A Monocentric Observational Study of Darbepoetin Alfa in Anemic Hepatitis-C-Virus Transplant Patients Treated With Ribavirin

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Abstract

Objectives: **Darbepoetin alfa is used to treat renal anemia; however, little information is available concerning its use during the posttransplant period, especially in HCV-positive patients treated with ribavirin for active hepatitis C.**

Materials and Methods: **This study investigated the efficacy and safety of using darbepoetin alfa in this population during a 6-month treatment period. All anemic patients were HCV/RNA-positive, treated with ribavirin, and had impaired renal function. Patients (n=7) who had not been treated previously with recombinant human erythropoietin (rHuEPO) were placed in "group no rHuEPO." Patients previously with recombinant human erythropoietin (n=16; "group rHuEPO") were switched to darbepoetin alfa according to the European summary of product characteristics.**

Results: **Seventy-three percent of the patients were men. The mean creatinine clearance at baseline was 58.7 ± 21.5 mL/min. All patients received an immunosuppressive treatment. Although mean hemoglobin levels remained stable in group no rHuEPO and increased in group rHuEPO, the difference was not statistically significant. Also, the median darbepoetin-alfa–weighted dose in group no rHuEPO increased while it remained stable in group rHuEPO, as did the median daily dosage of ribavirin; however, these differences were not statistically significant. Creatinine levels and creatinine clearance levels remained stable throughout the study. No significant medical events related to the treatment were reported during the study.**

Conclusions: **Darbepoetin alfa was found to be efficient and well tolerated in correcting renal anemia in transplant recipients treated with ribavirin for active hepatitis C.**

Key words: *Hepatitis C, Ribavirin, Observational study, Organ transplant, Transplant patients*

Anemia is a common complication of chronic kidney disease, where it is related to a decrease in the synthesis of erythropoietin. Residual chronic kidney disease also frequently occurs in renal-transplant recipients, but the importance of anemia among such patients has long been underestimated. Allograft dysfunction, iron deficiency, immunosuppressive treatments, and various other medications are well-known contributing factors (1). A combination therapy that includes alpha-interferon and ribavirin is currently the reference therapy in patients infected with hepatitis C virus, because it ensures a sustained virologic response. However, a common adverse effect associated with this therapy is anemia, secondary to several mechanisms including bone-marrow suppression and hemolysis (2). Ribavirin has been contraindicated in chronic kidney disease for a long time, mainly because of this adverse effect (3).

Transplant patients with chronic kidney disease and treated with ribavirin for chronic hepatitis C, therefore, have twice the risk of becoming anemic: this status being frequently referred to as mixed anemia. Moreover, when patients are treated with alpha-interferon and ribavirin, anemia may result, necessitating a reduction in the ribavirin dosage,

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which might, in turn, compromise the antiviral effectiveness of the dual therapy.

When treating renal anemia, the use of erythropoiesis-stimulating agents is a well-established practice (4). However, clinical standards are lacking concerning the use of recombinant human erythropoietin (rHuEPO) to manage anemia in patients with hepatitis C virus, despite a growing body of evidence and increasing clinical experience (5).

Darbepoetin alfa is an engineered rHuEPO analogue. Compared with standard rHuEPO, it has longer in vivo activity and therefore, can be administered less frequently (6). Although intravenous or subcutaneous routes are possible, the subcutaneous route is preferred when patients are not on dialysis, owing to a lack of vascular access. Darbepoetin alfa is generally well tolerated, and clinical trials of 20 to 52 weeks' duration have demonstrated the efficacy of subcutaneous and intravenous administration of treating anemia associated with chronic kidney disease in both dialysis and predialysis patients (7).

This study assessed the efficacy and safety of darbepoetin alfa in anemic transplant recipients with both chronic kidney disease and hepatitis C, for which they were treated with ribavirin.

Patients and Methods

This monocentric, observational, nonrandomized pilot study was done during a 6-month period to assess the efficacy and safety of darbepoetin alfa in posttransplant anemic patients treated with ribavirin for chronic hepatitis C.

The patients' data from the 3 months before entering the study also were considered. The study lasted 9 months: beginning with a retrospective 3-month phase before darbepoetin alfa treatment, followed by a prospective 6-month darbepoetin alfa intervention period.

Eligible transplant patients were recipients of a liver or a kidney graft for at least 3 months. To be included in the study, patients had to have had anemia defined as a hemoglobin level of 11 g/dL or less, or had been treated with rHuEPO for chronic anemia. They also had to have had chronic kidney disease, that is, a creatinine clearance level of less than 80 mL/min. To ensure adequate iron stores to support erythropoiesis, serum ferritin was required to be 100 μg/L or more and/or transferrin saturation had to be 20% or more. Exclusion criteria were uncontrolled hypertension (diastolic blood pressure ≥ 110 mm Hg), heart failure (NYHA class III or IV), progressive hematologic conditions, or clinical status leading to suspect anti-erythropoietin antibodies. Pregnant women were also excluded.

