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NANDROLONE DECANOATE VERSES ERYTHROPOIETIN FOR TREATMENT OF ANEMIA CAUSED BY CHRONIC KIDNEY DISEASE

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ABSTRACT

Androgens which are comparatively cheap were used in the treatment of anaemia (due to chronic kidney diseases) in dialysis patients before the development of Erythropoietin (EPO). However, there aresome concerns related to their efficacy and side effects. Study aims are to examine the efficacy and harms of Nandrolone Decanoate for the treatment of anaemia caused by chronic kidney disease (CKD) compared to recombinant erythropoietin. A systematic analysis and review revealed no difference between Nandrolone Decanoate and recombinant erythropoietin for the treatment of anaemia caused by CKD in men over 50 years. Therefore, nandrolone Decanoate can be used for the treatment of anaemia caused by CKD in this category of patients, in developing countries. However, further studies are required to determine the long-term efficacy and safety of nandrolone Decanoate in men over 50 years of age, also its safety and effectiveness in females, and in males less than 50 years of age.

KEYWORDS

Anemia, Erythropoietin (EPO), Nandrolone Decanoate, Androgens and Chronic kidney Diseases (CKD).

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INTRODUCTION

Erythropoietin and other erythropoietin stimulating agents (ESAs) like Nandrolone Decanoate are the main stay for the treatment of anemia caused due to chronic kidney disease (CKD)[1]. The main limitation of EPO use in developing countries is cost, making it unavailable to most patients. Androgens which are relatively cheap were used in the treatment of anaemia in dialysis patients before the invention of recombinant EPO[2,3]. However, there are concerns about their efficacy and side effects. The aim of this

systematic review and analysis was to examine the efficacy and harms of androgens for the treatment of anaemia of CKD compared to EPO.

Etiology of Anemia in CKD

In anemia body have fewer red blood cells than normal person. Red blood cells supply oxygen to tissues and organs throughout the body and enable them to utilize energy from the food. In anemia, red blood cells carry less oxygen to tissues and organs[4,5]. Anemia is the most important consequence of CKD that prevails early in the course of illness and affect patients who have some degree of reduced renal function. Anemia appears to have pronounced effect on patient's well-being and may ultimately determine the prognosis both before and after initiation of renal replacement therapy. Anemia in CKD is characterized by normochromic normocytic red blood cells. Although several factors (e.g. decreased red cell production or survival, blood loss) may contribute to development of anemia in patients with CKD, the primary cause is believed to be a reduction in erythropoietin production by the failing kidneys. Support for this belief includes the presence of serious anemia in a nephric patients, the condition of relative erythropoietin deficiency in CKD patients, when compared with normal individuals, also the almost uniform increase in red blood cell count seen in CKD patients following initiation of exogenous erythropoietin therapy. Nandrolone Decanoate increases production and urinary excretion of erythropoietin. It may also have a direct action on bone marrow. Iron deficiency is the second common cause of anemia in CKD. Other secondary cause of anemia in CKD patients include severe hyperparathyroidism, hypothyroidism, acute and chronic inflammatory conditions, aluminium toxicity, folate and vitamin B12 deficiency, decreased red blood cell survival span, and hemoglobinopathies[6-10]. Anemia in CKD is shown in Figure No.1.

Schematic representation of the mechanisms underlying anemia of CKD. Iron and EPO are important for red blood cell production in the bone marrow. Iron availability is controlled by the liver hormone hepcidin, which further regulates dietary iron absorption and macrophage iron recycling from senescent red blood cells. There are several feedback loops that control hepcidin levels, including iron and EPO. In CKD patients (particularly in end stage kidney disease patients on hemodialysis), hepcidin levels have been found to be highly elevated, probably due to reduced renal clearance and induction by inflammation, leading to iron-restricted erythropoiesis. CKD also inhibits EPO production by the kidney, and may also lead to circulating uremic-induced inhibitors of erythropoiesis, shortened red blood cell lifespan, and increased blood loss. Black and gray arrows represent normal physiology (black for iron and hormonal fluxes, gray for regulatory processes). Coloured arrows represent the additional effects of CKD (blue for activation, red for inhibition). RBC, red blood cell[11].

Nandrolone enters the cell and binds to and activates "erythropoietic" erythropoietin receptor in responsive tissue, including the prostate, seminal vesicles, scrotum, penis, larynx, hair follicles, muscle, and bone. The resulting activated hormone receptor complex translocates into the nucleus and binds to androgen response elements (ARE) in the promoter region of targeted genes, where the complex promotes gene expression necessary for maintaining male sex characteristics. This agent also stimulates erythropoietin production by enhancing the production of erythropoietic stimulating factors. Furthermore, mimicking the negative feedback mechanism of testosterone, Nandrolone Decanoate also suppresses the secretion of luteinizing hormone (LH).

