ejpmr, 2024, 11(4), 180-184

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

A COMPARATIVE STUDY ON SAFETY, EFFICACY AND AFFORDABILITY BETWEEN ERYTHROPOIETIN VS DARBEPOIETIN IN DIALYSIS PATIENT TO TREAT ANEMIA

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Article Received on 12/02/2024 **Article Revised on 4/03/2024** **Article Accepted on 25/03/2024**

ABSTRACT

Study Objective: To compare the safety, effectiveness, and affordability of erythropoietin alfa with Darbepoetin alfa for achieving increasing haemoglobin concentration in ESRD patients associated with dialysis to treat anemia. **Design:** A prospective, comparative study. **Methods:** In this randomised study, end-stage renal disease (ESRD) patients on dialysis were considered, who are anaemic or whose haemoglobin levels are<10gm/Dl. Among a total population of 80 patients, half of them received erythropoietin alfa and the other half received Darbepoetin alfa via I.V or S.C route of administration and was then observed for the next 26 weeks. The efficacy was compared by observing the mean change in haemoglobin level from baseline to the end of the study. Safety was also evaluated by comparing ADRs observed in both groups. **Results:** In the patient population (n = 80), 40 patients were given erythropoietin alfa (Epofit 4k IU) and the remaining 40 patients were given Darbepoetin alfa (Cresp 40mcg). The mean change in haemoglobin levels to achieve the target haemoglobin levels (10.5-12.5 g/Dl) between these 2 groups during monthly follow up and at the end of 6 months was superior in group A 1(65.2%) than in group B (52.2%). The safety of the drug was evaluated by comparing the ADRs observed in each group. Group b- with Darbepoetin alfa (23.2%) showed significantly similar ADRs when compared to group A- with erythropoietin alfa (21.2%). Although the ADR's were not severe. **Conclusion:** Both the drugs are safe and effective for treating anaemia in dialysis patients, but erythropoietin alfa tends to be superior to Darbepoetin alfa. Darbepoetin alfa is superior as it is a long- acting drug which is generally administered only 1 to 2 times a week, whereas erythropoietin alfa is a short-acting drug which is administered 3 times a week (Doses are adjusted according to HB levels). Although both the drugs are safe and effective, erythropoietin alfa is preferred due to its availability, cost effectiveness, and domestic production.

INTRODUCTION

CKD (chronic kidney disease)

Chronic Kidney Disease (CKD) is a condition in which the kidneys have been damaged and are unable to filter the blood properly.[1]

ESRD (End stage renal disease)

End-stage renal failure (ESRD) is the last stage of CKD, in which the kidneys functions have deteriorated to the point that they can't function. A patient with end-stage renal failure requires dialysis or a kidney transplant to live.[2]

ANEMIA

Anemia is a common complication in chronic kidney disease (CKD) and is associated with a reduced quality of life and increased mortality and morbidity. The mechanisms involved in anemia associated with CKD are diverse and complex. They include a reduction in endogenous erythropoietin (EPO) production, absolute and/or functional iron deficiency, and inflammation with increased hepcidin levels, among others. Oral or intravenous iron supplements, as well as erythropoiesis-stimulating medications, are widely used to treat patients (ESA).

ERYTHROPOIETIN ALFA

Erythropoietin is a glycoprotein that stimulates red blood cell production. It is produced in the kidney. Recombinant human erythropoietin (Epoetin Alfa) is a 165 amino acid glycoprotein produced using recombinant DNA technology that has the same biological properties as endogenous erythropoietin.[3]

Pharmacology

Erythropoietin is a glycoprotein that leads to the stimulation of RBC production. This hormone regulates the differentiation and proliferation of committed

erythroid progenitors in the bone marrow. rHuEPO also speeds up the discharge of reticulocytes without changing the duration of the cell cycle or the number of mitotic divisions required for differentiation. It also raises the number of developing erythroid precursors in the bone marrow. This is followed by an increase in RBC count and hemoglobin.[4]

Pharmacokinetics

In patients with CKD, intravenously given erythropoietin is removed at a pace consistent with first order kinetics, with a circulating half-life ranging from 4 to 13 hours. Detectable levels of plasma erythropoietinare maintained for at least 24 hours within the therapeutic dosing range. Peak levels of erythropoietin are reached between 5 and 24 hours following subcutaneous erythropoietin delivery to individuals with CKD.

