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# Pharmacologic Adjuvants to Reduce Erythropoietin Therapy Dose in Anemia of Chronic Kidney Disease and End Stage Renal Disease

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## 1. Introduction

Anemia is one of the leading causes of morbidity in chronic renal failure.[1] Chronic kidney disease (CKD) associated anemia is largely due to reduced erythropoietin (EPO) release and, to a lesser degree, to shortened red cell survival.[2] To overcome EPO deficiency in this population, the development and administration of erythropoiesis-stimulating agents (ESAs) such as recombinant human EPO and darbepoetin alfa (DPO) has resulted in substantial health benefits, including improved quality of life, reduced blood transfusion requirements, decreased left ventricular mass, diminished sleep disturbance and enhanced exercise capacity.[1-7] Unfortunately in recent clinical trials, a proportion of patients exhibited complications such as fatal or nonfatal stroke, access thrombosis, increase in thrombotic events and exacerbation of malignancy associated with overly aggressive correction of anemia. [8-10] It is not established whether these complications are related to higher dose of EPO, underlying EPO resistance factors (i.e. inflammation) or achieving higher hematocrit (HCT). A multifactorial combination of predisposing circumstances is possible. A number of pharmacologic agents have been evaluated as adjuvant to ESAs therapy. These agents include iron, L-carnitine, ascorbic acid, androgens, statins, pentoxifylline and N-acetylcysteine. In this review article we will focus on the agents that have been used in conjunction with EPO to correct anemia in patient with chronic kidney disease and end-stage renal disease in an effort to reduce the dose requirement of EPO.

## 2. Iron

Iron is one of the most integral components of hematopoiesis in the anemia of kidney disease. "Trapped" iron storage or decreased availability of iron is the most common factor for the resistance to the effect of ESAs. Absolute iron deficiency is likely to be present in patients with CKD when**:** the percent transferrin saturation (plasma iron divided by total iron binding capacity x 100) falls below 20; the serum ferritin concentration is less than 100 ng/mL among advance CKD("predialysis") and peritoneal dialysis patients and less than

200 ng/mL among home hemodialysis patients.[11] However, functional iron deficiency is associated with transferrin saturation (TSAT) ≤20 percent and elevated ferritin levels (between approximately 200 to 800 ng/mL) or higher. An elevated ferritin level in this condition is likely secondary to the acute phase reaction of underlying inflammation. The 2006 K/DOQI guidelines recommend goals of iron therapy during administration of ESAs**.** For predialysis and peritoneal dialysis patients: TSAT >20 percent or content of hemoglobin (Hb) in reticulocytes >29 percent and serum ferritin concentration >100 ng/mL. For patients undergoing hemodialysis: transferrin saturation >20 percent or content of Hb in reticulocytes >29 percent and serum ferritin concentration >200 ng/mL.[12]

A number of clinical trials have compared which route of iron administration Intravenous (IV) vs Oral (PO) is superior in treating anemia of CKD. [13-22]

First we will discuss this issue in the Chronic Kidney Disease (CKD) population.

