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TOPIC HIGHLIGHT

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Use of agents stimulating erythropoiesis in digestive diseases

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Abstract

Anemia is the most common complication of inflammatory bowel disease (IBD). Control and inadequate treatment leads to a worse quality of life and increased morbidity and hospitalization. Blood loss, and to a lesser extent, malabsorption of iron are the main causes of iron deficiency in IBD. There is also a variable component of anemia related to chronic inflammation. The anemia of chronic renal failure has been treated for many years with recombinant human erythropoietin (rHuEPO), which significantly improves quality of life and survival. Subsequently, rHuEPO has been used progressively in other conditions that occur with anemia of chronic processes such as cancer, rheumatoid arthritis or IBD, and anemia associated with the treatment of hepatitis C virus. Erythropoietic agents complete the range of available therapeutic options for treatment of anemia associated with IBD, which begins by treating the basis of the inflammatory disease, along with intravenous iron therapy as first choice. In cases of resistance to treatment with iron, combined therapy with erythropoietic agents aims to achieve near-normal levels of hemoglobin/hematocrit (11-12 g/dL). New formulations of intravenous iron (iron carboxymaltose) and the new generation of erythropoietic agents (darbepoetin and continuous erythropoietin receptor activator) will allow better dosing with the same efficacy and safety.

Key words: Erythropoiesis-stimulating agents; Recombinant human erythropoietin; Darbepoetin; Continuous erythropoietin receptor activator; Inflammatory bowel disease; Anemia

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INTRODUCTION

Anemia is a frequent complication in patients with digestive diseases, especially chronic processes such as inflammatory bowel disease (IBD)[1,2], and is associated with a higher rate of hospitalization and worse quality of life[3,4]. The main cause of anemia associated with IBD is iron deficiency, but there is also a component of anemia that is associated with chronic diseases. Therefore, when there is no good response to intravenous iron therapy, combination with erythropoietic agents, erythropoietin (EPO) or darbepoetin, may assist in the management of anemia[3,5-7]. The other subgroup of patients with digestive diseases in whom we can use erythropoiesis-stimulating agents (ESAs) are those being treated for chronic hepatitis C, whose anemia is caused by the use of rivabirin[8,9].

Human EPO is a glycoprotein hormone of 30.4 kDa, which is composed of 165 amino acids, and is the main regulator of erythropoiesis. It inhibits the apoptosis of erythroid progenitors and induces the clonal proliferation of normoblasts[10-12]. In adults, it is synthesized mainly in the kidney, which produces 90%-95% of the total circulating EPO; the remainder, about 10%, is synthesized by liver[13,14]. In addition to kidney and liver, it has been shown that other organs can secrete EPO, including peripheral endothelial cells, vascular smooth

muscle cells, neurons, astrocytes, cardiomyocytes and microglia[15].

The basal production maintains a relatively constant level of EPO in plasma, within a range between 5 and 29 U/L, which can increase up to 100 times in the presence of serious anemia[16]. Tissue hypoxia is the most important trigger for increased synthesis of EPO[10,17].

In 1977, Miyake *et al*[18] purified EPO molecule, which enabled cloning of the gene in 1983, and the subsequent development of recombinant EPO in mammalian cell lines[19]. The clinical use of EPO was started in 1986[20] for the treatment of anemia of chronic kidney disease (CKD)[21]. Treatment with EPO was able to eliminate almost completely transfusion dependence in hemodialysis patients, who in turn achieved a significant improvement in quality of life[22-24]. Treatment of anemia with EPO has helped to reduce the need for transfusions and the associated risks: transmission of infection, allogeneic iron overload and immunological damage[25].

