Name of journal: *World Journal of Clinical Urology*

ESPS Manuscript NO: 10897

Columns: REVIEW

**Benefits and risks of erythrocyte-stimulating agents**

Katagiri D *et al.* Benefits and risks of ESA

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**Received:** April 24, 2014 **Revised:** June 5, 2014

**Accepted:** July 17, 2014

**Published online:**

**Abstract**

Chronic kidney disease (CKD) is a common and serious clinical problem. Anemia in patients with advanced CKD, frequently called renal anemia, causes disabling fatigue and diminishes patients’ quality of life. Frequent and excess transfusions or iron supplementation are potentially hazardous. Although it remains unclear whether the main factor in the development of renal anemia is the failure of erythropoietin (EPO) production in the kidney or a dysfunction in oxygen sensing exogenous EPO administration is considered a rational treatment. The advent of recombinant human erythropoietin (rHu-EPO) products has dramatically changed the therapeutic strategy for renal anemia. Although rHu-EPO therapy has improved patients’ quality of life and decreased the need for blood transfusions, some potential adverse effects have been reported till date. This brief review discusses the treatment of renal anemia with regard to the following: (1) historical background; (2) effectiveness of rHu-EPO; (3) some topics regarding the treatment of anemia, including EPO resistance, hemoglobin (Hb) cycling, and adequate Hb levels; (4) major adverse effects of rHu-EPO, including hypertension, thrombotic complications, and pure red cell aplasia; and (5) future problems to be resolved.

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**Key words:** Chronic kidney disease; Erythrocyte-stimulating agents; Renal anemia; erythropoietin; Pure red cell aplasia

**Core tip:** Renal anemia is a common clinical problem in patients with severe chronic kidney disease. To overcome the shortage of endogenous erythropoietin (EPO), administration of exogenous EPO is an effective treatment. The advent of recombinant human erythropoietin (rHu-EPO) products has dramatically changed the therapeutic strategy and has shown outstanding effectiveness in patients with renal anemia. Here we discuss the treatment of renal anemia and the adverse effects of rHu-EPO.

Katagiri D, Hinoshita F. Benefits and risks of erythrocyte-stimulating agents. *World J Clin Urol* 2014; In press

**HISTORICAL BACKGROUND**

Serious anemia requiring transfusion and/or iron supplementation is one of the frequent complications in patients with progressed chronic kidney disease (CKD)[1]. This type of anemia is also known as renal anemia, and it causes disabling fatigue and diminishes the quality of life (QOL) in patients with CKD. Excessive blood transfusions and/or iron supplementation are potentially hazardous. Rare but serious risks associated with transfusion include procedural complications, pulmonary congestion, electrolyte imbalance, metabolic alkalosis, hypocalcemia, and severe lung injury (Table 1)[1]. Moreover, the great risk of transfusion-related infections, such as hepatitis virus, West Nile virus, and human immunodeficiency virus infections, cannot be ignored. The other important and common therapy for renal anemia is iron supplementation. Iron deficiency is a serious clinical problem in patients with chronic heart failure[2,3]. However, iron overload has potentially adverse outcomes, including hypotension and dyspnea[4,5], transfusional hemosiderosis, and increased risk of infection[6-8].

The advent of recombinant human erythropoietin (rHu-EPO) was a major breakthrough in the treatment of renal anemia. Although it remains unclear whether the leading factor in the development of renal anemia is the failure to produce EPO in the kidney or a dysfunction in oxygen sensing[9], exogenous EPO administration is considered a rational method to treat anemia in patients with CKD. Human EPO, which is derived from the urine of patients with aplastic anemia (AA), is purified to apparent homogeneity. In 1977, Miyake and colleagues first purified human EPO in an amount sufficient for chemical characterization[10]. Recombinant human EPO was subsequently produced and became available for clinical use more than two decades ago. Consequently, it completely altered the medical management of renal anemia.

