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ORIGINAL ARTICLE

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Efficacy and safety of darbepoetin alfa injection replacing epoetin alfa injection for the treatment of renal anemia in Chinese hemodialysis patients: A randomized, open-label, parallel-group, noninferiority phase III trial

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Abstract

Background: This study was to explore the clinical efficacy and safety of darbepoetin alfa injection replacing epoetin alfa injection (recombinant human erythropoietin injection, rHuEPO) for the treatment of anemia associated with chronic kidney failure in Chinese patients undergoing hemodialysis.

Method: This study was a multicenter, randomized, open-label, inter-group parallel control phase III noninferiority trial from April 19, 2013 to September 9, 2014 at 25 sites. In this study, the members of the darbepoetin alfa group underwent intravenous administration once per week or once every two weeks. The members of the control drug epoetin alfa group underwent intravenous administration two or three times per week. All subjects underwent epoetin alfa administration during the 8-week baseline period. After that, subjects were randomly assigned to the darbepoetin alfa group or epoetin alfa group. The noninferiority in the changes of the average Hb concentrations from the baseline to the end of the evaluation period (noninferiority threshold: −1.0 g/dl) was tested between the two treatments. The time-dependent hemoglobin (Hb) concentration and the maintenance rate of the target Hb concentration (the proportion of subjects with Hb concentrations between 10.0 and 12.0 g/dl) were also evaluated. Iron metabolism, including changes in the serum iron, total iron-binding capacity, ferritin, transferrin saturation, and comparisons of the dose adjustments between the two groups during the treatment period were analyzed further. Adverse events (AEs) were also observed and compared, and the safety was analyzed between the two treatment groups. The conversion rate switching from epoetin alfa to darbepoetin alfa was also discussed. SAS® software version 9.2 was used

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to perform all statistical analyses. Descriptive statistics were used for all efficacy, safety, and demographic variable analyses, including for the primary efficacy indicators.

Results: Four hundred and sixty-six patients were enrolled in this study, and ultimately 384 cases were analyzed for safety, including 267 cases in the darbepoetin alfa group and 117 cases in the epoetin alfa group. There were 211 cases in the per-protocol set, including 152 cases in the darbepoetin alfa group and 59 cases in the epoetin alfa group. The changes in the average Hb concentrations from the baseline to the end of the evaluation period were −0.07 and −0.15 g/dl in the darbepoetin alfa group and epoetin alfa group respectively. The difference between the two groups was 0.08 g/dl (95% confidence interval [CI]: −0.22 to 0.39), and the lower limit of the 95% CI was −0.22 > −1.0 g/dl. The average Hb concentrations of the two groups were 10.88–11.43 g/dl (darbepoetin alfa) and 10.91–11.38 g/dl (epoetin alfa) during the study period of Weeks 0–28, with the maintenance rates of the target Hb concentration ranging within 71%–87% and 78%–95% in the darbepoetin alfa group and epoetin alfa group respectively. During the period of comparison between the two groups, the incidence of AEs in the darbepoetin alfa group was 61.42%, while in the epoetin alfa group it was 56.41%. All of the adverse events and reactions in the study were those commonly associated with hemodialysis.

Conclusion: The overall efficacy and safety of darbepoetin alfa for the treatment of Chinese renal anemia patients undergoing hemodialysis are consistent with those of epoetin alfa.

KEYWORDS

anemia, conversion ratio, darbepoetin alfa, epoetin alfa, hemodialysis

Research Highlights

- Efficacy and safety of darbepoetin alfa are good for Chinese renal anemia patients.
- Efficacy and safety of darbepoetin alfa are consistent with those of epoetin alfa.
- Darbepoetin alfa is convenient in clinical use due to the low frequency of dose adjustment.

1 | INTRODUCTION

Patients with chronic kidney failure are prone to renal anemia due to inadequate production of erythropoietin induced by kidney injury.[1–3] In the 1990s, epoetin alfa (recombinant human erythropoietin, rHuEPO) was approved for renal anemia in patients undergoing hemodialysis and patients with pre-dialysis chronic kidney disease, which resulted in significant improvements in Hb concentrations and associated quality of life (QOL).[4–6] However, the half-life of epoetin alfa preparations administered intravenously is short, approximately

4–8 h.[7] Darbepoetin alfa as a second-generation and long-acting recombinant erythropoietin preparation is a new recombinant glycoprotein introducing 2 N-linked glycosylation sites by replacing 5 amino acid residues in 165 amino acid residues of epoetin alfa.[8] Compared with endogenous erythropoietin and epoetin alfa, darbepoetin alfa has the characteristics of a prolonged half-life in the blood and increased biological activity in vivo.[9]

Several clinical studies on darbepoetin alfa in patients with chronic kidney insufficiency have been carried out in Japan, the United States, and some other countries. It has been confirmed that darbepoetin alfa can not only reduce the frequency of administration but can also have the same anemia improvement effects and safety as short-acting rHuEPO preparations.[10–13] Darbepoetin alfa has been approved for marketing in more than 70 countries and regions worldwide, such as in the United States, Japan, and European countries. It has also been widely used in practical medical treatments. However, a large sample study on it has not yet been conducted in China. This study intended to explore the noninferior efficacy of darbepoetin alfa compared with epoetin alfa in Chinese hemodialysis patients with renal anemia, and to evaluate the efficacy and safety of darbepoetin alfa during hemodialysis and provide a basis for clinical treatment. This study was a PhIII clinical trial for new drug application and passed the National Medical Products Administration review.