## 3. Anemia in chronic kidney disease

In a prospective trial by Stoves et.al, PO vs IV route of iron administration was studied. Forty five anemic patients with CKD, not on dialysis, were randomized to receive oral (ferrous sulfate 200 mg tid) or intravenous (300 mg iron sucrose monthly) iron therapy. EPO was started at the same time and the dose adjusted according to a pre-established protocol. After an average follow up of 5.2 months, there were no significant differences in Hb response and EPO dose between the two groups.[13] A prospective study by Charytan et. al. in 96 CKD anemic patients on EPO compared the efficacy of IV iron (5 doses of 200 mg iron sucrose weekly) to oral iron (ferrous sulfate 325 mg tid). They found an increase in Hb and ferritin following IV iron, whereas the oral iron group demonstrated an increase in Hb without increase in iron stores.[14] Both of the above studies failed to show IV iron superior to PO in either selected group of CKD patients. Van Wyck et.al. conducted a larger study of 182 non dialysis-dependent CKD (stages 3 to 5) patients to compare oral iron vs. IV iron. That randomized, controlled, multicenter trial tested IV iron as sucrose 1 g in divided doses over 14 days vs oral ferrous sulfate 325 mg three times a day for 56 days. Inclusion criteria for the group were Hb ≤11 g/dL, TSAT ≤25%, and ferritin ≤300ng/mL. EPO/DPO dose was not changed for eight weeks prior to or during the study. The proportion of patients achieving the primary outcome (Hb increase ≥1 g/dL) was greater in the IV iron treatment group than in the oral iron treatment group (44.3% vs. 28.0%, P = 0.0344), as was the mean increase in Hb by day 42 (0.7 vs. 0.4 g/dL, P = 0.0298).[15] Agarwal and colleagues conducted a randomized, multicenter, controlled trial in 75 adult, anemic, iron-deficient, non-dialysis CKD patients not receiving ESAs. The patients were randomly assigned to receive either IV ferric gluconate 250 mg weekly for 4 weeks or oral ferrous sulfate 325 mg three times a day for 42 days. Both oral and IV iron similarly increased Hb in anemic CKD patients not receiving ESAs.[16]

A new IV iron preparation, ferumoxytol has been approved in the United States. It appears to be safe and effective when given as a rapid infusion of up to 510 mg in patients with CKD and patients on dialysis. A Phase III trial randomly assigned 304 patients with CKD in a 3:1 ratio to two 510-mg doses of intravenous ferumoxytol within 5 ± 3 days or 200 mg of elemental oral iron daily for 21 days. Among patients who were not receiving ESAs, Hb increased 0.62 ± 1.02 g/dL with ferumoxytol vs. 0.13±0.93

g/dL with oral iron. Among patients who were receiving ESAs, Hb increased 1.16±1.49 g/dL with ferumoxytol vs. 0.19±1.14 g/dL with oral iron. The increase in Hb at day 35, the primary efficacy end point, was 0.82+/-1.24 g/dL with ferumoxytol and 0.16+/-1.02 g/dL with oral iron (P<0.0001).[17] The authors concluded that a regimen of two doses of 510 mg of intravenous ferumoxytol administered rapidly within 5±3 days was well tolerated and had the intended therapeutic effect. The side effects associated with IV iron in the above-mentioned studies were headache, myalgia, and hypotension (particularly in thin, older women<65 kg). Intravenous iron sucrose has shown better tolerability. Oral iron has more GI associated side effects including constipation, diarrhea, nausea and vomiting.[13-17]

As a result of these studies the K/DOQI guidelines have recommended that either oral iron therapy or intravenous iron therapy can be given in CKD patients.

## 4. Anemia in end stage renal disease

Among hemodialysis patients, studies show that transferrin saturation and serum ferritin levels usually continue to fall and anemia fails to correct despite ongoing oral iron therapy. MacDougall et.al. studied 37 iron-replete hemodialysis patients beginning EPO therapy randomized into three groups with different iron supplementation: Group1, IV iron dextran 5 ml (equivalent to 250 mg of elemental iron) every 2 weeks; Group 2, oral ferrous sulfate 200 mg tid; Group 3, no iron. Subjects were treated with 25 U/kg of EPO thrice weekly subcutaneously. After a period of 16 weeks, the Hb response in the group receiving IV iron (7.3+/-0.8 to 11.9+/-1.2 g/dL) was significantly greater than that for the other two groups (7.2 +/-1.1 to 10.2 +/-1.4 g/dL and 7.3+/-0.8 to 9.9+/-1.6 g/dL for Groups 2 and 3, respectively; $p < 0.005$ for both groups vs. Group 1 at 16 weeks). Serum ferritin levels remained constant in those receiving IV iron (345 +/-273 to 359+/-140 mcg/L) in contrast to the other two groups in which ferritin levels fell significantly (309+/-218 to 116+/- 87 mcg/L and 458+/-206 to 131+/- 121 mcg/L for Groups 2 and 3, respectively; $p < 0.0005$ for Group 1 vs. Group 2, and $p < 0.005$ for Group 1 vs. Group 3 at 16 weeks). Dosage requirements of EPO were also less in Group1.These results suggested that even in iron-replete patients, those supplemented with IV iron have an enhanced Hb response to EPO with better maintenance of iron stores and lower dosage requirements of EPO.[18]