There is a general consensus, as stated by the recommendations of panels of international experts (The National Kidney Foundation Dialysis Outcomes Quality Initiative[26], the Canadian Society of Nephrology[27], the European Renal Association/European Dialysis and Transplantation Association[28,29], Kidney Disease: Improving Global Outcomes[30] and the Japanese Society for Dialysis Therapy[31,32]), that the partial correction of anemia in patients with CKD improves clinical parameters and quality of life compared with the lowest levels of hemoglobin[26-32]. At present, for instance, in the United States, > 90% of patients on chronic dialysis and 30% on pre-dialysis are treated with EPO, with an average hemoglobin level of 12.0 g/dL[33-35]. Subsequently, its use has been extended to the treatment of anemia associated with other diseases such as cancer[36-38], IBD[3,5-7], heart failure[39,40] and the anemia associated with hepatitis C virus treatment[8]. In addition to its role as an erythropoietic agent, EPO has other potential therapeutic uses currently under extensive investigation[41,42], for use as a cytoprotective agent in the central nervous system[43,44] and intestinal mucosa[45-47]. Other possible applications include are cytoprotection in peripheral neuropathy, retinopathy and myocardial ischemia[48,49].

TYPES OF EPO

In clinical practice there are several forms of EPO available for the treatment of anemia (Table 1). The first generation are two forms of recombinant human EPO (rHuEPO): epoetin α (Epogen, Amgen and Procrit/Eprex; Johnson & Johnson/Janssen-Cilag) and EPO β (NeoRecormon; Roche), which are administered three times a week[50]. The development during the last decade of ESAs with a higher degree of glycosylation and prolonged half-life has allowed less frequent administration. A preparation called long-acting darbepoetin α (Aranesp; Amgen) produces a similar physiological response compared with rHuEPO[51]. It has more chains of carbohydrates and sialic acidic residues, which gives it a different pharmacokinetic profile from that of rHuEPO, with a half-life approximately three times higher (25.3 h *vs* 8.5 h by iv administration), and a plasma clearance four times slower. This allows a frequency of administration of once weekly, or even every 2-4 wk[52,53]. The equivalence relationship between rHuEPO and darbepoetin α from the molecular weight of both proteins is 1:200[54]. In clinical practice, the multiplication factor is not so simple, as the required dose of rHuEPO can be higher, which probably is related to an increase in resistance to EPO[55]. A pegylated derivative, the continuous EPO receptor activator (CERA) (epoetin β-methoxy polyethylene glycol, CERA; Roche) is another erythropoietic agent that activates repeatedly the EPO receptor. It has an elimination half-life in humans of about 130 h, and so can be administered every 3-4 wk[56-59]. Several studies have shown an effect similar to EPO in maintaining hemoglobin levels[60-65]. CERA is not available in United States, but is currently used in Europe. An additional advantage is that CERA can be kept out of the fridge and used for up to 1 mo (at < 25℃).

There is a new generation of erythropoietic analogues: synthetic erythropoiesis protein and peptide mimetics of EPO. These new agents stimulate erythropoiesis through activation of EPO receptors[66-69]. Hematide (developed by Affymax) is a synthetic peptide agonist of the EPO receptor, and although it has no structural homology with EPO, it is able to activate the EPO receptor and stimulate erythropoiesis over a 1-mo period, with good tolerance and stability at room temperature[66].

SIDE EFFECTS OF ESAs

The use of ESAs is related to several common side effects that should be well known by clinicians. Hypertension is the most common side effect, with an overall incidence of 5%-24%[70]. Vascular access thrombosis occurs with higher incidence[71,72], although it is not found in other small studies[73,74]. The risk of serious cardiovascular events, such as thromboembolism and death, increases when hemoglobin levels increase rapidly (> 1 g/dL every 2 wk)[75]. The development of anti-EPO antibodies is a very rare but serious complication of treatment with erythropoietic agents. From 1998 to 2004, it was apparent that there was a significant increase in the number of patients who developed pure red-cell aplasia (PRCA) secondary to the appearance of neutralizing anti-EPO antibodies[76,77]. PRCA is characterized by severe anemia, high transfusion requirement and a total lack of response to increasing doses of rHuEPO. Most of the reported cases have been patients with chronic renal failure who received rHuEpo α (Eprex) subcutaneously. PRCA was related to a change of formulation of Eprex (replacement of human serum albumin by polysorbate 80, because of the risk of bovine spongiform encephalopathy) and formation of immunogenic micelles. Alternatively, it has been suggested that leachates released by the uncoated rubber stoppers of the pre-filled syringes may interact with polysorbate 80 and