In this study, we aimed to verify the safety of darbepoetin alfa in achieving the target hemoglobin (Hb) concentration (10.0 g/dl ≤ Hb concentration ≤ 12.0 g/dl) in Chinese patients undergoing hemodialysis with anemia induced by chronic kidney failure, and that its efficacy in improving anemia was not inferior to that of short-acting epoetin alfa preparations.

2 | METHODS

2.1 | Study design and procedures

This study was a multicenter, randomized, open-label, intergroup parallel control phase III noninferiority trial taking place between April 19, 2013 and September 9, 2014 at 25 sites. According to the relevant phase III clinical trials conducted in Japan, it was assumed that the standard deviation was 1.5 g/dl, α was 0.025 [set according to the bilateral (100 – 2α)% confidence interval] and the noninferiority margin $\delta = 1.0$ g/dl. To ensure 90% power, there were 168 subjects in the darbepoetin alfa group and 70 subjects in the epoetin alfa group, and in consideration of the fact that about 30% of the subjects discontinue the treatment before the end of the evaluation period, noninferiority can be verified with a total of 340 subjects, so there should be 240 in the darbepoetin alfa group and 100 in the epoetin alfa group.

In this study, the darbepoetin alfa group was given darbepoetin alfa injections (Kyowa Kirin Co., Ltd./Kyowa Kirin China Pharmaceutical Co.) intravenously once per week or once every 2 weeks. The control drug epoetin alfa (Kyowa Kirin Co., Ltd./Kyowa Kirin China Pharmaceutical Co.) was administered intravenously two or three times per week. All subjects were administered epoetin alfa during the 8-week baseline period. After that, subjects were assigned to groups using a central randomization system for dynamic stratified randomization, with random assignments to the test (darbepoetin alfa) and control (epoetin alfa) groups at a 12:5 ratio. After randomization, the two groups entered the comparison period (0–28 weeks), during which Weeks 0–20 was the dose adjustment period according to the changes in the Hb concentrations to maintain the Hb target value (10 g/dl ≤ Hb concentration ≤ 12 g/dl), and Weeks 21–28 was the efficacy evaluation period.

The first doses and the dosage forms for subjects converted to the administration of darbepoetin alfa once randomly were calculated according to Table 1.

2.2 | Selection criteria

The inclusion criteria for this study included: (1) chronic kidney failure, age ≥18 years, ≤70 years; (2) undergoing hemodialysis two or more times in 1 week, and short-acting rHuEPO preparation administration during the 12 weeks before the study; (3) Hb levels in the range of 10 g/dl to 12 g/dl before the study; (4) transferring

TABLE 1 Darbepoetin alfa first dose conversion and frequency adjustment

First epoetin alfa and darbepoetin alfa dose conversion: Baseline epoetin alfa dose per week		
Dose number	**Epoetin alfa (once/week)**	**Darbepoetin alfa (once/week)**
1	3000 IU	10 μg
2	4500 IU	20 μg
3	6000 IU	30 μg
4	7500 IU	30 μg
5	9000 IU	40 μg
Darbepoetin alfa once a week to 2 weeks: Baseline darbepoetin alfa dose once/week		
Dose number	**Darbepoetin alfa (once/week)**	**Darbepoetin alfa (once/2 weeks)**
1	10 μg	20 μg
2	20 μg	40 μg
3	30 μg	60 μg
4	40 μg	80 μg
5	60 μg	120 μg

saturation (TSAT) ≥ 20% or serum ferritin ≥100 ng/ml during the 4 weeks before the study.

The exclusion criteria in this study were: (1) uncontrollable hypertension (diastolic blood pressure > 100 mmHg before hemodialysis); (2) congestive heart failure (New York Heart Association Class III or IV); (3) subjects having undergone surgery with massive bleeding within 12 weeks before the study; (4) malignant tumors, hematological system diseases or other hemorrhagic disorders; (5) subjects undergoing blood transfusions, or the administration of protein anabolic hormone, testosterone heptane, mepitiostane or other experimental drugs within 12 weeks before the study; (6) AST or ALT values >3 times the upper limit of normal; (7) severe drug allergies, including epoetin alfa allergy.

2.3 | Efficacy and safety assessments

During the trial, the dose of the study drug was adjusted according to the changes in the Hb concentrations of the subjects so that they were kept within the target range (10.0 g/dl ≤ Hb concentration ≤ 12.0 g/dl). The main observation index was the changes in the average Hb concentrations in the baseline period and the average Hb concentrations in the evaluation period (noninferiority limit: −1.0 g/dl). The secondary evaluation indexes were the changes of the Hb concentrations and the maintenance rate of the target Hb concentration (the proportion of subjects whose Hb concentrations were between 10.0 and 12.0 g/dl). The main standard of the safety assessment was the incidence of adverse events, and the incidences of adverse reactions such as stroke and hypertension were analyzed.

The subjects in the full analysis set (FAS) were those who were administered the test drug for at least 1 week (can be withdrawn) after being randomly divided into groups; subjects from whom measured values that can be used to evaluate the effectiveness were obtained (definition of validity: Hb concentrations at the baseline and at least 1 week after administration), and discontinued subjects for whom the average Hb concentrations of the evaluation period were evaluated using the average Hb concentrations 4 weeks before the suspension.

