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Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial

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Abstract

Background. Several studies with erythropoiesis-stimulating agents claim that maintenance therapy of renal anaemia may be possible at extended dosing intervals; however, few studies were randomized, results varied, and comparisons between agents were absent. We report results of a multi-national, randomized, prospective trial comparing haemoglobin maintenance with methoxy polyethylene glycol-epoetin beta and darbepoetin alfa administered once monthly.

Methods. Haemodialysis patients ($n = 490$) on stable once-weekly intravenous darbepoetin alfa were randomized to methoxy polyethylene glycol-epoetin beta once monthly or darbepoetin alfa every 2 weeks for 26 weeks, with dose adjustment for individual haemoglobin target (11–13 g/dL; maximum decrease from baseline 1 g/dL). Subsequently, patients entered a second 26-week period of once-monthly methoxy polyethylene glycol-epoetin beta and darbepoetin alfa. The primary endpoint was the proportion of patients who maintained average haemoglobin ≥10.5 g/dL, with a decrease from baseline ≤1 g/dL, in Weeks 50–53; the secondary endpoint was dose change over time. The trial is registered at www.ClinicalTrials.gov, number NCT00394953.

Results. Baseline characteristics were similar between groups. One hundred and fifty-seven of 245 patients treated with methoxy polyethylene glycol-epoetin beta and 99 of 245 patients with darbepoetin alfa met the response definition (64.1% and 40.4%; $P < 0.0001$). Doses increased by

6.8% with methoxy polyethylene glycol-epoetin beta and 58.8% with darbepoetin alfa during once-monthly treatment. Death rates were equal between treatments (5.7%). Most common adverse events included hypertension, procedural hypotension, nasopharyngitis and muscle spasms, with no differences between groups.

Conclusions. Methoxy polyethylene glycol-epoetin beta maintained target haemoglobin more successfully than darbepoetin alfa at once-monthly dosing intervals despite dose increases with darbepoetin alfa.

Keywords: anaemia; chronic kidney disease; darbepoetin alfa; erythropoiesis-stimulating agent; methoxy polyethylene glycol-epoetin beta

Introduction

Anaemia is a common complication of chronic kidney disease, and correction of anaemia with erythropoiesis-stimulating agents is associated with improved patient outcome [1] and quality of life [2].

Approved erythropoiesis-stimulating agents with short half-lives generally require short dosing intervals and frequent administration (mainly two to three times per week) to maintain stable haemoglobin concentrations [3]. An erythropoiesis-stimulating agent with a longer half-life and correspondingly longer dose interval might improve anaemia management and provide greater convenience to patients [4] while decreasing the impact on health-care resources, especially given the increasing incidence and prevalence of chronic kidney disease [5]. This has led to clinical testing of available erythropoiesis-stimulating agents at dosing intervals longer than those in approved labelling. However, most published studies tested dosing intervals shorter than once monthly and used uncontrolled designs [6,7].

Methoxy polyethylene glycol-epoetin beta, a continuous erythropoietin receptor activator (C.E.R.A.), is approved without restrictions for once-monthly maintenance therapy for anaemia in patients with chronic kidney disease, while once-monthly administration of darbepoetin alfa is approved in Switzerland [8] but restricted to pre-dialysis patients stable at the 2-week dosing interval in the EU [9]. The aim of the PATRONUS (comPArator sTudy of C.E.R.A. and darbepOetin alfa in patieNts Undergoing dialySis) study was to compare the efficacy and safety of methoxy polyethylene glycol-epoetin beta and darbepoetin alfa, each ultimately administered intravenously once monthly for the maintenance of haemoglobin concentrations in dialysis patients, in a prospective, parallel-group design.

Materials and methods

Study participants

Patients were screened from 82 centres in Europe, Canada and Australia and were aged ≥18 years, had stable chronic renal anaemia (with a haemoglobin range of 11–13 g/dL) and were on regular haemodialysis (Figure 1). To be included in the study, patients must have received haemodialysis three times weekly for ≥12 weeks before screening and during the 4-week screening/baseline period. Eligible patients must have had stable haemoglobin concentrations, defined as a maximum variation of 1 g/dL during the screening/baseline period. They must have undergone continuous once-weekly maintenance intravenous darbepoetin alfa therapy for ≥8 weeks before screening and during the screening/baseline period. Patients were not selected on the basis of darbepoetin alfa dose. Only one dose change was allowed during the screening/baseline period. Patients also had to have adequate iron status, defined as serum ferritin ≥100 μg/L, transferrin saturation ≥20% or <10% hypochromic red blood cells. Patients were excluded from the study if they had overt bleeding that necessitated red blood cell transfusion within 8 weeks of the start of screening or during the screening/baseline period; a non-renal cause of anaemia; C-reactive protein >30 mg/L; the likelihood of early withdrawal; or life expectancy of <12 months.

