Anemia management in patients on peritoneal dialysis: efficacy and safety of epoetin δ

Bruce S. Spinowitz

New York Hospital, Queens, Cornell University Medical Center, New York, NY, USA

ABSTRACT

In a one-year, multicenter, open-label, uncontrolled trial, epoetin δ was given subcutaneously, 1–3-times weekly to peritoneal dialysis patients who had previously received an epoetin. Dose was adjusted to maintain hemoglobin at 10.0–12.0 g/dL. The primary endpoint was mean hemoglobin over weeks 12–24. Safety was assessed. Mean±SD baseline hemoglobin was 11.2±0.9 g/dL. Hemoglobin over weeks 12–24 was 11.6±1.1 g/dL. Adverse events were those expected in this patient population. No life-threatening adverse events occurred. Subcutaneous epoetin δ was effective and well tolerated for the treatment of anemia in peritoneal dialysis patients.

Key words: anemia, peritoneal dialysis, epoetin.

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Introduction

Progression of chronic kidney disease (CKD) is often associated with severe anemia,[1] and epidemiological studies have shown that hemoglobin levels are correlated with creatinine clearance.[1,2] This anemia primarily results from the failure of the diseased kidney to produce sufficient quantities of erythropoietin, although factors such as shortened erythrocyte lifespan, deficiencies of iron and vitamins, and the bleeding tendency associated with uremia may be involved.[3,4] Anemia in patients with CKD is associated with fatigue, and with cognitive and sexual dysfunction.[5] In addition, anemia also has important effects on the cardiovascular system, increasing the risk of left ventricular hypertrophy[6,7] and leading to reduced survival.[7,8]

Recombinant erythropoietins, which are produced in Chinese hamster ovary (CHO) cell lines, have been available for the treatment of anemia since the 1980s. Epoetin δ (Dynepo®, Shire plc.) differs from the currently available erythropoietins as it is produced in a human cell line. This results in a protein that has a different glycosylation profile compared with CHO-cell-derived epoetins.[9] Epoetin δ has been shown to be effective and well tolerated for the treatment of anemia of CKD in predialysis[10] and hemodialysis patients.[11,12] This paper reports the results of a study assessing the efficacy and safety of subcutaneous (sc.) epoetin δ in patients receiving peritoneal dialysis.

Design and Methods

Study design

The study was a multicenter, open-label, uncontrolled trial to assess the efficacy and safety of sc. epoetin δ during one year of treatment in patients who had previously received epoetin therapy.

Clinical trial registration: ISRCTN68321818 (*http://www.controlled-trials.com/ISRCTN68321818*). Patients receiving peritoneal dialysis formed a subgroup of the total trial population.

Sc. epoetin δ was to be given once, twice or three-times weekly at the discretion of the investigator. The starting dose was identical to that of the last dose of recombinant erythropoietin received by the patient, and this dose was maintained for two weeks. After this time, the dose of epo-

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Correspondence: Bruce S. Spinowitz, M.D. FACP, Associate Director, Nephrology, Associate Chairman, Medicine, New York Hospital, Queens, Clinical Professor of Medicine, Cornell University Medical Center, New York, NY, USA. E-mail: bss9001@nyp.org

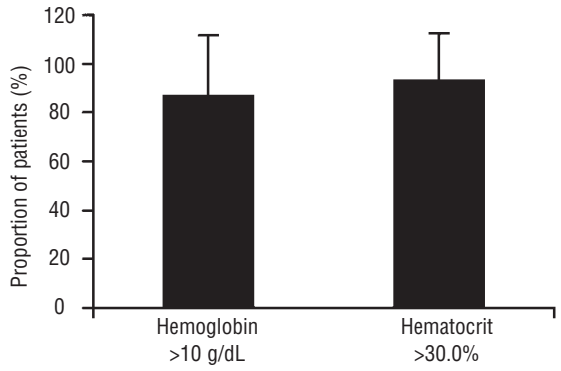

Figure 1. Mean±SD proportion of patients having hemoglobin levels >10.0 g/dL or hematocrit >30% during Weeks 12 to 24 (modified intent-to-treat population; n=91).