ADRS

1. In CKD Patients: Hypertension, Headache, Tachycardia, Nausea, Vomiting, Clotted vascular access, Hyperkalemia, SOB, and diarrhea.[5]
2. In cancer patients on chemotherapy treated with erythropoietin, may show pyrexia, diarrhoea, nausea, vomiting, edema, asthenia, fatigue, shortness of breath, and upper respiratory infection.[6]
3. In surgery patients treated with erythropoietin includes pyrexia, nausea, constipation, skin reaction at medication site, vomiting, skin pain, insomnia, headache, dizziness.

DARBEPOIETIN

Darbepoetin Alfa is an erythropoiesis-stimulating protein that works in the same way that erythropoietin does. Darbepoetin Alfa is a 165-amino-acid protein with a molecular weight of roughly 37 kDa that is synthesized using recombinant DNA technology in the Chinese Hamster Ovary (CHO) cell. Darbepoetin Alfa contains two more N-linked glycosylation sites than erythropoietin, for a total of five N-linked glycosylation sites. In the human body, the extra N-linked glycosylation sites result in a prolonged half- life.[7]

Pharmacokinetics

To achieve the same biological response, Darbepoetin Alfa's level in the circulation remains above the minimum stimulatory concentration for erythropoiesis for longer than the equivalent molar dose of r- HuEPO due to its increased carbohydrate content. To achieve the same biological response, Darbepoetin Alfa should be administered less frequently.

ADVERSE REACTIONS

Adverse reactions have been reported with Darbepoetin Alfa and include: patients with cancer have a higher risk of death, myocardial infarction, stroke, and thrombosis, as well as a higher chance of tumour progression or recurrence, seizures, hypertension, serious allergic reactions, PRCA.

1. Patients with Chronic Renal Failure: In adult patients, adverse reactions occurring in patients treated with Darbepoetin Alfa are: hypertension, dyspnea, peripheral edema, cough, procedural hypotension, angina pectoris, vascular access complications, fluid overload, rash, and arteriovenous graft thrombosis. In pediatric patients, the clinical studies often reported significantadverse effects of Darbepoetin Alfa were hypertension and seizures. Hypertension, injection site soreness, rash, and convulsions were the most frequently reported side effects. Studies have not evaluated the effects of Darbepoetin Alfa when administered to pediatric patients as the initial treatment for the anaemia associated with CKD.
2. Chemotherapy Treatment for Cancer Patients: Hypersensitivity, convulsions, hypertension, thromboembolic events, including pulmonary embolism, myocardial infarction, cerebrovascular disorders, including CNS haemorrhages and cerebrovascular accidents (ischemic and haemorrhagic), rash, edema, and injection site pain have all been reported in controlled clinical trials and post-marketing experience.[8]

REVIEW OF LITERATURE

1. **Yves Vanrenterghem, Peter Barany et al (2002):** This was a multicenter, randomized, open- label comparative study designed to determine whether darbepoetin alfa is as effective and well tolerated as EPO when administered IV or SC for treatment of anemia in dialysis patients. Patients were required to be ≥18 years of age with CRF. They had to be on stable EPO (alfa or beta) therapy given one, two, or three times weekly by the IV or SC route for at least three months. Then the study concluded that Darbepoetin alfa maintains hemoglobin as effectively aserythropoietin, but with a reduced dose frequency.[9]
2. **Mehta KS, Sinha SD, Bandi Vamsi et al (2019):** This study was phase III, randomized, active-controlled, non-inferiority study, the pre-dialysis patients with CKD who had hemoglobin (Hb) levels less than 10 gm/dL received either EPO (thrice weekly) or DA-α (once weekly) subcutaneously for 12-24 weeks. The patients with Hb levels greater than10 gm/dL were switched directly to DA-α or EPO for 12 weeks maintenance phase. The primary efficacy endpoint was to compare the mean change in Hb level from baseline to end of correction phase between DA-α and EPO. Safety was also evaluated.[10]
3. **Wolf gang C.Winkelmaye, Tara I. Chang et al (2015):** This study was an Observational, registry-based, retrospective cohort study. Which was mimicked a cluster-randomized trial by comparing mortality and cardiovascular events in US patients initiating hemodialysis therapy in facilities (almost) exclusively using DPO and EPO. It was concluded that In incident hemodialysis patients, mortality and cardiovascular event rates did not differ between

patients treated at facilities predominantly using DPO versus EPO.[11]

4. **Joan C egrie, Erik Dwyer, Jeffrey K Browne et al:** This study was conducted to prove Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. Pharmacokinetic and Pharmacodynamics studies and biochemical analysesof Darbepoetin alfa and erythropoietin were performed to define the consequences of the increased carbohydrate content.Increasing the sialic acid-containing carbohydrate content beyond the maximum found in EPO leads to a molecule with a longer circulating half-life and thereby an increased in vivo potency that can be administered less frequently.[12]

AIMS AND OBJECTIVES OF THE STUDY

Primary Objective

To study or determine Safety, Efficacy and Affordability of DA-α against EPO-α for treating anemia amongdialysis patients or patients with ESRD.