This open-label, randomized, multicentre, parallel-group phase III study was designed in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice of the International Conference on Harmonisation. The design was approved by the review boards or ethics committees of participating institutions. All participants gave prior written informed consent.

Procedures

Figure 2 shows the treatment protocol. All patients entered a 4-week screening/baseline period during which they continued to receive their previous darbepoetin alfa treatment (Amgen, Thousand Oaks, CA, USA). Eligible patients were then randomly assigned (1:1) to receive intravenous methoxy polyethylene glycol-epoetin beta (F. Hoffmann-La Roche, Basel, Switzerland) once monthly or darbepoetin alfa every 2 weeks for a first 26-week treatment period. Patients were randomized between December 2006 and November 2007.

The starting dose of methoxy polyethylene glycol-epoetin beta was based on the previous weekly dose of darbepoetin alfa in the week before randomization. For patients who previously received <40 μg of darbepoetin alfa per week, the starting dose of methoxy polyethylene glycol-epoetin beta was 120 μg. Patients who had received 40–80 μg or >80 μg of darbepoetin alfa per week were given 200 or 360 μg of methoxy polyethylene glycol-epoetin beta, respectively. The starting dose of darbepoetin alfa every 2 weeks was twice the weekly dose of darbepoetin alfa in the week before randomization.

After an initial 26-week period, patients entered a second 26-week treatment period, during which both study medications were administered once monthly: the first once-monthly dose of darbepoetin alfa was double the last dose of the first 26-week treatment period, while methoxy polyethylene glycol-epoetin beta was continued at the same dose and interval as in the first 26-week period.

Doses for all patients were to be adjusted so that haemoglobin concentrations would remain within a target range of 11–13 g/dL and not decrease >1 g/dL compared with each individual patient's baseline. Doses of methoxy polyethylene glycol-epoetin beta were to be adjusted according to protocol and not more often than once monthly. Doses of methoxy polyethylene glycol-epoetin beta were to be decreased by 25% for haemoglobin >13 and ≤14 g/dL and increased by 25% for haemoglobin decreases >1 g/dL versus baseline or for haemoglobin <11 and ≥9 g/dL. Methoxy polyethylene glycol-epoetin beta dose decreases of 50% were to be made for haemoglobin increases >2 g/dL versus baseline and increases of 50% for haemoglobin decreases >2 g/dL versus baseline or haemoglobin <9 g/dL. Treatment was to be interrupted temporarily if haemoglobin exceeded 14 g/dL.

Darbepoetin alfa doses were to be adjusted according to the approved prescribing information, without additional restrictions.

Iron supplementation was to be initiated or intensified according to centre practice in cases of iron deficiency (serum ferritin <100 μg/L, transferrin saturation <20%, or hypochromic red blood cells >10%) and discontinued in patients who had serum ferritin levels >800 μg/L or transferrin saturation >50%.

Randomization and masking

Randomization numbers were generated by computer at a coordinating centre and allocated to the two treatment groups in a 1:1 ratio using a permuted block randomization with a block size of four, in the order in which patients were enrolled. Randomization was not stratified by centre; therefore, identification of the next patient in the sequence was impos-

