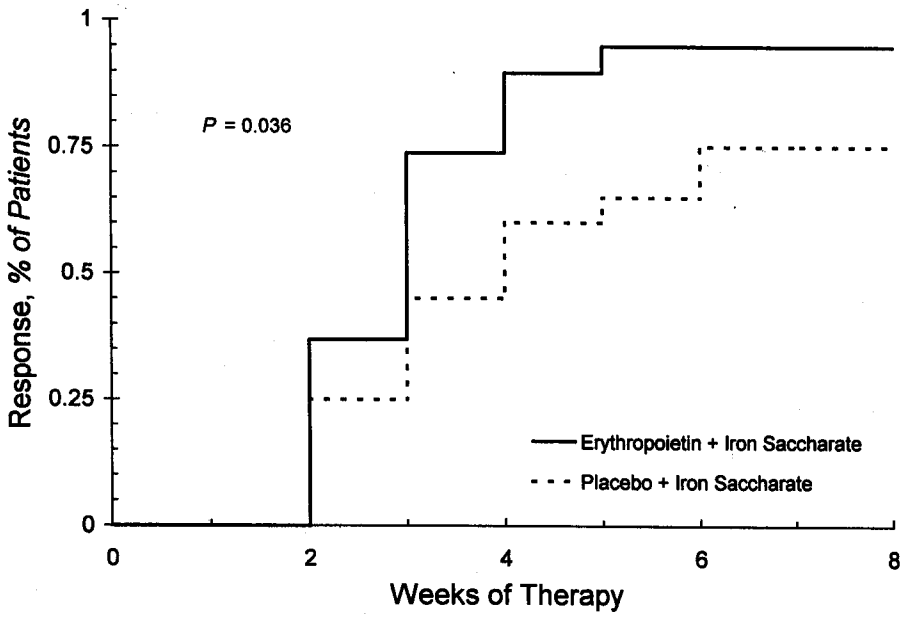

Figure 1. Kaplan–Meier estimation of the cumulative response to erythropoietin and iron saccharate or placebo and iron saccharate. Response was defined as an increase in hemoglobin concentration of 2 g/dL or more.

ranged in age from 18 to 68 years (mean, 32 years). Nine patients had received blood transfusions during the previous year. At baseline, the groups were similar with respect to all characteristics except for sex: There were 3 men in the erythropoietin group (15%) and 10 men in the placebo group (50%). The baseline hemoglobin level was 8.7 ± 1.4 g/dL in the erythropoietin group and 8.5 ± 1.5 g/dL in the placebo group. Both groups had substantial reductions in ferritin level (erythropoietin group, 32 ± 50 μg/L; placebo group, 15 ± 23 μg/L; $P = 0.176$) and transferrin saturation (erythropoietin group, 4% ± 3%; placebo group, 4% ± 6%; $P = 0.152$), indicating iron deficiency. Serum erythropoietin concentrations were moderately elevated (erythropoietin group, 82 ± 88 mU/mL; placebo group, 129 ± 171 mU/mL; $P > 0.2$), and an inverse relation between the logarithm of erythropoietin and hemoglobin levels was seen:

$$\log(\text{erythropoietin}) = 3.80 - 0.23 \times \text{hemoglobin concentration}; r = -0.82, P < 0.001$$

Outcome of the Blinded Phase

Twenty patients in the placebo group and 19 patients in the erythropoietin group completed the trial. One patient in the erythropoietin group was lost because of noncompliance. Fifteen patients in the placebo group (75% [95% CI, 51% to 91%]) and 18 patients in the erythropoietin group (95% [CI, 74% to 100%]) responded to intravenous iron therapy ($P = 0.20$). The cumulative response rate was higher in the erythropoietin group ($P = 0.036$) (**Figure 1**). The mean increase in hemoglobin concentration was 4.9 g/dL in the erythropoietin group and 3.3 g/dL in the placebo group, a difference of 1.6 g/dL (CI, 0.6 g/dL to 2.5 g/dL) ($P = 0.004$).

The increases in serum ferritin levels (116 μg/L [CI, 83 μg/L to 171 μg/L] in the erythropoietin group compared with 282 μg/L [CI, 205 μg/L to 360 μg/L] in the placebo group; $P < 0.001$) and transferrin saturation (5% [CI, 3% to 7%] in the erythropoietin group compared with 10% [CI, 6% to 13%]; $P = 0.032$) were significantly less in the erythropoietin group than in the placebo group. C-reactive protein levels did not change. The patients who did not respond to treatment (1 in the erythropoietin group and 5 in the placebo group) had normal ferritin levels (mean, 298 μg/L [range, 61 μg/L to 495 μg/L]) and low transferrin saturation (mean, 9% [range, 2% to 17%]) at the end of this phase of the trial.

