EVALUATING EPOETIN ALFA 40,000 U SUBCUTANEOUSLY EVERY 2 WEEKS TO MAINTAIN HEMOGLOBIN LEVELS IN ANEMIC HIV-INFECTED PATIENTS

AM Levine, 1 GJ Leitz, 2 and the Community HIV Anemia Management Protocol Sites 2 (CHAMPS 2) Study Group

1University of Southern California, Keck School of Medicine, Los Angeles, CA; 2Ortho Biotech Products, L.P., Bridgewater, NJ

ABSTRACT

Background: Previous studies have shown that initial dosing of epoetin alfa 40,000 U SC subcutaneously (SC) once weekly (QW) is safe and effective at increasing hemoglobin (Hb) levels and improving quality of life (QOL) in anemic, HIV-infected patients (pts). However, in a population already burdened with complex medication regimens, the efficacy, safety, and convenience of epoetin alfa 40,000 U SC every 2 weeks (Q2W) to maintain Hb needs further exploration.

Methods: In a 24-week, multicenter, open-label study, HIV-infected pts with Hb ≤12 g/dL were administered epoetin alfa 40,000 U SC Q2W until target Hb (≥13 g/dL) was achieved. Patients were then switched to a maintenance phase during which epoetin alfa was given at a dosage of 40,000 U SC Q2W. If, during Q2W dosing, Hb measured ≤11 g/dL, pts were switched back to QW dosing; if Hb was >14 g/dL, dosing was temporarily withheld until Hb reached <14 g/dL, when previous maintenance dose resumed.

Results: At the time of this preliminary analysis, 63 pts were enrolled. Baseline characteristics are: median age 43 y (range, 25-74 y); 57% men; 82% on HAART; median CD4+, 233 cells/μL (range, 3-1308); median HIV-RNA, 770 copies/mL (range, 49,533-000); median Hb, 11.2 g/dL (range, 7.2-12.8 g/dL). Fifty pts entered maintenance phase, having reached target Hb (≥13 g/dL) in a median of 3.1 wk (range, 1-7 wk). During maintenance, median dosing interval of epoetin alfa 40,000 U SC was Q2W (range, 1.1-9.5 wk). Target Hb (≥13 g/dL) was maintained in 6 pts with Q2W dosing, 25 (50%) with Q2W, 10 (20%) with Q2W, 4 (8%) with Q2W, and 2 (4%) with Q4W. In 3 pts with only a few days in maintenance, dosing interval was not assessed. Median weekly dose of epoetin alfa was 16,697 U (range, 4211-37,333 U).

Conclusions: These preliminary data suggest that the majority of anemic, HIV-infected pts in this study can maintain a target Hb level of ≥13 g/dL with the more convenient Q2W or Q4W dosing regimens.

REFERENCES

7. Gerhard Leitz, MD, PhD, UCSF/Norris Comprehensive Cancer Center and Hospital 1441 Eastlake Avenue, MS 34 Los Angeles, CA 90033-0804 Telephone: 323-865-3913 Fax: 323-865-0060 E-Mail: hornor@usc.edu
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ABSTRACT
Background: Previous studies have shown that weekly dosing of epoetin alfa (SC) every 2 weeks (Q2W) is safe and effective at increasing hemoglobin (Hb) levels and improving quality of life (QoL) in anemic HIV-infected patients (pts). However, in a population already burdened with complex medication regimens, the efficacy, safety, and convenience of epoetin alfa SC every 2 weeks (Q2W) to maintain Hb needs further exploration.

Methods: In a 24-week, multicenter, open-label study, HIV-infected pts with Hb ≤12 g/dL were administrated epoetin alfa 40,000 U SC every 2 weeks until target Hb (≥13 g/dL) was achieved. Patients were then switched to a maintenance phase during which epoetin alfa was given at a dosage of 40,000 U SC every 2 weeks (Q2W), during Q2W dosing, Hb measured ≥11 g/dL, pts were switched back to QW dosing if Hb ≥14 g/dL, dosing was temporarily withheld until Hb reached <14 g/dL, when previous dosing maintenance resumed.

Results: At the time of this preliminary analysis, 43 pts were enrolled. Baseline characteristics are mean age 45 ± 10 years, 20 (47%) white, 34 (80%) HAART, median CD4+ 225 cells/µL (range, 3-1300), median HIV-RNA 775 copies/mL (range, 4.3-16,935,000), median age 40.5 ± 20.6 (range, 1.2-94; 75% of pts entered maintenance phase, having reached target Hb (≥11 g/dL) in a median of 5.1 wk (range, 1.1-31). In a median of 2.1 wk (range, 1-11) patients achieved target Hb. Median duration of maintenance, median dosing interval of epoetin alfa 40,000 U SC was Q2W 1 wk (range, 1-11), 1�2 wk (range, 1-11.6 wk). Target Hb (≥11 g/dL) was maintained in 8/43 pts with QW dosing, 25/37 (67%) with Q4W dosing, 4 (9%) with Q2W, and 1 (2%) with Q1W in 3 pts with only a few days in maintenance, dosing interval was not assessed. Median weekly dose of epoetin alfa was 16,847 U (range, 411-37,332 U).