Table 1 Erythropoietic agents available

Half-life (h)			Periodicity	Initial dose	Target levels
	iv	sc			
Epoetin β	9	24	1-3 times per week	100-150 IU/kg per week, (max 300 IU /kg)	
Epoetin α	7	20	1-3 times per week	100-150 IU/kg per week, (max 300 IU /kg)	Hemoglobin: 11-12 g/dL, Hematocrit: 33%-36%,
Darbepoetin α	25	48	Every 1-2 wk	0.45 μg/kg every 2 wk	↑ hemoglobin every 2 wk: 0.5-1 g/dL
CERA	133	137	Every 2-4 wk	0.6 μg/kg every 2 wk	

act as an adjuvant to the immune response. Failure in the cold chain is also a potential factor involved[78-80]. The number of cases reported has dropped significantly from 2003, with none in 2007. This may have resulted from a change in the route of administration (at present the iv route is used in most patients on dialysis), maintenance of the cold chain, or elimination of uncoated rubber syringe stoppers[75]. Should this complication occur, clinical guidelines for diagnosis and treatment are readily available[81-84]. It has been suggested that the use of the new analogue hematide in these cases may be effective[85].

Other possible side-effects are edema, fever, dizziness, insomnia, headache, pruritus, constipation, among other.

USEFULNESS OF ESAs IN DIGESTIVE DISEASES

IBD

Anemia is the most common complication of IBD[86,87]. Inadequate monitoring and treatment leads to a worse quality of life[88,89] and increased morbidity and hospitalization[90-92]. Repeated loss of blood, and to a lesser extent malabsorption of iron are the main causes of iron deficiency in IBD[86]. There is also a variable component of anemia that is related to chronic inflammation[3,4,7,87,93]. This involves failure of iron transport that is mediated by inflammatory cytokines, such as hepcidin, which is the main negative regulator of iron absorption in the small intestine and of iron sequestration by macrophages[94-101], and an inappropriately low production of EPO for the degree of anemia[16,90,101-103]. The management of anemia in IBD should focus on proper control of the inflammatory process, as well as iron supplementation, and in cases of resistance, to assess iron therapy in combination with erythropoietic agents[3,87,91,104]. Up to 25%-30% of patients with anemia associated with IBD combination therapy may require iron and erythropoietic agents to correct anemia[3,105,106]. In other diseases (cancer, rheumatoid arthritis, AIDS), EPO levels < 500 mU/mL (some authors suggest < 100 mU/mL) may respond to administration of rHuEPO[107-112].

In patients with anemia associated with IBD, high levels of transferrin (iron deficit indicators) as well as high levels of serum EPO (an indicator of a correct response to anemia) may predict a good response to treatment with iv iron. In contrast, low levels of serum EPO indicate the need to associate agents erythropoietic in addition to iron treatment[3].

Since the increased production of hepcidin in anemia of chronic diseases may limit the oral absorption of iron, it should be given by the iv route. The iv administration of iron has proven its efficacy, safety and tolerability, with iron sucrose[7,89] as the new formulation iron carboxymaltose, that allows the administration of 1 g of iron in 15 min[112,113]. The use of erythropoietic agents in the treatment of anemia associated with IBD is useful for patients who do not respond to treatment with iv iron, and in whom the aggressive treatment of IBD (including immunosuppressive therapy) has not abolished the mucosal inflammation, and who require additional blood transfusions[5,7,114-116].

Hemoglobin target

Previous studies on the use of EPO in patients with CKD have found different results concerning the desirable target level of hemoglobin and its effect on cardiovascular prognosis. In 1997, the KDOQI guidelines[117] recommended target levels for hemoglobin/hematocrit between 33% (11 g/dL) and 36% (12 g/dL). A similar recommendation was made in the 2006 update of the KDOQI guidelines[26] although on that occasion, an upper limit for hemoglobin was set, because there was no evidence to maintain a target ⩾ 13 g/dL. The European Best Practice Guidelines Working Group did not recommend the complete correction of hemoglobin levels in patients with diabetes or cardiovascular disease[29].

