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Darbepoetin in chronic kidney disease and dialysis patients; an updated review of outcomes

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ABSTRACT

Individuals with chronic renal failure in stage three and after demonstrate anemia as a frequent complication. Although target hemoglobin levels remain debatable in pre-dialysis and dialysis patients, correction of anemia with erythropoiesis-stimulating agents (ESAs) has resulted in reduced need for blood transfusions, improved survival and enhanced overall quality of life. Owing to longer half-life and greater biological activity, darbepoetin alfa can maintain stable hemoglobin levels at extended dosing intervals. It is also economical and convenient with no compromise in efficacy. Studies have shown similar dose requirements for both intravenous versus subcutaneous darbepoetin in pre-dialysis and dialysis patients. This review article focuses on clinical outcomes of darbepoetin including the achieved hemoglobin target, maintenance of hemoglobin levels, all-cause mortality, cardiovascular events, additional blood transfusion, quality of life, and economic outcomes in patients with chronic kidney disease (CKD). This review also outlines the risk associated with darbepoetin administration and changes in guidelines recommendation for improving its use.

Implication for health policy/practice/research/medical education:

The main advantages of darbepoetin are efficacious anemia correction and reduction of blood transfusions.

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Introduction

In India, the prevalence of chronic kidney disease (CKD) varies from less than 1% to 13% with around 48% of patients presenting in Stage 5 (1,2). In 2016, the International Society of Nephrology Kidney Disease Data Center Study showed an estimated prevalence of 17% in Indian patients (2). Over 130 000 people are on dialysis in India and every year it is added up by about 232 per million (3). About 79%–97% of individuals with chronic renal failure stages 3-5 suffer from anemia, which increases the risk of cardiovascular disease (CVD) and all-cause mortality (1).

The current standard therapy for anemia in CKD patients (both pre-dialysis and dialysis) includes the use of oral or intravenous (IV) iron supplementation and erythropoiesis-stimulating agents (ESAs). In clinical studies, ESAs have been shown to increase the hemoglobin

(Hb) levels (4). However, Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline recommends ESA therapy initiation if Hb concentration remains <10 g/dL despite repletion with oral or IV iron therapy (5). Depending on half-life, two types of ESAs have got regulatory approval for the treatment of CKD: short-acting [epoetin alfa, recombinant human erythropoietin (rHuEPO; approved by Food and Drug Administration (FDA) in June 1989)] and long-acting [darbepoetin alfa (approved by FDA on September 17, 2001), continuous erythropoietin receptor activator (CERA), approved by FDA on November 14, 2007)].

Darbepoetin alfa has simplified the management of anemia because of its equivalent dose requirement for both IV and subcutaneous (SC) administration and extended dosing intervals over rHuEPO (6). In addition, several studies have confirmed the efficacy of darbepoetin

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alfa in CKD and dialysis patients (CKD5D) (7-10). Over the years, comparison of the efficacy of epoetin alfa and darbepoetin alpha has contradictory results (4,6). The current review focuses on the efficacy and safety outcomes with darbepoetin alfa directly compared with placebo or other ESAs while treating the anemia of CKD/CKD5D.

Materials and Methods

Search strategy

Article searches were carried out on PubMed and Google Scholar from 1999 to 2019. The keywords used were anemia, darbepoetin alfa, CKD, epoetin alfa, erythropoiesis-stimulating agent, renal replacement therapy and hemodialysis. Literature was not limited by study design and all types of studies including randomized, double-blind, cohort, case-control, observational and retrospective studies were included. Animal studies were not considered for the efficacy and safety review. All relevant literature has been included in this study; however, any literature not included is unbiased, unintentional and unconditional.

Darbepoetin alfa; a second-generation erythropoietin (EPO) analogue

Darbepoetin alfa is a hyper-glycosylated EPO analogue that has prolonged survival in the circulation (11). Darbepoetin alfa was approved by the FDA and the European Medicines Agency EMA in 2001 for the treatment of anemia in patients with CKD and cancer (11). The terminal half-life of IV darbepoetin-alfa was approximately three times longer than that of IV epoetin-alfa (25.3 versus 8.5 hours) (11).

