PROCRIT® (epoetin alfa)
PROCRIT - Once Every-Four-Weeks Dosing in Chronic Kidney Disease

SUMMARY

- **Spinowitz et al (2008)**[1] assessed hemoglobin (Hb) response in nondialysis chronic kidney disease (CKD) patients with anemia, treated with 1 of 4 initiation regimens of epoetin alfa (EPO) (10,000 international units [IU] once weekly [QW]; 20,000 IU once every 2 weeks [Q2W]; 20,000 IU once every 4 weeks [Q4W]; and 40,000 IU Q4W; N=262). The mean Hb change from baseline was not inferior for the Q4W EPO group vs the Q2W group and adverse events (AEs) were similar between groups.
- **Provenzano et al (2005)**[2] evaluated EPO dosing schedules of up to Q4W, in the PROMPT study (N=519), and found that Hb levels ≥11.0 g/dL were maintained in ~90% of patients receiving EPO 10,000 IU subcutaneously (SC) QW and 20,000 IU SC Q2W and >75% of patients administered EPO 30,000 IU SC once every 3 weeks (Q3W) and 40,000 IU SC Q4W. The most frequent AEs were hypertension (HTN), peripheral edema, urinary tract infection, and headache.
- **Pergola et al (2010)**[3] conducted a study in nondialysis patients with CKD and anemia (N=430) where Q2W and Q4W dosing with EPO demonstrated noninferiority to QW dosing with respect to the change in Hb concentration from baseline to the average of the last 12 weeks of treatment. The most common serious adverse (SAEs) were congestive heart failure (CHF), acute renal failure, chest pain, and anemia.
- **Patel et al (2012)**[4] evaluated the use of extended-dosing frequencies of EPO in patients residing in long-term care facilities (N=157). The administration of EPO at intervals of Q2W followed by Q4W was effective for the treatment of anemia in nondialysis patients with CKD. AEs were similar between the EPO and the standard of care (SOC) treatment groups. Thrombovascular events (TVEs) were reported in 5.9% of patients in the EPO group compared with 2.5% of patients in the SOC group.
- **McGowan et al (2008)**[5] conducted a study in nondialysis patients with CKD and anemia (N=39) and reported that each of the 4 different dosing regimens of EPO (3 times a week [TIW], QW, Q2W, and Q4W) administered SC resulted in a similar pharmacodynamic (PD) response, despite modest differences in pharmacokinetic (PK) response.
- A single-center prospective study investigating Q4W EPO dosing has been published.[6] Post hoc analyses of the PROMPT study[2] are also available.[7-9] In addition, Q4W EPO dosing has been evaluated in other retrospective analyses.[10-12]

CLINICAL DATA

Q4W Initiation EPO

Spinowitz et al (2008)[1] evaluated the feasibility of initiating therapy with EPO using dosing intervals of up to Q4W in anemic CKD patients not receiving dialysis (N=262).

Study Design/Methods

- This was a prospective, open-label, randomized, multicenter, 16–week study.
- The study enrolled adult patients with Hb <11 g/dL.
- CKD was defined as glomerular filtration rate (GFR) 15–90 mL/min/1.73 m^2.
- Target Hb was 11–12 g/dL.
- Patients were randomized in a 1:2:2:2 ratio to receive the following extended EPO regimens SC for 16 weeks: 10,000 IU QW; 20,000 IU Q2W; 20,000 IU Q4W; or 40,000 IU Q4W.
- Dose titrations were allowed starting at week 5.
- The maximum doses allowed were: 20,000 IU for QW; 40,000 IU for Q2W; 35,000 IU for 20,000 IU Q4W; and 70,000 IU for 40,000 IU Q4W dosing groups, respectively.

Results

Patient Characteristics

- The mean Hb level was 10.2 g/dL and the mean GFR was 30.2 mL/min/1.73 m^2.

