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Review Article

Darbepoetin alfa: review in the management of anemia in patients with chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a significant clinical problem across the world including India. The SEEK (Screening and Early Evaluation of Kidney Disease) study from India reported the prevalence of CKD as 17.2%. Diabetic nephropathy, undetermined etiology, chronic glomerulonephritis and hypertensive nephrosclerosis are the common causes of CKD in India. Rising rates of diabetes and hypertension, late presentation of patients to nephrologists and limited number of nephrologists in India adds to the concerns related to management of CKD. Considering the pathophysiology of CKD, anemia is almost an inevitable complication in these patients. Untreated anemia significantly contributes to the morbidity and mortality associated with CKD. Early recognition, timely management with appropriate therapy helps to reduce the complications of anemia. Erythropoiesis-stimulating agents (ESAs) are one of the important measures for correction of anemia in CKD patients. Darbepoetin, an ESA is a valuable therapeutic option for the treatment of anemia in CKD patients and has played a vital role in enhancing anemia management. In this article we reviewed the efficacy and safety data along with key benefits and place of darbepoetin alfa in the management of anemia in CKD patients.

Keywords: Anemia, Chronic kidney disease, Darbepoetin, India

INTRODUCTION

Chronic kidney disease (CKD) is a global clinical concern across the world. With increased life expectancy and rising rates of lifestyle disorders, prevalence of CKD majorly contributed by non-communicable diseases such as diabetes and hypertension is on rise. These two common conditions are the major contributors for CKD in India too.[1] The prevalence of CKD is high both in rural and urban parts of India. The rates of CKD in different studies differ because of the different methods used for estimating the prevalence. For instance, a study from rural population in Karnataka reported CKD in 6.3% by using glomerular filtration rate (GFR) estimation by modification of diet in renal disease (MDRD) and 16.54% by Cockcroft-Gault equation corrected to the body surface area.[2] The SEEK (Screening and Early Evaluation of Kidney Disease) study from India with a

cohort of 5588 subjects reported the prevalence of 17.2% with approximately 6% patients presenting in stage 3 or above (stage 3-4.3%; stage 4-0.8% and stage 5-0.8%) with large variations among different centers. Hypertension, anemia, diabetes, obesity, history of ischemic heart disease and history of hypercholesterolemia was significantly more common in patients with CKD compared to those with non CKD.[3] According to the first report of Indian registry published in 2012 diabetic nephropathy (31%) is the commonest cause of CKD.[4] The reported rates of CKD in India due to undetermined etiology, chronic glomerulonephritis and hypertensive nephrosclerosis in this registry were 16%, 14% and 13% respectively.One of the major challenges for management of CKD in India is late presentation of patients to the nephrologist. Indian CKD registry reported close to 48% patients presenting in stage V.

Among different problems associated with CKD, anemia is a common clinical concern and is an early complication in this patients.[5-7] The prevalence of anemia defined as hemoglobin less than 12 g/dL is progressively higher from stage 1 to stage 5 CKD. In a study, anemia was reported among 42% patients of stage 1 whereas it was seen in 82% patients of stage 5. The corresponding percentage of patients with hemoglobin less than 11 g/dL was 21% (stage 1 CKD) and 72% (stage 5 CKD).[6] In Indian studies anemia has been shown to be present in 94%-100% patients with CKD.[8-10]

The pathophysiology of anemia is complex. Cardiorenalanemia syndrome is a vicious cycle wherein congestive heart failure can lead to CKD as well as it can be the result of CKD (Figure 1). Congestive heart failure can either directly cause renal injury or through inflammation initiated by cytokines which adversely affect the erythropoiesis and iron metabolism. Diminished cardiac output impairs the blood supply to kidneys resulting in renal ischemia, the consequence of which is progression of anemia due to impaired hormonal function of the kidney.[11]

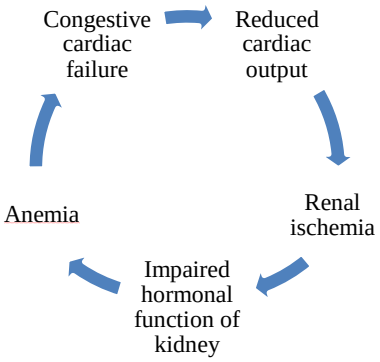

Figure 1: Vicious cycle of congestive heart failure and renal disease.

