

# A comparative observational study on desidustat to erythropoiesis-stimulating agent for anemia management in dialysis-dependent patients

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**Abstract: Background:** Anaemia is the most common complication observed as renal disease worsens. Conventionally used recombinant human erythropoietin (rHuEPO) agents have significantly altered how anemia is treated in CKD patients. A novel drug, desidustat, which is a HIF (hypoxia-inducible factor)-PH (prolyl hydroxylase) inhibitor, has been approved recently in India for the management of anemia in dialysis-dependent and dialysis-non-dependent patients. **Aims and Objectives:** The key objective of this research is to compare Desidustat and ESAs' effectiveness in treating anemia in individuals who are reliant on dialysis. **Materials and Methods:** This study was conducted at the Asian Institute Of Nephrology and Urology, Banjara Hills, for 6 months. A total of 64 patients were included. Informed consent was obtained from all the subjects who had undergone dialysis at least twice a week in the hospital. **Results:** The time taken and change in mean hemoglobin values were contrasted with an unpaired t-test, and the p-value was found to be  $>0.05$ , not statistically significant. There were very mild adverse events observed in both treatment groups, which were usually relieved by symptomatic treatment. **Conclusion:** This study identifies the non-inferiority of desidustat over erythropoiesis-stimulating agents in the treatment of anemia in dialysis-dependent chronic kidney disease patients. Patients on desidustat attained normal hemoglobin levels within a shorter time frame and maintained this range for a longer duration as compared to ESAs. There were no severe adverse events observed in either of the groups.

**Keywords:** Chronic Kidney Disease, Anemia, Dialysis, Erythropoiesis-stimulating Agent, HIF (hypoxia-inducible factor)-PH (prolyl hydroxylase) inhibitor, Desidustat

## I. INTRODUCTION

According to KDIGO guidelines, CKD is classified into 5 stages named 1, 2, 3, 4, and 5 based on Glomerular Filtration Rates (GFR). GFR rates below 15 millilitres per min per  $1.73 \text{ m}^2$  body surface area belong to stage 5, or End-stage renal failure/End-stage renal disease, a condition when mortality is likely without renal replacement therapy [RRT], such as hemodialysis, peritoneal dialysis, hemodiafiltration, or a renal transplant. The majority of people are asymptomatic until they reach stage 4 or stage 5. <sup>(1)</sup> As per the World Health Organization (WHO),  $<13.0 \text{ g/dL}$  for men and  $<12.0 \text{ g/dL}$  for premenopausal women are typically considered to be anemic. CKD-related anemia is a type of normocytic, normochromic, or hypoproliferative anemia. It is usually linked to poor outcomes in CKD and increased mortality, among other CKD comorbidities. Anemia in chronic kidney disease is associated with poor quality of life, a higher risk of cardiovascular disease, hospitalizations, cognitive impairment, and mortality <sup>(2)</sup>. As the GFR drops  $<60 \text{ mg/ml}$ , the condition begins to manifest. When the GFR is  $>80 \text{ millilitre per min}/1.73 \text{ m}^2$ , anemia is unlikely to occur. Yet the anemia worsens as the GFR declines. Anemia is the most common complication observed as renal disease worsens, affecting almost all patients with stage 5 CKD. Later stages of CKD have greater rates of anemia both in terms of prevalence and severity; among patients on dialysis at stage 5, anemia prevalence is above 90%. <sup>(2)</sup> Chronic renal illness-linked anemia is multifactorial. Anemia can be result of various factors, including reduction in the lifespan of red blood cells, functional iron deficit, decreased erythropoietin (also called EPO) production, or resistance to EPO signaling. Decreased renal erythropoietin (EPO) production, the hormone that stimulates the synthesis of RBC's —is the most likely cause. Hypoxia-inducible factor (HIF), a transcription factor that is responsible for controlling the gene expression of erythropoietin, has recently been linked to decreased erythropoietin. Additional causes of bleeding include malfunctioning platelets, iron insufficiency, folate, vitamin B12 deficiency, uremia (which causes RBC malformation that causes hemolysis), and, in rare cases, blood loss during HD In renal glomerulopathies, such as glomerulonephritis and diabetic nephropathy, anemia can be especially severe. Depending on the level of excretory failure, RBC

fragmentation by injured renovascular endothelium in certain conditions, such as glomerulopathy and malignant hypertension, worsens anemia.

### **ERYTHROPOIESIS:**

The erythropoietic system preserves homeostasis in the red blood cell supply to ensure an appropriate tissue oxygen supply. If the blood loss is not substantial, balance is achieved by replacing the erythrocytes lost owing to senescence and bleeding. Following the prediction that a circulating factor controlled the erythropoietic response, ERYTHROPOIETIN was discovered, and its gene was cloned in 1985. The availability of oxygen in tissue is continuously sensed at the molecular level. A complex reaction is activated if hypoxia is detected. Erythropoietin glycoprotein hormone production is boosted, which plays a significant part in the reaction. The main stimulant for mammalian erythrocyte formation is this 30.4-kDa molecule. Due to its synthesis in the kidneys, systemic circulation, and ability to bind to tissue receptors, particularly those in the bone marrow, erythropoietin works as a true hormone. To promote erythropoiesis, erythropoietin binds to receptors on the surface of cells in the bone marrow. The method by which cells detected hypoxia and the crucial function of the transcriptional factor HYPOXIA INDUCIBLE FACTOR 1 (HIF-1) was discovered shortly after.