The per-protocol set (PPS) satisfies the selection criteria in the FAS and does not meet the exclusion criteria, satisfies the measured values that can be evaluated for effectiveness (valid Hb concentration measurements at 4 weeks and later for the baseline period as well as for the evaluation period, including data falling within the time window at the time of discontinuation), good medication compliance (compliance ≥ 80%, i.e., wrong medication for no more than 7 weeks during the entire study period), and includes subjects who did not seriously violate the protocol. The safety set (SS) includes all subjects who were randomly assigned to the group and who used the test drug at least once. The effectiveness analyses were based on FAS and PPS, and mainly on PPS. Safety evaluations were based on SS.

To evaluate the iron metabolism, the changes of the serum iron, the total iron-binding capacity (TIBC), the ferritin and TSAT in the darbepoetin alfa group and epoetin alfa group were, respectively, measured during the treatment. Meanwhile, the amounts of dose adjustments between these two groups were compared after the change to darbepoetin alfa.

2.4 | Statistical analyses

SAS® software version 9.2 (SAS Institute Inc.) was used to perform all statistical analyses. For the main efficacy measurement, the changes in the Hb concentrations in each subject from the baseline period (−4 to −1 weeks) to the evaluation period (21–28 weeks) were calculated, and the difference in the mean Hb concentration (i.e., darbepoetin alfa-epoetin alfa) and the bilateral 95% confidence intervals (CIs) of the subjects in the two groups were calculated via an analysis of covariance. Other efficacy measures were calculated with the mean ± the standard deviation (SD) and the rate. In addition, descriptive analyses and χ^2 tests were used for subgroup analyses of the incidences of adverse events between the two groups.

All safety results were analyzed according to the Medical Dictionary for Regulatory Activities (MedDRA 19.0), which is used to summarize adverse events, adverse reactions, and serious adverse events. The severity and causality among these events should be classified with respect to the System Organ Class (SOC) and the preferred term (PT).

3 | RESULTS

3.1 | Epidemiology

A total of 492 patients were screened, and 466 patients were successfully enrolled in this study. All enrolled patients entering into the baseline period were treated with epoetin alfa for 8 weeks. During this period, 78 patients withdrew from the study and 388 patients who completed the baseline period were randomly assigned into the darbepoetin alfa group (271 patients) and epoetin alfa group (117 patients). Due to 4 patients being untreated in the darbepoetin alfa group, 384 cases were finally analyzed for safety, including 267 cases in the darbepoetin alfa group and 117 cases in the epoetin alfa group. A total of 380 cases were enrolled in the FAS, including 263 cases in the darbepoetin alfa group and 117 cases in the epoetin alfa group. While there were a total of 211 cases in the PPS, which included 152 cases in the darbepoetin alfa group and 59 cases in the epoetin alfa group.

In this study, males accounted for 55.26% of subjects in the darbepoetin alfa group and 64.41% of subjects in

the epoetin alfa group, and the average ages were 47.79 ± 12.33 and 49.03 ± 12.49 years old in the darbepoetin alfa group and epoetin alfa group respectively. The primary diseases in both groups were chronic glomerulonephritis, followed by diabetic nephropathy and polycystic kidney disease. The dialysis history concerning hematodialysis and hemodiafiltration in the darbepoetin alfa group was 53.52 ± 44.20 months, and that of the epoetin alfa was 62.58 ± 39.81 months. The two groups were comparable in demographic characteristics, previous histories, baseline Hb concentrations, baseline ferritin, and TSAT (Table 2).

3.2 | Main efficacy analysis

The results showed that the average variation in the Hb concentrations from the baseline period to the evaluation period between the darbepoetin alfa group and epoetin alfa groups was −0.22 to 0.39 g/dl (95% CI). The lower limit of the 95% CI was greater than −1.0 g/dl, which met the noninferiority standard (Table 3).

TABLE 2 Epidemiologic features (per-protocol set)

Characteristics	Darbepoetin alfa	Epoetin alfa
Gender		
Male	55.26%	64.41%
Female	44.74%	35.59%
Age (years)	47.79 ± 12.33	49.03 ± 12.49
BMI (kg/m^2)	21.52 ± 3.66	21.71 ± 3.26
Primary disease		
Chronic glomerulonephritis	83 (54.61%)	38 (64.41%)
Diabetic nephropathy	17 (11.18%)	4 (6.78%)
Polycystic kidney	10 (6.58%)	2 (3.39%)
History of dialysis	53.52 ± 44.20	62.58 ± 39.81
Dialysis frequency		
Twice a week	15 (9.87%)	7 (11.86%)
3 times a week	132 (86.84%)	51 (86.44%)
5 times 2 weeks	5 (3.29%)	1 (1.69%)
Previous history	52 (34.21%)	15 (25.42%)
Baseline Hb concentration	11.07 ± 0.79	11.16 ± 0.70
0Weekly ferritin	385.90 ± 380.16	317.13 ± 231.17
0Weekly TSAT	32.30 ± 24.37	28.88 ± 14.58

Note: Data were presented as *n* (%) or mean ± SD. Fisher's test was used to compare categorical variables. Wilcoxon's rank-sum test was used to compare measurement data between groups.

Abbreviations: BMI, body mass index; Hb, hemoglobin; SD, standard deviation; TSAT, transferring saturation.

The gender, age, body mass index (BMI), dialysis history, and primary medical history of the subjects in the baseline period as multiple factors were stratified to analyze the correlation with the changes in the Hb concentrations in the main efficacy assessment.

