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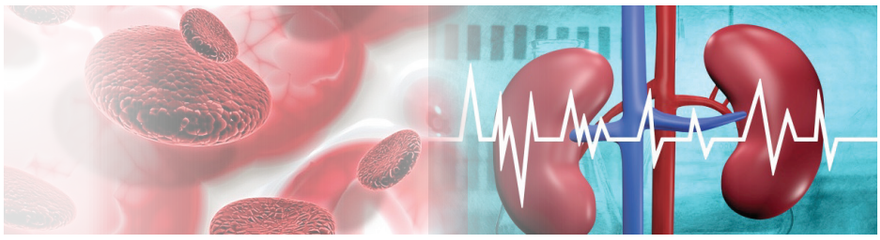
Renal Anemia



Efficacy, tolerability and safety of darbepoetin alfa injection for the treatment of anemia associated with chronic kidney disease (CKD) undergoing dialysis: a randomized, phase-III trial

Sinha SD, Bandi VK, Bheemareddy BR et al. *BMC Nephrol.* 2019 Mar 13;20(1):90.

Introduction

Anemia is an inevitable complication of chronic kidney disease (CKD) and is caused predominantly by insufficient production of erythropoietin from the failing kidneys and circulating levels of erythropoietin. In patients with CKD, untreated anemia has been associated with poor outcomes such as deterioration of cardiac function, decreased cognition, mental acuity, fatigue, and mortality.

Erythropoietin alfa (EPO) is a short acting erythropoiesis-stimulating agent (ESA) and has been a primary choice for treating anemia in patients with CKD for the past twenty years. However, the optimal route of EPO administration and dosage are debatable due to its short half-life. Intravenous (IV) administration of EPO should be limited to haemodialysis patients at a dosage of three times per week, as any dose reduction can lead to a major increase in the dose requirement. In addition, high doses of epoetin alfa increase the risk of poor outcomes including cardiovascular events. On the other hand, subcutaneous (*sc*) EPO therapy is efficacious during hemodialysis, peritoneal dialysis, and pre-dialysis in patients with CKD. The frequent dosing regimen of EPO poses a constant strain on patients and health care staff. Thus, long-acting ESAs are favored over short-acting ESAs.

Darbepoetin alfa

Darbepoetin alfa is the first long-acting ESA with extended dosing intervals and thus has an advantage over epoetins alfa and beta. DA-α has played an important role in the effective management of anemia and is preferred over epoetins/biosimilar epoetins for patients requiring less-frequent administration of ESAs. DA-α owing to its longer half-life, maintains target hemoglobin levels (10-12g/dL) with low dosing frequency (once weekly or biweekly), benefiting patients and health care staff equally. The dose requirement of EPO by the *sc* route is 22% lesser than that by the IV route; however, DA-α has similar dose requirements by both the *sc* and IV routes, which simplifies management of anemia. Clinical studies have shown that DA-α administered once every 2 weeks or every month improves convenience and saves costs with no compromise in its efficacy while maintaining the target hemoglobin (Hb) range in patients.

Treatment of renal anemia in Indian ESRD patients undergoing dialysis

This study aimed to determine whether a biosimilar DA-α has similar efficacy and safety as that of EPO when given at a reduced dose frequency for the treatment of renal anemia in Indian patients with end-stage renal disease (ESRD) undergoing dialysis.

Efficacy assessment

- In the intention-to-treat (ITT) population, Hb levels were increased gradually from baseline to the end of first evaluation period, with the mean change in Hb levels of 1.84 and 1.85 in DA-α and EPO group, respectively (within group comparison, $p < 0.001$ for each). Change from baseline to the end of first evaluation period in Hb levels was equal in per protocol (PP) population for both treatment groups.
- The difference in the mean change in Hb levels amongst the two groups was − 0.01 g/dL (95% CI − 0.68 to − 0.66, $p = 0.97$). It was not statistically significant even with the

low frequency of DA-α administration.

- The difference in the mean Hb change amongst the two groups was − 0.2878 g/dL (95% CI − 0.936 to − 0.360) when adjusted for covariates (using analysis of covariance).
- The lower limit of the two-sided 95% CI of primary endpoint was above the pre-specified non-inferiority margin of − 1.0 g/dL, irrespective of being adjusted (− 0.936) or unadjusted (− 0.68) for covariates, establishing that DA-α was equally effective as EPO, in maintaining mean Hb despite the reduced dosing frequency in patients undergoing dialysis.
- The results of PP population analysis set further confirmed the robustness of ITT analysis. In PP population, the lower limit of the 95% CI was − 0.994 (adjusted) and − 0.81 (unadjusted), which was above the pre-specified non-inferiority margin of − 1.0 g/dL.