### **IRON AND HEPCIDIN:**

Iron and erythropoietin must be available in sufficient amounts for effective erythropoiesis to occur. Iron deficiency is commonly observed in patients with chronic kidney disease (CKD); its prevalence is higher in those receiving dialysis and approximately 50% in those with non-dialysis-dependent CKD. Iron shortage can be caused by occult blood loss, disease - condition, systemic inflammation, surgery, venepuncture, impaired absorption due to high hepcidin concentrations, and blood retention by the dialysis machine, among other things. These variables are thought to cause patients to lose around 2,000 mg of iron annually<sup>(5)</sup>. Uncertainty surrounds the extent of iron loss in non-dialysis-dependent CKD. A blockage in iron absorption from the intestines and reduced iron release from storage in macrophages and the liver commonly exacerbate the iron shortage in CKD which affects the availability of iron for erythropoiesis. Hepcidin, a circulating protein, produced by the liver, serves as the primary regulator of iron homeostasis and mediates this iron blockage phenomenon. Hepcidin plays an important role in the pathogenesis of anemia and inflammation. The cellular iron transporter ferroprotein is internalized into cells as a result of elevated hepcidin levels. As a result, neither iron from storage tissues nor that derived from enterocytes enters the circulation.<sup>(12)</sup> Hepcidin levels rise in reaction to the body's enhanced iron store and fall in response to iron insufficiency.<sup>(13)</sup> Inflammation is a secondary but significant factor in elevated hepcidin levels. This reaction restricts the amount of iron that bacteria can access during infection. It may be a maladaptive response in CKD patients.<sup>(11)</sup> Hepcidin concentration rises as a result of an occult state of inflammation, which also prevents iron from being accessible for erythropoiesis. This is often discernible by the relatively frequent observation of decreased transferrin saturation (TSAT; decreased circulating iron) combined with an unexpectedly raised serum ferritin content (elevated iron storage) in haemodialysis patients<sup>(10)</sup>. Increased mortality, cardiovascular disease, and atherosclerosis are linked to elevated serum hepcidin levels in CKD<sup>(12)</sup>.

### **TREATMENT FOR IRON DEFICIENCY AND REPLACEMENT:**

As iron is typically poor in this population, it is advised that all CKD patients, dialysis-dependent or independent should be tested for iron insufficiency. Patients taking iron replacement medication should have their iron status evaluated at least once a month, and those not receiving it should have it done once every three months. Before administering ESA, we should think about iron replacement therapy if serum ferritin falls below 100 ng/ml without it. According to the KDIGO 2012 guideline, ESA should be taken into account when serum ferritin is less than 500 ng/ml and TSAT is less than 30%<sup>(5)</sup>. The rationale for the recommendation is that high serum ferritin levels may cause iron to accumulate in reticuloendothelial system organs, increasing the risk of infections and CVD. When serum ferritin falls below 100 ng/ml or TSAT drops below 20% in patients receiving adequate dosages of ESA, iron replacement therapy should be explored. It is yet unknown, though, the safety of long-term iron replacement therapy. In these populations, careful iron status monitoring is necessary both to start iron supplementation therapy on time and to prevent giving too much iron.

### **ERYTHROPOIESIS STIMULATING AGENTS (ESA):**

For normal erythropoiesis, the kidney's peritubular cells produce erythropoietin (EPO), a sialo glycoprotein hormone which is of MW 34000. It is also produced in small amounts by the spleen, liver, bone marrow, and lungs<sup>(21)</sup>. There is no storage of erythropoietin within the cells in which it is made; instead, it is released directly into the bloodstream after production. When in circulation, the distribution's volume is similar to the plasma's volume. Erythropoietin stimulating agents (ESAs) are pharmacologically manufactured recombinant forms of EPO produced from cell cultures using recombinant DNA technology. Recombinant erythropoietin circulates with a t<sub>1/2</sub> of ~ 5 - 12 hours, as does likely native

erythropoietin and is secreted directly into the bloodstream. Recombinant human erythropoietin (rHuEPO) has significantly altered how anemia is treated in CKD patients. Examples of erythropoietin-stimulating agents include epoetin alfa, darbepoetin, and methoxy polyethylene glycol-epoetin beta. Since ESAs have a risk of side effects, they are usually reserved for individuals whose hemoglobin level is less than 10 g/dL. Owing to the possibility of side effects, individuals with hemoglobin levels below 10 g/dL are typically the only ones who can use ESAs. The amount of EPO produced increases with decreasing pO<sub>2</sub>. Anemia and hypoxia are sensed by kidney cells and induce rapid secretion of EPO, which acts on the erythroid marrow and stimulates the proliferation of CFUs in the erythroid series. It causes erythroblasts to mature and produce hemoglobin; it also releases reticulocytes into the bloodstream<sup>(21)</sup>.

#### DOSAGE REGIMEN:

According to KDIGO guidelines: -

Initiation therapy: For adult CKD 5 patients, ESA therapy should be considered when hemoglobin is between 9.0 and 10.0 g/dl, in order to prevent the Hb concentration from dropping below 9.0 g/dl.

Maintenance therapy: In all adult patients, ESAs are not used to deliberately raise the Hb levels above 13 g/dl.

These ESAs are to be administered in parenteral form, either intravenous or subcutaneously. Recent research suggests that administering epoetin SC rather than IV may result in a dosage reduction of roughly 30%. The recommended dosage of Epoetin alfa-50-100 U/kg, 3×/WK, Darbepoetin alfa-0.45 µg/kg every WK<sup>(5)</sup>.

#### USES:

Epoetin is primarily used to treat anemia of chronic renal failure, which is caused by low EPO levels. For EPO therapy, only individuals with symptoms and Hb ≤ 8 g/dL should be evaluated. Epoetin increases hematocrit and hemoglobin, decreases the need for transfusions, and enhances quality of life when administered 25–100 U/kg SC or IV three times a week (maximum of 600 U/kg/week). As a result, it is being used by patients who are eligible more frequently. Starting low and titrating up is an effective method to maintain a hematocrit of 30–36% and a maximum of 12 g of hemoglobin per deciliter. Higher mortality has been observed in trials when the Hb level is brought up to normal (13.5 g/dl). Therefore, it is recommended to use the lowest dose of epoetin that is necessary to prevent blood transfusions or to maintain a level between 10 and 11 g/dl. Patients' ability to exercise and general well-being both improve. Since the majority of patients have low iron stores, concurrent parenteral and oral iron therapy is necessary to get the best results.