**THE EFFECTIVENESS OF ERYTHROCYTE-STIMULATING AGENTS**

### The introduction of exogenous rHu-EPO into clinical practice dramatically altered the treatment of renal anemia in patients with CKD[11]. Some of the beneficial effects of rHu-EPO therapy include elevated hemoglobin (Hb) levels, improved QOL and cognitive function[12-14], and decreased left ventricular mass, among others[15]. In 1990, Evans *et al*[16] reported that rHu-EPO therapy led to significant improvements in personal activity levels, functional ability, appetite, sleeping hours, condition or satisfaction with health, and happiness. However, no significant differences were observed in patients’ working capacity or job status[16]. Overall, the spread of exogenous rHu-EPO treatment diminished the need for transfusion[17] and the risk of transfusion-related complications. Roth *et al*[18] reported that rHu-EPO therapy improves anemia in patients with stage 3 or 4 CKD [glomerular filtration rate (GFR) = 15–59 mL/min per 1.73 m2] and does not increase the severity of CKD[18]. The administration of rHu-EPO is definitely regarded as an effective therapy for transfusion-dependent long-term dialysis patients (GFR < 15 mL/min per 1.73 m2 and use of maintenance renal replacement therapy; CKD 5D) with extremely low Hb levels.

**EPO-RELATED TOPICS**

***EPO resistance***

Erythrocyte-stimulating agents (ESA) resistance is a serious clinical problem that physicians often encounter in patients with renal anemia. It has been reported as the most predominant predictor of cardiovascular events and fatality[19]. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines describe the evaluation and management of ESA resistance (Table 2)[20]. Table 3 presents a clinical approach to manage ESA resistance. Among many factors associated with ESA resistance, including hyperparathyroidism, inflammation, and underdialysis, iron deficiency is the leading cause. Iron supplementation often results in the improvement of anemia[1].

***Hb cycling***

Fishbane *et al*[21] previously defined Hb cycling as cycles with > 1.5 g/dL and > 8 wk and excursions as half of a cycle. In their report, more than 90% hemodialysis (HD) patients were reported to experience Hb cycling. The mean duration of Hb excursions was 10.3 ± 5.1 wk. An increase in the rHu-EPO dose, intravenous iron treatment, and post-hospital discharge were the factors associated with upward excursions[21]. Yang *et al*[22]reported that Hb variability is related to severe mortality in CKD 5D patients in the United States. However, this trend was negated in a subsequent study conducted in Europe[23] and remains to be verified in future research.

***Adequate Hb levels***

According to recent major randomized controlled trials (RCTs), more harm than benefit may be caused by higher Hb levels. Therefore, setting the Hb level at < 11.5 g/dL in adult patients with CKD is suggested by the KDIGO 2012 guidelines[20]. In the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial[24], 603 CKD 3–5 patients (GFR < 59 mL/min per 1.73 m2) treated with rHu-EPO were evaluated. The number of patients who required HD was greater in the high Hb group (13.0–15.0 g/dL) than in the low Hb group (10.5–11.5 g/dL). The rate of decrease in GFR between the two groups was similar. On the other hand, 1432 CKD 3–4 patients (GFR, 15–59 mL/min per 1.73 m2) were studied in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial[25]. Patients receiving strong treatment for anemia (aiming at 13.5 g/dL) experienced a greater incidence of combined cardiovascular adverse events compared with those receiving standard treatment (11.3 g/dL). Considering these findings, the adequate and appropriate range of Hb levels that should be achieved with rHu-EPO therapy remains to be determined. Intentionally increasing Hb levels to > 13 g/dL using ESAs is not recommended for all adult patients according to the KDIGO guidelines[1,20]. In addition, an excessively high dose of ESA is reported to be potentially harmful for patients according to the results of post-hoc analysis of RCTs[26,27], notably in concurrence with high Hb levels[28].

**ADVERSE EFFECTS OF ESA**

Table 4 shows the major complications associated with EPO therapy[11].

***Hypertension***

Hypertension has been considered a common complication of ESA therapy, particularly in the early phase of indication for rHu-EPO therapy[29]. Previous studies have noted that rHu-EPO is the leading factor in approximately 20% patients with clinically important increases in blood pressure during amelioration of anemia. Hb levels, history of hypertension, and previous antihypertensive drug use were not confirmed as risks[30,31]. Similar to the observation in essential hypertension and CKD-associated hypertension, in which an increase in peripheral vascular resistance is the main cause, rHu-EPO-induced hypertension manifests hemodynamic changes[11]. An approximately 30% increase in systemic vascular resistance has been reported[32,33]. Management of this adverse event includes the adjustment of dry weight or limiting the rate of Hb increase and prescription of antihypertensive medication.