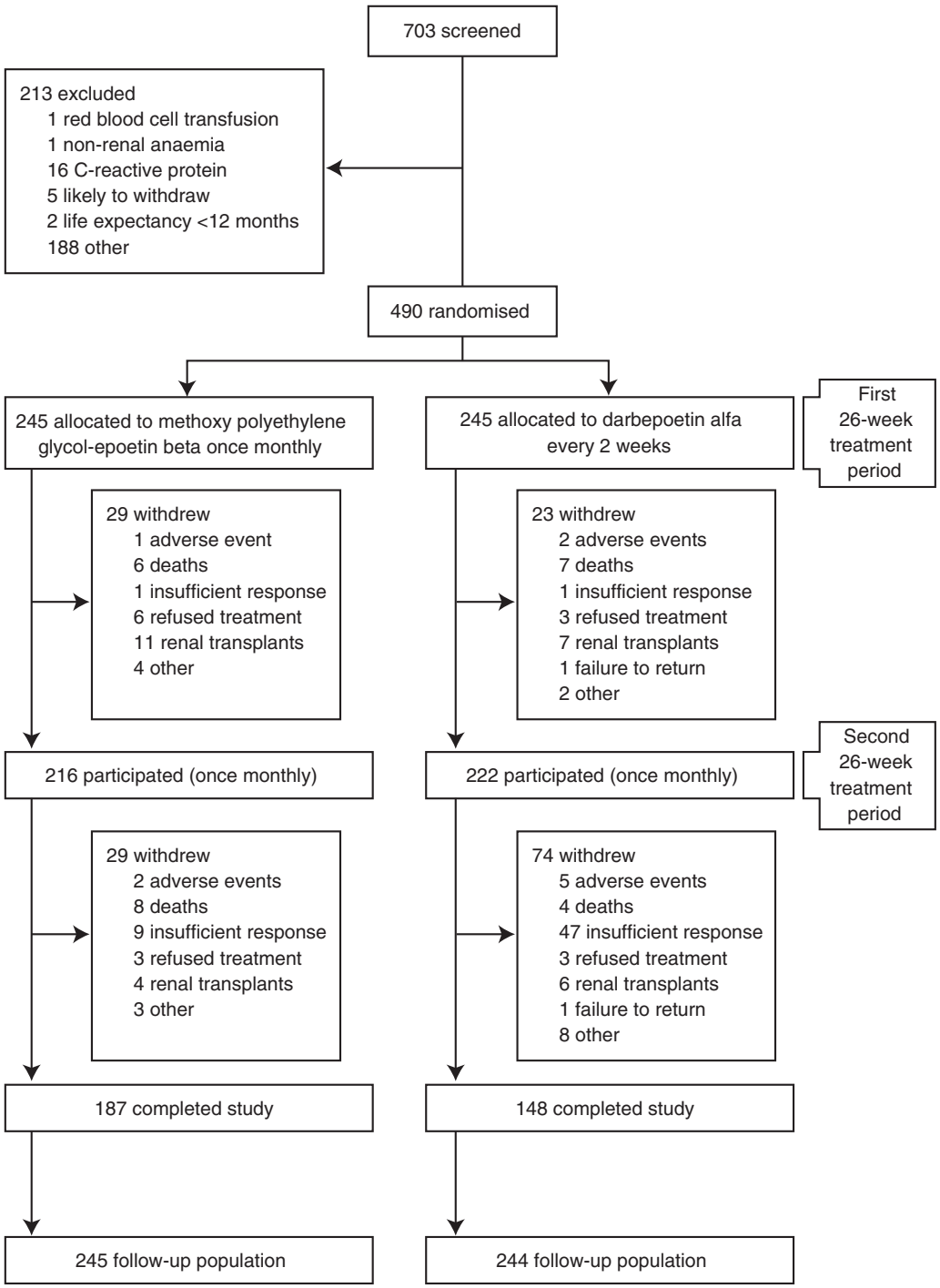

Fig. 1. Screening and enrolment of study patients.

sible. Investigators received numbers by telephone and recorded them on patients' electronic case-report forms. This was an open-label study; therefore, the treatment assignment was not masked.

Study outcomes

The primary efficacy endpoint was the proportion of responders on once-monthly treatment in the second treatment period in the intent-to-treat population, i.e. all randomized patients with a haemoglobin decrease from baseline ≤1 g/dL and an average haemoglobin ≥10.5 g/dL during the evaluation period (Weeks 50–53).

The secondary efficacy endpoint was the difference between the monthly dose in Week 27 and the average dose in months 11 and 12 for the two study groups.

Assessments

Patients were assessed every week during the screening/baseline period, the 52-week treatment period and at the final visit. At each assessment, all patients who had received at least one dose of study drug throughout the treatment protocol were asked whether they had experienced any adverse events. Blood pressure, heart rate, haemoglobin and haematocrit

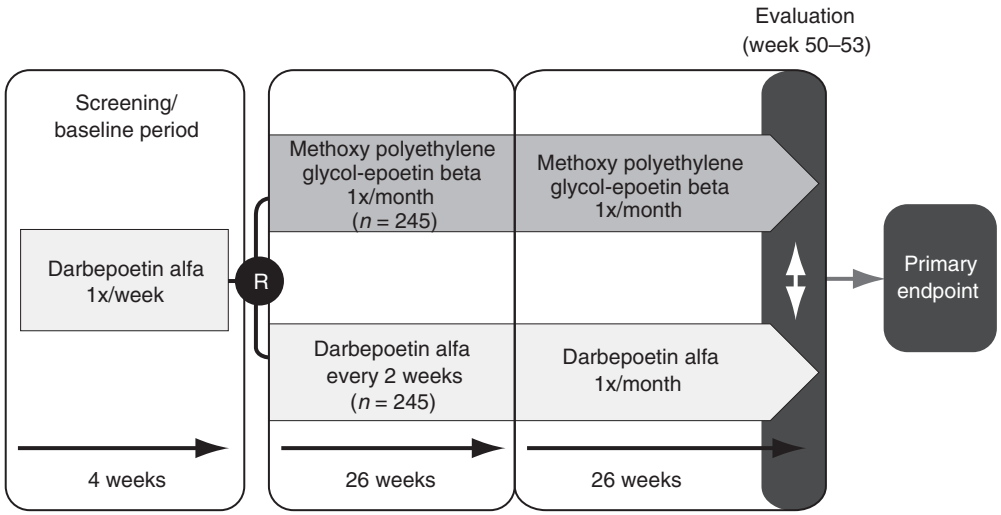

Fig. 2. Treatment protocol. *R* = randomization.

were measured at every visit. White blood cell count, platelet count, aspartate amino transferase, alanine aminotransferase, albumin, alkaline phosphatase, C-reactive protein, potassium, phosphorus, serum ferritin, serum iron, serum transferrin, total iron-binding capacity or proportion of hypochromic red blood cells were measured every 8 weeks and at the final visit.