#### ADVERSE EFFECTS:

Adverse effects occur as a result of sudden increases in hematocrit, blood viscosity, and peripheral vascular resistance (due to the correction of anemia).

- EPO's most severe adverse effects have been associated with a higher risk of thrombotic events, particularly in surgical patients. Blood viscosity increases when erythropoietin-stimulating medications are used in conjunction because they stimulate erythrocyte production. This adds to the reduced vasodilatory effect caused by a low baseline pO<sub>2</sub>, raising the risk of ischemic stroke and myocardial infarction.
- Additionally, there exists an increased possibility of venous thromboembolism, prompting some to suggest antithrombotic prophylaxis for individuals undergoing ESA therapy.
- The majority of patients who receive dialysis have a high risk of elevated clot formation in the AV shunts; hypertensive episodes or consistently elevated blood pressure; significant thromboembolic events; seizures; and in certain cases, flu-like symptoms lasting 2-4 hours.
- Headache, rash, nausea, and joint pain are typical adverse effects. Heart attacks, strokes, increased cancer growth, and pure red cell aplasia are some of serious adverse effects that may occur.
- The safety of using it while pregnant is uncertain<sup>(21)</sup>.

However, the use of ESA is linked to harmful cardiovascular events, and many CKD patients do not respond well to ESA in terms of hematology, primarily because the erythron does not receive enough iron. Infection, neoplasia, severe hyperparathyroidism, aluminum toxicity, a lack of vitamin B12, inadequate renal replacement therapy, myelosuppressive medications, and immune-mediated pure red cell aplasia are additional reasons for ESA resistance<sup>(6)</sup>. Patient responses to rhEPO have a high degree of heterogeneity and sensitivity loss, and this resistance to rhEPO therapy can raise mortality and morbidity rates in CKD patients. In addition, rhEPO can produce antibodies that are directed against it. Moreover, even in the presence of adequate EPO secretion in the body, anemia and hyperresponsiveness to rhEPO within CKD patients may be caused by an inadequate reaction of the body to hypoxia. Iron absorption and utilization are abnormal in CKD patients because of ongoing inflammation and elevated hepcidin levels. By blocking ferroportin, the tissue iron exporter, hepcidin, a hepatic hormone, reduces the amount of iron absorbed from the GI tract and locks the iron in tissue like the liver and macrophages. There is also a considerable

unmet need to treat CKD-induced anemia since rhEPO is hyporesponsive. Inhibitors of prolyl hydroxylase (PHD) present a viable therapeutic alternative for anemia brought on by CKD<sup>(18)</sup>.

#### **DESIDUSTAT:**

A small molecule belonging to the class HIF-PH inhibitor that is orally available was created by Zydus Cadila under the brand name OXEMIA to treat anemia brought on by CKD, COVID-19 infections, and chemotherapy-induced anemia<sup>(23)</sup>. In phase 2 and 3 studies, HIF-PHIs consistently demonstrated clinical efficacy in patients with anemia of non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD. They promote erythropoiesis in a dose-dependent manner. On March 7th, 2022, desidustat gained its first approval in India for the treatment of CKD in patients who were either receiving dialysis-dependent or independent.

#### **HIF-PHD SYSTEM:**

The HIF system is responsible for the body's detection of tissue hypoxia and subsequent recognition of anemia. The HIF transcription factors- HIF-1 and HIF-2 are made up of two subunits: an oxygen-sensitive  $\alpha$ -subunit (HIF-1  $\alpha$ , HIF-2  $\alpha$ , or HIF-3  $\alpha$ ) and a constitutively expressed  $\beta$ -subunit. These proteins control responses to environmental stimuli. HIF-1  $\alpha$  and HIF-2  $\alpha$  generate HIF-1 and HIF-2 transcription factors, respectively, when they heterodimerize with HIF  $\beta$ . HIF-1 primarily controls genes that are sensitive to hypoxia, such as those that produce angiogenic factors like vascular endothelial growth factor (VEGF) and glycolytic enzymes like phosphoglycerate kinase-1 and lactate dehydrogenase-A. Initially identified as a vascular HIF-1  $\alpha$ -like factor, its  $\alpha$ -subunit is sometimes referred to as endothelial PAS domain protein-1. It soon discovered that HIF-2  $\alpha$  was not exclusive to endothelial cells<sup>(8)</sup>. HIF-2 promotes the expression of EPO in the liver and kidneys, as well as the transcription of other genes involved in iron metabolism and transport, such as ferroportin (FPN1), divalent metal transporter 1 (DMT1), and duodenal cytochrome b (DCYTB)<sup>(8)</sup>. Although HIF-1 and HIF-2 share many of the same targets, some genes are controlled more by one than the other. HIF-2 seems to be more important in the control of erythropoietin synthesis and the activation of iron metabolism genes. It has been demonstrated that TF, TF receptor 1, and ceruloplasmin (CP) are all regulated by HIF-1 and HIF-2. Under conditions of rapid erythropoiesis, erythroferrone (ERFE) mediates the reduction of hepcidin synthesis in the liver. The oxidation of ferrous (Fe<sup>2+</sup>) to ferric (Fe<sup>3+</sup>) iron is catalyzed by the copper-carrying ferroxidase known as ceruloplasmin (CP), which is controlled by the HIF. Pharmacologic HIF activation is therefore expected to improve enteral iron absorption and transport by upregulating the expression of iron metabolism and transport genes. Later, it was discovered that the oxygen-regulated HIF-1 subunit's proline residues, which are hydroxylated to cause ubiquitylation and proteasomal degradation, govern HIF transcriptional activity. Prolyl-4-hydroxylases, or PHD enzymes, act as the main oxygen sensors in the HIF pathway and mediate HIF hydroxylation.