Secondary Objective

- To determine or to find improvement of hemoglobin and creatinine levels in renal anemic patients.
- To asses the demographic details and medication history of the patients.
- To asses the comorbidities of patients if present.
- To compare ADRs of both drugs.
- To determine economic or cost effectiveness among both the drugs.
- To provide patients counselling about disease and drugs.

METHODS AND MATERIALS

Study Design

The Study is Prospective and comparative study.

Source of Data and Materials

- Patient data collection form.
- Patient case note/prescription.
- Patient consent form.

Inclusion Criteria

- Patients on dialysis.
- Anemic patients.
- Patients above 18 years.
- Patients below 80 years.

Exclusion Criteria

- Patients who are not willing to give the consent.
- Hypersensitive patients.
- Pediatrics and geriatrics.
- Sickle cell anemia.
- Pregnant or breastfeeding patient.

PARAMETERS

Primary Parameters

HaemoglobinCreatinine

Secondary Parameters

GRBS
Comorbidities

Method of Data Collection

Data collection from patient's medication notes

Study Procedure

This is a comparative study between 2 drugs where dialysis patients are enrolled in the study after obtaining the consent. The data collection form will be prepared and used. This form mainly consists of the demographic details of patients their HB levels, creatinine levels and about their disease condition and present history followed by medication chart. Patient counseling will be done using leaflets and there will be constant follow up. This study is conducted at care hospitals. All the information related to study will becollected and data will be analyzed using suitable method for analysis.

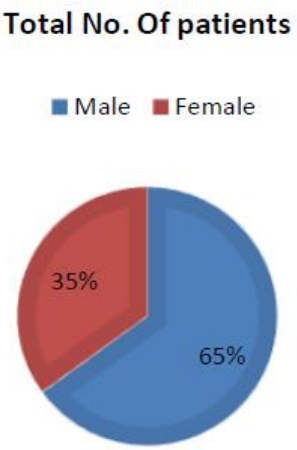
RESULTS

The work entitled Comparative study on safety, efficacy and affordability between Erythropoietin Alpha and Darbepoetin Alfa in dialysis patients to treat anemia was carried out in the Nephrology Department at Care Hospitals, Hitech City, Hyderabad. A total number of 80 patients were enrolled in this study. The patients were divided into 2 groups (A&B). Group A (40 Patients) were treated with Erythropoietin Alpha and Group B (40 Patients) were treated with Darbepoetin Alfa.

Group A: Erythropoietin Alpha
Group B: Darbepoetin Alfa.

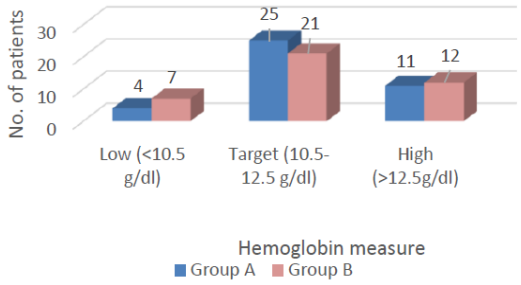
1. **Total No. of Dialysis Patients.**

Gender	Male	Female	Total No. Of Patients
No. Of patients	52 (65%)	28 (35%)	80



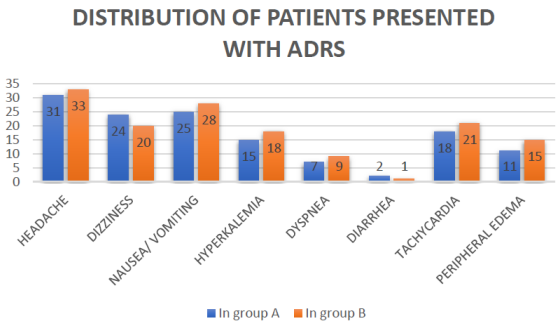
2. Target Hemoglobin In Each Group

TOTAL HB MEASURES	GROUP A	GROUP B
Hb level		
Low (<10.5 g/dl)	4 (10%)	7(17.5%)
Target (10.5-12.5 g/dl)	25(62.5%)	21(52.5%)
High (>12.5g/dl)	11(27.5%)	12(30%)
Total	40(100%)	40(100%)