Anemia treatment in CKD

Exogenous erythropoietin injection in pre-dialysis phase of care. Reported benefit of anemia correction in CKD are (1) improved sense of well-being, quality of life, neurocognitive function and work capacity (2) reduced need for packed red blood cell transfusions; (3) reduced allo-sensitization prior to renal transplantation and (4) reduced hospitalization. Newer experimental data suggest that long-term benefits could be due not only to antianemic effect, but also to a direct organ protective effect of (rHu)-

Epo mediated through a receptor complex different from the "erythropoietic" erythropoietin receptor.

Androgen verses Erythropoietin

A study conducted by B.Adamu using several databases (MEDLINE, EMBASE, The Cochrane library, LILACS, AJOL, and CINAHL) for randomized controlled trials using the key terms anaemia, chronic kidney disease, and androgens, without language restrictions concluded that there was significant heterogeneity for the outcome of haemoglobin across studies (I2 of 82%), all individual effect estimates did not favour EPO over androgens (neither clinically meaningful nor statistically significant estimates). Also, there is a trend towards less increase in blood pressure requiring adjustment of blood pressure medications in the androgen arm with a relative risk, although the difference is not statistically significant[12].

Cost is a major limitation for the routine use of ESAs in developing countries. In a study from Tunisia, only 10.8% of patients on hemodialysis were on EPO, while 38% required regular transfusions.

Prior to the advent of EPO in the 1980s and subsequently other ESAs, androgens such as nandrolone were used in the treatment of anaemia of CKD. Androgens are thought to correct anaemia of CKD by enhancing the conversion of the pluripotent stem cell to erythroid colony forming and burst forming units. In addition, 5-α metabolite of androgens stimulates erythropoiesis by enhancing erythropoietin production by the kidney, while the 5-β metabolite stimulates the bone marrow directly.[6] However, there are concerns about their efficacy and potential side effects such as hepatotoxicity, dyslipidemia, virilization, priapism, and hyperglycaemia[7]. In the current era of evidence-based medicine, it is important to study systematically the efficacy and potential side effects of androgens for the treatment of anaemia of CKD before sanctioning or discouraging their use. This is particularly important for many developing countries where patients cannot afford to buy ESAs. Androgens are much cheaper than ESAs being five-times cheaper than EPO treatment in the study by Aggarwal *et al*[12]. Also, a study was conducted by *Paul. AK*to see the efficacy of Nandrolone Decanoate, a cheaper alternative; in comparison with recombinant human erythropoietin for management of anemia of predialysis diabetic chronic kidney disease. Sixty adult diabetic patients with anaemia of chronic kidney disease on conservative treatment [Not on Hemodialysis (HD)] were enrolled. All the relevant haematological and renal parameters were evaluated at the end of 3rd and 6th months. Study concluded that Nandrolone Decanoate, though not equally effective, may be considered as a valid alternative therapy for the treatment of anemia of pre-dialysis diabetic chronic kidney disease to that of erythropoietin[13].

Exogenous erythropoietic proteins

During the last decade, two alternative treatments for renal anemia have been approved: darbepoetin and CERA. Both are direct agonists of the "erythropoietic" receptors and both were derived from rHu-Epo. Molecularly, they differ from rHu-Epo in that they are much larger molecules (darbepoetin is genetically modified rHu-Epo with a higher sugar content and CERA is pegylatedrHu-Epo) with lower affinity for the erythropoietin receptor but with a longer circulating time. It has been proposed that high doses of erythropoietin are likely to exert toxic effects and pleiotropic systemic actions. More specifically, antiapoptotic, anti-inflammatory, angiogenetic and cytoprotective effects have been revealed in the kidneys, cardiovascular system, brain and retina.

Potential concern related to erythropoietin proteins administration

Effect on renal function: Studies reported the rapid prognosis of renal diseases with exogenous erythropoietin in renal insufficiency. Collective data is summarized in Table No.1. Preliminary data from several studies suggested that correction of anemia may actually slow the prognosis of CKD[1].

Effect on blood pressure control: During initial use of rHuEpo to treat anemia, concerns about severe hypertensive crisis and seizers were prominent. However, these concerns are nearly eliminated. The increase in blood pressure that

develop with rHuEpo is most likely due to an increase in systemic vascular resistance that occur with rapid anemia correction[1].

B.Adamu also concluded that there is a trend towards less increase in blood pressure requiring adjustment of blood pressure medications in the androgen treated Patient with a relatively lesser risk of, although the difference is not statistically significant.

DISCUSSION

Anemia is an important complication of CKD which can occur even at early stages of the disease[14] and is important both from the point of view of morbidity and mortality. Erythropoietin and other related erythropoiesis stimulating agents (ESAs) are currently the main stay of the treatment of anemia of CKD. However, recently there are concerns that the use of ESAs in the treatment of anemia in CKD needs to be reevaluated. Cost is a major limitation for the routine use of ESAs in developing countries. In a study from Tunisia, only 10.8% of patients on hemodialysis were on EPO, while 38% required regular transfusions[13]. In developing countries where patients cannot afford EPO, anemia is treated mainly with recurrent blood transfusions with attendant risks of complications such as transfusion transmissible infections, especially in the current pandemic of human immune deficiency virus infection.