#### **MECHANISM OF HIF-PHD SYSTEM:**

HIF- $\alpha$  is constantly synthesized; when enough oxygen is supplied, it is quickly hydroxylated for breakdown by the enzymes known as HIF-prolyl hydroxylases. Since they need oxygen as a co-substrate, prolyl hydroxylases serve as oxygen sensors. HIF $\alpha$  is polyubiquitinated and eliminated by the von Hippel-Lindau protein after hydroxylation. While HIF $\beta$  is constitutively produced, it is not susceptible to oxidative damage.<sup>(9)</sup> When there is tissue hypoxia, HIF $\alpha$ - builds up, translocates to the nucleus, forms a heterodimer with HIF- $\beta$ , and binds to the hypoxia response elements of several oxygen-sensitive genes. The erythropoietin gene is one of these, increasing the synthesis of erythropoietin. Several additional genes are also activated, including those that code for enzymes and transporters related to iron metabolism, angiogenesis, and mitochondrial genesis. Hence, through enhanced expression of iron metabolism and transport genes, pharmacologic HIF activation is predicted to enhance enteral iron absorption and transport. The HIF/PHD oxygen-sensing system controls biological processes crucial for cell viability and plays a central role in cellular adaptation to hypoxia. They include erythropoiesis, angiogenesis, immunological responses, mitochondrial metabolism, and glycolysis.

#### **MECHANISM OF ACTION:**

Hypoxia-inducible factor (HIF), which is stabilized by prolyl hydroxylase inhibitors (PHI), promotes erythropoiesis by boosting the production of erythropoietin and lowering hepcidin. Hypoxia-inducible factor (HIF) is a heteromeric transcription factor (HIF-1Alpha, HIF-2Alpha, and HIF-3Alpha) that is essential for the control of iron metabolism, erythropoiesis, and several other processes related to homeostasis. These factors control the cellular response to hypoxia by changing gene expression in a particular cell type. The regulation of iron metabolism and erythropoiesis is mostly controlled by HIF-2alpha. Since prolyl hydroxylases need oxygen as a co-substrate, they function as oxygen sensors. HIF-PHIs chelate at the iron in the catalytic site, stabilizing HIF-1 and HIF-2 and increasing HIF-regulated gene expression in a dose-dependent manner. Prolyl hydroxylase domain proteins hydroxylate hypoxia-inducible factor HIF-

$\alpha$ , which is subsequently degraded by proteases in a normoxic environment. When there is hypoxia, HIF- $\alpha$  does not degrade; instead, it moves to the nucleus, attaches to HIF- $\beta$ , and triggers the hypoxia response element, which commences the transcription of the erythropoietin gene<sup>(5)</sup>.

#### PHARMACOKINETICS:

Healthy volunteers, CKD patients requiring dialysis, and pre-dialysis CKD patients have all had their oral desidustat pharmacokinetics evaluated. After a single oral dosage of 50 mg of desidustat while fasting, the peak plasma concentration (C<sub>max</sub>) of desidustat is attained in 1.3 hours on average in healthy individuals. Consuming food decreased desidustat exposure [C<sub>max</sub> and area under the concentration-time curve from time 0 to t (AUC<sub>t</sub>)] and delayed desidustat t<sub>max</sub><sup>(23)</sup>. In patients with dialysis-dependent CKD who received desidustat 50, 100, or 150 mg as a single dose within two hours of dialysis (n = 8/dose), T<sub>max</sub> was attained 2.5 hours after administering the medication. Desidustat exposure (C<sub>max</sub> and AUC<sub>t</sub>) increased in pre-dialysis CKD patients in a dose-dependent manner after single and multiple doses of therapy with desidustat 100, 150, or 200 mg (n = 11/dose) on alternate days for six weeks<sup>(24)</sup>. Desidustat did not accumulate following the administration of several doses (accumulation index = 1). Desidustat has no preferential distribution in erythrocytes and is primarily (99%) bound to plasma proteins. Desidustat was metabolically stable in vitro when it was treated with recombinant human CYP isoforms, human hepatocytes, or human liver microsomes. Desidustat was converted into the minor metabolites hydroxylated and hydroxyl-glucuronide in pre-dialysis patients. Desidustat does not create reactive glutathione-protein adducts. Following a single oral dose of 10-300 mg in fasting healthy volunteers, Desidustat was eliminated as an unchanged drug in the urine; hydroxylated and hydroxyl-glucuronide metabolites were also detected in the urine. Desidustat's mean elimination half-life was 6–15 h in dialysis-dependent CKD patients receiving a single dosage of 50–150 mg and 6–14 h in pre-dialysis CKD patients receiving repeated doses of 100–200 mg on alternate days for six weeks. The kinetics of HIF $\alpha$ -stabilization and the relative expression of HIF regulatory genes impacting the entire erythropoiesis process were shown to differ amongst other medications in this class, including daprodustat, molidustat, Roxadustat, and vadadustat.

#### DOSAGE REGIMEN:

The recommended dose of desidustat is 100mg given orally three times a week, which is the suggested starting dose for patients who are dialysis dependent. In phase 1 studies, desidustat was discovered to be well-tolerated in single and multiple doses up to 300 mg, while in phase 2 studies, desidustat was discovered to be safe, efficacious, and bearable up to 200 mg in patients with CKD and anemia<sup>(24)</sup>.