Wingard et.al. conducted a prospective study on 46 EPO treated hemodialysis patients and randomized them into four different oral iron preparations. These four preparations included Chromagen (ferrous fumarate from Savage Laboratories), Feosol (ferrous sulphate from Smith Kline Beecham), Niferex (polysaccharide, Central Pharmaceutical) or Tabron (ferrous fumarate; Parke-Davis). All patients were prescribed approx 200 mg of elemental iron daily with at least 100 mg of ascorbic acid for six months. The study concluded that with emphasis on compliance, oral iron supplementation at the dose used for this study was able to maintain adequate iron status in the short term (less than 6 months) without the need for IV iron dextran. However, IV iron dextran eventually (after 6 months) would be necessary because of the downward trend in iron stores.[19]

Ferumoxytol was studied in a randomized, open-label, controlled, multicenter Phase 3 trial by Provenzano et.al. to evaluate the safety and efficacy of IV ferumoxytol compared with oral iron.[20] Anemic patients on HD and on a stable ESA regimen received either two injections of 510 mg of ferumoxytol within 7 days (n = 114) or 200 mg elemental oral iron

daily for 21 days (n = 116). Ferumoxytol resulted in a mean increase in Hb of 1.02+/-1.13 g/dL at day 35 compared with 0.46+/-1.06 g/dL with oral iron (p = 0.0002). There was a greater mean increase in TSAT with ferumoxytol compared with oral iron at day 35 (p < 0.0001).

## 5. Conclusion

For patients with chronic kidney disease who are not on dialysis, oral iron or IV iron can be used for iron supplementation. This conclusion is consistent with the opinion of the Work Group from K DOQI guidelines.

The preferred route of administration of iron in patients with chronic kidney disease on hemodialysis is intravenous as supported by K DOQI guidelines as of 2006.

## 6. Ascorbic acid

Vitamin C or ascorbic acid has been studied in the metabolism of iron and anemia management. The first studies were performed in guinea-pigs. It was found that ascorbic acid deprivation increased the total non-haem iron concentration in the spleen and reduced it in the liver, and in both organs ferritin was diminished and haemosiderin increased. Repleting the ascorbic acid restored the normal distribution of iron between the two storage compounds, and in the spleen the total storage iron concentration returned to control levels within 24 hours.[21] Another important property of ascorbic acid is its ability to increase the availability of storage iron to chelators.[22] In hemodialysis patients this role of ascorbic acid was investigated by Deicher who conducted a cross-sectional, single-centre observational study. Pre-dialysis plasma Vitamin C concentrations were measured and response to EPO (Hb concentration/ international units EPO/kg/week) was recorded. Univariate analysis yielded a significant correlation between Vitamin C plasma levels and response to EPO. It was found that in unselected hemodialysis patients Vitamin C plasma levels account, at least partially for the response to EPO.[23] That work led to ascorbic acid investigations for use in EPO-treated hemodialysis patients, particularly those with EPO- hypo responsiveness, elevated serum ferritin levels, and functional iron deficiency (transferrin saturation ≤20 percent and elevated ferritin level between 200 to 800 ng/ml or higher). Studies evaluated the role of IV Vitamin C in hemodialysis patients and showed that in those patients who develop resistance to EPO with "functional iron deficiency", the resistance can be overcome by giving Vitamin C instead of iron,thus avoiding hemosiderosis.[24] In another comparative larger study, Tarng et.al. were able to show similar results in a prospective trial of dialysis patients. Sixty-five HD patients with serum ferritin levels greater than 500 mcg/L were recruited and divided into the control (N = 19) and intravenous ascorbic acid IVAA (N = 46) groups. IVAA patients with a hematocrit (HCT) of less than 30% received 300 mg of ascorbic acid three times per week for eight weeks. Controls had a HCT of more than 30% and did not receive the adjuvant therapy. Red blood cell and reticulocyte counts, iron metabolism indices, erythrocyte zinc protoporphyrin (E-ZPP), and the concentrations of plasma ascorbate and oxalate were examined before and following the therapy. Thirteen patients (four controls and nine IVAA patients) withdrew by the end of the study. Eighteen patients had a dramatic response to IVAA with a significant increase in Hb and reticulocyte index and a concomitant 24% reduction in EPO dose after eight weeks. This paralleled a