Untreated anemia in patients with chronic renal failure can lead to several consequences including increased need for hospitalizations, serious cardiovascular problems such as left ventricular dysfunction and left ventricular hypertrophy, increased requirement for blood transfusions, impaired quality of life and increased risk of death.[7,12] Left ventricular hypertrophy is a known risk factor for cardiac morbidity and mortality.[7]

In diagnosed cases of anemia with hemoglobin levels less than 11g/dl, other causes should be ruled out. Iron deficiency, as a cause of anemia, if present should be corrected. Early and effective treatment of anemia is important for achieving positive outcome in terms of morbidity and mortality.[7] The optimal hemoglobin level is a subject of debate.[5] Generally it is agreed that evaluation of anemia in CKD is started when hemoglobin level is reduced to 12g/dL and the therapy should be started when hemoglobin level goes below 11g/dL.[5] Data suggest that hemoglobin level should be maintained above 11g/dL in order to protect the cardiac functions.[12] Hemoglobin level of around 12 g/dL seems to be better in improving left ventricular mass index and the quality of life in pre-dialysis patients compared to conventional hemoglobin levels.[5]

Introduction of erythropoiesis-stimulating agents (ESAs) is a major advance in the management of anemia associated with CKD. Correction of anemia by ESAs can reduce left ventricular hypertrophy and stress on the heart, resulting in reduced risks for cardiovascular disease in CKD patients.[13] Effective therapy of anemia helps in improving overall survival of the patients and also the quality of life.[14] In this regards, ESA represents one of the most important means and mainstay of correcting anemia in CKD patients.[15] These agents cause increase in the level of hemoglobin in patients with anemia in CKD and reduce requirement for blood transfusion. In CKD patients, administration of these agents helps to improve the survival.[16]

In this article, we reviewed data on darbepoetin by systematically searching publications identified by PubMed, Google scholar from 1999 to 2016 with search items: anemia, darbepoetin alfa, chronic kidney disease, epoetin alfa, erythropoiesis stimulating agent, renal replacement therapy. 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. Though we have taken utmost care to include all relevant literature, non-inclusion of any literature is unconditional, unbiased and unintentional.

DARBEPOETIN ALFA

The commonly used ESAs are epoetin alfa and darbepoetin alfa, both of them have the same protein sequence but there is difference in their glycosylation. Darbepoetin stimulates the process of erythropoiesis by similar mechanism as that of endogenous erythropoietin.

Darbepoetin offers advantages of greater potency and longer half-life and potential for extended dosing.[17,18]

PHARMACOKINETICS

Pharmacokinetics of darbepoetin alfa has been studied with intravenous (IV) and subcutaneous (SC) administration. The pharmacokinetic parameters in CKD patients are shown in the Table 1.[17,19]

Table 1: Pharmacokinetic parameters of intravenous darbepoetin alfa.

Pharmacokinetic parameter	Darbepoetin alfa
Absorption (SC administration)	Slow
Bioavailability in patients on dialysis (SC administration)	~37%
Volume of distribution (IV administration)	52.4+2.0 mL/kg
Cmax (SC administration)	48 hours (12-72 hours)
Area under the serum concentration (IV administration)	291.0+7.6 ng.h/mL
Clearance (IV administration)	1.6+0.3mL/h/kg
Terminal elimination half-life (IV administration)	25.3 hours
Terminal elimination half-life in patients on dialysis (SC administration)	46 hours (range 12-89 hours)
Terminal elimination half-life in patients not on dialysis (SC administration)	70 hours (range 35-139 hours)