## II. MATERIALS AND METHODS

This observational study was carried out at the NEPHROLOGY department at the ASIAN INSTITUTE OF NEPHROLOGY AND UROLOGY hospitals. A sample size of 64 was taken and observed for 6 months. Out of which, 30 patients were receiving erythropoiesis-stimulating agents (ESA), and 34 patients were on desidustat.

**STUDY CRITERIA:** Age more than 18 years, hemoglobin values during the screening period < 11 g/dl, patients on hemodialysis atleast  $\geq 2$  times in a week, patients who had no planned kidney transplant and no planned change in treatment (dialysis modality), history of cancer - either concurrent or current, serologic status indicating the presence of an active HIV infection or hepatitis B or C infection, history of autoimmune hemolytic anemia untreated, thalassemia/bleeding disorders, idiopathic thrombocytopenic purpura (ITP), or renal transplant, past history of allergic responses linked to substances with chemical or biologic compositions comparable to those of Epoetin alfa, Desidustat, or any other erythropoiesis-stimulating drug, pregnant and breast feeding women, the existence of additional clinically significant systemic diseases or disorders (e.g., immune system, gastrointestinal, respiratory, mental, or involving any other body system), history of significant alcoholism or drug abuse were excluded from the study.

## III. RESULTS

All the qualitative factors like gender, comorbidities, side effects, and dialysis type are represented with frequencies and percentages. All the quantitative parameters, like Age, HB, SBP, DBP, and K<sup>+</sup>, at different time points, are represented with means and standard deviation. To compare the mean difference between the two groups, we used a t-test for independent samples. All the data will be entered in MS Excel and analyzed using the SPSS 23.0 version. P value less than 0.05 will be considered significant.

## IV. DISCUSSION

We have conducted a study to assess the efficacy of desidustat and ESAs in the management of anemia in people who are dialysis dependent. In this observational study, a total of 64 patients were recruited, out of whom 34 patients were on desidustat and 30 were on ESA agents. In this study, out of 34 patients in the desidustat group, the majority were 61 and above, and the number of males and females was equal with a mean of 64.54 kg, whereas out of 30 patients in the

ESA group, the majority were belonging to the age group of 45–60 and males had a mean weight of 64.5 kg, which was similar to the study conducted by Sishir Gang et al. The majority of the patients in the desidustat group had hypertension as a common comorbid condition, whereas hypertension and type 2 diabetes mellitus were more common in the ESA-receiving group, which was similar to the study conducted by the DREAM-D phase 3 study. Epoetin  $\alpha$  was the most commonly prescribed EPO analog, followed by epoetin  $\beta$ . A very small number of patients were prescribed darbepoetin  $\alpha$ . All 64 patients in both groups were usually prescribed iron supplements, which are usually composed of iron sucrose or ferric carboxymaltose, with a dose ranging from 500mg in 100 mL of NS given through the IV route every one week, 10 days, 1 month, or 45 days, depending on the body weight and hemoglobin levels. Out of 34 patients, 27 were receiving dialysis three times a week and were given desidustat with an initial dose of 100mg after every dialysis session. For the seven patients who presented twice a week for dialysis, the third dose was administered 48 hours after the second dose. 30 patients were administered various types of ESA agents at a dose of 50 IU/kg and were observed for 24 weeks. Dosage adjustments were made during the course of treatment based on changes in hemoglobin levels. Thus, our study was in accordance with Prakash Khetan et al. Out of available EPO analogues in India, 87% of 30 patients were receiving epoetin  $\alpha$ , followed by 10% epoetin  $\beta$ , and 3% of darbepoetin  $\alpha$ . The patients receiving desidustat who were previously not on an ESA analogue for at least 4 weeks prior to screening were included in accordance with the study conducted by Deepak Varade et al. Most of the patients in the desidustat group started their dialysis session in the year between 2018-2022 whereas patients received EPO agents between 2021 and 2022. Chills, hypotension, dry cough, generalized weakness, and SOB were commonly reported in the desidustat group. SOB was more commonly presented in patients administering ESAs, which was common to the results obtained by a phase 3 study conducted at Muljibhai Patel Urology Hospital, Nadiad, India. Each patient in both groups was observed for 24 weeks. Patients in the desidustat group achieved a significant change in mean from baseline at week 8 ( $11 \pm 1.37$ ), whereas the desirable mean was achieved at week 18 ( $11.33 \pm 1.23$ ) in the ESA treatment group. A study conducted by Umesh Gupta et al. showed similar results. Both of the treatment groups, desidustat, and ESAs, were compared using an unpaired t-test, and the difference in mean values showed non-significant values ( $p > 0.05$ ), inferring the inferiority of efficacy in both treatment groups. These results were in accordance with the phase-3 DREAM-D study reported by Sohitha Dhillon et al. There is no change in serum potassium levels from baseline to week 24 in both groups during the course of treatment, in accordance with the study conducted by Pooja Kanani et al. Though the majority of the patients in both groups presented a history of hypertension as a comorbid condition, there were no clinically significant changes observed in systolic blood pressure or diastolic blood pressure. In a report, Desidustat: First Approval, Sohitha Dhillon, et al. concluded similar results.