significant rise in serum iron and TSAT and a fall in E-ZPP and serum ferritin (baselines vs. 8 weeks, serum iron 68+/-37 vs. 124 +/-64 mcg/dL, TSAT 27+/-10 vs. 48+/-19%, E-ZPP 123+/-44 vs. 70+/-13 micromol/mol heme, and serum ferritin 816+/-435 vs. 587+/-323 mcg/L, $p<0.05$). Compared with responders, mean values of Hb, EPO dose, iron metabolism parameters, and E-ZPP showed no significant changes in controls (N = 15) and in non-responders (N = 19).[25]

A single PO study by Benz et. al. was conducted in 21 EPO resistant anemic hemodialysis patients with ferritin levels greater than 350 ng/mL had received oral daily ascorbic acid at a dose of 500 mg/day and were retrospectively studied. Hemoglobin, HCT, EPO dose, ferritin, and transferrin saturation were recorded at baseline and after three months of treatment. EPO dose/HCT was calculated. Serum oxalate levels were also measured. In this study, daily oral ascorbic therapy decreased ferritin levels and EPO dose requirements while raising Hb and HCT level. Hb increased 9% from 11.4 to 12.2 gm/dl ($p$ = 0.05), HCT increased 10% from 33.3 to 36.7% ($p$ = 0.05), and EPO dose requirement decreased 33% from 26,229 to 17,559 U/week ($p$ = 0.03). Ferritin levels decreased 21% from 873 to 691 ng/mL ($p$ = 0.004) Patients with oxalate levels >27 micromol/L were instructed to stop ascorbic acid treatment, and mean levels decreased from 107 to 19 micromol/L ($p$ = 0.01) over a mean time of 71 days. This beneficial profile of the effects of ascorbic acid therapy is consistent with improvement of EPO resistance and cost savings in this population.[26]

The primary concern for using Vitamin C in dialysis patients is secondary oxalosis because of the impairment in renal excretion and inadequate removal by dialysis procedures.[27-28] Tarng et.al. showed that oxalate levels increase modestly after 8 weeks of IV Vitamin C but information on longer courses of treatment is limited.[25] Canavese prospectively studied the dose of Vitamin C and effect on oxalate levels in 30 dialysis patients. Eighteen patients were administered intravenous ascorbate during 18 months (250 mg/wk, subsequently increased to 500 mg), and 12 patients were taken as reference untreated cases. The study found that plasma oxalate levels progressively increased as the dose of IV Vitamin C was increased from 250 to 500 mg/week. After six months at a dose of 500 mg per week, 7 of 18 patients (40 percent) attained plasma oxalate levels that exceeded the range that would be associated with calcium oxalate super saturation at usual calcium concentrations.[29]

The 2006 K/DOQI guidelines for anemia in CKD stated that there was insufficient evidence to recommend Vitamin C as an adjuvant to EPO therapy.[30] However, several of the clinical studies were published subsequent to the development of those guidelines.