Blood samples for assessment of study-drug immunogenicity were collected at Weeks 1, 13, 27 and 40 and at the final visit. Physical examinations were performed at baseline and at the final visit. Fractional clearance of urea (Kt/*V*) or urea reduction ratio was used to assess adequacy of haemodialysis at baseline. The use of any red blood cell transfusions, iron supplementation and all concomitant treatments were recorded throughout the study. The study ended in November 2008.

Statistical analyses

The study was powered to demonstrate an absolute difference of 15% in the primary endpoint between the two groups. On the assumption that 60% of patients receiving methoxy polyethylene glycol-epoetin beta and 45% of patients receiving darbepoetin alfa would fulfil the response definition, a sample size of 244 patients per group would be adequate to demonstrate a 15% higher response rate in the methoxy polyethylene glycol-epoetin beta arm with 90% power and a significance level of 5%.

The two treatment arms were tested for a difference in the response rate at the once-monthly dosing interval—the proportion of responders in each group—using a two-sided Chi^2-test with Schouten correction [10] at the 5% α-level.

The proportion of responders was analysed using frequency rates and two-sided 95% confidence intervals based on the exact method of Clopper and Pearson [11]. For the difference in proportions, the 95% confidence interval with Hauck–Anderson correction [12] was calculated. In addition, the risk ratio and the corresponding 95% confidence intervals were determined.

Baseline haemoglobin was calculated by a time-adjusted mean of all values recorded between the day of first study-drug administration and the previous 30 days. The haemoglobin value on the day of the first dose was included in the baseline calculation as this assessment was performed before the first dose was administered. A similar time-adjusted mean was calculated using all haemoglobin values recorded in the evaluation period. Subtracting the baseline value from the evaluation period value gave the change in haemoglobin concentration between the baseline and evaluation period. In the case of patients who entered the second treatment period (once-monthly dosing schedule), missing haemoglobin values before Week 53 were handled using the last-observation-carried-forward method. To correct for any increase in haemoglobin caused by red blood cell transfusions, the haemoglobin values measured within 3 weeks after a transfusion were replaced by the haemoglobin value measured immediately before the transfusion.

For the secondary efficacy endpoint, the percentage change between the monthly dose at Week 27 and the average dose in months 11 and 12 was calculated in each treatment group. Five patients in the methoxy polyethylene glycol-epoetin beta group and three patients in the darbepoetin alfa group had a dose at Week 27 but not thereafter and were not included in the analysis of dose change on the once-monthly dosing schedule.

Descriptive safety analyses of adverse events, serious adverse events and deaths were performed on all patients who received at least one dose of study medication (safety follow-up population).

To ensure the safety of trial participants and the integrity of the trial, an independent data and safety monitoring board (DSMB), consisting of two clinical experts in nephrology and one statistician, monitored the trial for evidence of beneficial or adverse effects. The DSMB was to review safety results every 3 months. The DSMB could make recommendations for continuation, modification or termination of the study. The trial is registered at www.ClinicalTrials.gov, number NCT00394953.

Results

Study population

A total of 490 patients were randomized from 82 centres in 13 countries. One patient assigned to the darbepoetin alfa group did not receive any study medication and was excluded from the safety follow-up population (n=489).

Figure 1 shows that 335 patients completed the study (187 given methoxy polyethylene glycol-epoetin beta and 148 given darbepoetin alfa), while 155 withdrew: 58 of 245 (24%) patients in the methoxy polyethylene glycol-epoetin beta group and 97 of 245 (40%) patients in the darbepoetin alfa group. Reasons for withdrawal were balanced between groups and in each study period, with the exception of 'insufficient therapeutic response' as assessed by the investigator, primarily in the once-monthly treatment period [10 (4%) and 48 (20%) patients treated with methoxy polyethylene glycol-epoetin beta and darbepoetin alfa, respectively; $P<0.0001$].