**Figures and Tables**

**TABLE 1: DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

	STATISTICS	DESIDUSTAT TABLET(n=34)	ORAL ERYTHROPOIETIN STIMULATING AGENT INJECTION(n=30)
<b>AGE, YEARS</b>	MEAN $\pm$ SD	52.15 $\pm$ 13.994	58.20 $\pm$ 12.770
<b>GENDER, n (%)</b>	FEMALE	17(50.00%)	13(56.67%)
	MALE	17(50.00%)	17(56.67%)
<b>WEIGHT, kg</b>	MEAN $\pm$ SD	64.54 $\pm$ 11.526	64.55 $\pm$ 18.038
<b>COMORBID CONDITIONS, n (%)</b>	-	7	13
<b>DIABETES MELLITUS TYPE 2</b>	-	27	27
<b>HYPERTENSION</b>	-	2	2
<b>CARDIAC DISORDERS</b>	-	8	8
<b>HYPOTHYROIDISM</b>	-		
<b>DIALYSIS TYPE, n (%)</b>			
<b>HD</b>	-	28(82.35%)	28(93.33%)
<b>HDF</b>	-	6(17.65%)	2(6.67%)
<b>DIALYSIS VINTAGE, n (%)</b>			
<b>2012-2014</b>	-	2(5.88%)	1(3.33%)
<b>2015-2017</b>	-	3(8.82%)	2(6.67%)
<b>2018-2020</b>	-	15(44.11%)	13(43.33%)

<b>2021-2022</b>	-	14(41.17%)	14(46.67%)
<b>FREQUENCY OF DIALYSIS PER WEEK, n (%)</b>			
<b>2</b>	-	7 (20.59%)	9 (30.00%)
<b>3</b>	-	27 (79.41%)	21 (70.00%)
<b>SIDE EFFECTS, n (%)</b>			
<b>ABDOMINAL PAIN</b>	-	2(5.88%)	0(0%)
<b>CHILLS</b>	-	5(14.70%)	0(0%)
<b>CONSTIPATION</b>	-	0(0%)	1(3.33%)
<b>DRY COUGH</b>	-	4(11.76%)	2(6.66%)
<b>FEVER</b>	-	2(5.88%)	1(3.33%)
<b>GASTRIC IRRITATION</b>	-	0(0%)	1(3.33%)
<b>GENERALIZED WEAKNESS</b>	-	3(8.82%)	2(6.66%)
<b>HEADACHE</b>	-	1(2.94%)	2(6.66%)
<b>HEMATURIA</b>	-	1(2.94%)	0(0%)
<b>HYPOTENSION</b>	-	4(11.76%)	0(0%)
<b>MUSCLE SPASMS</b>	-	1(2.94%)	0(0%)
<b>NAUSEA</b>	-	2(5.88%)	0(0%)
<b>SHORTNESS OF BREATH</b>	-	3(8.82%)	3(10%)
<b>VERTIGO</b>	-	0(0%)	1(3.33%)
<b>GENERIC NAME</b>		<b>NO. OF PATIENTS</b>	
<b>EPOETIN ALFA</b>	-	1(3.33%)	0(0%)
<b>EPOETIN BETA</b>	-	2(6.66%)	0(0%)
<b>EPO ALFA</b>	-	3(10%)	3(10%)
<b>r-HUMAN EPO</b>	-	5(16.67%)	1(3.33%)

HD-HEMODIALYSIS, HDF-HEMODIAFILTRATION

**TABLE 2: DISTRIBUTION BASED ON TYPE OF EPO AGENTS**

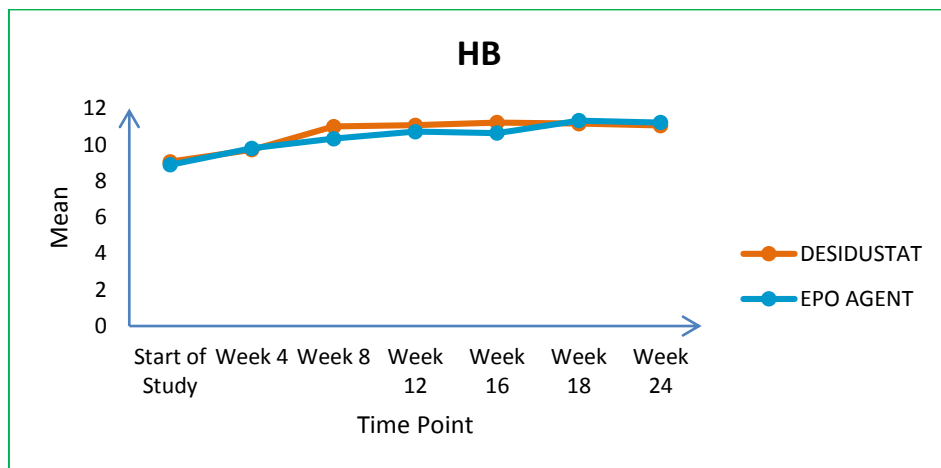
**TABLE 3: COMPARISON OF SUBJECTS BASED ON HAEMOGLOBIN LEVELS**

HB	Group		P value
	Desidustat	EPO Agent	
<b>Start of Study</b>	9.06 ± 1.17	8.89 ± 1.227	0.591
<b>Week 4</b>	9.72 ± 1.253	9.8 ± 1.394	0.819
<b>Week 8</b>	11.00 ± 1.37	10.33 ± 1.54	0.745
<b>Week 12</b>	11.07 ± 1.32	10.72 ± 1.566	0.346
<b>Week 16</b>	11.22 ± 1.633	10.64 ± 1.286	0.117
<b>Week 18</b>	11.16 ± 1.672	11.33 ± 1.323	0.654
<b>Week 24</b>	11.06 ± 1.717	11.22 ± 1.354	0.684