3.3 | Hb concentration changes

During the comparison period (0–28 weeks), the average Hb concentration was maintained at a stable level between 10.88 g/dl and 11.43 g/dl in the darbepoetin alfa group and 10.91–11.38 g/dl in the epoetin alfa group. The general tendencies of the changes in the Hb concentrations between the darbepoetin alfa and epoetin alfa were almost overlapping (Figure 1).

3.4 | Target Hb concentration maintenance rate

The target Hb concentration maintenance rate in this study refers to the proportion of subjects whose Hb concentrations were between 10.0 g/dl and 12.0 g/dl. During the comparison period, the overall maintenance rates of the Hb concentration in the darbepoetin alfa group ranged between 71%–87%, 80% at the baseline and 81% at 28 weeks respectively, and those of the epoetin alfa group ranged from 78% to 95%, 83% at the baseline and 82% at 28 weeks respectively. There were no significant differences in the maintenance rates between the two groups after the last administration ($p = 0.81$, $p > 0.05$).

The results showed that the maintenance rates of the target Hb in the darbepoetin alfa group were roughly consistent with those of the epoetin alfa group during the comparison period. Most subjects in both groups were able to stay within the target Hb concentration range during the study (Figure 2).

3.5 | Changes in iron metabolism, including serum iron, TIBC, ferritin, and TSAT

In this study, we also discussed the iron metabolism which was detected by the serum iron, TIBC, ferritin, and TSAT both at the baseline (Week 0) and after the treatment (Weeks 0–28). However, there were no significant differences between various points in time (Figure 3).

3.6 | Comparisons of dose adjustment times between groups

In the 0–28 weeks, the times of dose adjustments in the darbepoetin alfa group and epoetin alfa group were 5.16 ± 2.81 and 13.02 ± 9.85, respectively (Table 4).

TABLE 3 Changes of Hb concentration in the evaluation period compared with the baseline period (per-protocol set)

Items	Number of subjects	mean value (g/dl)	95% confidence interval (g/dl)
Darbepoetin alfa	152	−0.07	
Epoetin alfa	59	−0.15	0.08
Difference (darbepoetin alfa group-epoetin alfa group)	−0.24 to 0.10	−0.39 to 0.09	−0.22 to 0.39