Table No.1: Study of the effect of Anemia correction with Erythropoietin on progression of renal diseases

S.No	Year	Author	Patient	Duration	Serum Cr, mg/dl	Effect on renal diseases prognosis
1	1989	Kleinman	14	12 Weeks	3 - 11	Neutral
2	1990	Lim	26	52 Weeks	6.0 ± 2.05	Neutral
3	1990	Watson	11	12 Weeks	6.6 ± 1.3	Acceleration
4	1991	US Study	117	26 Weeks	5.9 ± 2.5	Neutral
5	1992	Austrian Study	123	12 Weeks	6.2 ± 0.2	Neutral
6	1995	Sevica	16	52 Weeks	3.45 ± 1.9	Neutral
7	1997	Portoles	11	26 Weeks	6.3 ± 1.3	Neutral
8	2000	Silverberg	26	30 Weeks	2.59 ± 1.77	Neutral
9	2001	Jungers	20	92 Weeks	5.96 ± 0.84	Slowing

Sr = Serum Creatinine; CrCl = creatinine clearance; G = glomerular filteration; I = slope of I/Cr over time.

Table No.2: Studies of the Hypertensive effect of Anemia Correction with Erythropoietin

S.No	Year	Author	Patient, N	Duration (Weeks)	%age change in Hct/month	Hypertensive effect, % age of patient
1	1989	Eschbach	17	20	5 - 9	59
2	1989	Lim	14	8	3 - 4	0 - 21
3	1990	Lim	26	52	n/a	0
4	1991	US Study	117	26	5 - 6	22
5	1992	Austrian Study	123	12	2 - 3	0
6	1994	Roth	83	48	3	0
7	1997	Portholes	11	26	3	55
8	2000	Hayashi	9	12	4.25	44
9	2001	Jungers	20	92	0.9 g/Dl (Hg)	0

Hct = Hematocrit; Hg = Hemoglobin; n/a = not available

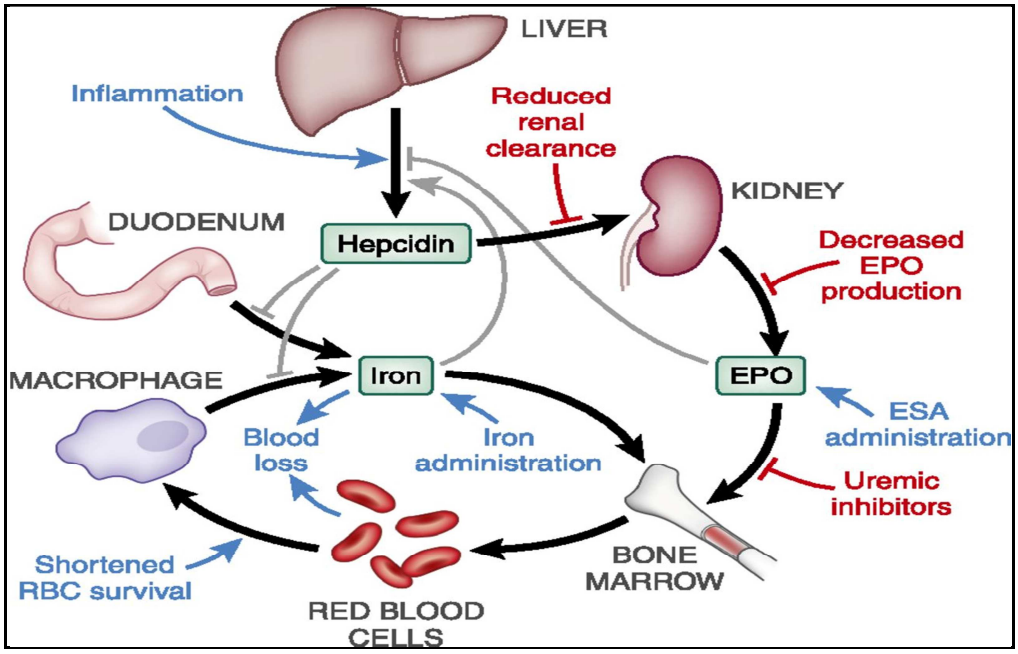

Figure No.1: Etiology of anemia in CKD

CONCLUSION

Review conclude that the results of this analysis revealed no difference between the Nandrolone Decanoate and Erythropoietin for the treatment of anaemia of CKD in men over 50 years. Many subjects with poor socioeconomic status having chronic kidney disease (CKD) and anaemia in a developing country cannot afford the treatment with erythropoietin. Therefore, Nandrolone Decanoate can be used for the treatment of anaemia of CKD in this category of patients, in Developing countries. However, further studies are needed to determine their long-term safety in men over 50 years old, as well as their effectiveness and safety in females in general, and males less than 50 years of age.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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