The increase in hemoglobin concentration was associated with positive changes in the quality-of-life score (Spearman rank correlation coefficient: $r = -0.372$; $P = 0.020$) and the Crohn's disease activity index ($r = -0.356$; $P = 0.026$). The feeling of well-being, mood, physical ability, and social activities accounted for most of the improvement in quality of life. Improvement in the Crohn's disease activity index was derived primarily from changes in two items: hematocrit and general well-being.

Outcome of the Open Phase

A total of 39 patients entered the open phase of the trial. Eighteen responders from the erythropoietin group and 15 responders from the placebo

group were treated with iron infusions alone. The single nonresponder in the erythropoietin group received erythropoietin, 300 IU/kg, and the 5 nonresponders in the placebo group received erythropoietin, 150 IU/kg, in addition to iron infusions. All previous nonresponders had an increase in hemoglobin concentration between the beginning and the end of the open phase (increase in the nonresponder in the erythropoietin group, 3.6 g/dL; mean increase in the nonresponders in the placebo group, 3.6 g/dL [CI, 2.5 g/dL to 4.6 g/dL]) (**Figure 2**). During the open phase, 27 of the 33 patients who received iron saccharate alone had changes in hemoglobin concentration of less than 2 g/dL (mean change, 0.3 g/dL [CI, −0.1 g/dL to 0.7 g/dL]). Three patients (1 in the erythropoietin group and 2 in the placebo group) had a further increase (mean, 2.4 g/dL), and three (all in the previous erythropoietin group) had a decrease in hemoglobin concentration (mean, −2.5 g/dL).

During the study, 12 patients in the erythropoietin group and 13 patients in the placebo group received prednisolone therapy. No patients received red blood cell transfusions.

Adverse Events

Six different side effects were noted in 14 patients. Local burning at the site of injection was reported by 5 patients in the erythropoietin group and 2 patients in the placebo group ($P = 0.24$). All other side effects were related to iron saccharate infusions: burning at the site of venipuncture ($n = 3$), bitter taste ($n = 2$), transient fever (body temperature < 38 °C) ($n = 3$), and transient hypotension ($n = 2$). In 2 patients, transferrin saturation increased more than 50% (to 51% and 55%, respectively) and returned to normal within 2 weeks after iron infusions were withheld.

Discussion

We conducted this randomized clinical trial to investigate the effect of intravenous iron therapy alone or in combination with recombinant human erythropoietin for the treatment of anemia associated with Crohn disease. Seventy-five percent of patients had a substantial response to intravenous iron alone. The addition of erythropoietin was associated with a somewhat greater and more rapid increase in hemoglobin concentrations and with concurrent lower iron deposition into the storage pool (as measured by serum ferritin and transferrin saturation) during the blinded phase of the trial. Adding erythropoietin or increasing the erythropoietin dose produced a response in all previous nonresponders during open-label treatment. The increase in hemoglobin concentration was associated with an improvement in quality of life.

In a previous trial of erythropoietin (11), patients with inflammatory bowel disease and severe anemia received oral iron supplementation. Mean hemoglobin concentrations decreased by 0.9 g/dL in the placebo group (which was receiving oral iron therapy alone) and increased slightly (by 1.7 g/dL) in the erythropoietin group. In that study, the thera-