***Thrombotic complications***

The increased incidence of vascular access thrombosis or serious cardiovascular events associated with rHu-EPO therapy is multifactorial and controversial[34,35]. Churchill *et al*[36] reported an insignificant difference between patients treated with rHu-EPO and comparison groups in the time to development of the first thrombosis of fistula. However, rHu-EPO treatment increased the frequency of graft thrombosis[36]. Tang *et al*[37] confirmed that the occurrence of thrombosis in rHu-EPO–treated patients was not related to patients’ hematological responses to the drug; rather, it depends on the integrity of patients’ vasculature and the type of vascular access used.

***Pure red cell aplasia***

Normocytic anemia with decreased reticulocytes and absence of erythroblasts is the main feature of Pure red cell aplasia (PRCA). The onset of secondary PRCA may follow parvovirus infection, leukemia, lymphoma, collagen disease, or rHu-EPO treatment. In Europe, the frequency of rHu-EPO-associated PRCA reached a peak in 2001–2002, in connection with Eprex (Johnson & Johnson, New Brunswick, NJ, United States)[38]. It was suggested that subepidermal immune reactions play an essential role in PRCA induced by rHu-EPO, as the condition was mostly induced by subcutaneous administration[39]. To guide the close examination and therapy of patients with a strong possibility of developing antibody-associated PRCA, recommendations based on expert opinions have been published[40,41]. The two major clinical features of antibody-mediated PRCA are as follows: (1) An associated decline in blood Hb levels of 4 g/dL per month; (2) A decrease in the number of reticulocytes to < 10000/mL (Table 5)[20].

Currently, the incidence rate of PRCA is very low. However, PRCA may still occur even though rHu-EPO is thought to be well preserved under good storage conditions. This is because rHu-EPO has been more popular for the treatment of renal anemia[42,43].

We previously reported an elderly patient with PRCA who was positive for anti-erythropoietin (anti-rHu-EPO) antibodies[43]. Transfusions for symptomatic anemia and discontinuation of rHu-EPO treatment are important for the initial management of anti-EPO antibody-mediated PRCA[44]. Subsequent immunosuppressive therapy should be considered because PRCA in this setting is immune-mediated and because spontaneous remission is rare. In a previous study related to anti-EPO antibody-mediated PRCA (N = 47), 78% (N=29/37) patients who received immunosuppressive therapy recovered[45], whereas all patients without immunosuppressive drug therapy (N = 9) did not recover from PRCA. According to another report of 62 PRCA patients who did not receive immunosuppressive therapy, only one patient showed spontaneous recovery[46].

Fisch *et al*[47] reviewed serum antibodies and natural killer (NK) cells or T-lymphocyte associated mechanisms of erythropoiesis. Rituximab (an anti-CD20 monoclonal antibody)[48] and alemtuzumab (an anti-CD52 monoclonal antibody)[49] are expected to represent an alternative therapeutic strategy for patients with refractory PRCA. However, the patient in our presented case report refused immunosuppressive treatment, and successful remission was achieved with cessation of rHu-EPO treatment alone. The patient’s severe anemia gradually ameliorated along with a decrease in antibody titer[43]. In 1997, Prabhakar and Muhlfelder reported the first case of a patient with PRCA caused by rHu-EPO who recovered after the discontinuation of ESA therapy[50]. In 1996, Casadevall *et al*[51] reported a patients with PRCA and spontaneously decreasing anti-EPO antibodies. It should be emphasized that spontaneous PRCA remission following the cessation of rHu-EPO therapy is extremely unlikely. Early recognition as well as appropriate and prompt management is important for managing the consequences of this antibody-related PRCA.

**FUTURE PROBLEMS TO RESOLVE**

Peginesatide is an rHu-EPO receptor agonist without cross-reactivity with anti-EPO antibodies[52]. Peginesatide is expected to be a potential alternative therapy for managing patients with anti-EPO antibody-associated PRCA[53]. In February 2013, the drug industry recalled peginesatide because the Food and Drug Administration (FDA) received reports of anaphylactic reactions following peginesatide administration, some of which resulted in death[54].