3. DISTRIBUTION OFPATIENTS PRESENTED WITH ADRS

ADRs Reported	In group A	In group B
HEADACHE	31	33
DIZZINESS	24	20
NAUSEA/ VOMITING	25	28
HYPERKALEMIA	15	18
DYSPNEA	07	09
DIARRHEA	02	01
TACHYCARDIA	18	21
PERIPHERAL EDEMA	11	15



DISCUSSION

In our 6 months study 80 patients were observed patients with ESRD or patients on dialysis were enrolled for the study as per inclusion and exclusion criteria. They were divided into Group A (40 patients who were treated with Erythropoietin alfa) &Group B (40 patients who were treated with Darbepoetin alfa).

Both the groups were compared by using following parameters

Gender: A total of 80 patients were screened and randomized into two treatment group. Out of which 40 patients were of GROUP A, 24 patients (60%) were male, 16 patients (40%) were female. In case of GROUP B, 28, patients (70%) were male, 12 patients (30%) were female.

Haemoglobin levels in the patients

All the patients haemoglobin values were recorded with an interval for 30 to 60 days from baseline to 6 months. From the collected data, we analyzed that 62.5% of Group A and 52.5% of Group B has achieved target haemoglobin measure where as 10% of Group A and 17.5% of Group B has achieved low HB measure and 27.5% of Group A and 30% of group B has achieved High level.

Both the groups produced increase in the haemoglobin levels during the study time, the erythropoietin isfound to be superior in maintaining haemoglobin levels when compare to darbepoetin.

Creatinine levels in the patients

All the patients' creatinine levels were recorded with an interval for 30 to 60 days from baseline to 6 months.From the collected data, we analysed that about 75% of Group A patients and 58% of Group B patients have achieved the targeted creatinine levels during the treatment.

Although both the groups achieved the target creatinine levels, the erythropoietin alfa shows superiority. **Secondary parameters include:** The parameters that used to the Safety comparison were **Comorbidities:**

In our study, patients were associated with comorbid conditions, Mostly with 81.25% HTN, 72.5% DM, 31.25% Thyroid, 45% Anaemia, 10% Diabetic Neuropathy, 18.75% UTI, 8.75% AKI, 12.5% Coronary Artery Disease and 6.25% Depression.

ADRS

In our study ADRs were observed from the patients- 80% of the total patient populated reported headache as the most common ADR followed by nausea vomiting 66%, Dizziness 55%, Tachycardia 48% Hyperkalaemia 41%, Peripheral edema 32%, Dyspnea 20% and Diarrhoea 4%.

CONCLUSION

Erythropoietin is a hormone secreted by the kidneys that increases the rate of production of red blood cells in response to falling levels of oxygen in the tissues.

Most people on dialysis have anemia because

The kidneys are not making enough erythropoietin hormones to help patient's body in making red blood cells. Patients often lose some blood during hemodialysis treatments and blood testing. Patient may have low levels of iron. To make hemoglobin, Iron is essential.

In order to treat these patients are generally given epoetin which is a human erythropoietin produced in cell culture using recombinant DNA technology. It helps in treating

anemia in dialysis patients.

In this study comparison of safety, efficacy and affordability between erythropoietin Alfa and Darbepoetin Alfa for treating renal anemia in dialysis patients was done. Patients with end stage renal disease (ESRD) /Dialysis patients were enrolled for the study as per inclusion and exclusion criteria. With sample size of 80, patients were divided into two groups i.e., Group A (40 patients who were treated with Epofit 4000 IU) & Group B (40 patients who were treated with cresp 40mcg). The parameters that were used to the safety efficacy comparison were – CBP (hemoglobin levels), Creatinine levels were recorded from baseline to six months with an interval of 30 to 60 days. Then the comparison was done using statistical method.

In this prospective comparative study, we observed that both erythropoietin alfa (epofit) and darbepoetin alfa (cresp) treats anemia in dialysis patients. However, the erythropoietin alfa was significantly superior to Darbepoetin alfa in maintaining the hemoglobin levels as well as creatinine levels whereas darbepoetin alfa was superior to erythropoietin alfa with its long-acting capacity and better half-life.

According to the study's secondary goal/objective

The use of erythropoietin alfa (Epofit) and darbepoetin alfa (cresp) can treat anaemia in dialysis patients, using erythropoietin is preferred due to its availability, cost effectiveness and domestic production.

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