This study was conducted in accordance to the ethical principles of the Helsinki Declaration: patients were informed of the study protocol and gave their written consent to the data collection. The follow-up conditions were those of daily practice, and the protocol ensured that posttransplant patients would not have complementary visits or biological assessments done outside the standard follow-up regimen.

Patient characteristics

Twenty-six patients were included in the study: 9 in group no rHuEPO, and 17 in group rHuEPO. The mean age of patients was 54.5 years (range, 30-74 years), and 19 patients were men. All had received a liver (n=18) or a kidney (n=5) graft; the mean duration of transplant was 5.3 ± 5.2 years (range, 0.2-18.1 years). Mean creatinine clearance at baseline was 58.7 ± 21.5 mL/min. All subjects were being treated with ribavirin for chronic hepatitis C and were receiving immunosuppressive therapies, that is, tacrolimus (n=16), cyclosporin (n=9), azathioprine (n=5), and mycophenolate mofetil (n=3). Eighty-eight percent of patients were also treated with corticosteroids. Immunosuppressive therapy averaged 2.2 medications per patient.

Erythropoietin-naïve patients (group no rHuEPO) were given darbepoetin alfa at a dosage of 0.45 μg/kg/week. When anemia occurred, that is, when their hemoglobin level went below 11.5 g/dL, and previously rHuEPO-treated patients (group rHuEPO) were switched to darbepoetin alfa using an initial conversion factor of 1:200, as set forth in the European summary of product characteristics (SmPC) (ARANSEP 2004). Only the subcutaneous route was used. Dose adjustments were done to ensure hemoglobin levels of between 11 and 13 g/dL, according to SmPC guidelines. Blood samples were drawn at baseline and at monthly intervals to measure hemoglobin levels. Safety assessments considered were the nature, seriousness, and relation of all adverse events to the study drug. Laboratory parameters were also monitored.

The intent-to-treat population consisted of all patients who had received at least 1 dose of darbepoetin alfa. The main criterion was assessed on the completer-analysis-set population who had been predefined as all patients who had completed the study and had hemoglobin-level assessments available at baseline and months 3 and 6. Because of 3 premature withdrawals, the CAS population comprised 23 patients: 7 in group no rHuEPO, and 16 in group rHuEPO.

Statistics

Descriptive statistics were applied to demographics at baseline as well as assessed variables. The main criterion was the variation in hemoglobin level throughout the darbepoetin alfa intervention period, and was defined as the mean change in hemoglobin level from baseline to month 6. Comparisons were done by paired *t* tests. Secondary criteria comprised the variation of darbepoetin alfa dosage from baseline to months 3 and 6: owing to the small number of subjects and dispersion of values, the median values are more robust and were considered more appropriate. Variation of hemoglobin according to duration of transplant and baseline creatinine clearance was also assessed. Iron supplementation and number of transfusions were quantified.

Results

Darbepoetin alfa efficacy on anemia

The variation in hemoglobin levels in the CAS population is presented in Table 1. Mean hemoglobin remained stable in EPO-naïve patients (group no rHuEPO), while it increased by 1.04 g/dL [95% confidence interval (CI) -0.05, 2.12] in previously treated patients (group rHuEPO) after 6 months of darbepoetin alfa-treatment. However, the mean difference did not reach statistical significance (P = .059). In group rHuEPO, the percentage of patients with hemoglobin levels greater than 11 g/dL increased from 44% at baseline to 81% at month 6, whereas it remained stable at 71% in the patients in group no rHuEPO.

Table 1. Hemoglobin levels during follow-up

Mean Hb (g/dL)	Baseline	M3	M6	Change (M6 - Baseline) Mean	95% CI*
All patients (n=23)	11.2	11.9	12.0	0.82	(-0.02, 1.65)
group no rHuEPO (n=7)	11.2	11.5	11.6	0.31	(-1.30, 1.92)
group rHuEPO (n=16)	11.1	12.0	12.2	1.04	(-0.05, 2.12)

*CI: confidence interval

In previously rHuEPO-untreated patients (group no rHuEPO), the stability of hemoglobin levels was achieved with a nonsignificant increase in the weighted dose of darbepoetin alfa from baseline to month 6 (Table 2). For group rHuEPO patients, the 12-g/L target hemoglobin level was achieved from month 3 onwards, with a weekly injection at a dosage equivalent to that which patients were receiving before baseline.

Table 2. Evolution of darbepoetin alfa (DA)-weighted doses during follow-up

Median DA weighted dose (µg/kg/week)	All patients (n=23)	Group I (n=7)	Group II (n=16)
Before baseline*	0.68		0.68
Baseline	0.90	0.70	1.00
M3	0.75	0.90	0.68
M6	0.90	0.90	0.65

*The equivalent dosage of DA was calculated using the ratio: weekly 200 IU rHuEPO = 1 µg weekly DA.