As an alternative to the administration of exogenous rHu-EPO or its mimetics, induction of endogenous EPO production by several mechanisms, including prolyl hydroxylase domain protein inhibitors and GATA-binding protein inhibitors, is considered to have potential advantages of better availability and lower immunogenicity[55].

Further research in this field is required to answer the following clinical questions[20]: (1) Is there any difference in outcomes between intravenous and subcutaneous ESA administration? (2) Can any vascular complications occur in association with normalization of Hb levels using ESA therapy? (3) Are there any potential risks associated with ESA use in patients with a history of cancer?

**CONCLUSION**

rHu-EPO therapy is undoubtedly an effective strategy for renal anemia. However, clinicians must balance the benefits, such as a decrease in the requirement of transfusions and amelioration of anemia-related symptoms, with the potential side effects of rHu-EPO administration. Further research is expected to answer some interesting clinical questions related to the use of rHu-EPO therapy for renal anemia.

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**P-Reviewer:** Trumper L **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Risks associated with blood transfusions[1]**

|  |  |
| --- | --- |
| Adverse effects | |
|  | Fever/allergic reactions |
| Hemolytic reaction |
| TRALI |
| Anaphylaxis |
| Fatal hemolysis |
| GVHD |
| Thrombotic complications |
| Mistransfusion |

TRALI: Transfusion-related acute lung injury; GVHD: Graft-versus-host disease.

**Table 2 Erythrocyte-stimulating agents hyposensitivy (Kidney Disease Improving Global Outcomes Guideline 2012)[20]**

|  |  |
| --- | --- |
| Initial ESA hyporesponsiveness | |
|  | 1 Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing |
|  | 2 In patients with ESA hyporesponsiveness, avoid repeated escalations of the ESA dose beyond double the initial weight-based dose |
| Subsequent ESA hyporesponsiveness | |
|  | 1 Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require two increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration |
|  | 2 In patients with acquired ESA hyporesponsiveness, avoid repeated escalations in ESA dose beyond double the dose at which they had been stable |
| Management of poor ESA responsiveness | |
|  | 1 Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response |
|  | 2 For patients who remain hyporesponsive despite the correction of treatable causes, accounting for relative risks and benefits: decline in Hb concentration; continuing ESA if needed to maintain Hb concentration, with due consideration of the doses required; blood transfusions |

ESA: Erythrocyte-stimulating agents; Hb: Hemoglobin.

**Table 3 Practical approach in the presence of erythrocyte-stimulating agents resintance (Kidney Disease Improving Global Outcomes Guideline 2012)[20]**

|  |  |
| --- | --- |
| Tests | Finding and action |
| 1 Check adherence | If poor, attempt to improve (if self-injection) |
| 2 Reticulocyte count | If > 130000/**μ**L, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen |
| Serum vitamin B12, folate | If low, replenish |
| Iron status | If low, replenish iron |
| Serum PTH | If elevated, manage hyperparathyroidism |
| Serum CRP | If elevated, check for and treat infection or inflammation |
| Underdialysis | If underdialyzed, improve dialysis efficiency |
| ACEi/ARB use | If yes, consider reducing dose or discontinuing drug |
| 3 Bone marrow biopsy | Manage condition diagnosed e.g., dyscrasia, infiltration, fibrosis |

ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; CRP: C-reactive protein; PTH: Parathyroid hormone.

**Table 4 Nonhematologic complications associated with erythropoietin therapy[11]**

|  |  |
| --- | --- |
| Adverse effects | |
|  | Hypertension |
| Injection site pain |
| Seizure |
| Pure red cell aplasia |
| Liver dysfunction |
| Shock, anaphylaxis |
| Thrombotic complications |

**Table 5 Evaluation for pure red cell aplasia (Kidney Disease Improving Global Outcomes Guideline 2012)[20]**

|  |
| --- |
| Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 wk develops the following:  (1) Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dL (5 to 10 g/L) per week OR requirement of transfusions at the rate of approximately 1 to 2 per week  (2) Normal platelet and white cell counts  (3) Absolute reticulocyte count less than 10000/mL |
| ESA therapy should be stopped in patients who develop antibody-mediated PRCA |
| Peginesatide should be used to treat patients with antibody-mediated PRCA. |

PRCA: Pure red cell aplasia; ESA: Erythrocyte-stimulating agents; Hb: Hemoglobin.