## 7. Pentoxifylline

Pentoxifylline (PTX) is a methyl xanthine derivative, which is approved for use in peripheral vascular disease and may also have anti-inflammatory effects according to studies. Benbernou et. al. studied pentoxifyline and examined its regulatory effect on T helper (TH1-and TH2) cell-derived cytokines in human whole blood and peripheral blood mononuclear cells stimulated with phytohemagglutinin and phorbol myristate acetate. The results showed that PTX at the appropriate concentrations ($5 \times 10^{(-4)}$M ) could induce selective suppression of interleukin (IL) -2 and interferon (INF) -gamma, whereas at high concentrations this drug could act as a suppressive agent of both TH1- and TH2-derived cytokines.[31] Bienvenu showed similar results that PTX possesses a much broader spectrum

of activity on cytokine production than was initially described, and it appears to be a potential and promising immunotherapeutic agent.[32] These studies led to PTX's possible role in treating EPO resistant anemia. Navarro et. al. conducted a prospective small study of 7 anemic patients with CKD, who were treated with pentoxifylline (400 mg orally daily) for 6 months with the goal of defining the effects of pentoxifylline, as an agent with anti-tumor necrosis factor (TNF)-alpha properties. The results showed Hb significantly increased in the pentoxifylline-treated patients at the 6th month (9.9+/-0.5 g/dL at baseline;10.6+/-0.6 g/dL at the 6th month, respectively, $p < 0.01$), whereas no increase was seen in the control group. Serum EPO levels remained stable in all patients. However, the serum TNF-alpha concentration decreased significantly in patients receiving pentoxifylline. The study suggested that the inhibition of erythropoiesis by cytokines may play a significant role in renal anemia. The administration of agents with anti-cytokine properties, such as pentoxifylline, can improve the hematologic status in this population.[33] Another small study was conducted by Cooper and colleagues on 16 dialysis EPO resistant anemic patients. The patients were treated with oral pentoxifylline 400 mg daily for 4 months. Ex-vivo T cell generation of TNF-alpha and IFN-gamma from the patients was assessed before and 6 to 8 weeks after the therapy. A total of 12 of 16 patients completed the study. Before therapy, mean Hb concentration was 9.5+/-0.9 g/dL. After 4 months, the mean Hb concentration increased to 11.7+/-1.0 g/dL (p = 0.0001). Baseline ex vivo T cell expression of TNF-alpha decreased from 58% +/-11% to 31%+/-23% (p= 0.0007) after therapy. Likewise, IFN-gamma expression decreased from 31%+/-10% to 13%+/-10% (p = 0.0002). EPO doses remained unchanged in all but one patient in whom the dose was reduced in response to a higher Hb. One patient who was previously transfusion dependent was able to stop receiving monthly transfusions. Pentoxifylline therapy may significantly improve Hb response in patients with EPO–resistant anemia in renal failure.[34]

This small, open-label, uncontrolled study suggests the need for a larger, controlled trial with this agent. Until such a trial is conducted, pentoxifylline is not recommended as an EPO-adjuvant except in the experimental setting.

## 8. Statins

Statins (HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. As mentioned above, cytokines play a role in inhibition of erythropoiesis. Statins have been evaluated as an adjuvant to EPO with the thought that they have anti-oxidant and anti-inflammatory properties. In one retrospective study, 70 HD patients were treated with statins for a period of 4.7 months and were found to have the mean Hb level rise from 10.6 to 12.5 g/dL ($p < 0.0005$) with an associated 25 percent decrease in EPO requirements.[35] Another study investigated whether the anti-inflammatory effect of statins improved EPO responsiveness in hemodialysis patients. It examined patients with Type 2 diabetes mellitus, who had been shown to have EPO resistance. One hundred and three patients were stratified into statin and non-statin groups.The outcome of interest was EPO dose. The mean EPO dose (units/kg per week) was significantly lower in the statin group (275.6 ± 273.2, vs. 449.5 ± 555.9, $p < 0.05$). Twenty percent of patients in the

statin group required EPO dose in excess of an EPO equivalent of 500 units/kg per week, compared to 30.88% in the non-statin group. The two-way analysis of variance showed no interaction between the use of statins and the presence of Type 2 diabetes mellitus on EPO dose. This study demonstrated that hemodialysis patients who were on statins had a significantly lower EPO requirement. This association is possibly due to the pleiotropic effect of statins.[36]