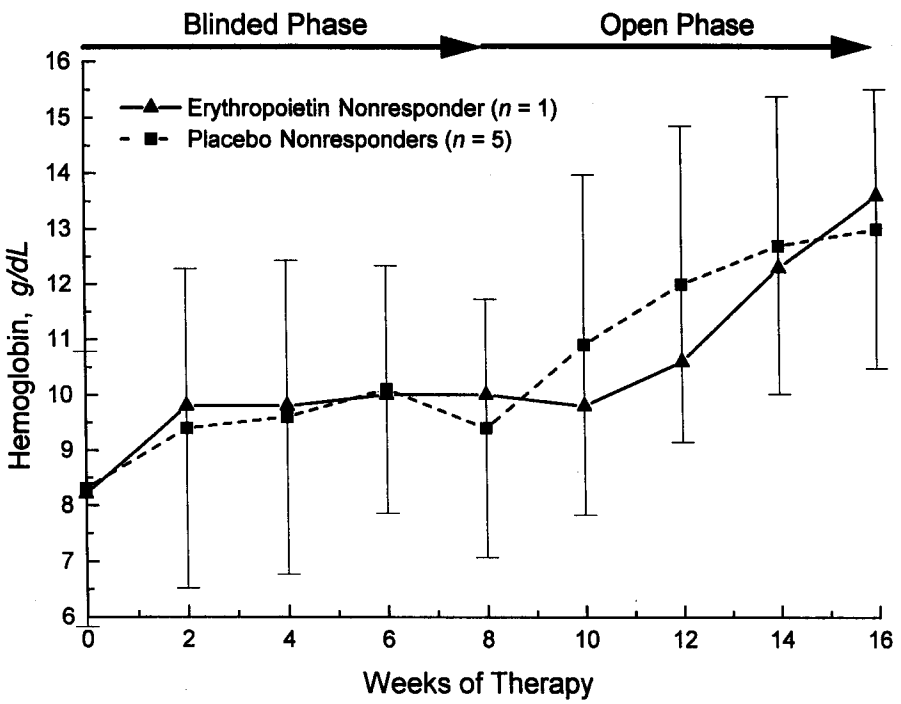

Figure 2. Mean hemoglobin concentrations in five nonresponders in the placebo group and one nonresponder in the erythropoietin group during the blinded and open phases of the study. Bars represent 95% CIs for the nonresponders in the placebo group. All patients had been treated without response for 8 weeks in the blinded phase of the trial (*left*). In the open phase of the trial (*right*), nonresponders in the placebo group received erythropoietin, 150 IU/kg of body weight, and the one nonresponder in the erythropoietin group received erythropoietin, 300 IU/kg. To convert g/dL to g/L, multiply by 10.

peutic potency of erythropoietin appeared to be limited by concomitant iron deficiency. We therefore chose to use intravenous iron in our trial to avoid the difficulties associated with oral iron therapy (16). In contrast to iron dextran, which may cause anaphylactic reactions, iron saccharate is well tolerated, particularly when used as a dilute solution (17–19). Indeed, no serious adverse event related to intravenous iron therapy occurred in our trial. Temporary hypotension or local burning were easily controlled by reducing the speed of infusion. We suggest that the amount and route of iron were responsible for the high efficacy of iron therapy in our study. Intravenous iron alone had twice the effect (an increase in hemoglobin concentration of 3.3 g/dL within 8 weeks) of erythropoietin combined with oral iron (an increase in hemoglobin concentration of 1.7 g/dL within 12 weeks). These results underscore the potential value of intravenous iron supplementation in severe anemia associated with Crohn disease.

The lack of a true placebo group (a group receiving both placebo injections and placebo infusions) limits the interpretation of our results because subjective outcome measurements, such as quality of life, can be influenced by the placebo effect. Before study entry, however, our patients did not respond to or tolerate oral iron therapy; this is generally true in about half of patients with severe anemia associated with Crohn disease (11). Because the need for an adequate supply of iron in this group was clear, the inclusion of a true placebo group was considered unethical. The fact that the quality-of-life score did not improve in the few nonresponders argues against the presence of such a placebo effect in our trial. It is also unlikely that prednisolone therapy for Crohn disease affected our results because the mean prednisolone dose was similar in both groups and did not change until the end of the trial. Compliance was controlled by the administration of iron infusions at our outpatient clinic and by the weekly counting of empty erythropoietin and placebo vials. All patients but one achieved full compliance during the blinded phase of the trial. The failure of randomization to balance sex distribution between the groups happened by chance. However, the number of women in the erythropoietin group was larger than that in the placebo group, and this may have been associated with additional blood loss in this group due to menstrual flow. Thus, the mismatch in sex might have resulted in an underestimation rather than an overestimation of the effects of erythropoietin.

Anemia in patients with Crohn disease can present a serious therapeutic challenge. Our study shows that the optimal management of anemia in this young population is associated not only with changes in laboratory values but, most importantly, with an improvement in quality of life (for example, the ability to work or to engage in social activity). The cost of iron saccharate therapy is only 0.8% of the cost of erythropoietin therapy. The responsible use of medical resources therefore suggests that iron saccharate should be considered first-line therapy in patients with severe anemia. Erythropoietin may have a secondary therapeutic role in patients who do not respond to intravenous iron. Unfortunately, we have not yet found a variable that predicts the need for erythropoietin therapy.

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Requests for Reprints: Christoph Gasché, MD, Klinik für Innere Medizin IV, Neues AKH, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

Current Author Addresses: Drs. Gasché, Dejaco, Tillinger, Reinisch, and Gangl: Klinik für Innere Medizin IV, Neues AKH, Währinger Gürtel 18-20, A-1090 Vienna, Austria.
Dr. Waldhoer: Institute of Tumor Biology, Department of Epidemiology, Borschkegasse 8a, A-1090 Vienna, Austria.
Dr. Fueger: Division of Nuclear Medicine, Department of Radiology, University Hospital Graz, Auenbruggerplatz 15, A-8036 Graz, Austria.
Dr. Lochs: IV. Medizinische Klinik/Charité, Schumannstrasse 20/21, D-10117 Berlin, Germany.

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