Secondary analyses

- Improvement in Hb levels was observed as early as week 4 in both treatment groups which showed similar mean Hb change in the DA-α (0.30 g/dL, 95% CI − 0.01 to − 0.61, p = 0.0566) and EPO (0.74 g/dL, 95% CI 0.29 to 1.19, p = 0.0019) groups.
- The difference in mean Hb change between the two groups was − 0.44 g/dL (95% CI − 0.97 to − 0.09, p = 0.105), which was not statistically significant irrespective of the reduced frequency of DA-α administration.
- Increase in Hb levels from baseline was also similar in PP population even at week 4 (mean Hb change: − 0.62, 95% CI − 1.14 to − 0.10, p = 0.0209).
- In ITT population, the similar proportions of patients were observed to achieve target Hb level at the end of the first evaluation visit (DA-α vs. EPO: 52.38% vs. 49.2%; OR [95% CI] = 0.96 [0.46 to 1.99], p = 0.90). Similar results was observed in PP population (DA-α vs. EPO: 68.08% vs. 69.56%; OR [95% CI] = 0.94 [0.39 to 2.30], p = 0.89).
- In ITT and PP population, the Kaplan-Meier estimated median time to achieve the target Hb level was 9 weeks and 7 weeks after DA-α and EPO treatment, respectively.
- In ITT population, the proportion of patients who maintained their Hb levels within the target Hb range (10–12 g/dL) till the end of maintenance was similar in both the treatment groups (DA-α vs. EPO: 38.10% vs. 57.14% respectively; OR [95% 314 CI] = 0.57 [0.26 to1.25], p = 0.16). Similar result was observed in PP population for both treatment groups (DA-α vs. EPO: 34.09% vs. 57.50% respectively; OR [95% CI] = 0.46 [0.17 to 1.22], p = 0.11).
- This demonstrates that, compared to EPO, DA-α does not increase Hb variability despite reducing the dosing frequency. Furthermore, fewer dose adjustments were observed in DA-α treated patients.

Safety assessment

- In the DA-α group, 25 (39.7%) patients and 32 (50.8%) patients in EPO group experienced at least one treatment-emergent adverse event (TEAE) during the study period.
- Patients mostly reported TEAEs of mild-to-moderately severe in nature except one (1.58%) from the EPO group who experienced severe TEAEs.
- None from the DA-α group reported any TEAE related to the study drug; whereas, 4 patients from the EPO group reported 5 AE related to the study drug.
- In the EPO group, 4 patients reported 5 AEs that were related to the study drug. Severe adverse events were reported by 9 patients (5 from EPO group and 4 from the DA-α group).
- The commonly reported events in both the treatment groups were pyrexia (DA-α vs. EPO: 9.5% vs. 7.9%), cough (9.5% vs. 15.9%), vomiting (4.8% vs. 6.3%), nasopharyngitis (4.8% vs. 6.3%), increased blood creatinine and urea (4.8% vs. 4.8% for each) and decreased glomerular filtration rate (4.8% vs. 4.8%).

Conclusion

The results of this study demonstrated that, the efficacy of DA-α, when administered at reduced dose frequency, is similar to EPO for treating renal anaemia in patients undergoing dialysis. In this study, patients who were treated with DA-α could effectively maintain their Hb levels in the target therapeutic ranges and required with fewer dose adjustments than those treated with EPO. Therefore, the treatment using DA-α rules out the need for frequent monitoring and dose adjustments. In addition, both groups showed similar increases in Hb levels.

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Evaluating the iron availability for erythropoeisis is crucial in treating anaemia patients with CKD. Iron deficiency can interfere with the response to EPO and DA-α and affect the efficacy. Thus, according to clinical practice guidelines and recommendations, iron supplements were given to all the patients in this study. To help maintain serum ferritin within recommended levels, most patients from both treatment arms received iron supplements. Additionally, serum ferritin levels were similar in both treatment groups.

In this study, DA-α was as safe as EPO. A majority of the reported AEs were due to the underlying disease and its treatment. In addition, only few AEs were associated with EPO use, and none were related to DA-α use. This study showed that safety profile of DA-α similar to those in other clinical trials conducted in pre dialysis stage of patients. Also, it was observed that DA-α was well tolerated and had similar safety profile to EPO.

Low-normal hemoglobin levels and anemia are associated with increased risk of end-stage renal disease in general populations: A prospective cohort study

Yi SW, Moon SJ, Yi JJ. *PLoS One*. 2019 Apr 25;14(4):e0215920.