etin δ could be altered to maintain hemoglobin levels at 10.0–12.0 g/dL, in line with the European Best Practice Guidelines at the time of the study.[13]

Patients

Adults (≥18 years of age) with CKD and a medical history of anemia were eligible to enter the study if they had received a stable dose (i.e. no dose change of >50%) of sc. recombinant erythropoietin at least once weekly for 30 days before entering the study. Patients were also required to have had hemoglobin levels of 9.6-12.4 g/dL in the two weeks before entering the study, and transferrin saturation ≥18% and serum ferritin levels ≥90 ng/mL at the pre-study measurement. Sufficient iron to maintain transferrin saturation ≥20% and serum ferritin levels ≥100 ng/mL was specifically required during the study. If iron status measurements fell short of these criteria patients received intravenous (iv.) iron supplementation of at least 1,000 mg over a maximum of ten weeks. At trial centers in France oral iron supplementation was attempted before use of the iv. route.

Exclusion criteria included: uncontrolled hypertension; concomitant illness that could reduce life expectancy to less than 12 months; thrombocytopenia (platelet count <75,000/mm^3); active bleeding; use of immunosuppressive drugs (other than corticosteroids for a chronic condition) or androgen therapy within 30 days of entering the study; impaired hepatic function or major systemic disease. Women of child-bearing potential, who were pregnant, breastfeeding or not using medically approved contraception were also excluded.

The study was performed in accordance with the Declaration of Helsinki and all patients gave written, informed consent. The clinical study protocol, informed consent documentation and other appropriate study-related documentation were reviewed and approved by an independent ethics committee or an institutional review board at each center.

Endpoints and analysis

Hematologic parameters were assessed weekly and the primary efficacy endpoint was the mean hemoglobin level over weeks 12-24. Secondary endpoints included the mean treatment dose, mean hematocrit, and percentage of hemoglobin measurements >10 g/dL and hematocrit measurements >30%. Efficacy data were assessed using a modified intent-to-treat (mITT) group consisting of all treated patients who had a baseline hemoglobin measure and at least one such measure at week 12, 16, 20 or 24. Descriptive statistics were calculated for efficacy endpoints.

Safety was assessed by recording and monitoring adverse events at each visit. In addition, laboratory safety assessments were carried out every four weeks, and physical examinations and ECG at baseline, mid-study and at study end (or early withdrawal). The safety-evaluable population included all patients who received at least one dose of study medication.

Results and Discussion

In total, 102 peritoneal dialysis patients entered the study and were included in the safety-evaluable population. Of these, 91 were included in the mITT group. Baseline characteristics are shown in Table 1. At baseline, mean±SD hemoglobin level was 11.9±0.9 g/dL and mean hematocrit was 34.4±2.8%.

The majority of patients in the mITT population received epoetin δ once weekly (68/91; 74.7%), with the remainder receiving epoetin δ either twice weekly (17/91; 18.7%) or three-times weekly (6/91; 6.6%). Mean hemoglobin during weeks 12–24 was 11.6±1.1 g/dL and mean hematocrit was 37.0±3.5%. Most patients had hemoglobin levels that were above 10.0 g/dL and hematocrit above 30% during weeks 12–24 (Figure 1). The median proportion of patients who reached these targets was 100% in both cases.

Control of anemia over weeks 12–24 was achieved with a mean dose per administration of epoetin δ (62.5±52.2 IU/kg) that was numerically lower than the baseline dose of epoetin (83.5±47.7 IU/kg). Treatment with epoetin δ continued to control anemia throughout the 52 weeks of the study. Mean hemoglobin level from week 12 to the end of the study was 11.2 g/dL and mean hematocrit over the same period was 35.7%. In total, 90.2% of patients experienced an adverse event during the study (Table 2), of which the most common were infection, peritonitis, headache and upper respiratory tract infection. The majority of events were mild to moderate in intensity. Only 8.8% of patients experienced an adverse event that was considered by the investigators to be possibly related to treatment (Table 2). Serious adverse events were reported by 50% of patients, of whom 5 patients experienced serious adverse events considered to be possibly related to treatment. These consisted of 3 cases of anemia, one of hypertension and one of pancreatitis. None of these events was life threatening. Mean changes in laboratory parameters, vital signs and ECG were minimal; all clinically important changes were related to infection, inflammatory disease or renal failure. No patient in the study developed neutralizing anti-erythropoietin antibodies.