Routes of administration

Darbepoetin alfa can be used by both intravenous (IV), and subcutaneous (SC) routes (12). Previous studies have demonstrated that dose requirements for darbepoetin alfa IV or SC are comparable and target hemoglobin or hematocrit levels can be achieved and maintained using either an IV or SC route with darbepoetin alfa (12). Aarup et al conducted a crossover study to compare IV versus SC dose requirements of darbepoetin alfa in 71 stable hemodialysis patients. IV darbepoetin alfa was associated with 95% probability of a mean dose reduction between 1.2% and 28% ($P = 0.036$) (13). Absorption with SC route is more rapid in children (14).

Dose and frequency

The labeling for darbepoetin alfa recommends that it be given either IV or SC at the dose of 0.45 µg/kg per week or 0.75 µg/kg once every two weeks for patients with CKD on dialysis. The approved dosage for patients with CKD not on dialysis is 0.45 µg/kg at four-week intervals (15). Darbepoetin alpha at lower dose frequency (0.45 µg/kg, once weekly), showed similar mean change in Hb levels as EPO in Indian pre-dialysis in individuals with chronic

renal failure with anemia (11.28 g/dL versus 11.02 g/dL; 95% CI -0.62, 1.09; $P = 0.5837$) (16). Another randomized phase-III trial from India, comparing the efficacy and safety of darbepoetin alfa and EPO in patients with end-stage renal disease (ESRD), has also demonstrated similar results with the difference in mean Hb change between these two groups being insignificant - 0.01 g/dL (95% CI - 0.68 to -0.66, $P = 0.97$) (17).

In 2009, a meta-analysis investigated the relative dose savings in patients receiving dialysis when switched from epoetin alfa or beta to darbepoetin alfa. Using the conversion ratio of 200:1, it reported an average 30% dose savings (18). In 2018, Woodland et al reported a dose conversion ratio, from EPO to darbepoetin alpha, of greater than 350:1 by 3-month in hemodialysis (HD) patients (19).

Achieved Hb target

About 95% to 97% of CKD patients (ESA naive) had achieved Hb levels between 11 and 13 g/dL, after almost 5 weeks of starting de novo Q2W administration of SC darbepoetin alfa (10,20). Administration of darbepoetin alfa either at Q2W or QM could maintain the Hb levels ≥ 10 g/dL in most of the patients with CKD (77.78%), not on dialysis (21). In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study, over 4,000 diabetics with CKD stages 3 and 4 were randomly assigned to darbepoetin alfa ($n=2012$) to achieve a target Hb level of 13g/dL and to placebo ($n=2026$) with rescue darbepoetin alfa when the Hb level was <9 g/dL. At three months of post-treatment, the darbepoetin alfa group significantly achieved the median Hb level of 12.5 g/dL, as compared with 10.6 g/dL in the placebo group (22). A review (33 studies, $n=5526$) found longer-acting ESAs (darbepoetin and CERA) to be non-inferior to rhuEPO in achieving the Hb target (23).

Maintenance of Hb levels with darbepoetin alfa

In 2009, Krause and colleagues compared the efficacy and safety profile of *de novo* every-other-week darbepoetin alfa in ESA-naive subjects aged <65 , 65–74 and ≥ 75 years of age with CKD (not receiving dialysis). The analysis suggested that darbepoetin alfa can achieve and maintain Hb levels in patients with CKD with de novo every-other-week administration (24).

All-cause mortality

In 2017, a systematic review (27 studies involving 5410 adults with CKD) compared the risk of mortality between patients randomly assigned to CERA, darbepoetin and EPO and reported no significant difference between the treatment (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65) (25). Similar results have been reported from another systematic review of 9 trials involving 2024 individuals with chronic renal failure (odds ratio [OR] 1.33; 95% CI: 0.88–2.01) (26). A Quasi-experimental

cohort study, comparing CV mortality rates of darbepoetin alfa versus EPO in patients with ESRD initiating HD, reported no difference between groups (HR, 1.05; 95% CI, 0.94–1.16) (27).

Cardiovascular events

Randomized controlled trials (RCTs) on pre-dialysis patients with renal anemia conducted in Japan, found no difference between the darbepoetin group (target Hb, 11.0–13.0 g/dL) and the rHuEPO group (target Hb, 9–11.0 g/dL) in terms of safety, including risk for CV events. However, a significant decrease in the left ventricular mass index was seen in the darbepoetin group (28). The Darbepoetin Alfa for Renal Anemia Management in Japan (DREAM-J) surveillance study has also found no increase in the incidence of CV-related adverse events (AEs) with higher Hb levels (29).