Intravenous administration of darbepoetin in CKD patients on dialysis results in biphasic serum concentration pattern, with distribution half-life of about 1.4 hours and a longer terminal elimination half-life.[19] Darbepoetin has almost three times longer half-life compared to IV recombinant human erythropoietin (rHuEPO). The half-life of darbepoetin is about 25.3 hours compared to 8.5 hours of rHuEPO.[18] Apparent clearance is faster in patients on dialysis compared to those not on dialysis. In children with CKD, Cmax and half-life is similar to those in adult patients with CKD on dialysis. However, subcutaneous dose in children results in higher average bioavailability compared to adult patients on dialysis.[19]

EFFICACY IN PRE-DIALYSIS PATIENTS

Darbepoetin alfa can be used as effective and safe maintenance therapy for anemia in pre-dialysis patients. A 24 week clinical trial evaluated efficacy and safety of darbepoetin alfa in predialysis patients (n=42) previously treated with once-weekly epoetin alfa. The patients were switched to once in two week to darbepoetin alfa administered subcutaneously, dose of which was given to adjust hemoglobin between 11 and 13g/dL. Follow up of 39 patients showed consistently significant increase in hemoglobin levels at eight weeks (0.39; $p < 0.002$), 16 weeks (0.58; $p < 0.001$), and 24 weeks (0.83g/dL; $p < 0.001$). The rise in hemoglobin was seen despite reduction of darbepoetin dose up to 15% at 24 weeks. There were no adverse events related to the drug.[20] Another clinical trial showed that darbepoetin alfa administered once monthly is an efficacious option for the treatment of anemia in patients with CKD.[21]

Continuous erythropoietin receptor activator (CERA) is gaining importance for the treatment of anemia in CKD patients because of its potential to maintain a stable hemoglobin level due to its longer half-life compared to darbepoetin alfa. However, the results of comparative clinical trials are not consistent. One study concluded that CERA could be more effective for correction of anemia in pre-dialysis patients.[22] The results of another study conducted in predialysis patients suggested no significant difference in the effects in regards to achievement of target hemoglobin levels in both groups (Table 2).[23]

Table 2: Summary of studies with darbepoetin alfa for the treatment of anemia in CKD patients not on dialysis.

Reference	Number of patients	Study design	Administration of darbepoetin	Outcome with darbepoetin alfa
Molina M, et al[20]	42	Prospective, comparative study	S.C. darbepoetin alfa once every other week	Superior to epoetin alfa
Martinez PM, et al[21]	12 (three months) and seven (one year)	Prospective study	S.C. darbepoetin alfa once a month	Effective in maintaining hemoglobin >11 g/dL
Koibuchi K, et al[22]	128	Retrospective study	As per approved usage in Japan	Significant decrease in hemoglobin over 6 months in darbepoetin alfa group compared to CERA
Furukawa T, et al[23]	29	Randomized, controlled trial	subcutaneous CERA or DA once every four weeks	Similar effects on hemoglobin levels
Hoggard J, et al[24]	442	Prospective study	Darbepoetin once monthly or Epoetin alfa once-weekly or once-every-other-weekly	Higher preference to once a month darbepoetin alfa

Compliance is an important factor that determines the success of treatment and in this regards, patient's preference is considered as one of the important factors. Medicines which are preferred by the patients are more likely to be taken by them for longer period. A study has shown that patients usually prefer once monthly darbepoetin alfa compared to once week epoetin alfa.[24]

In pre-dialysis patients, poor nutrition and presence of inflammation may need higher doses for the correction of anemia.[14,25] Moreover, female sex and cardiovascular disease have also been shown to be risk factors for requirement of high dose.[25]