Table 1 shows baseline characteristics for all randomized patients, which were similar in the two treatment groups and comparable to those in previously reported studies of dialysis patients. Mean haemoglobin concentra-

Table 1. Baseline characteristics

	Methoxy polyethylene glycol-epoetin beta (n = 245)	Darbepoetin alfa (n = 245)
Sex (male)	148 (60%)	156 (64%)
Age (years)	66.2 (13.6)	65.5 (13.9)
Race		
Caucasian	233 (95%)	225 (92%)
Black	5 (2%)	12 (5%)
Oriental	5 (2%)	7 (3%)
Other	2 (<1%)	1 (<1%)
Weight (kg)	72.3 (15.1)	73.8 (16.9)
Haemoglobin (g/dL)	12.09 (0.56)	12.07 (0.55)
Ferritin (μg/L)	427 (276–614)	446 (282–663)
TSAT	26.5% (19.5–33.0)	26.6% (21.0–32.8)
Iron supplementation	208 (85%)	209 (85%)
Kt/V	1.54 (0.29)	1.52 (0.27)
Albumin (g/L)	38.9 (4.4)	39.2 (4.3)
Time since first dialysis (years)	4.20 (5.92)	4.15 (5.55)
Aetiology of kidney disease		
Hypertension/large vessel disease	71 (29)	84 (34)
Diabetes	74 (30)	72 (29)
Glomerulonephritis	31 (13)	37 (15)
Interstitial nephritis/pyelonephritis	27 (11)	30 (12)
Polycystic kidney disease (adult type, dominant)	25 (10)	11 (4)
Previous median weekly darbepoetin alfa dose (μg)	30.0	20.0
Darbepoetin alfa dose per week before randomization		
<40 μg	155 (63%)	164 (67%)
40–80 μg	80 (33%)	65 (27%)
>80 μg	10 (4%)	16 (7%)

Data are numbers (%), mean (SD) or median (IQR).
TSAT = transferrin saturation.

tions at baseline, approximately 12.1 g/dL in both, did not differ between groups. Both ferritin and transferrin saturation were well within recommended limits; 85% (417 of 490) of patients received supplementary iron before randomization.

During the study, a similar percentage of patients in each group received concomitant iron treatment (91% in the methoxy polyethylene glycol-epoetin beta group and 92% in the darbepoetin alfa group). The most common supplements administered were intravenous iron sucrose to 62% of patients in both groups and intravenous ferrous gluconate to 24% of patients in the methoxy polyethylene glycol-epoetin beta group and 23% in the darbepoetin alfa group. Cumulative doses [median (interquartile range, IQR)] of each of the preparations were roughly equal in the two groups: iron sucrose 2100 mg (1325, 3200) and 1900 mg (1100, 2700); ferrous gluconate 2062 mg (1406, 2937) and 2154 mg (1062, 2687) for methoxy polyethylene glycol-epoetin beta and darbepoetin alfa, respectively.

Angiotensin-converting enzyme inhibitors were administered to 31% of patients and angiotensin II receptor antagonists to 22% of patients in each group.

Thirty-nine patients (15.9%) in the methoxy polyethylene glycol-epoetin beta group and 32 (13.1%) in the darbepoetin alfa group received at least one red blood cell transfusion. The mean number of units of blood transfused per patient was 1.56 and 1.64, respectively. Reasons given for transfusions (in descending order of frequency) were surgery, infection/inflammation, blood loss and anaemia and were balanced between groups.

Efficacy

The response rate in the evaluation period was higher in patients treated with methoxy polyethylene glycol-epoetin beta than with darbepoetin alfa: 157 of 245 (64.1%) versus 99 of 245 (40.4%). The absolute difference of 23.7% (95% CI 14.9–32.5) was statistically significant ($P < 0.0001$). The relative risk of response with methoxy polyethylene glycol-epoetin beta was 1.59 compared with darbepoetin alfa (95% CI 1.33–1.90).

In the intent-to-treat population, the proportion of patients on the once-monthly treatment regimen who did not fulfil the response criteria when treated with darbepoetin alfa was more than double that in the methoxy polyethylene glycol-epoetin beta group (50.2% versus 24.1%, respectively; $P < 0.0001$).

As an additional exploratory assessment of treatment effect at the once-monthly dosing interval, response was calculated in a subset of patients who entered the second treatment period: 157 of 216 (72.7%) versus 99 of 222 (44.6%) ($P < 0.0001$). The difference in response rates was also found in an analysis of all patients who completed the study: 148 of 187 (79.1%) versus 91 of 148 (61.5%) ($P < 0.0005$).

The mean and median haemoglobin values for the two treatment groups were close to 12 g/dL at baseline. During the first treatment period, there was a parallel decline in the median haemoglobin values in the two treatment groups, with a nadir of the median haemoglobin at 11.1 g/dL at Week 14 for methoxy polyethylene glycol-epoetin beta and 11.2 g/dL for darbepoetin alfa at Week 16 (Figure 3).