A prospective study tested the effect of statin therapy on ESA hypo- responsiveness, and emphasized its anti-inflammatory benefits in maintenance hemodialysis patients. This study enrolled 30 patients with baseline cholesterol >220 mg/dL. Low-dose atorvastatin (10 mg/day) was prescribed for 12 weeks. They prospectively recorded biochemistry and hematological profiles, ESAs prescription and inflammatory markers at baseline, 4 weeks and 12 weeks. Statistically significant changes were noted after 4 and 12 weeks of statin therapy for cholesterol (272.5 to 184.4 and 196.4 mg/dL, $p < 0.05$) and ESA hypo-responsiveness, reported as EPO to HCT ratio (EHR) (129.3+/-58.2 to 122.3+/-53.5 and 121.0+/-53.3 EPO U/HCT/week, $p < 0.05$). Mean values for proinflammatory cytokines included interleukin-6 and TNF-alpha levels decreased by 30.8 and 10.6%, respectively. These data suggest that statin therapy may benefit patients with ESA hypo-responsiveness. This benefit in ESA hypo-responsiveness is associated with the effects of statins on inflammation.[37]

These preliminary studies may justify future studies to use statins as an EPO dose reducing adjuvant in patients with inflammation-mediated EPO resistant anemia of CKD.

## 9. Carnitine

L-carnitine is a small molecule (molecular weight: 161.2) that is derived from dietary products, mainly red meat and milk. Endogenous carnitine production takes place in the liver from lysine, methionine, ascorbate, niacin and pyridoxine. L-carnitine is required for the transport of long-chain fatty acids into the mitochondria and is an integral part of energy metabolism via ATP formation.

L-carnitine has been shown to improve anemia in uremic patients by stabilizing erythrocyte membrane function or erythropoiesis. End-stage renal disease patients are known to have carnitine deficiency.[38] This could be a contributing factor of anemia requiring higher dose of EPO. Thus, it has been used therapeutically in dialysis patients with and without concomitant EPO. Carnitine's role as an adjuvant to EPO in kidney disease is unclear. Most studies have involved HD patients with IV carnitine administration.

A 2002 meta-analysis evaluated the efficacy of IV carnitine supplementation in lowering the required dose of EPO using data from six randomized trials. The EPO dose was found to be significantly lower among those administered carnitine, with a beneficial response reported in four of the six studies.[38] Two studies showed improvement in Hb and HCT with PO carnitine but they were published before EPO was available.[39,40] In one study, 24 dialysis anemic patients were divided into two groups, controls (inert placebo), treated patients (L-carnitine 1.6 g PO daily) for one year. A significant increase in HCT, Hb, red cell count and mean corpuscular Hb concentration was observed. In comparison with the control group, an

early improvement could be detected by the 3rd month, with further increases in the successive months of treatment in the L-carnitine cohort.

There is some evidence in the literature suggesting that accumulation of metabolites (trimethyleamine and trimethylamines-N-oxide)of oral carnitine, may have potential toxicity[41]. Marcus et.al. conducted a study using oral carnitine and showed that a small dose of L-carnitine is sufficient to increase the blood concentration of carnitine.[41] The concern remains about the accumulation of trimethylamines-N-oxide and its potential toxicologic effects include neurological toxicity and uremic breath.

The 2006 K/DOQI guidelines for anemia in CKD stated that there was insufficient evidence to recommend L-carnitine.[42]

## 10. Androgens

There is no literature available in CKD patients not on dialysis. Before EPO was available, androgens (which may increase endogenous EPO production, sensitivity of erythroid progenitors to the effects of EPO, and red blood cell survival) were used regularly in the treatment of anemia in dialysis patients.[43-46] Their use for anemia in dialysis patients has declined markedly since EPO was approved.