Cerebrovascular thrombosis and stroke

The results of TREAT study confirmed an increased incidence of cerebral infarction among CKD patients in the higher hematocrit arm, while the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study pointed to an increase in stroke rates among CKD patients with the higher target for Hb concentration (22,30). However, systematic reviews of ESA therapy have demonstrated that higher target Hb (13–15 g/dL) could lead to increased risk of stroke, worsening hypertension, and vascular access thrombosis (31,32). A study by Akizawa et al reported stroke only in one patient from the high Hb group receiving darbepoetin and in three patients from the low Hb group receiving rHuEPO (28). Another study by Vanrenterghem et al also showed no significant difference ($P \geq 0.682$) in incidence rate of vascular access thrombosis between treatment groups (darbepoetin alfa 10%, rHuEPO 9%) (8).

Additional blood transfusions and iron therapy

ESAs have shown to reduce the need for RBC transfusions and iron therapy in CKD patients with anemia (33–35). A systematic review (32 studies, $n=9414$) by Palmer et al reported a significant reduction in the need for blood transfusions among adults with CKD stages 3–5 receiving darbepoetin alfa (32). Another study involving 4038 adults with diabetes and CKD stage 3 to 4 indicated that the need for blood transfusions as well as iron therapy was reduced by darbepoetin alfa than placebo group (22). The administration of CERA in CKD patients to treat anemia with a twice-monthly schedule (ARCTOS) extension study in patients with CKD who were not on dialysis, reported a total of 109 (37%) patients requiring iron supplementation during a 24-week extension period (36).

Quality of life outcomes with darbepoetin alfa

A randomized single-blind study reported statistically significant improvements in some SF-36 and FACT-An

subscale score, with darbepoetin alfa. However, mean SF-36 score was comparable between the darbepoetin alfa (51.4 [95 % CI 48.0, 54.9]) and placebo (46.7 [40.9, 52.5]) groups (37). In addition, it has shown improvement in FACT-Fatigue and EQ-5D scores (37). Various studies have also shown moderate-to-large improvements in fatigue with ESA treatment for anemia (38). Interestingly, the striking improvements in fatigue symptom among patients treated to achieve Hb level lower than a target of 10–12 g/dL show the significance of partial anemia correction with ESA therapy (38). One meta-analysis by Palmer et al found limited and inconclusive evidence for effects of ESAs on health-related quality of life (HRQoL) due to the selective reporting by the RCTs (32). This finding was further supported by Collister et al wherein significant heterogeneity amongst studies ruled out meaningful positive effects of ESAs on HRQoL in patients with CKD (39). However, another systematic literature review by Gandra et al reported that the treatment of anemia with ESA therapy improved energy and physical function in CKD patients, not on dialysis (40).

Safety outcomes with darbepoetin alfa

The tolerability and safety profile for darbepoetin alfa is as good as rHuEPO. A prospective, phase IV, observational registry reported 434 AEs in 162 children with CKD who received darbepoetin alfa; peritonitis (10.0 %) was most common AEs followed by gastroenteritis (6.0 %), and hypertension (4.1 %). In this study, only 48 children received ≥ 1 transfusion (41). A multicenter prospective study by Hattori et al reported 24 AEs in 44% of patients receiving darbepoetin for CKD associated anemia; however, no definite relation was observed between darbepoetin alfa and AEs (42). Another Japanese study, evaluating the safety and efficacy of darbepoetin alfa in children ($n=31$) with CKD on peritoneal dialysis (PD)/HD or pre-dialysis, reported total 87 AEs in 87.1 % children; none of which were related to the study drug (43). The results regarded darbepoetin as an effective and safe alternative to rHuEPO in children with CKD.

In 2019, a study comparing the safety of two darbepoetin alfa formulations in healthy male volunteers reported negative anti-drug antibody reactivity for all samples collected for up to 360 or 264 hours after SC or IV administration from both intervention groups (44). Few cases of pure red cell aplasia (PRCA) have been reported in CKD patients receiving treatment with darbepoetin, predominantly by SC route (45). However, Prospective Immunogenicity Surveillance Registry (PRIMS) found low PRCA risk after SC administration of a new coated-stopper syringe presentation of different ESAs (46).

Economic outcomes

In Greece, an analysis conducted from public third-party-payer perspective, demonstrated the lowest overall costs per patient with darbepoetin alfa compared to other ESAs

at €8210 and €6689, for patients on HD or PD, respectively (47). In 2017, a randomized controlled trial by Woodland et al reported reduction in cost of \$1876 per patient per year for darbepoetin alpha than EPO ($P = 0.02$) in HD patients (19).