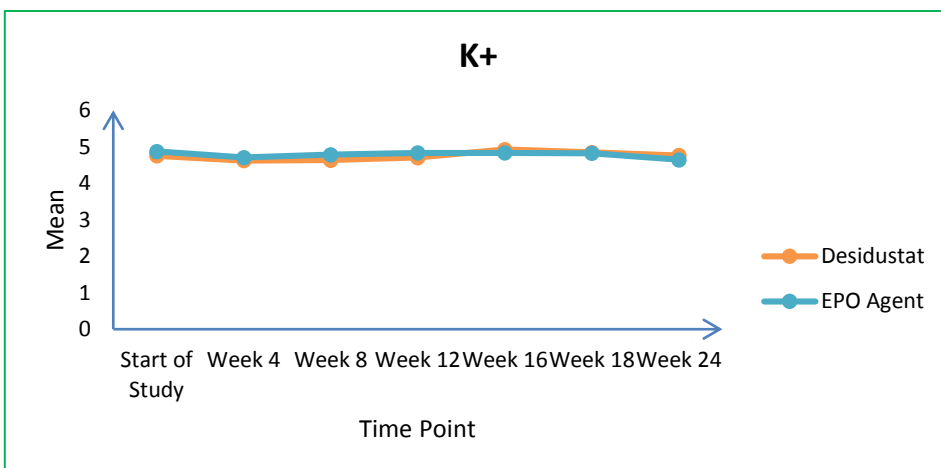
**TABLE 4: COMPARISON OF SUBJECTS BASED ON SERUM POTASSIUM LEVELS**

SERUM K+	Group		P value
	Desidustat	EPO Agent	

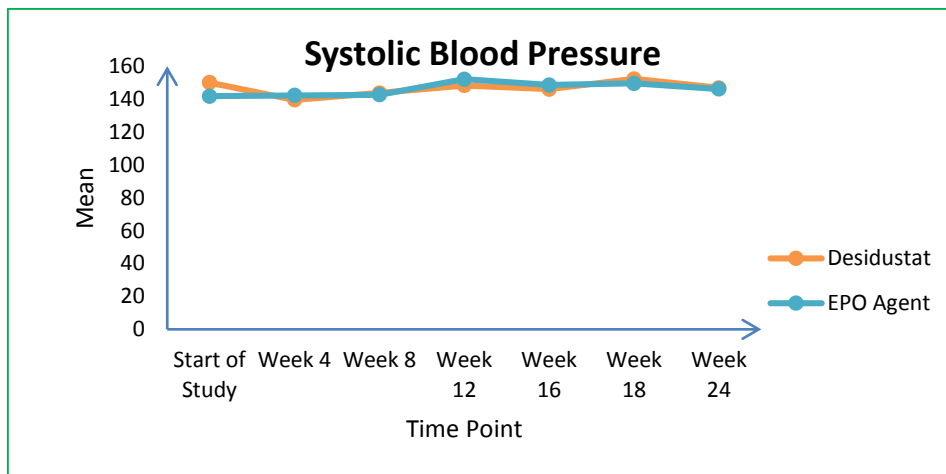
<b>Start of Study</b>	4.75 ± 0.808	4.87 ± 0.736	0.539
<b>Week 4</b>	4.62 ± 0.609	4.7 ± 0.68	0.609
<b>Week 8</b>	4.63 ± 0.491	4.78 ± 0.654	0.299
<b>Week 12</b>	4.7 ± 0.513	4.83 ± 0.633	0.368
<b>Week 16</b>	4.92 ± 0.524	4.83 ± 0.711	0.575
<b>Week 18</b>	4.84 ± 0.448	4.82 ± 0.585	0.888
<b>Week 24</b>	4.76 ± 0.39	4.64 ± 0.48	0.293



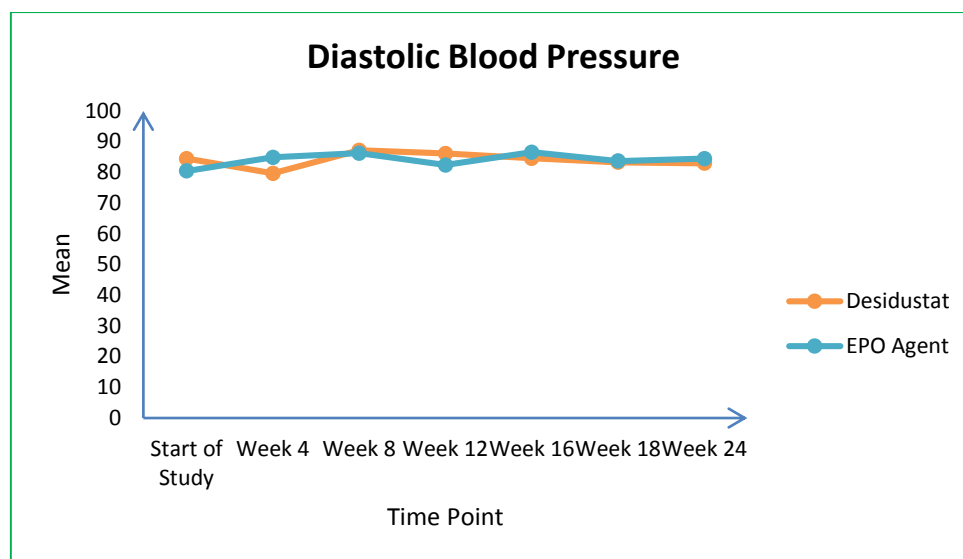
**FIGURE 1: SUMMARY OF HAEMOGLOBIN LEVELS OVER TIME.**