The clinical benefits and adverse effects associated with normal or near normal hemoglobin values were evaluated in multiple randomized studies that assessed mortality and morbidity from cardiovascular or cerebrovascular events, good control of blood pressure, quality of life, functional status and vascular access thrombosis[71,118-126]. The results of these studies have not suggested any improvements after correction of anemia, except in quality of life. Despite differences in their populations, two large randomized studies published in November 2006, the CHOIR[127] and CREATE[128] studies have shown that attempts to correct anemia completely did not reduce mortality or cardiovascular disease in CKD patients, compared with partial correction. A meta-analysis that included these two studies concluded that patients with a higher target hemoglobin have a significantly higher risk of all-cause mortality and vascular access thrombosis[129].

In light of these data, the KDOQI guidelines were reviewed and updated in 2007, with a recommended hemoglobin level of 11-12 g/dL, and not exceeding 13 g/dL[130]. Also the European Best Practice Guidelines Working Group[75] has concluded that hemoglobin

> 13 g/dL may be associated with cardiovascular events in these patients.

Factors that influence the increase in mortality with higher hemoglobin targets may include the impossibility of achieving the target hemoglobin, a too high hemoglobin target, the toxic effects of high doses of ESAs, the presence of comorbidity and other features[131-135]. These factors were evaluated in a second analysis of the CHOIR study[136] that found no clinical factor associated with risk, after adjustment and multivariate analysis, except for high dose of epoetin (> 20000 U/wk), which was an independent risk factor for death, myocardial infarction, heart failure, or stroke. This increased risk was observed in the high and low hemoglobin groups, particularly among those who did not reach the target hemoglobin. These results suggest that increased mortality is due to high doses of ESAs rather than higher hemoglobin targets[137]. Epoetin α dose should not exceed 20000 U/wk in patients with CKD, and probably in other diseases. These patients should be assessed for other causes of poor response to treatment with EPO. Some studies have suggested the possible relationship between the variability of the hemoglobin level and the patient[138,139]. Although there is variability in the results of different studies[120,131,140-143], the most consistent observation is that there are better results in terms of quality of life, with no increase in adverse reactions of hemoglobin in the range of 11-12 g/dL (hematocrit 33%) compared with lower levels[139-144]. There is a large study under way in relation to the normalization of hemoglobin. The Trial to Reduce Cardiovascular Events with Aranesp Therapy study is a randomized, placebo-controlled trial in pre-dialysis CKD patients with type 2 diabetes mellitus[145,146], which is due to end in 2011.

In clinical practice, given the difficulty of maintaining standards within the narrow target range of 11-12 g/dL[147-149], it's accepted the range 10-12 g/dL, particularly in patients with good tolerance.

The target haemoglobin level in patients with IBD is still to be determined. Data from recent studies in CKD patients indicate increased morbidity and mortality in relation to high levels of hemoglobin (normal)[130-133], as in patients with cancer[103,104]. It seems appropriate to establish a target hemoglobin level of 11-12 g/dL, which demonstrates greater benefit in quality of life and cost-effectiveness in renal patients[120,133,139-145].

Dosage, monitoring and control

To maintain adequate levels of hemoglobin with erythropoietic agents iron stores must be normalized. Iron should be administered in sufficient quantity to achieve a transferrin saturation ⩾ 20% and a ferritin level ⩾ 100 ng/mL[7,87,150]. The response to EPO is dose dependent, but varies from patient to patient, depending on the frequency and route of administration (iv or sc), although to a lesser extent with darbepoetin[151,152]. The hypertension may complicate treatment, particularly if hemoglobin level rises quickly (> 1 g/dL every 2 wk)[153]. With the present preparations, sc and iv administration are indistinguishable; however, sc administration presents some advantages over iv, such as a lower incidence of hypertension, and a 25%-50% reduction in dose compared with iv administration[154-157]. Another important advantage of iv administration is a longer half-life (24 h *vs* 9 h)[158,159]. Daily sc EPO is more effective than administration 2-3 times weekly[160], although administration less frequently than every 2 wk is also effective[161-163]. Discomfort at the injection site is minimal. It is important to remember to maintain the cold chain at 4℃ to preserve a high effectiveness[164].