Conclusions: Those preliminary data suggest that the majority of anemic HIV-infected pts in this study can maintain a target Hb level of ≥13 g/dL with the more convenient Q2W dosing regimen.

INTRODUCTION
Anemia remains the most common hematologic abnormality in patients infected with HIV infection.1,2 Anemia is strongly associated with decreased survival in HIV-positive patients.1,2,3 Recent studies have shown that once-weekly (QW) administration of epoetin alfa 40,000 U is effective in improving anemia and quality of life in HIV-infected patients receiving highly active antiretroviral therapy (HAART).4,5 This rationale formed the basis for the current study, in which syngeneic monkeys, target Hb levels were achieved more rapidly with a Q2W dosing regimen, compared with a larger dose given less frequently, and epoetin alfa was effective at maintaining target Hb levels with an every 2- or 3-week dosing schedule when initiated at higher Hb levels.6,7

METHODS
Inclusion Criteria
• HIV-infected men or women ≥ 18 years of age
• Currently on stable antiretroviral regimen for at least 6 months prior to enrollment
• Epoetin alfa was well tolerated

Exclusion Criteria
• Acute, symptomatic opportunistic infection or other acute AIDS-defining illness within 6 months of screening
• History of primary hematologic disease
• Anemia attributable to factors such as iron, B12 or folic deficiency, hemolysis, or gastrointestinal bleeding
• Hepatitis C virus coinfection unless treatment with interferon/interferon+ribavirin had been completed at least 12 weeks prior to study entry
• Fertility level with oophorectomy
• Pregnancy or lactation

STUDY DESIGN
Phase II, open-label, randomized, multicenter study (Figure 1).

RESULTS
Patient Demographics
BL characteristics: Median age = 43 years (range: 23-74 years); Ethnicity: 53% black, 34% white, 8% Hispanic, 5% other; 60% on HAART; Median CD4+ count = 130 cells/µL (range, 1-5,308 cells/µL); Median HIV-RNA = 1,240 copies/mL (range, 31-6,250,000 copies/mL); and Median Hb = 11.5 g/dL (range, 7.2-12.8 g/dL).

Table 1: Disposition of Evaluated Patients

<table>
<thead>
<tr>
<th>TABLE 1. Disposition of Evaluated Patients</th>
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<tbody>
<tr>
<td>Total number of patients evaluated 120</td>
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<tr>
<td>Patients transfused 3</td>
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<tr>
<td>Initiation phase 119</td>
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<tr>
<td>Number of patients who did not reach target Hb 17</td>
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<tr>
<td>Maintenance phase (Hb ≥11 g/dL) 94</td>
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<tr>
<td>Number of patients who achieved MP and had no subsequent assessment available 8</td>
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Patient Monitoring
• Complete blood count including Hb, baseline (BL), Weeks 1–4, and every 2 weeks thereafter or on early withdrawal
• Adverse events monitored throughout the study and collected at each study visit

RESULTS (cont’d)

Safety
• A total of 227 adverse events were reported; most were mild to moderate in severity and not related to epoetin alfa; 1 adverse event (mild muscle spasm in lower back) was considered possibly related to epoetin alfa; 1 patient experienced serious adverse events, including 1 death—none were related to study epoetin alfa.
• 74 yr old admitted to hospital with fractured hip requiring surgery; suspected probably due to pulmonary embolism

CONCLUSIONS
In this preliminary analysis of 120 patients, 86% had Hb increases of ≥1 g/dL, 77% achieved target Hb ≥13 g/dL, with epoetin alfa 40,000 U QW.

Once patients reached target Hb ≥13 g/dL, ability to maintain Hb levels at ≥13 g/dL, using epoetin alfa once every 2 weeks to once every 4 weeks.

The calculated median dosing interval for efficacious epoetin alfa maintenance was on average 40,000 U every 2 weeks.

The longer dosing intervals of epoetin alfa in maintenance provide greater patient and provider ease, while potentially increasing compliance.

Epoetin alfa was well tolerated.
ABSTRACT

Background: Previous studies have shown that weekly dosing of epoetin alfa (40,000 U subcutaneously, SC) every 28 days (Q28) is safe and effective at increasing/hemoglobin (Hb) levels and improving quality of life (QOL) in anemic, HIV-infected patients (pts). However, a population currently burdened with complex medication regimens, the efficacy, safety, and convenience of epoetin alfa 40,000 U SC every 2 weeks (Q2W) to maintain Hb needs further exploration.

Methods: A 24-week, multicenter, open-label, study, HIV-infected with Hb <12 g/dL were administered epoetin alfa 40,000 U SC QW until target Hb (13 g/dL) was achieved. Patients were then switched to a maintenance phase during which epoetin alfa was given at a dosage of 40,000 U SC Q2W. During Q2W dosing, Hb measured ≤11 g/dL, pts were switched back to QW dosing if Hb was ≤11 g/dL, dosage was temporarily withheld until Hb reached ≥11 g/dL, when previous dosing maintenance resumed.