EFFICACY IN PATIENTS ON DIALYSIS

Epoetin alfa and darbepoetin alfa both can be used for the treatment of anemia in patients on dialysis. Several studies have evaluated efficacy and safety of darbepoetin alfa in the treatment of anemia in these patients. In a Phase IIIb study of 24 weeks patients on dialysis receiving rHuEPO twice or twice a week were switched to darbepoetin alfa once a week whereas those receiving once a week were switched to darbepoetin alfa once every two weeks. The route of administration was not changed while switching to darbepoetin alfa. The study involved patients on both hemodialysis as well as peritoneal dialysis. Treatment-related adverse events were observed in 3% patients.[26] Many hemodialysis centers use darbepoetin-alfa as the preferred agent for the treatment of anemia in CKD patients. In a study 98 hemodialysis outpatients, were switched from twice to thrice weekly epoetin alfa to darbepoetin alfa. Both the agents were similar in effectiveness.[27]

In another small clinical trial, efficacy of darbepoetin was examined with monthly dosage frequency. Patients receiving mean initial biweekly dose of 57±10.0µg were switched to monthly regimen with increase in dosage once they maintained target levels of hemoglobin. After switching to darbepoetin monthly regimen, hemoglobin levels were maintained in the therapeutic range throughout the study. Thus, monthly dosing frequency was found to be effective and safe over one year. Dosage schedule of monthly administration has significant potential to improve the compliance because of the convenience to patients.[28]A retrospective study involving 150 adult patients on chronic hemodialysis receiving darbepoetin to achieve target hemoglobin levels of 11-13 g/dL proved its efficacy.[29]

Darbepoetin has also been studied in patients on peritoneal dialysis who were switched from epoetin alfa. Darbepoetin-alfa was successful in maintaining stable hemoglobin levels in these patients without any significant adverse events. The percentage of patients with hemoglobin between 11-13g/dL was higher with the darbepoetin (85% vs73%).[30]

In a large multicenter observational study (n=741) darbepoetin alfa has also been studied with once every 2 weeks administration for one year in adult patients with mean age of 61 years. The study is significant in terms of high completion rate. A total of 86% patients completed the study and 70% were on darbepoetin alfa once every 2 week dose schedule. Mean hemoglobin level 6 months before conversion, at the time of conversion and 12 months after conversion was 11.69, 12.25 and 11.88g/dl respectively.

Table 3: Summary of studies with darbepoetinalfa for the treatment of anemia in dialysis patients.

Reference	Number of patients	Study design	Administration of darbepoetin	Outcome with darbepoetin
Bristoyiannis G, et al[26]	173 patients on dialysis	Phase IIIb, multi center, open-label study	Darbepoetin alfa once a week or once in two weeks; intravenous or subcutaneous.	Effective maintenance of hemoglobin at less frequent dosing interval
Agrawal V, et al[27]	98 patients on hemodialysis	Observational study	Darbepoetin alfa once a week	As effective as epoetin alfa
Alsaran K, et al[28]	26 patients on hemodialysis	Prospective study	Darbepoetin- alpha fortnightly to monthly intravenous	Effective and safe for 12 month treatment period
Nguyen T, et al[29]	150 patients on chronic hemodialysis	Retrospective study	Darbepoetin alfa intravenously every week or two-weekly	Effective in controlling anemia
Remon C, et al[30]	35 patients on peritoneal dialysis	Not specified	Darbepoetin alfa, subcutaneously	Percentage of patients with hemoglobin between 11-13g/dL increased from 73% in epoetin to 85% in darbepoetin
Feriani M, et al[31]	741 patients on peritoneal dialysis	Multicenter, observational study	Darbepoetin alfa once in two weeks	Effective in maintaining hemoglobin level >11.0 g/dL in 73% patients
Locatelli F, et al[32]	341 patients on dialysis	Multicenter, open label study	Darbepoetin alfa once a week or once in two weeks intravenously or subcutaneously	Effective and safe in maintaining target hemoglobin level