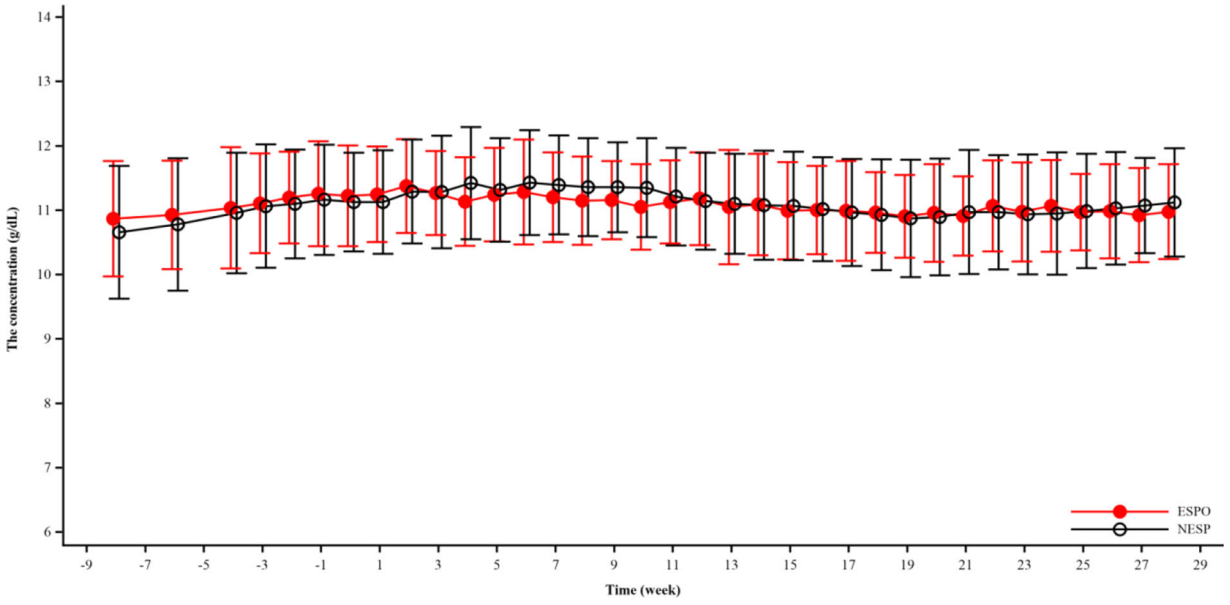

FIGURE 1 Change of Hb concentration (mean ± SD). Hb, hemoglobin

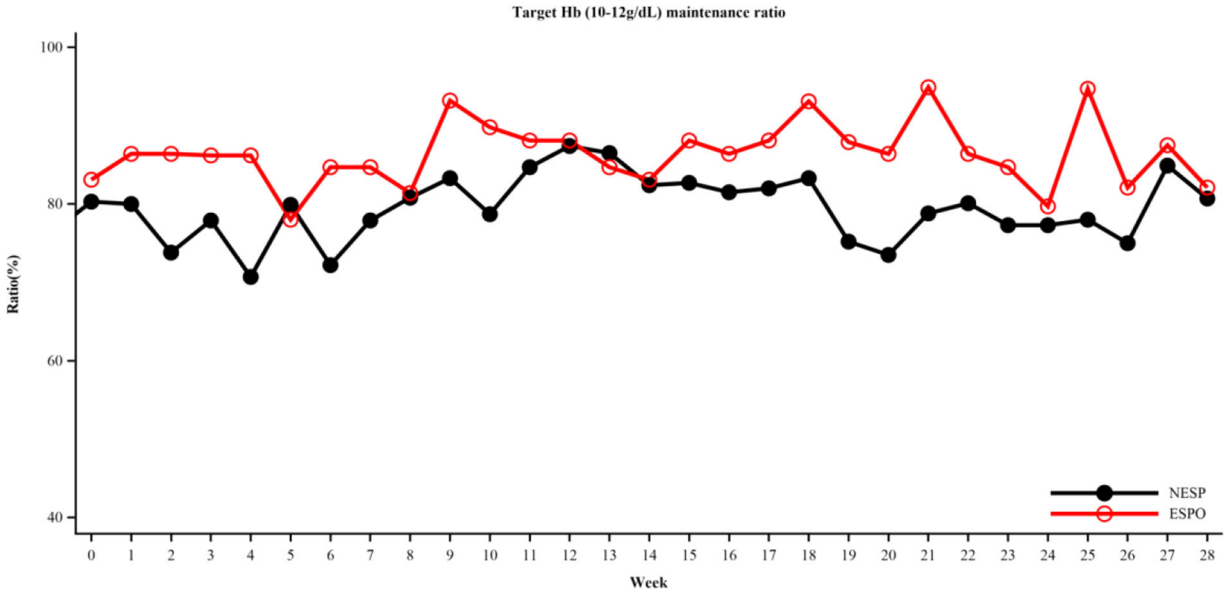

FIGURE 2 Maintenance rate of target Hb concentration (10 g/dl ≤ Hb ≤ 12 g/dl). Hb, hemoglobin

During the evaluation period, 5%–15% of patients did not need medication for maintenance in the darbepoetin alfa group, and the number of patients maintained with doses ≥30 μg shrank by approximately 30% after switching from epoetin alfa to darbepoetin alfa (Figure 4). The mean conversion ratio for the doses of darbepoetin alfa in the evaluation period to the doses of epoetin alfa was 310.2.