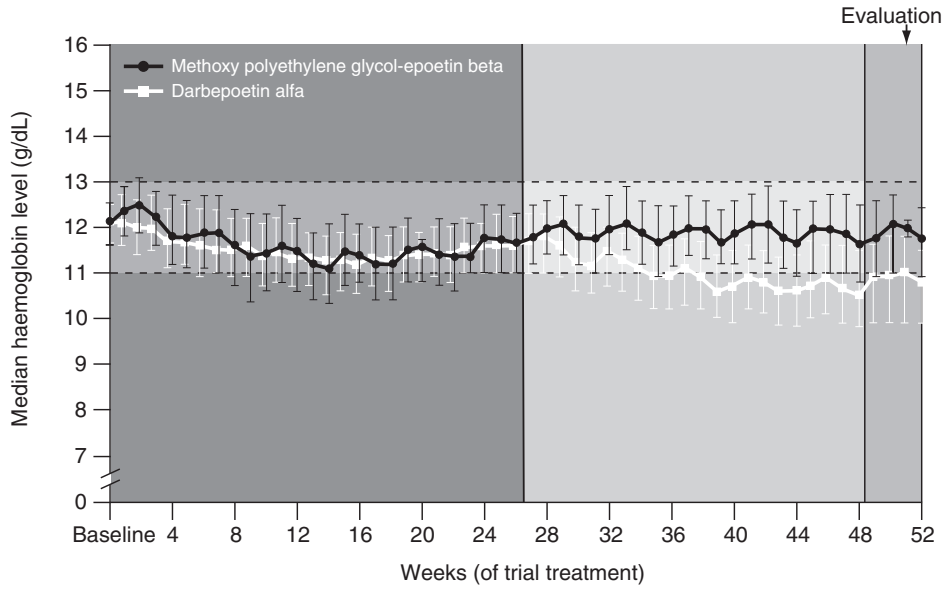

Fig. 3. Median haemoglobin values over time with interquartile range (intent-to-treat population).

Median haemoglobin values increased by approximately 0.5 g/dL from the nadir in both treatment arms until Week 26. During the 26 weeks of the second treatment period, the haemoglobin curves diverged, with methoxy polyethylene glycol-epoetin beta remaining essentially unchanged, while the median haemoglobin values with darbepoetin alfa declined by 1.2 g/dL from baseline to the evaluation period.

The patients assigned to darbepoetin alfa once every 2 weeks were given double the dose administered in the week before randomization (initial dose: mean 64.85 and median 48.00 μg/2 weeks), while patients treated with methoxy polyethylene glycol-epoetin beta received their initial dose according to the conversion table (initial dose: mean 159.38 and median 128.00 μg/month). Following dose adjustments according to protocol in order to achieve and maintain target (baseline) haemoglobin, doses were increased in 50% of patients in both treatment groups. The final doses in the first 26-week treatment period were: mean 102.46 and median 75.00 μg/2 weeks for darbepoetin alfa; mean 262.94 and median 200.00 μg/month for methoxy polyethylene glycol-epoetin beta.

At Week 27, at the time of conversion to once-monthly administration in the darbepoetin alfa treatment arm, the mean (median) dose was 260.4 μg (200.0 μg) in the methoxy polyethylene glycol-epoetin beta group and 202.8 μg (150.0 μg) in the darbepoetin alfa group (Table 2). In months 11 and 12, the mean (median) doses were 273.0 μg (196.0 μg) and 302.8 μg (225.0 μg) for methoxy polyethylene glycol-epoetin beta and darbepoetin alfa, respectively. The mean (median) dose change per patient was 6.8% (0%) with methoxy polyethylene glycol-epoetin beta and 58.8% (34.7%) with darbepoetin alfa. In the second 26-week treatment period, more patients receiving darbepoetin alfa required a dose increase to maintain target (baseline) Hb compared with those receiving methoxy polyethylene glycol-epoetin beta (58.4% versus 31.8%, respectively), while fewer patients receiving darbepoetin alfa required a dose decrease (4.6% versus 17.5%, respectively).

Adverse events

Of the 490 randomized patients, 489 received at least one dose of study drug. In total, 90% (439 of 489) had at least one adverse event, most of which were mild to moderate in intensity (Table 3). The incidence of adverse events did not differ between groups (P = 0.55). Six were judged to be related to treatment (four with methoxy polyethylene glycol-epoetin beta and two with darbepoetin alfa, respectively).