Introduction

Early detection and primary prevention in high-risk individuals are strategies used to reduce the burden of CKD. However, since most patients are asymptomatic until the advanced stages of CKD, determination of who should be screened and who is at high risk in asymptomatic adults has been a challenge. Few studies examined the impact of low-normal hemoglobin (Hb) levels and anemia on development of ESRD, despite the fact that low Hb levels per se may contribute to the progression of CKD to ESRD, while Hb decline and anemia may occur as a consequence of CKD even at early stages. Low-normal Hb levels, such as 13–13.9 g/dL in men, have been paid little attention.

Furthermore, it has been rarely examined and is unclear whether low-normal Hb levels and anemia increase ESRD incidence in individuals with normal kidney function, namely no albuminuria and normal glomerular filtration rate (GFR). A better understanding of the impact of low-normal Hb and anemia on ESRD may help identify high-risk groups and target Hb levels for the prevention, surveillance, and management of CKD in both general populations and CKD patients.

In this prospective cohort study, ESRD incidence was assessed according to Hb levels and albuminuria measured by the dipstick test, and the interaction between Hb levels and albuminuria was examined. In individuals with information on serum creatinine levels, these associations were examined after further consideration of the estimated GFR (eGFR).

Associations of Hb and albuminuria with ESRD incidence

A similar reverse-J-curve association of Hb and a linear association of albuminuria with ESRD incidence were found in both men and women. The age-adjusted incidence of ESRD was generally higher at lower levels of Hb and with more severe albuminuria in each sex. The age-adjusted incidence per 10,000 person-years was 1.07 and 1.67 in men and women with no albuminuria and the highest Hb levels, respectively, while it was 986.1 and 820.6 in men and women with albuminuria ≥3+ and the lowest Hb levels, respectively.

In the multivariable analysis, the pattern of hazard ratios (HR) was generally similar to that of age-adjusted incidence. The risk associated with the lowest Hb category and no albuminuria was greater than the risk associated with the highest Hb category and albuminuria of 1+. In the analysis of 15 combined Hb-albuminuria groups, the associations of lower Hb with ESRD generally did not weaken at ages ≥60 years in comparison to younger ages. Assuming a linear association, women had greater inverse associations with Hb than men. In women, but not in men,

the HRs associated with lower Hb were stronger at ages ≥60 years than at ages <60 years. Additionally, the effect size of 1 g/dL lower Hb was not different according to 5 albuminuria categories in both men and women.

Analysis after further consideration of the eGFR

Among 349,993 participants with information on eGFR, during the mean follow-up of 4.0 years, 316 individuals were diagnosed with ESRD. Individuals with a lower eGFR tended to be older, female, and to have comorbid diabetes and hypertension. The age-adjusted incidence and multivariable-adjusted HR of ESRD were generally higher at lower levels of Hb, with more severe albuminuria, and at a lower eGFR. The multivariable-adjusted HRs associated with 1 g/dL lower Hb in participants with eGFR values ≥60, 30–59, and <30 mL/min/1.73 m^2 were 1.34 (95% CI, 1.17–1.54), 1.55 (1.38–1.74), and 1.75 (1.47–2.09), respectively ($P_{interaction}$ between eGFR groups = .057).

In the analysis of 9 combined albuminuria-eGFR subgroups, HRs associated with 1 g/dL lower Hb were generally lower in persons with eGFR ≥60 than with <60 mL/min/1.73 m^2, regardless of albuminuria categories.

When biological interaction between low Hb, albuminuria, and eGFR groups was assessed using multivariable-adjusted HRs, the synergy index was 45.5. These results suggest a strong synergistic interaction.

Conclusion

Low-normal Hb levels and anemia were risk factors for ESRD incidence in general population without CKD as well as for the progression of CKD to ESRD. Lower Hb had synergic biological interactions with lower eGFR and albuminuria to increase the risk of ESRD incidence. Hb of 13–13.9 g/dL in men, 11–11.9 g/dL in women, and trace albuminuria by dipstick urinalysis were associated with a more than doubled risk of ESRD. The impacts of lower Hb may be stronger in older than younger women. The inclusion of persons with anemia or low-normal Hb in surveillance and management programs for the primary and secondary prevention of CKD may reduce the burden of CKD.

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Dpoetin™
Darbepoetin Alfa Injection 25 µg, 40 µg, 60 µg
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Feroneph®
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Feroneph®-O
Ferrous Ascorbate equivalent to elemental iron 100 mg, Folic Acid 10 mg, Methylcobalamin 500 mcg, Biotin 300 mcg, Calcium Pantothenate 6 mg, Vitamin B1 2 mg, Vitamin B2 3 mg, Vitamin B3 25 mg, Vitamin B6 10 mg
Effective & Tolerable Oral Iron Supplement