EPO can be started at a dose of 100-150 U/kg per week sc with iron supplements. The dose can be increased by 25% every 2-4 wk to reach 300 U/kg per week. It is not worthwhile to continue increasing the dose in patients who do not respond after 12 wk, and in these patients, the dose should be kept to the minimum effective dose to avoid transfusion[97,131]. The appropriate response should increase the hemoglobin level at least 0.5 g/dL at 2-4 wk. It is recommended analytical control in this period of time and if the hemoglobin increase is over target (> 10-12 g/dL) or > 1 g/dL in 2 wk, we must reduce dose by 25%. In contrast, if the hemoglobin level is < 10 g/dL (with adequate iron deposits) or hemoglobin increase < 1 g/dL in 4 wk, then we must increase dose by 25%[101,104,165]. Children usually require higher doses than adults to achieve a similar response[29,166]. In practice, most patients are dosed per unit dose (syringe) rather than kg. There are wide range of doses in pre-filled syringes.

Darbepoetin α can be administered iv and sc, with the main advantage of the half-life three times longer than epoetin. Effectiveness of Darbepoetin has been proved with administration weekly, every 2 wk[167] and monthly[117,168,169]. The initial dose of darbepoetin is 0.45 μg/kg every 2 wk and that of CERA is 0.6 μg/kg every 2 wk. Once the patient has been stabilized, the monthly dose may be doubled. Several well-designed prospective studies in renal patients have demonstrated the safety and effectiveness of weekly or even monthly treatment with epoetin α[170-174] in a similar way to new formulations of ESAs with long half-life[175].

Resistance

Evidence of EPO resistance stems from studies with an inadequate response EPO in 5%-10% of patients[176] or in patients who develop EPO resistance after a good initial response. There is a resistance to EPO when a sufficient dose of it, equal to or greater than 300 U/kg per week is not reached the desired concentration of hemoglobin[28].

It has been shown that the most frequent and important cause of resistance to EPO is iron deficiency, but there are other less frequent factors[28,177].

Blood loss is the most frequent cause of absolute iron deficiency, which is defined by ferritin levels < 100 ng/mL, transferrin saturation < 20%, and/or hypochromic red cells increased by 10%. Relative or functional iron deficiency results from difficulty in transferring stored iron to red blood cells and is defined by the existence of transferrin saturation < 20% while

maintaining high levels of ferritin > 100 ng/mL. The main causes of relative iron deficiency are acute and chronic inflammatory processes and chronic liver diseases[178]. Elevated levels of parathyroid hormone in CKD patients are another cause of non-negligible resistance to EPO[179]. The presence of an inflammatory disorder increases the resistance to treatment with erythropoietic agents, including the production of inflammatory cytokines that interfere with iron metabolism, reducing their availability in the bone marrow and causing functional iron deficiency. The process of dialysis may be associated with an increase in the induction of cytokines and the appearance of an inflammatory response syndrome[180].

In patients undergoing hemodialysis, carnitine metabolism is altered and carnitine deficiency is more likely in patients with a protein-deficient diet and high dialysis dose[181]. Carnitine may improve anemia in hemodialysis patients with EPO resistance[182] by mechanisms not yet known[183], or stabilizing the membrane as an antioxidant agent, or by stimulating erythropoiesis, by the increase in the number of reticulocytes demonstrated in some patients on hemodialysis treated with L-carnitine[184]. The dose used in patients with EPO resistence is 1 g iv post-hemodialysis[185].

Folic acid is involved in the process of regeneration and maturation of hematopoietic precursors. Folic acid deficiency is associated an ineffective erythropoiesis, and a megaloblastic anemia. Malnutrition, malabsorption, alcoholism, and various drugs that lower intestinal absorption, such as diphenylhydantoin, contraceptives and barbiturates, can cause folic acid deficiency. In dialysis patients with resistance to EPO, with normal ferritin levels, adjuvant treatment with folic acid may be attempted. It has been shown that the use of folic acid (10 mg/d) in hemodialysis patients improves the response to EPO, especially when presented high mean corpuscular volume, even with normal levels of folic acid[186].