EPO and androgen's combination in hemodialysis patients has been studied:

Ballal et.al. performed a study in a group of 15 adult male hemodialysis patients.[47] Seven patients were treated with EPO alone at a dose of 2,000 U intravenously (IV) three times a week. An additional group of eight patients was treated with 2,000 U of EPO three times a week and also received 100 mg of nandrolone decanoate intramuscularly (IM) each week. After 12 weeks of therapy, HCT values increased slightly in the group receiving EPO alone, from 25.3+/-0.8 to 27.4+/-1.5. In contrast, EPO in combination with nandrolone decanoate resulted in a greater increase in HCT values, from 24.4+/-1.4 to 32.9 +/-1.8 ($p < 0.001$). The results showed that the groups receiving low-dose EPO alone had a poor erythropoietic response. In contrast, patients receiving androgen in addition to EPO had a significantly greater increase in HCT values with treatment. These data show that androgen therapy significantly augments the action of exogenous EPO such that lower doses of EPO may be sufficient for an adequate hematopoietic response.

In a prospective, randomized study by Berns et al. in a chronic hemodialysis population, patients received EPO 40 U/kg intravenously three times weekly either alone (Group 1, n = 6) or with weekly intramuscular injection of 2 mg/kg nandrolone decanoate (Group 2, n = 6) for up to 16 weeks. Baseline HCT, ferritin, N-terminal parathyroid hormone, and aluminum levels were similar. The mean weekly rate of rise in HCT was 0.32+/-0.13% in Group 1 and 0.37+/-0.11% in Group 2, (p = NS). Three of 6 patients in Group 1, but only 1 of 6 patients in Group 2, reached the target HCT of 30% within 16 weeks. Two patients in Group 2 requested that the nandrolone decanoate be stopped prior to reaching target HCT because of unacceptable side effects (acne). [48] Nandrolone decanoate did not enhance the response rate to this EPO dose and is associated with significant side effects.

In a longer open-label study with low-dose EPO therapy, 19 chronic hemodialysis patients were randomly assigned to receive EPO (1,500 units IV at each HD treatment) either alone

or with nandrolone decanoate (100 mg intramuscularly weekly) for 26 weeks.[49] The mean increase in HCT and the final achieved HCT were greater in the nandrolone decanoate treated group (8.2 and 33.2 percent, respectively) than in the group treated with EPO alone (3.5 percent and 28.3 percent, respectively). No serious side effects were reported.

Thirty two hemodialysis patients were randomly assigned to receive low dose EPO therapy (1,000 units SC at each HD treatment) either alone or with nandrolone decanoate 50 mg intramuscularly twice weekly for six months.[50] The increase in Hb in the nandrolone decanoate treated group (from 7.5 to 10.4 g/dL) was not statistically different from the control group (7.3 to 10.0 g/dL). Side effects, including gynecomastia, hirsutism, menstrual irregularity, and increases in liver enzymes and triglyceride levels, were common.

The limiting factor in these studies was small size and relatively short follow ups, and none attempted to maintain currently recommended Hb levels. The 2006 K DOQI guidelines for anemia in CKD stated that androgens should not be used as an adjuvant to EPO.

## 11. N-acetylcysteine

N–acetylcysteine (NAC) is a drug and nutritional supplement used primarily as a mucolytic agent and also in the management of acetaminophen overdose. To explore the efficacy of oral NAC supplementation for anemia and oxidative stress in hemodialysis patients, Chien et al studied 325 dialysis patients. In this study, 49 pateints received NAC 200 mg orally three times a day during the first 3 months of dialysis, while the other 276 patients not receiving NAC were observed. During the 4-month study, 11 patients receiving NAC withdrew but had no severe adverse effects, while 49 patients not receiving NAC had negative confounding events. Thus only the data of the remaining patients, 38 taking NAC and 227 not taking NAC, were analyzed for efficacy.