After one year of conversion, 73% patients were having hemoglobin level above 11.0g/dL. There was no increase in the mean dosage.[31] In another study involving 341 patients on dialysis rHuEpo treatment was changed to darbepoetin alfa with reduced frequency of administration with same route of administration i.e. intravenous or subcutaneous (Table 3). Those receiving rHuEpo two/ three times weekly were given once-weekly darbepoetin alfa whereas for those on once weekly regimen, darbepoetin was given once in two week which was proved to be effective and safe in maintaining target hemoglobin concentration.[32]

A Spanish study showed that darbepoetin alfa is more cost efficient compared with epoetin alfa for the management of anemia in patients with hemodialysis and pre-dialysis.[33]

IN PATIENTS WITH POST-TRANSPLANTATION

Anemia is commonly observed after renal transplantation. Darbepoetin alfa has also been evaluated as a treatment option for anemia after transplantation.[34] Pankewycz and colleagues in a prospective study have shown correction of anemia in 60% post transplant patients at 3 months. A retrospective study (n=129) demonstrated effectiveness of darbepoetin alfa in reducing anemia in renal transplant patients without rise in cardiovascular events.[35]

In a case report, darbepoetin alfa has even been shown to be successful for the treatment of severe anemia in a pregnant woman who underwent transplant.[36]

In a small study (n=20) subcutaneous darbepoetin alfa 200μg was given every 2 weeks to the patients with post stem-cell transplantation anemia. Darbepoetin was found to be effective without any major safety concerns.[37]

In an observational, single center study among renal transplant patients, darbepoetin corrected anemia both in previously treated as well as EPO naïve patients. It was found to be well tolerated (Table 4).[38]

Table 4: Summary of studies with darbepoetin alfa for the treatment of post-renal transplant anemia.

Reference	Number of patients	Study design	Darbepoetin administration	Outcome with darbepoetin
Pankewycz O, et al[34]	75 (total patients evaluated for anemia)	Prospective study	Standard doses for three months	Correction of anemia in 60% patients at three months.
Jimenez C, et al (35)	60	Retrospective, observational study	Darbepoetin was given according to clinical practice	Given in the first week after transplant, darbepoetin is effective in reducing anemia during the first month without increased drug related cardiovascular events
Ribes D, et al (38)	73	Observational study	Darbepoetin given subcutaneously	Darbepoetin was found to be effective without any major safety concerns.

CHILDREN AND ELDERLY

Darbepoetin alfa has also been evaluated for its efficacy and safety in special population including children and elderly. The results in terms of outcomes in both these populations are promising. A Japanese multicentre study in children (n=25) undergoing peritoneal dialysis evaluated efficacy and safety of darbepoetin for 28 weeks. Darbepoetin was administered intravenously every 2 weeks in order to keep the hemoglobin levels between 11.0 to 13.0g/dL. If needed, dose was administered once every 4 weeks. Eighty percent patients achieved the target hemoglobin levels whereas in 60% patients the target values were maintained. Though the adverse events were reported in 44 %, no definite relation was observed with study drug.[39] Another Japanese study evaluated efficacy and safety in CKD children (n=31) on peritoneal dialysis/hemodialysis or not on dialysis. Patients on hemodialysis received IV darbepoetin alfa every week for 24 weeks whereas those on peritoneal dialysis or not on dialysis received bi-weekly dose either IV or SC. The target hemoglobin level was same as previous study. In some patients on peritoneal dialysis and not on dialysis, the dosage interval was extended to once every four weeks. In this study, all children achieved the target level of hemoglobin whereas 64.5 % were in the target range at the end of the study. There was no difference in the efficacy between SC or IV route of administration. None of the adverse events reported in this study too were related to the study drug.[40] Can C and investigators compared efficacy and safety of darbepoetin versus rHuEPO in 34 children with mean age of 11.42±4.05 years.[41] The study population included children on hemodialysis, peritoneal dialysis as well as not on dialysis. There was no significant difference in the hemoglobin at the end of six months (P >0.05) between two groups. The results suggest that darbepoetin can be an effective and safe alternative to rHuEPO even in children with CKD.