The effectiveness of erythropoietic response to stimulation can be assessed by resistance index of ESAs. This expresses the relationship between the dose of erythropoietic agents and hemoglobin concentrations maintained (IU/kg per week divided by hemoglobin). Resistance index of ESAs varies from one patient to another and also in the same patient over time. These values range from 0 in patients able to maintain adequate hemoglobin level through the endogenous production of EPO, to > 50 IU/kg per week and per g/dL of hemoglobin in patients who cannot maintain adequate hemoglobin, even after high-dose EPO therapy (> 300 IU/kg per week)[187-189].

Anemia following treatment with ribavirin in HCV patients

Hemolytic anemia is a frequent side effect of early use of ribavirin in the treatment of hepatitis C. It has a negative impact on quality of life, and it can, in extreme cases, cause deterioration in brain function and even death. Furthermore it is a common reason for reduction or discontinuation of antiviral therapy, which compromises the effectiveness and reduces the sustained viral response. The administration of EPO can improve anemia, without the need to reduce the dose of ribavirin[190-194].

FUTURE EXPECTATIONS WITH THE USE OF EPO

It has been discovered in recent years that the EPO is also synthesized locally by many tissues, especially in response to metabolic stress. EPO functions as a protective molecule that inhibits apoptosis in a wide variety of cell types, and reduces inflammation and local edema, as well as improving tissue regeneration[195]. The mechanisms of tissue protection are mediated by a receptor. This receptor is different other than that mediates the effects erithropoyetics of EPO[196]. The future of EPO therapy in ischemic diseases, and as protective cytotoxic therapies appears promising. Of course clinical trials comparing its efficacy with other conventional therapies are needed[197]. Also being evaluated is the effect of EPO on intestinal endothelial cells[45], and in the maintenance and repair of the mucosa[46].

SUMMARY AND PROSPECTS

For nearly 25 years, the anemia of chronic renal failure has been treated with rHuEPO, which has resulted in a significant improvement in quality of life and survival and avoidance of dependence on repeated transfusions[22-24]. Subsequently, rHuEPO has been used in other conditions that occur with anemia of chronic diseases such as cancer, rheumatoid arthritis[109] or IBD[3,5,114-116], and anemia associated with the treatment of hepatitis C[190-194]. It has also been investigated for its protective effects in other acute diseases such as myocardial ischemia and brain and kidney diseases[198]. The classical dosing schedule of three times weekly has been simplified with the advent of new generations of erythropoietic agents such as darbepoetin α, which allows administration every 2 wk, and CERA, which has a longer half-life that allows prolonged administration monthly. Research continues to develop new biologically similar molecules such as agonists of the EPO receptor as hematide, which allows the treatment of patients with PRCA and monthly administration[85]. As well as searching for orally active formulations that will simplify the management of anemia[199-202]. There have also been negative aspects of treatment with EPO, as the cases of pure red cell aplasia[64,80], or poor outcomes in relation to death and cardio vascular events in study of normalization of hemoglobin (in connection especially with high doses of EPO in patients with poor response)[127-129,137] and worse survival in patients with cancer[103,104]. However, EPO has been shown to be effective and safe in the treatment of anemia of chronic renal failure and has improved significantly quality of life of patients with chronic anemia[22-25].

Similarly, the development of iv iron therapy was a major breakthrough in the management of chronic anemia. Iron sucrose has demonstrated its safety, efficacy and tolerance[7,86,87]. Other new formulations of iron

that allow rapid iv administration of large doses with good efficacy and tolerance will make administration easier[5,110,202].

CONCLUSION

To summarize we can say that erythropoietic agents come to complete the range available therapeutic for treatment of anemia associated with IBD that begins by treating the inflammatory disease basis, as well as intravenous ferroterapia first choice. In cases of resistance to treatment with iron may raise a combined therapy with erythropoietic agents to try to achieve near-normal levels of hemoglobia/hematocrit (11-12 g/dL). The new formulations of iv iron (iron carboxymaltose) and the new generation of erythropoietic agents (darbepoetin and CERA) will allow a more comfortable and spaced dosage schedule, with the same efficacy and safety.

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