When the EPO dosage was stable, only the NAC group had a significant increase in HCT, accompanied with a decrease in plasma levels of 8-isoprostane and oxidized low-density lipoprotein. Analyzed as a nested case-control study, NAC supplementation was also found to be a significant predictor of positive outcomes in uremic anemia. [51] To determine the contribution of injectable iron administered to hemodialysis patients in causing oxidative stress and the beneficial effect of NAC in reducing it, Swarnalatha et al conducted a prospective, double blinded, controlled, cross over trial on 14 adult hemodialysis patients who were randomized into two groups; one group received NAC in a dose of 600 mgs by mouth twice daily for 10 days prior to intravenous iron therapy and the other group received placebo. Both groups received intravenous iron therapy, 100 mg of iron sucrose in 100 mL of normal saline given over a period of one hour. Blood samples for the markers of oxidative stress were taken before and after the iron therapy. After a week of wash-out period for the effect of NAC, subjects crossed over to the opposite regimen. They measured the lipid peroxidation marker, malondiaaldehyde (MDA), to evaluate the oxidative stress and total anti-oxidant capacity (TAC) for the antioxidant level in addition to the highly sensitive C-reactive protein (HsCRP). Non-invasive assessment of endothelial dysfunction was measured by digital plethysmography before and after intravenous iron therapy. There was an increase of MDA (21.97 + 3.65% vs 7.06 + 3.65%) and highly sensitive C-reactive protein (HsCRP) (11.19 + 24.63% vs 13.19 + 7.7%) after iron administration both in the

placebo and the NAC groups. NAC reduced the baseline acute systemic generation of oxidative stress when compared to placebo, which was statistically significant with MDA (12.76 +/- 4.4% vs 9.7 +/- 4.4%) but not with HsCRP. Pre-treatment with NAC reduced the endothelial dysfunction when compared to placebo, but it was not statistically significant.

The author concluded that in those HD patients, NAC reduced the oxidative stress before and after the administration of intravenous iron therapy in addition to the endothelial dysfunction induced by this treatment. [52]

Finnigan and Benz reported the results of treating 12 ESRD EPO resistant hemodialysis subjects with oral NAC 600 mg by mouth twice daily for 6 months. In that small pilot study, NAC therapy was associated with a 53% reduction in the EPO Resistance Index (weekly EPO dose/weight in Kg/Hb). [53]

These preliminary studies suggest the need for a larger, controlled trial with NAC. Until then, routine use of NAC as an EPO- adjuvant cannot be recommended.

## 12. Discussion

Anemia of CKD/ESRD has multiple etiologies, although the decrease in EPO production by the diseased kidneys is the major contributor. Recently, studies targeting higher Hb levels or using higher EPO dosing regimens in the correction of anemia have shown detrimental effects including increased all cause mortality, cardiac and cerebral vascular events and vascular access thrombosis[8-10,54] It is not clear whether this is due to higher HCT or EPO the molecule itself at higher concentration. This review article focused on adjuvant oral and parenteral agents that have been used along with EPO to reduce its dose and give foundation to research in randomized control trials. There may also be a potential benefit of these agents to use along with EPO in reducing cost and expenditures especially when the bundling method of dialysis payment is in effect.

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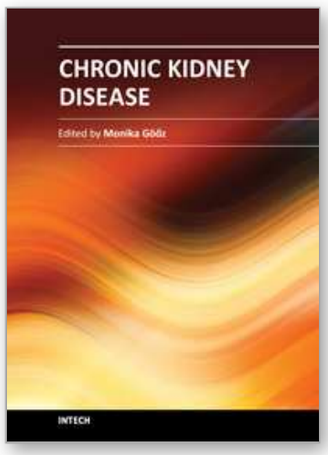


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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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