Efficacy

- A total of 230 (87.8%) patients completed the study and 32 (12.2%) withdrew.
- Modified intent-to-treat (mITT) or safety population (randomized patients who received ≥1 dose of EPO) consisted of 259 patients.
- The mean change in Hb for Q4W dosing regimens was not inferior to that of the Q2W dosing regimen. The difference in mean Hb change for 40,000 IU Q4W group vs 20,000 IU Q2W group was 0.12 (95.2% confidence interval [CI], -0.21 to 0.44). The difference in mean Hb change for 20,000 IU Q4W group vs 20,000 IU Q2W group was –0.05 (95.2% CI, -0.38 to 0.28).
- Hb >11 g/dL and increase ≥1 g/dL were achieved during the study: 10,000 IU QW (85%); 20,000 IU Q2W (81%); 20,000 IU Q4W (65%); 40,000 IU Q4W (77%).
- Mean weekly dose was 5943 IU, 7376 IU, 4522 IU, and 8660 IU for 10,000 IU QW, 20,000 IU Q2W, 20,000 IU Q4W, and 40,000 IU Q4W groups, respectively.
- Majority of dose adjustments were dose reductions which were most frequent in the 10,000 IU QW group and least frequent in the 20,000 IU Q4W group.

Safety

- The overall incidence of AEs was similar amongst all groups.
- The most common AEs (≥10%) were diarrhea, constipation, and headache; these events were considered possibly, probably, or very likely related to study drug in only 1 patient for each event.
- The following TVE were noted: 10,000 IU QW: n=1 (chest pain); 20,000 IU Q2W: n=0; 20,000 IU Q4W: n=1 (myocardial infarction [MI]); and 40,000 IU Q4W: n=3 (MI, chest discomfort, and peripheral vascular disorder). MI and peripheral vascular disorder were considered clinically relevant. Of the 5 patients who experienced a TVE, none had a Hb >12 g/dL or a Hb rise in excess of 1.0 g/dL over the previous 2–week period at the time that the event occurred.
- Two deaths were reported in the 20,000 IU Q2W group and 1 in the 20,000 IU Q4W group during the study.

Q4W Maintenance EPO

Provenzano et al (2005)[2] evaluated if extended EPO dosing schedules of up to Q4W were as effective as QW dosing in maintaining Hb levels ≥11 g/dL in CKD patients not on dialysis (N=519).

Study Design/Methods

- This was a prospective, randomized, open-label, multicenter, 16–week study.
- The clinical evaluation of EPO for maintenance phase treatment of patients with anemia due to CKD (PROMPT) study included CKD patients (serum creatinine: 1.5-6.0 mg/dL for females, 2.0-6.0 mg/dL for males) receiving maintenance EPO for treatment of anemia for ≥2 months.
- Patients were randomized to receive 1 of 4 dosing regimens SC for up to 16 weeks: 10,000 IU SC QW; 20,000 IU SC Q2W; 30,000 IU SC Q3W; or 40,000 IU SC Q4W.
- Dose reductions were allowed during the study, but dose escalations were not.

Results

Patient Characteristics

- Mean baseline Hb and GFR for all patients were 11.9±0.8 g/dL and 21.1±8.0 mL/min/1.73m^2, respectively.

Efficacy

- Of the 519 patients enrolled, 413 (79.6%) completed the 16-week study.

PROMPT Study Results[2]

	QW	Q2W	Q3W	Q4W
n=445[a]	108	114	114	104
Mean baseline Hb, g/dL (95% CI)	11.9 (11.7-12.0)	11.9 (11.8-12.0)	11.9 (11.8-12.1)	11.9 (11.8-12.0)
Mean final Hb, g/dL (95% CI)	12.2 (12.0-12.4)	11.9[b] (11.7-12.2)	11.2 (11.0-11.4)	11.4[b] (11.1-11.7)
% of patients maintaining Hb ≥11 g/dL	93.5	89.5	77.2	76.0

Abbreviations: CI, confidence interval; Hb, hemoglobin; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.
[a]Five patients did not have a final Hb measurement and are not included in the above analysis.
[b]Significant 1-sided *P*-value testing noninferiority from QW (defined as greater than -10% of the final mean Hb measurement of the QW group).