The evolution of hemoglobin levels was similar, whatever the time after transplant, to values of creatinine clearance at baseline. However, in those patients with low creatinine clearance rates (≤ 60 mL/min), the hemoglobin response appeared faster: median hemoglobin level increased by 1.4 g/dL within the first 3 months, and remained stable thereafter. For those patients with creatinine clearance greater than 60 mL/min, the median hemoglobin level increased steadily throughout the study period. Overall, the increase was similar in both groups.

Six patients received red-blood-cell transfusions before inclusion into the study: of these, 3 were treated by rHuEPO. During the darbepoetin alfa-treatment period, 2 subjects received a transfusion: 1 during the first month, and 1 during month 6. One patient was iron-supplemented during rHuEPO treatment, and another subject received iron supplementation at months 1 and 2.

Ribavirin treatment

The median daily dosage of ribavirin throughout the study period was 600 mg, as recommended for the SmPC product when hemoglobin levels are low. At baseline, there was, as expected, a direct positive

correlation between ribavirin dosage and hemoglobin levels (P = .02): patients with higher hemoglobin levels could accept higher ribavirin dosages. At month 6, there was a positive correlation between darbepoetin alfa and ribavirin dosages (P = .01).

Safety
No significant adverse events related to the treatment were reported during the study period. Of the 3 premature withdrawals, 1 patient discontinued intervention on the investigator's request because of normalization of the patient's hemoglobin level. One patient was hospitalized when diagnosed with a colic adenocarcinoma with a pulmonary metastasis. One patient interrupted darbepoetin alfa treatment at month 3 because of a high hemoglobin value (15.5 g/dL). No signs of deterioration in renal function were shown during the 6-month darbepoetin alfa treatment: serum creatinine and creatinine clearance remained stable.

Discussion

Anemia has long been known to be a complication of end-stage renal disease, and has been linked to cardiovascular morbidity and mortality. Erythropoiesis-stimulating agents have been used successfully for more than 10 years to treat anemia in patients with chronic kidney disease (4) including renal-transplant recipients (8, 9).

Anemia is also well-known to occur during combination therapy with pegylated (or standard) interferon and ribavirin, and often leads to ribavirin dose reduction or discontinuation (10). Ribavirin is known to accumulate extensively within erythrocytes, and exert direct toxicity through inhibition of intracellular energy metabolism and oxidative membrane damage (11). Bone-marrow suppression also contributes to this anemia and is the predominant mechanism for interferon-induced neutropenia and thrombocytopenia (11).

Although dose reduction or discontinuation of combination therapy can reverse these abnormalities, they also may reduce the virologic response. Erythropoiesis-stimulating agents, including darbepoetin alfa, have been shown to be a useful alternative for managing these hematologic adverse effects without reducing the optimal dosage of the combination antiviral regimen (12-15).

Very little is known about managing patients with mixed anemia because of the association between chronic kidney disease and hepatitis C. In fact, ribavirin has long been contraindicated in renal insufficiency owing to the adverse effect of anemia, and because of insufficient knowledge regarding dosing. In recent years, however, Bruchfeld and colleagues (3) demonstrated that, in a small series (7 patients), it was reasonably safe to use interferon and ribavirin in hepatitis-C-virus–related vasculitis and glomerulonephritis, irrespective of renal function. More recently, the same team published work done with hepatitis C virus patients undergoing hemodialysis (16). Patient management required reduced ribavirin dosages (170-300 mg/day), and high-dosage erythropoietin treatment, as well as ensuring adequate iron stores for erythropoiesis.

It is difficult to methodologically perform robust trials (randomized and controlled) in transplant recipients with hepatitis-C–associated renal impairment: the subjects' enrollment may last too long to achieve a statistically sufficient number to demonstrate significant effects of erythropoiesis-stimulating therapies.

To the best of our knowledge, this is the first study to assess the efficacy and safety of darbepoetin alfa in transplant recipients with hepatitis-C–associated renal impairment. It is a prospective, observational study, conducted as a routine follow-up. The fact that it is monocentric ensures a relatively homogeneous population and that there are no variations in assessing the biological parameters.

Both groups of patients had comparable hemoglobin levels at baseline, and the aim of darbepoetin alfa treatment, which was to ensure a hemoglobin level between 11 and 13 g/dL, was achieved in both groups by the end of the study. Previously, rHuEPO-treated patients were switched to higher darbepoetin alfa dosages than those of initial doses of EPO-naïve patients; however, it is possible to rapidly decrease the dosages of patients in the previously treated group and still maintain or achieve anemia correction with less frequent injections.

In this routine follow-up, some patients benefited from all possible management options for their anemia, and underwent red-blood-cell transfusions and/or iron supplementations, either during the 3-month retrospective phase or the 6-month prospective phase. However, it is interesting to note

that the need for these additive therapies was decreased during the darbepoetin alfa-treatment period.

Conclusions

In this pilot study, the first ever performed in ribavirin-treated transplant recipients with hepatitis-C–associated renal impairment—and thus having mixed induced anemia—darbepoetin alfa was shown to be well tolerated and effective in correcting hematologic abnormalities. This is, however, a small series, and further studies are needed to confirm our results.

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