Schaefer F and colleagues examined the long term effects (up to 2 years) of darbepoetin in a prospective, phase IV observational study in children (n=319). [42] There were no additional safety signals. These studies demonstrate the effectiveness and safety of darbepoetin in the treatment of anemia in children with CKD. Darbepoetin has also been examined for its efficacy and safety in elderly patient population. Krause MW and colleagues conducted a post hoc subanalysis of data from two clinical trials (n=203).[43] In this paper the authors compared efficacy and safety of darbepoetin administered every 2 weeks in patients not on dialysis with patients younger than 65 years. The analysis suggests that elderly patients can achieve and maintain hemoglobin levels between 11.0-13.0g/dL.

Darbepoetin alfa offers some clinical benefits over epoetin alfa:

- The half-life of darbepoetin is longer (up to three times) than rHuEPO which allows the extended dosing with darbepoetin alfa providing potential for improved compliance.[20]
- Subcutaneous administration of epoetin alfa is associated with the risk of pure red cell aplasia in patients with chronic renal failure. This results in limitation of its use in outpatients such as those patients not on dialysis or those receiving peritoneal dialysis. In this regards darbepoetin alfa scores over epoetin-alfa.[30]
- A real-world study, has showed switching from epoetin alfa to darbepoetin alfa may result in economic advantage with less administration related errors.[44]

DOSE OF DARBEPOETIN

Different starting doses are recommended for CKD patients on dialysis and for those who are not yet on dialysis. The recommended dose for patients receiving dialysis is 0.45 mcg/kg (IV/SC) weekly or 0.75mcg/kg (IV/SC) every two weeks. Intravenous administration is recommended for patients who are on hemodialysis. The initial dose for CKD patients not on dialysis is 0.45mcg/kg (IV/SC) every four weeks.[19]

SAFETY OF DARBEPOETIN

Generally darbepoetin is well tolerated. However, like other ESAs some patients may develop adverse events following administration of darbepoetin. Adverse event profile of darbepoetin is more or less similar to that of rHuEPO. The commonly reported adverse events include hypertension (31%), dyspnea (17%), peripheral edema (17%), cough (12%), postural hypotension (10%), vascular access complications (8%) and angina pectoris (8%).[19] One of the rare but clinical relevant complications associated with ESAs is development of pure red blood cell aplasia due to anti-erythropoietin antibodies against exogenously administrated ESAs.[15] There is a theoretical concern regarding development of antibodies against darbepoetin leading to loss of its effectiveness; however, long term experience shows no antibodies have been reported against it, possibly because of its protective structural nature.[18]

CONTRAINDICATIONS

Darbepoetin alfa should be avoided in patients with history or presence of serious allergic reaction to product or excipients, uncontrolled hypertension, pure red cell aplasia after darbepoetin or other ESA.[19]

PLACE IN THERAPY

Erythropoietin stimulating agents have been shown to be beneficial in terms of correction of anemia, reduced need of blood transfusion improvement in quality of life, beneficial effect on left ventricular hypertrophy. However, if they are used to increase hemoglobin level more than recommended, they may cause adverse cardiovascular outcomes.

The KDIGO guideline suggests not starting ESA therapy in adult CKD patients not on dialysis if hemoglobin level is at least 10g/dl whereas the decision to initiate can be individualized if level is <10g/dl. For adult patients with CKD 5D, the guideline suggest to use ESA therapy when hemoglobin level is between 9.0-10.0g and individualization of decision if level is above 10g/dl. Generally, ESAs are not suggested for maintaining hemoglobin level above 11.5 g/dl. For children with CKD, the suggested hemoglobin level is between 11-12g/dl.[45] The type of ESA is selected considering its pharmacology, safety, evidence, affordability and availability.[45]

Darbepoetin should be used to correct anemia in CKD patient to keep the hemoglobin level between 10-12g/dl. Overuse of darbepoetin can be avoided by treating correctable cause of anemia in this patients.[46]

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