Table 3 also shows the serious adverse events, which were comparable in the two groups (P = 0.71). The most

Table 2. Monthly dose of study drug

	Methoxy polyethylene glycol-epoetin beta (n = 211)	Darbepoetin alfa (n = 219)
Monthly dose in Week 27 (μg)		
Mean (SD)	260.4 (193.8)	202.8 (183.5)
Median (IQR)	200.0 (120.0–313.0)	150.0 (80.0–280.0)
Monthly dose in Months 11 and 12 (μg)		
Mean (SD)	273.0 (264.1)	302.8 (288.2)
Median (IQR)	196.0 (120.0–351.0)	225.0 (106.0–400.0)
Change in the monthly dose (%)		
Mean (SD)	6.8 (51)	58.8 (76.5)
Median (IQR)	0.0 (-25.0–25.1)	34.7 (1.9–95.3)

Table 3. Adverse events

	Methoxy polyethylene glycol-epoetin beta (n = 245)		Darbepoetin alfa (n = 244)	
	Patients with AEs n (%)	Events n	Patients with AEs n (%)	Events n
Hypertension*	36 (15%)	41	26 (11%)	29
Procedural hypotension*	21 (9%)	23	27 (11%)	39
Nasopharyngitis*	25 (10%)	32	20 (8%)	25
Muscle spasms*	21 (9%)	28	19 (8%)	23
Urinary tract infection*	23 (9%)	31	17 (7%)	19
Arteriovenous fistula site complication*	22 (9%)	29	17 (7%)	24
Diarrhoea*	18 (7%)	23	19 (8%)	20
Bronchitis*	20 (8%)	28	16 (7%)	19
Any adverse event	222 (91%)	1225	217 (89%)	1023
Serious adverse events	99 (40%)	167	94 (39%)	169
Adverse events leading to withdrawal	3 (1%)		7 (3%)	
Deaths†	14 (6%)		14 (6%)	

*Types of adverse events with incidence <7%.
†Twenty-five patients died before the end of the study and three after they had withdrawn from the study for other reasons.

common serious adverse events were arteriovenous fistula site complication, arteriovenous fistula thrombosis and sepsis. No patient had a serious adverse event that was judged to be treatment related. Twenty-eight deaths (14 methoxy polyethylene glycol-epoetin beta patients and 14 darbepoetin alfa patients) occurred: 25 before the end of the study and 3 after withdrawal and within 30 days of last study-drug administration. When mortality was summarized by patient exposure years, the death rates per 100 patient exposure years were 6.46 in the methoxy polyethylene glycol-epoetin beta group and 6.57 in the darbepoetin alfa group. None of these 28 deaths were assessed as study drug-related. Among the 28 deaths, 22 individual causes were reported. The most common causes of death were infections (seven cases), cardiac disorders (four cases) and nervous system disorders (four cases). We noted no clinically relevant changes in laboratory tests or vital signs during the study. We did not detect antibodies to study drugs.

Discussion

This study showed that treatment with methoxy polyethylene glycol-epoetin beta administered intravenously once monthly was superior to treatment with darbepoetin alfa administered intravenously at the same dosing interval for the maintenance of haemoglobin concentrations in haemodialysis patients. The proportion of all patients who entered the study and met the response criteria of no haemoglobin decrease from baseline exceeding 1 g/dL and an average haemoglobin ≥10.5 g/dL during the final evaluation period almost a year later was significantly higher in patients treated with methoxy polyethylene glycol-epoetin beta than in those given darbepoetin alfa (64.1% versus 40.4%; $P < 0.0001$). The median decline in haemoglobin between baseline and the evaluation period was 0.25 g/dL in the methoxy polyethylene glycol-epoetin beta group and 1.09 g/dL in the darbepoetin alfa group, despite the best efforts of investigators to maintain haemoglobin by performing consecutive dose increases. It is likely that the higher response rate with methoxy polyethylene glycol-epoetin beta than with darbepoetin alfa can be explained primarily by the well-established difference in the pharmacokinetics of the two drugs, specifically the longer half-life of methoxy polyethylene glycol-epoetin beta, and possibly by a difference between the two drugs in the relationship between drug concentration and the pharmacodynamic effect, i.e. the red blood cell production rate [13,14].

A large majority of the patients completed the study, and completion rates with methoxy polyethylene glycol-epoetin beta were similar to those reported for other large studies with methoxy polyethylene glycol-epoetin beta and other erythropoiesis-stimulating agents administered at shorter dosing intervals of similar duration [15–17]. There were more premature withdrawals in the darbepoetin alfa group (40%) than in the methoxy polyethylene glycol-epoetin beta group (24%), and the difference was primarily attributable to insufficient therapeutic response.

The secondary efficacy parameter was the change in dose over time (difference between the monthly dose in Week 27 and the average dose in months 11 and 12). The virtually unchanged dose of methoxy polyethylene glycol-epoetin beta corresponds to a stable haemoglobin course with once-monthly dosing, while the dose increase with darbepoetin alfa reflects the haemoglobin decline in a large number of patients on the once-monthly regimen.