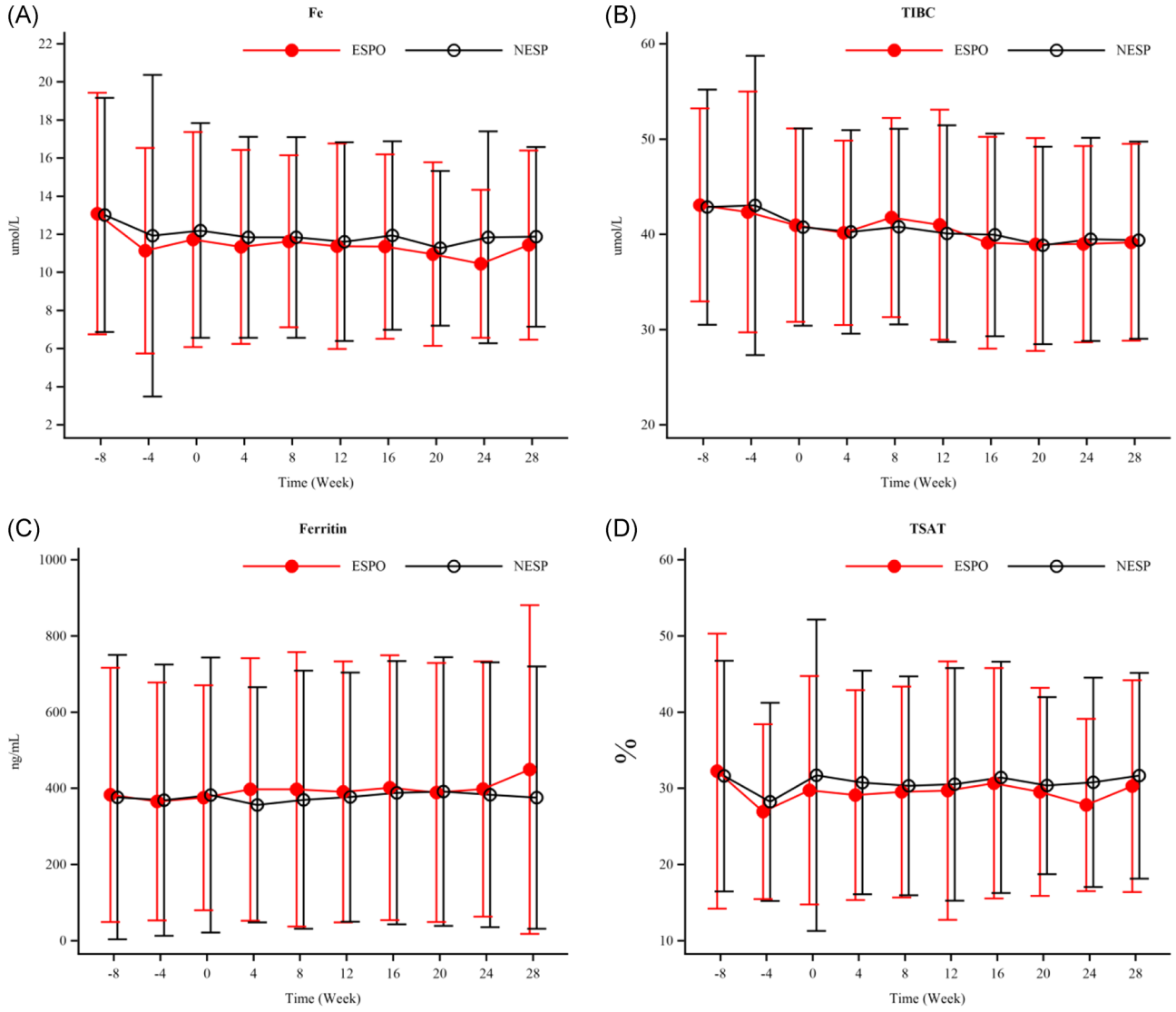

FIGURE 3 (A) Changes of serum iron, (B) Changes of TIBC, (C) Changes of ferritin, (D) Changes of TSAT. TIBC, total iron-binding capacity; TSAT, transferring saturation

TABLE 4 Comparison of dose adjustment times in 0–28 week between groups (per-protocol set)

Items	Number of cases (missing)	Mean ± SD	Median	Q1–Q3	Min–max
Darbepoetin alfa	152 (0)	5.16 ± 2.81	5.00	3.00–7.00	0.00–13.00
Epoetin alfa	59 (0)	13.02 ± 9.85	12.00	6.00–21.00	0.00–33.00

Abbreviation: SD, standard deviation.

3.7 | Safety assessment

The incidence of adverse events in the observation period, including the dose-adjusted period and evaluation period was 59.9% (230/384), among which the darbepoetin alfa group accounted for 61.42% (164/267) and the epoetin alfa group accounted for 56.41% (66/117). All of these outcomes were common adverse events in hemodialysis patients. In the darbepoetin alfa group (267 cases), there were 20 cases of hypertension (7.50%), 15 cases of increased blood pressure (5.62%), 11 cases of headache (4.12%), 19 cases of hyperkalemia (7.12%), 23 cases of muscle spasms (8.61%) and 4 cases of cerebral hemorrhage (1.50%), while in the epoetin alfa group (117 cases), there were 2 cases of cerebral infarction (1.71%), 4 cases of hypertension (3.42%), 3 cases of increased blood pressure (2.56%), 2 cases of headache (1.71%), 15 cases of hyperkalemia (12.82%) and 12 cases of muscle spasms

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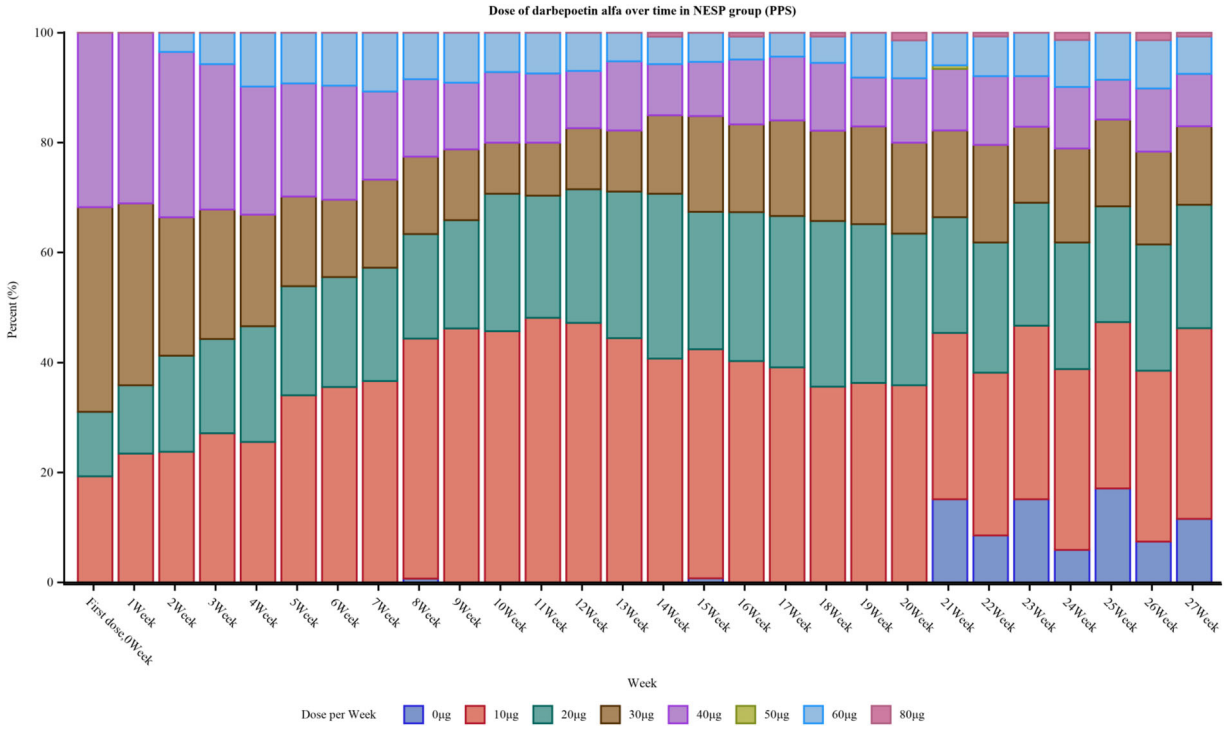

FIGURE 4 Dose adjustment of darbepoetin alfa during the treatment

TABLE 5 Incidence of adverse events and adverse reactions

Items	Darbepoetin alfa		Epoetin alfa	
	Number of people	incidence rate	Number of people	incidence rate
Adverse events	164	61.42%	66	56.41%
Cerebral hemorrhage	4	1.50%	0	0
Cerebral infraction	0	0	2	1.71%
Hypertension	20	7.50%	4	3.42%
Increased blood pressure	15	5.62%	3	2.56%
Hyperkalemia	19	7.12%	15	12.82%
Headache	11	4.12%	2	1.71%
Muscle spasm	23	8.61%	12	10.26%

(10.26%). All these events were clinically common in hemodialysis patients (Table 5).