**FIGURE 2: SUMMARY OF SERUM POTASSIUM LEVELS OVER TIME.**



**FIGURE 3: SUMMARY OF SBP OVER TIME.**



**FIGURE 4: SUMMARY OF DBP OVER TIME.**

## V. CONCLUSION

In conclusion, our 24-week observational study showed non-inferiority of the oral desidustat tablet compared to the subcutaneous ESA agents during the management of anemia in dialysis-dependent CKD patients. In the study we have conducted, the hemoglobin levels started to rise from week 8 in the patients receiving desidustat and week 18 in the patients receiving ESAs (Fig.1) and remained in the suggested normal ranges of 10–12 g/dl according to KDIGO guidelines up to week 24 in both treatment groups. In comparison to the ESA-receiving group, the desidustat group had a considerably larger rate of hemoglobin responders. Moreover, desidustat maintained the target hemoglobin range of 10–12 g/dl for a longer period compared to the group receiving ESAs. There were no severe adverse effects observed in either of the groups. Rather, the adverse effects presented were mild to moderate in severity, may or may not be related to the treatment, and were mostly resolved on symptomatic treatment without any change in the dosage of desidustat or ESAs. There was no significant change observed in groups receiving both the treatments, desidustat and ESAs, respectively, for their effects on serum potassium levels (Fig 2). No clinically significant changes in vitals were observed in either of the treatment groups (Fig 3 and 4). Though there were intradialytic changes such as hypertension or hypotension, which may or may not be solely due to either of the drugs, Moreover, intradialytic hypotension or hypertension was usually manageable by changing the head elevation. The major limitation of our study is that there is no relevant data on iron profiles, lipid profiles, or serum hepcidin levels, which may have an impact on distinguishing the efficacy of desidustat versus ESAs in the management of anemia in dialysis-dependent patients.

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## REFERENCES

- [1] Eckardt KU, Berns JS, Rocco MV, Kasiske BL. Questions to Be Addressed at the Planned KDIGO Controversies Conference. *American Journal of Kidney Diseases*. 2009;6(53):915-20.
- [2] DiPiro J.T., Talbert R.L., Yee G.C., Matzke G.R., Wells B.G., and Posey L. (Eds.), Eds. Joseph T. DiPiro, et al. McGraw Hill, 2017.
- [3] Babitt JL, Lin HY. Mechanisms of anemia in CKD. *Journal of the American Society of Nephrology: JASN*. 2012 Sep 9;23(10):1631.
- [4] Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Advances in chronic kidney disease*. 2019 Jul 1;26(4):253-66.

- [5] Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. *American Journal of Kidney Diseases*. 2018 Mar 1;71(3):423-35.
- [6] Fukuma S, Yamaguchi T, Hashimoto S, Nakai S, Iseki K, Tsubakihara Y, Fukuhara S. Erythropoiesis-stimulating agent responsiveness and mortality in hemodialysis patients: results from a cohort study from the dialysis registry in Japan. *American journal of kidney diseases*. 2012 Jan 1;59(1):108-16.
- [7] Hung SC, Lin YP, Tarng DC. Erythropoiesis-stimulating agents in chronic kidney disease: what have we learned in 25 years? *Journal of the Formosan Medical Association*. 2014 Jan 1;113(1):3-10.
- [8] Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. *Proceedings of the National Academy of Sciences*. 1993 May 1;90(9):4304-8.
- [9] Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, Kriegsheim AV, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH. Targeting of HIF- $\alpha$  to the von Hippel-Lindau ubiquitylation complex by O<sub>2</sub>-regulated prolyl hydroxylation. *Science*. 2001 Apr 20;292(5516):468-72.
- [10] Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *science*. 2004 Dec 17;306(5704):2090-3.
- [11] Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferrremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *The Journal of Clinical Investigation*. 2004 May 1;113(9):1271-6.
- [12] Pak M, Lopez MA, Gabayan V, Ganz T, Rivera S. Suppression of hepcidin during anemia requires erythropoietic activity. *Blood*. 2006 Dec 1;108(12):3730-5.
- [13] Liu Q, Davidoff O, Niss K, Haase VH. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. *The Journal of Clinical Investigation*. 2012 Dec 3;122(12):4635-44.
- [14] Yeh TL, Leissing TM, Abboud MI, Thinnes CC, Atasoylu O, Holt-Martyn JP, Zhang D, Tumber A, Lippl K, Lohans CT, Leung IK. Molecular and cellular mechanisms of HIF prolyl hydroxylase inhibitors in clinical trials. *Chemical science*. 2017;8(11):7651-68.
- [15] Liu J, Wei Q, Guo C, Dong G, Liu Y, Tang C, Dong Z. Hypoxia, HIF, and associated signaling networks in chronic kidney disease. *International journal of molecular sciences*. 2017 Apr 30;18(5):950.
- [16] Bonomini M, Del Vecchio L, Sirolli V, Locatelli F. New treatment approaches for the anemia of CKD. *American Journal of Kidney Diseases*. 2016 Jan 1;67(1):133-42.
- [17] Johnson BM, Stier BA, Caltabiano S. Effect of food and gemfibrozil on the pharmacokinetics of the novel prolyl hydroxylase inhibitor GSK1278863. *Clinical Pharmacology in Drug Development*. 2014 Mar;3(2):109-17.
- [18] Bernhardt WM, Wiesener MS, Scigalla P, Chou J, Schmieder RE, Günzler V, Eckardt KU. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *Journal of the American Society of Nephrology: JASN*. 2010 Dec;21(12):2151.
- [19] Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney international*. 2017 Aug 1;92(2):306-12.
- [20] Abrahams L. Hemin, erythropoietin and antithrombotics to treat Covid-19.
- [21] Tripathi KD. *Essentials of medical pharmacology*. 8th ed. New Delhi, India: Jaypee Brothers Medical; 2018.
- [22] National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 75593290, National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 75593290, Desidustat. Retrieved October 19, 2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/Desidustat>.
- [23] Zydus Cadifa, Zydus to launch Oxemia™ (Desidusta) a breakthrough treatment for patients suffering from chronic kidney disease (CKD) [media release]. [www.zyduslife.com](http://www.zyduslife.com)
- [24] Zydus Lifesciences Ltd. Oxemia™ (desidustat): summary of product characteristics. Ahmedabad: Zydus Lifesciences Ltd.; 2022.