Extension of the administration intervals of erythropoiesis-stimulating agents to a once-monthly regimen has been investigated in the interest of reducing the resources required for anaemia management without compromising haemoglobin control. Multiple studies with methoxy polyethylene glycol-epoetin beta have demonstrated stable haemoglobin values at the once-monthly dosing interval [7,15,16]. There are also studies with traditional erythropoiesis-stimulating agents, several in patients with chronic kidney disease not requiring dialysis [18–21] and one study of patients on dialysis [22]. While the studies in chronic kidney disease patients not on dialysis [18,20]

used multiple epoetin alfa doses and dosing intervals in a parallel-group study design with a treatment of 16 weeks, the only study in dialysis patients [22] was an uncontrolled, single-arm study in which administration intervals were extended in patients defined as responders. Patients stable on a once every 2 weeks darbepoetin alfa dosing regimen were assigned to once every 3 weeks dosing, and only those who maintained stable haemoglobin values according to the protocol definition in the first 20-week period were treated at the once every 4 weeks interval in the subsequent 20 weeks. Moreover, if the haemoglobin concentration was not within the target range, dosing could be changed to a shorter interval; thus, in this study, increasing the dosing interval out to once monthly was limited to 'responder' patients. In contrast, in the study reported here, response at the once-monthly dosing interval was tested in all patients randomized, allowing a direct comparison of once-monthly methoxy polyethylene glycol-epoetin beta and darbepoetin alfa.

The frequencies of adverse events and serious adverse events were similar in the two treatment groups and characteristic of the haemodialysis population. Adverse events considered related to trial treatment by the investigator were very rare in both treatment groups (four patients in the methoxy polyethylene glycol-epoetin beta group and two in the darbepoetin alfa group), whilst no serious adverse event was assessed as related to the trial medication. Twenty-eight deaths (14 methoxy polyethylene glycol-epoetin beta patients and 14 darbepoetin alfa patients) occurred during the study, none reported as related to the study drug.

These results may be generalized to the maintenance haemodialysis population. Patient characteristics at baseline, including typical comorbidities, were similar to those in other clinical trials of intravenous erythropoiesis-stimulating agents for maintenance of haemoglobin [15,23–25].

Limitations of our study include selection of patients with stable haemoglobin at baseline and potential biases in assessment of clinical endpoints, which are inherent to all open-label clinical trials. However, haemoglobin concentration, the primary measure of efficacy, is objective and not subject to bias. Since data on safety were collected by many investigators in 82 different centres, systematic skewing of the data is unlikely, and source data verification confirmed that safety reporting was similarly complete for both treatment groups.

In summary, treatment with methoxy polyethylene glycol-epoetin beta administered intravenously once monthly was superior to treatment with darbepoetin alfa administered intravenously at the same dosing interval for maintaining haemoglobin concentrations in patients with chronic kidney disease and renal anaemia ($P < 0.0001$) despite dose increases with darbepoetin alfa. Safety findings were characteristic of the population under study and similar between the two treatment groups.

Statement

The results presented in this manuscript have not been published previously in whole or part, except in abstract format.

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Conflict of interest statement: F.C. has received consultancy fees from Vifor and has received speaker's honoraria from Amgen and F. Hoffmann-La Roche. C.E.L. has received consultancy fees from F. Hoffmann-La Roche. A.deF. has served as an advisor for Amgen and F. Hoffmann-La Roche and has received speaker's honoraria from Gambro, Abbott and Shire. F.L. has served as an advisor for Amgen, F. Hoffmann-La Roche and Affymax. J.F.E.M. has received speaker's honoraria and grants from F. Hoffmann-La Roche and other companies that produce ESAs. B.C. has received speaker's honoraria from F. Hoffmann-La Roche, Amgen, Janssen-Cilag, Fresenius, Genzyme and Shire. P.G.K. has received speaker's honoraria from F. Hoffmann-La Roche. I.C.M. has received consultancy fees, research funding and honoraria from Amgen, Ortho Biotech, F. Hoffmann-La Roche, Affymax and Shire. A.B. has received consultancy fees and speaker's honoraria from Amgen and F. Hoffmann-La Roche and has acted as a paid fact witness for F. Hoffmann-La Roche. B.V.V. has received consultancy fees from Baxter, F. Hoffmann-La Roche, Fresenius Medical Care, AstraZeneca, Janssen-Cilag and Amgen. U.B. and F.C.D. are employees of F. Hoffmann-La Roche. G.V., I.K. and S.J. declare that they have no conflict of interest.

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Clinical importance of an elevated circulating chemerin level in incident dialysis patients

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Abstract

Background. Circulating chemerin, a novel adipokine linked to obesity, glucose tolerance and hyperlipidaemia, was recently reported to be increased in chronic kidney disease (CKD) patients. We explored possible links between chemerin and various clinical, nutritional and biochemical markers as well as its association with 5-year all-cause mortality.