Gender, age, BMI, dialysis histories, and primary medical histories of the subjects in the baseline period were stratified by multiple factors, and their correlation with the incidence of adverse drug events was analyzed. It can be seen from the forest plot that there is no significant correlation between the incidence of adverse events and the subjects' sex, age, BMI, duration of dialysis history, and different factors of primary diseases. There were no significant differences in the incidences of adverse events between the two groups (Figure 5).

4 | DISCUSSION

This study was conducted in anemia patients with stable chronic kidney failure undergoing hemodialysis to verify the safety and efficacy of darbepoetin alfa to achieve a target Hb concentration (10.0 g/dl ≤ Hb ≤ 12.0 g/dl) not inferior to that of epoetin alfa. The results showed that the efficacy of the intravenous administration of darbepoetin alfa once per week or once every two weeks was not inferior to that of epoetin alfa, which was administered intravenously two or three times per week.

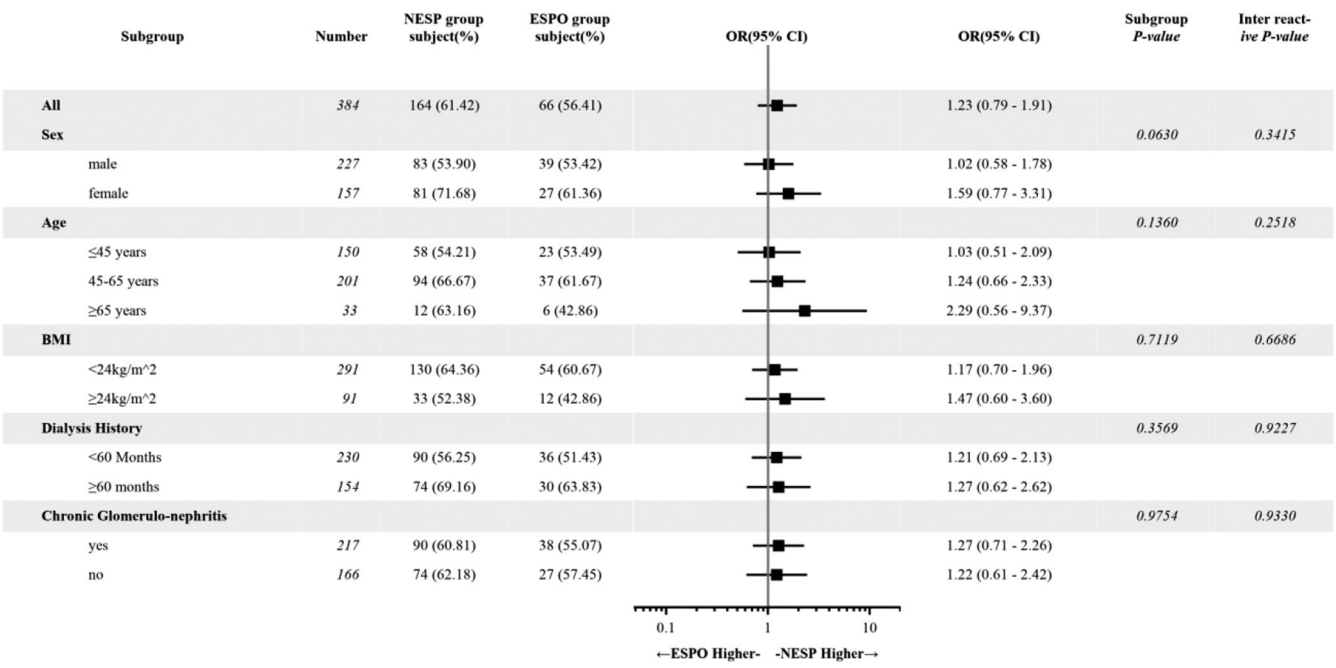

FIGURE 5 Subgroup analysis of the incidence of adverse events

The variation tendency of the Hb concentrations in the darbepoetin alfa group was near to that of the epoetin alfa group during the study. After switching, the times of the dose adjustments in the darbepoetin alfa group were obviously superior and significantly different from those of the epoetin alfa group ($p < 0.0001$). Overall, this study indicated that the administration of darbepoetin alfa when switching from epoetin alfa could excellently maintain the stability of the target Hb concentrations in Chinese patients with chronic kidney failure who are undergoing hemodialysis. The efficacy results were consistent with the previous darbepoetin alfa clinical study conducted in Japan with a similar experimental design.[14]

After random grouping, subjects who violated the inclusion criterias, used the wrong drugs or the forbidden drugs during the study were analyzed in the FAS rather than the PPS. The demographic characteristics, basic diseases, and baseline Hb concentrations of the subjects in the darbepoetin alfa group and the epoetin alfa group were well balanced and comparable. The results for the PPS population were basically consistent with those of the FAS population. The results of the efficacy analyses in the FAS population were basically consistent with those of the PPS population, and the noninferiority was also valid.