- Approximately 90% of patients administered EPO Q2W and >75% of patients administered EPO Q3W or Q4W maintained Hb levels ≥11 g/dL.
- Difference in mean final Hb between QW and both Q2W and Q4W met the criteria for noninferiority (*P*<0.001 and *P*=0.024, respectively) but did not meet criteria for noninferiority between Q3W and QW (-1.0 g/dL) (*P*=0.084, 1-sided). The intent-to-treat analysis showed that all 3 groups were noninferior to the QW group.
- GFR remained stable during the 16-week maintenance phase in all dosing groups and 14 patients progressed to dialysis.

Safety

- The incidence of AEs was low and comparable across the study groups.
- The most frequent AEs reported by at least 5% of patients in any group included HTN (6.8%), peripheral edema (5.7%), urinary tract infection (4.3%), and headache (3.3%).
- Clinically significant AEs possibly related to vascular thrombosis were reported in 13 (2.5%) of patients.
- Sixteen (3.1%) of patients withdrew from the study due to AEs.

Pergola et al (2010)[3] evaluated whether EPO treatment Q2W or Q4W was inferior to QW EPO in patients with anemia and CKD (N=430).

Study Design/Methods

- This was a randomized, open-label, multicenter, parallel-group study that included anemic patients with CKD (GFR ≥15 and <60 mL/min/1.73 m^2) not on dialysis.
- Patients maintained on a stable QW dose were randomized in a 1:1:2 ratio to receive 1 of 3 EPO dosing regimens SC: EPO QW for 36 weeks (initial dose: the same as the last prerandomization dose of EPO treatment), EPO Q2W for 36 weeks (initial dose: twice the QW prerandomization dose of EPO rounded to nearest 10,000 IU), or EPO Q4W for 36 weeks (initial dose: 4 times the QW prerandomization dose of EPO rounded to nearest 20,000 IU).
- The safety population was defined as receiving at least 1 dose of study drug (N=430).

- The mITT population was defined as receiving ≥1 dose of study drug and having ≥1 postrandomization Hb measurement (N=428).
- The maximum dose was 20,000 IU QW, 40,000 IU Q2W, or 80,000 IU Q4W.

Results

Patient Characteristics

- The median baseline GFR was 26 mL/min/1.73 m^2.
- At baseline, the mean Hb concentrations were 11.0, 11.1, and 11.2 g/dL for the QW, Q2W, and Q4W groups, respectively.

Efficacy

- Median weekly doses over the course of the study were 2967 IU for the QW group, 4529 IU for the Q2W group, and 5423 IU for the Q4W group.
- Hb maintenance was noninferior in both the Q2W and Q4W dosing groups compared with the QW dosing arm. For the Q2W and QW groups, the estimated mean difference was -0.03 g/dL (95% CI, -0.21 to 0.15); for the Q4W and QW groups, the estimated mean difference was -0.09 g/dL (95% CI, -0.25 to 0.06).
- In all 3 treatment groups, the mean final Hb levels were 11.0 g/dL (average Hb over last 12-week period).
- The mean proportion of weeks per subject in which the Hb concentration was 10.0-11.9 g/dL, inclusive, during weeks 13-37 was 81% of the 107 patients in the QW treatment arm, 81% of the 106 patients in the Q2W treatment arm, and 75% of the 215 patients in the Q4W treatment arm.
- A total of 24 subjects (5.6%) received transfusions: 3.7% in the QW treatment arm, 5.7% in the Q2W treatment arm, and 6.5% in the Q4W treatment arm.
- The majority of subjects receiving a transfusion (n=20) received transfusions for an acute decrease in Hb associated with hospitalization for an intercurrent medical illness or surgical procedure.