Results: At the time of this preliminary analysis, 69 pts were enrolled. Baseline characteristics are as follows: age 41 ± 10 yrs, 79% HIV, median CD4+ = 240 cells/µL (range, 3-1300), median HIV-RNA = 47,755 copies/mL (range, 1,300-1,308,000), median Hb = 9.0 g/dL (range, 7.2-12.8 g/dL), 97% pts entered maintenance phase, having reached target (Hb ≥11 g/dL). In a median of 5 wk (range, 1-17 wk) after initiation of maintenance, median dosing interval of epoetin alfa 40,000 U SC was Q2 W (median, 11 g/dL, to median of 13.4 g/dL (range 13.0-17.7 g/dL) upon reaching target (Hb ≥11 g/dL). Withdrawing or altering epoetin alfa was given at a dosage of 40,000 U SC QW until target Hb (13 g/dL) was achieved.

Conclusions: These preliminary data suggest that the majority of anemic, HIV-infected pts in the study can maintain a target Hb ≥11 g/dL with the more convenient Q2W dosing regimen.

STUDY OBJECTIVES

The present study sought to evaluate the efficacy and safety of Q2W dosing of epoetin alfa in maintaining Hb levels of approximately 13 g/dL in anemic HIV-infected patients.

METHODS

Inclusion Criteria

• HIV-infected men or women 18 to 75 years of age
• Currently on stable antiretroviral regimen for at least 4 weeks prior to enrollment
• Hemoglobin ≤13 g/dL

Exclusion Criteria

• Acute, symptomatic opportunistic infection or other acute AIDS-defining illnesses within 6 months of screening
• History of primary hematologic disease
• Anemia attributable to factors such as: tumor, or blood dilution due to transfusion or other causes
• Hematocrit ≥30% concomitant treatment with iron/iron chelator/interferon drug such as levamisole or interferon alfa-2a/b (where available)
• Fibrinoid-nephritis
• Pregnancy or lactation

Study Design

Phase I: Open-label, randomized, multicenter study (Figure 1).

RESULTS

Patient Demographics

BL characteristics: Median age = 43 years (range: 23-74 years); Ethnicity: 53% black, 34% white, 6% Hispanic; 5% other; 92% on HAART; Median CD4+ count = 198 cells/µL (range, 51-3,256 cells/µL); Median HIV-RNA = 1,240 copies/mL (range, 10-95,000,000 copies/mL) and Median Hb = 11.3 g/dL (range, 7.2-12.8 g/dL).

TABLE 1. Disposition of Evaluated Patients

| Total number of patients evaluated | 120
| Patients transfused | 1
| Initiation phase | 119
| Number of patients withdrawn* | 7
| Number of patients not yet achieving target Hb | 18
| Maintenance phase (Hb ≥11 g/dL) | 94
| Number of patients who reached NP but had no subsequent assessment available | 8
| Maintenance phase of patients who received epoetin alfa | 86

*The reasons for withdrawals are as follows: to follow-up (n = 2), patient request (n = 2), adverse events unrelated to epoetin alfa (n = 2), and noncompliance (n = 1).

RESULTS (cont’d)

Safety

• A total of 227 adverse events were reported, most were mild to moderate in severity and not related to epoetin alfa

• One adverse event (tympanic membrane perforation) was considered possibly related to epoetin alfa

• Seven patients experienced serious adverse events, including 1 death—their relative, who died of AIDS

CONCLUSIONS

In this preliminary analysis of 120 patients, 87% had Hb increases of ≥1 g/dL, 77% achieved target Hb ≥13 g/dL, with epoetin alfa 40,000 U QW

• Once patients reached target Hb, 83% were able to maintain Hb levels at ≥13 g/dL, using epoetin alfa once every 2 weeks to once every 4 weeks

• The calculated median dosing interval for efficacious epoetin alfa maintenance was on average 40,000 U every 2.7 weeks

• The longer dosing intervals of epoetin alfa in maintenance provide greater patient and provider ease, while potentially increasing compliance

• Epoetin alfa was well tolerated

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Methods: In a 24-week, multicenter, open-label study, HIV-infected pts with Hb ≤12 g/dL were administered epoetin alfa 40,000 U SC QW until target Hb (>13 g/dL) was achieved. Patients were then switched to a maintenance phase during which epoetin alfa was given at a dosage of 40,000 U SC Q2W. If, during Q2W dosing, Hb measured ≤11 g/dL, pts were switched back to QW dosing; if Hb was ≥14 g/dL, dosing was temporarily withheld until Hb reached <14 g/dL, when previous maintenance dose resumed.

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Conclusions: These preliminary data suggest that the majority of anemic, HIV-infected pts in this study can maintain a target Hb level of ≥13 g/dL with the more convenient Q2W dosing regimen.