In addition, a lower dose frequency followed by dose adjustments of lower necessity in the darbepoetin alfa group suggests its clinical advantage in maintaining Hb levels while minimizing the workloads of clinical practitioners. In this study, the mean conversion ratio during the evaluation period was 310.2:1 (310.2 IU/dose epoetin alfa: 1 μg/dose darbepoetin alfa) when switching from epoetin alfa to darbepoetin alfa, which was between the conversion ratios reported from Taiwan (296.4:1) and Japan (350:1).[15,16] Anemia in patients with chronic kidney disease is characterized by the decreased production of renal erythropoietin and reduced survival rate of red blood cells. In addition, patients undergoing hemodialysis are often iron-deficient. The most common cause of epoetin alfa resistance is a decrease in a patient's iron reserves or its availability. Therefore, sufficient iron reserves must be maintained to ensure the effective treatment of renal anemia with epoetin alfa.[17–20] During the entire observation period in this study, there were no significant differences in the serum iron, TIBC, ferritin, and TSAT between the two groups at any point in time. Previous studies have shown that compared with long-term erythropoietin receptor activators, there are no differences in the serum iron and TIBC in those treated with darbepoetin alfa, but the level of serum ferritin in the darbepoetin alfa group does show a downward trend.[21,22] Therefore, iron availability in patients treated with darbepoetin alfa and epoetin alfa requires further study.

As for safety, all of the adverse events and reactions observed in the study were those commonly associated with hemodialysis. The incidence of serious adverse reactions in the darbepoetin alfa group was 2.62% (7/267). Other important adverse reactions (incidence > 0.5%) in the darbepoetin alfa group included five cases of hypertension (1.87%) and four cases of increased blood pressure (1.50%). Hypertension and increased blood pressure were common adverse reactions in both groups, and they were reduced or

disappeared after treatment. Four cases (1.50%, 4/267) of death occurred in the darbepoetin alfa group, all of which occurred during the comparative period of the two groups, including three cases of stroke death and one case of multiple fractures with infection, heart failure, and circulatory respiratory failure. The mortality rates reported in the clinical studies of darbepoetin alfa conducted in the United States and Japan with similar trial designs were 5.33% (9/169) in the United States study and 1.64% (1/61) in the Japan study.

Studies at home and abroad have shown that hypertension and high blood pressure are the most common adverse reactions to epoetin alfa. The incidence rate of hypertension in hemodialysis patients is over 80% during the induction period, and the incidence rate during the dialysis maintenance period can reach 43%. Anemia is improved with the administration of epoetin alfa, and hypertension outbreaks become more frequent or worsen. Especially in cases of anemia improving faster or the higher target setting of anemia improvement, the incidence of hypertension increases. This is the pathogenesis of epoetin alfa-related hypertension. With the improvement of anemia, the increase of peripheral vascular resistance and adverse responses of the cardiovascular system to anemia are the main reasons for this. Darbepoetin alfa and epoetin alfa have the same mechanisms of action. Therefore, when darbepoetin alfa is administered, more attention should be paid to patients with hypertension. Stroke is a common complication in maintenance hemodialysis patients. Four cases (1.50%) of cerebral hemorrhage in the darbepoetin alfa group and two cases (1.71%) of cerebral infarction in the epoetin alfa group were observed in this study. Previous studies have confirmed that renal hypertension caused by renal insufficiency is one of the most important risk factors of a cerebral hemorrhage in hemodialysis patients. In addition, hypertensive nephropathy, diabetic nephropathy, polycystic kidney disease, and other primary diseases are also independent risk factors of a cerebral hemorrhage. In this study, the primary diseases of the four subjects in the darbepoetin alfa group who had adverse events of stroke (cerebral hemorrhage) were chronic glomerulonephritis, diabetic nephropathy, polycystic kidney disease, and hypertensive nephropathy, respectively. The incidence of stroke observed in the meta statistics of pre-market clinical trials for this product was 2.1%, which was similar to the incidence observed in each group of this study.

In summary, the results of our study demonstrated that the efficacy and safety of darbepoetin alfa are similar to that of epoetin alfa in Chinese patients with chronic kidney disease undergoing hemodialysis, and due to the low frequency of dose adjustment, darbepoetin alfa seems to be more convenient to use in clinical practice.

AUTHOR CONTRIBUTIONS

All authors participated in the study and contributed to the acquisition, analysis, and interpretation of data.

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CONFLICTS OF INTEREST

Kyowa Kirin Co., Ltd. (KKC) and Kyowa Kirin China Pharmaceutical Co., Ltd (KKCN) participated in and approved the design and conduct of the study. Professor Wenge Li is a member of Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review process of this article.

DATA AVAILABILITY STATEMENT

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

ETHICS STATEMENT

The implementation of this study respected each subject and strictly followed the protocol requirements, the ethical principles of the Declaration of Helsinki and the E6 guidelines of the ICH Clinical Trial Management Code, as well as the local laws and regulations of the various study sites. This study was approved by the Ethics committees (ECs) of all of the hospitals involved. The leading site EC approval number was 2013 (Ethical Review)-07. All patients who participated in this study gave their written informed consent.

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