Safety

- Among the 3 treatment groups, the incidence of AEs was comparable.
- The most commonly reported AEs across treatment arms: HTN (11%), urinary tract infection (8%), edema (8%), and hyperkalemia (2%).
- Death occurred in 4%, 3%, and 4%; TVEs occurred in 3%, 5%, and 3%; and SAEs occurred in 22%, 26%, and 26% of patients in the QW, Q2W, and Q4W treatment groups, respectively.
- The most commonly reported SAEs across treatment arms were CHF (4%), acute renal failure (3%), chest pain (2%), and anemia (2%).

Patel et al (2012)[4] evaluated the use of extended-dosing frequencies for EPO over a 27-week period for patients who resided in long-term care facilities (N=157).

Study Design/Methods

- This was a prospective, open-label, multicenter, controlled study and patients were randomized in a ratio of 3:1 to receive EPO (n=118) or SOC (n=39).
- Patients were initiated on EPO 20,000 IU SC Q2W. Doses were titrated to maximum doses of 60,000 IU.

Results

Patient Characteristics

- The mean baseline Hb level was 10.1±0.8 g/dL and the mean estimated glomerular filtration rate (eGFR) was 45.7±17.1 mL/min/1.73 m^2 in the EPO group; corresponding values in the SOC group were 10.2±0.9 g/dL and 43.4±15.1 mL/min/1.73 m^2, respectively.

Efficacy

- The mean change in Hb level from baseline to endpoint was 0.9 g/dL in the EPO group and 0.3 g/dL in the SOC group (*P*=0.006).
- Hb responses (2 consecutive Hb levels ≥11.0 g/dL or increases ≥1.0 g/dL) were achieved in 85.1% of patients in the EPO group and in 53.8% of patients in the SOC group (*P*<0.001).
- Thirty-three patients (28.9%) converted from the Q2W to Q4W dosing regimen.
- No patient who converted to the Q4W dosing regimen had to be returned to the Q2W dosing regimen.
- Median time to Hb response was 41 days in the EPO group and 114 days in the SOC group (*P*<0.0001).
- Four patients in the EPO group required transfusions. None of the patients in the SOC group required a transfusion.

Safety

- The percentages of patients who had treatment-emergent AEs, SAEs, or who died during or within 30 days of the end of the study were similar between the EPO group and the SOC group.
- The most frequent AEs reported by ≥10% of patients in the EPO group included pain in extremity (10.1%), peripheral edema (11.0%), and upper respiratory tract infection (16.9%).
- Thromboembolic vascular AEs occurred in 5.9% of patients in the EPO group and in 2.5% of patients in the SOC group.

PHARMACOKINETIC STUDY

McGowan et al (2008)[5] evaluated PK and PD profiles of 4 different dosing regimens of EPO administered SC in anemic CKD patients not on dialysis during a prospective, open-label, randomized, multicenter study (N=39). The following dosing regimens were studied: 50 U/kg TIW X 12 doses; 10,000 U QW X 4 doses; 20,000 U Q2W X 2 doses; and 40,000 U Q4W X 2 doses. Each of the 4 different dosing regimens of EPO (TIW, QW, Q2W, and Q4W) resulted in a similar PD response despite modest differences in PK responses. Median time to achieve maximum endogenous erythropoietin concentration ranged from 12 to 24 hours postdose across all treatment groups. Maximum observed serum concentration and area under the curve increased proportionally with increasing doses of EPO. With the exception of the TIW group, mean half-life ($t_{1/2}$) values were similar across all treatment groups. Terminal $t_{1/2}$ was difficult to determine in the TIW group due to more frequent dosing in this group.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 16 July 2024. In an effort to streamline this document to provide the most relevant information, only multicenter, prospective studies are described above. A single-center, prospective study and retrospective studies are cited in the Summary section.

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