Table 1. Baseline characteristics of the modified intent-to-treat population.

Characteristic	*Patients (n=91)*
Sex, n (%)	
Men	45 (49.5)
Women	46 (50.5)
Age, years (mean ± SD)	52.4±14.0
Race, n (%)	
Caucasian	47 (51.6)
Black	34 (37.4)
Asian/Oriental	4 (4.4)
Multi-racial	6 (6.6)
Primary diagnosis, n (%)	
Diabetic nephropathy	24 (26.4)
Hypertensive nephrosclerosis	33 (36.3)
Glomerulonephritis	18 (19.8)
Polycystic kidney disease	4 (4.4)
Other	12 (13.2)

Table 2. Adverse events occurring during treatment in >10% of the safety-evaluable population and those events considered possibly related to treatment.

Adverse event	*Number (%) of patients (N=102)*
Total	92 (90.2)
Infection	43 (42.2)
Peritonitis	30 (29.4)
Headache	21 (20.6)
Upper respiratory infection	21 (20.6)
Hypertension	16 (15.7)
Hypotension	16 (15.7)
Hypervolemia	15 (14.7)
Diarrhea	14 (13.7)
Dizziness	14 (13.7)
Vomiting	12 (11.8)
Pain	12 (11.8)
Asthenia	11 (10.8)
Cough increased	11 (10.8)
Possibly related to treatment	
Anemia	4 (3.9)
Hypertension	2 (2.0)
Polycythemia	1 (1.0)
Cholelithiasis	1 (1.0)
Pancreatitis	1 (1.0)

The results of this open-label study indicate that epoetin δ, given subcutaneously, is effective in controlling anemia in peritoneal dialysis patients. In this study, which enrolled patients who had reasonably well-controlled anemia at baseline, a switch from a conventional, CHO-cell-derived sc. epoetin to epoetin δ was associated with continued control of anemia up to one year.

Epoetin δ has demonstrated efficacy in pre-dialysis and hemodialysis patients[10-12] and most studies of anemia in patients requiring dialysis involve patients receiving hemodialysis rather than those receiving peritoneal dialysis. Accordingly, there is relatively little published evidence from patients undergoing peritoneal dialysis. However, the available evidence does suggest that anemia in patients receiving peritoneal dialysis is associated with a similarly increased risk of fatigue, hospitalization and death, as anemia in patients receiving hemodialysis.[14,15] Despite this, patients receiving peritoneal dialysis appear to require substantially lower doses of erythropoietin to control their anemia.[16,17] Possible reasons for this reduced epoetin dose requirement include a lower level of blood loss and inflammation in patients receiving peritoneal dialysis, the use of the subcutaneous route, as is usually the case in a peritoneal dialysis population, as well as improved dialytic removal of inhibitors of erythropoiesis.[16] Of interest in the present study, the mean dose of epoetin δ was numerically lower than the dose epoetin patients were receiving before entering the study.

Epoetin δ was well tolerated in the present study. The number and type of adverse events that occurred during treatment were generally in line with those expected for a peritoneal dialysis population. The incidence of adverse events considered possibly related to treatment was low, and no such event resulted in death or was considered to be life-threatening. No patient developed neutralizing anti-erythropoietin antibodies during epoetin δ treatment.

Unlike the existing epoetins derived from CHO cell lines, epoetin δ is produced in a human cell line by activation of the endogenous erythropoietin gene. Because the production cell is of human origin, the glycosylation profile of epoetin is different from ESAs produced in CHO cell lines.[9]

Further research is underway to assess any clinical impact of these differences in glycosylation. Subcutaneously administered epoetin δ is effective and well tolerated for the treatment of anemia in CKD patients requiring peritoneal dialysis.

Authorship and Disclosures

This paper presents data from a multicenter trial. The author was one of the leading recruiters in the trial and has been responsible for drafting, reviewing and approving this article. All other study investigators on the trial are acknowledged. The author reported no potential conflicts of interest.

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