Risk with darbepoetin

In 2007, the USFDA mandated a black box warning for all ESAs following reports of increased AEs with higher doses of ESAs. The deciding factor for this black box warning was the data obtained from the Normal Hematocrit Cardiac Trial (NHCT), the CHOIR study, and the CV Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study (30,48,49). An increased risk of vascular access thrombosis and heart attacks were reported by NHCT for dialysis patients in the higher hematocrit arm, while an increase in CV events and mortality rates among pre-dialysis patients with a higher target for Hb concentration were reported by the CHOIR study (30,48). These findings were further supported by few trials demonstrating that the correction of anemia in CKD patients with ESAs does not confer a beneficial effect on mortality, CV, or renal outcomes (22,29,50). The CREATE study showed a higher risk of ESRD requiring dialysis among the patients targeted to higher hematocrit levels (49).

Recommendations for improving administration of ESAs

In response to the three trials raising concerns on safety of ESAs in CKD patients with anemia, changes in position statements and management guidelines were published (Table 1) (5). KDIGO guideline recommends ESA therapy initiation in patients whose hemoglobin concentration has fallen below 10 g/dL even after addressing all the

reversible causes (5). In certain patients considered suitable for transplantation or who are likely to avoid blood transfusion, ESAs can be initiated to correct anemia in chronic renal failure patients (15). The US Food and Drug Administration (USFDA) has even obviated the need to mention target Hb on the label and recommends that ESA should be used in lowest possible dose to reduce red blood cell transfusion (51). Thus, ESA therapy should be initiated in CKD patients displaying moderate anemia who are moderately symptomatic. Various recommendations from different guidelines for ESA administration in patients with CKD have changed over the years owing to safety issues. These changes in guidelines are listed in Table 1 (5,15,51-55).

Conclusion

Over the past 10 years, clinical treatment strategies for anemia in CKD patients have changed markedly, which included ESA administration, IV iron supplementation, and red blood cell transfusions. The clinical approval of darbepoetin has brought about transformation in the treatment of anemia in CKD patients. The main advantages of darbepoetin are efficacious anemia correction and reduction of blood transfusions, as well as improvements in HRQoL. More population-specific studies are required as currently published studies are insufficient to delineate Hb limit and risk-benefit ratio for darbepoetin.

Authors' contribution

TJ and SJC searched the data and prepared the draft of the manuscript. JD and SVB edited and finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

Authors declare no conflict of interests.

Table 1. Change in guidelines recommendations for ESA administration in CKD patients

Guideline	Year	Recommendations for ESA use
NKF-DOQI	1997	<ul style="list-style-type: none"> Hb target range from 11 to 12 g/dL
FDA	2007	<ul style="list-style-type: none"> Issued a black box warning to maintain the Hb levels within the range of 10-12 g/dL and not to exceed 12 g/dL in ESA-treated patients
ERBP	2010	<ul style="list-style-type: none"> ESA therapy may be initiated in CKD ND patients with Hb concentration <10 g/dL In CKD 5D patients, it should be used to avoid Hb fall below 9 g/dL when the Hb is between 9.0–10.0 g/dL
FDA	2011	<ul style="list-style-type: none"> Remove the concept of a "target hemoglobin range" Use lowest ESA dose to reduce the need for red blood cell transfusions
KDIGO	2012	<ul style="list-style-type: none"> ESA therapy should not be initiated when the hemoglobin level is ≥ 10 g/dL Individualization of the ESA therapy should be considered in patients who are likely to benefit in terms of quality of life
NICE	2015	<ul style="list-style-type: none"> ESA therapy should be considered in patients who are more likely to benefit in terms of both physical functioning and quality of life Hb target range from 10 to 12 g/dL
Renal association	2017	<ul style="list-style-type: none"> ESA therapy should be considered in patients who are more likely to avoid blood transfusion and to have benefit in terms of both physical functioning and quality of life Hb target range from 10 to 12 g/dL

Abbreviations: CKD, Chronic kidney disease; CKD ND, non-dialysis chronic kidney disease; CKD 5D, indicate end-stage renal disease patients who undergo chronic dialysis; ESA, Erythropoiesis-stimulating agents; Hb, Hemoglobin.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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