

How the Target Hemoglobin of Renal Anemia Should Be?

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Key Words

Erythropoiesis stimulating agents · Cardiovascular disease · Erythropoietin · ESA resistance

Abstract

Renal anemia is caused by the deficiency of endogenous erythropoietin (Epo) due to renal dysfunction. We think that it is possible to slow the progression of chronic kidney disease (CKD) in case we initiate Epo early in pre-dialysis patients, especially in the non-diabetic population. Erythropoiesis stimulating agent (ESA) treatments targeting mild anemia (10–12 g/dl) can decrease the risk of occurrence of cardiovascular disease (CVD) in patients with hypertension, diabetes mellitus and congestive heart failure. As the large randomized controlled trials such as Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta, Correction of Hemoglobin and Outcomes in Renal Insufficiency and Trial to Reduce Cardiovascular Events with Aranesp Therapy in the Western countries suggested, we do not recommend high doses of ESA to achieve the target hemoglobin (Hb) level. The target Hb of >13 g/dl might lead to increase in the risk of CVD although maintaining a high Hb of >12 g/dl without ESA is not harmful for CKD patients. It is desirable to determine the target Hb in dialysis patients depending on their ages. Renal anemia should be monitored constantly to start ESA and iron replacement therapy at an appropriate time, while avoiding their excess in order to

minimize the occurrence of CVD and other complications. Taken all the international guidelines and our clinical experiences together, we should consider administration of ESA when the Hb level becomes <11 g/dl in pre-dialysis patients and <10 g/dl in dialysis patients. © 2015 S. Karger AG, Basel

Background

Renal anemia is one of the most frequent complications of chronic kidney disease (CKD). The majority of patients with CKD stage 5 suffer from anemia [1], which becomes evident at an earlier stage in the diabetic population [2]. Anemia leads to a decrease in oxygen delivery to vital organs, which is initially compensated for by tachycardia and cardiac hypertrophy, but eventually leads to the development of cardiovascular disease (CVD). CKD patients with anemia were reported to have 1.7 times higher risk of CVD [3]. Progression of renal anemia is not only associated with progression of CKD, as discussed below, but also with an increasing risk of CVD, causing a vicious cycle of the cardiorenal anemia syndrome.

The main cause of renal anemia is deficiency of endogenous erythropoietin (Epo). Some clinical studies have shown that the correction of hemoglobin (Hb) by erythropoiesis stimulating agents (ESAs) might retard the progression of CKD and decrease the occurrence of CVD.

However, recent large clinical studies have failed to demonstrate the beneficial effects of targeting high Hb levels for the improvement of CKD and CVD. Rather, excessive elevation of Hb might lead to higher risk of CVD. On the other hand, there are many papers showing that quality of life (QOL) was improved by ESA.

Content

The target Hb of renal anemia differs between pre-dialysis and dialysis patients, which will be discussed below.

Pre-Dialysis Patients with CKD

Does the Correction of Hb Using ESA Retard the Progression of CKD?

There are several randomized controlled trials (RCTs) or meta-analyses that studied whether targeting higher Hb levels might retard the progression of CKD [4–11]. A pioneering study by Kuriyama et al. [4] demonstrated that correction of anemia by ESA can retard the progression of renal failure especially in the non-diabetic patients. A recent report by Tsubakihara et al. [5] showed that maintaining higher Hb ($11.0 \leq \text{Hb} \leq 13.0$ g/dl) with darbepoetin alfa tended to preserve renal function better in patients with CKD not on dialysis, while obviously underpowered to evaluate renal outcomes. Gouva et al. [6] also performed a RCT of early versus deferred initiation of Epo in non-diabetic pre-dialysis patients with serum creatinine 2–6 mg/dl and Hb 9–11.6 g/dl. They concluded that early initiation of Epo in pre-dialysis CKD patients with non-severe anemia significantly slows the progression of CKD and delays the initiation of renal replacement therapy. Cody et al. [7] performed a meta-analysis of 15 trials (461 participants) and concluded that treatments with ESA in pre-dialysis patients corrects anemia, avoids the requirement for blood transfusions and improves QOL and exercise capacity. On the other hand, Palmer et al. [8] performed a meta-analysis of 27 RCTs (10,452 patients) examined since 2004 and concluded that corrections of Hb using ESA was not significantly useful in retardation of progression of CKD. It should be noted that some studies did not achieve differences in Hb levels designed in the original protocol. Studies that achieved differences of Hb levels of >2 g/dl between the 2 groups showed reno-protection.

Given all the results of RCTs, we conclude that it should be possible to slow down the progression of CKD in case we initiate Epo early in pre-dialysis patients, especially in the non-diabetic population.

Occurrence of CVD

Several RCTs or meta-analysis suggested that targeting higher Hb levels, in other words, complete correction of renal anemia with ESA, might increase occurrence of CVD [6, 8–11]. In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study, complete correction of anemia did not only effect a first cardiovascular event but dialysis also was required more often in patients with the high-target Hb group [9]. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, target Hb level of 13.5 g/dl was associated with increased risk for death, myocardial infarction, cardiovascular events including congestive heart failure (CHF) and cerebral infarction [10]. In addition, an RCT of pre-dialysis patients with type 2 diabetes (Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT] study) demonstrated that death due to cardiovascular event occurred more frequently in patients assigned to darbepoetin alfa than in patients assigned to placebo (hazards ratio 1.05, 95% CI 0.94–1.17; $p = 0.41$) [11]. Palmer et al. [8] showed that a higher Hb target was associated with increased risks for stroke, hypertension and vascular access thrombosis compared with a lower Hb target.

Results from the above-mentioned studies do not necessarily negate targeting higher Hb levels. Achieving higher Hb levels might still be beneficial in selected populations; ESA treatment in patients with symptomatic CHF and mild anemia (10.1–11.8 g/dl) improved anemia and exercise tolerance, reduced symptoms and had benefits on clinical outcomes [12]. According to a result of Japanese RCT, left ventricular mass index was improved in the high-Hb group compared with the low-Hb group [13]. It should be noted, however, that this study was performed in the population with low cardiovascular events and hypertension, as compared to countries in which preceding studies were performed.

As suggested by large RCTs such as the CREATE, CHOIR and TREAT in the Western countries, we think that a target Hb of >13 g/dl may be associated with higher risk of occurrence of CVD.

Improvement of QOL

Many clinical studies have shown that ESA is effective for improving QOL. For example, the Functional Assessment of Cancer Therapy–Fatigue score is improved in high-target Hb groups in the TREAT study [11]. However, there was no significant difference in energy and physical functioning between the high-target Hb group and low-target Hb group in the same study. As a

result of the CREATE study, general health and vitality showed higher scores in the high-target Hb group from a long-term perspective [9]. A Japanese RCT showed that the score for vitality was improved with ESA [13]. On the other hand, the CHOIR study concluded that there was no significant difference in QOL between the high- and the low-target Hb groups [10]. A subsequent meta-analysis by Clement et al. [14] demonstrated statistically significant changes in the physical function, general health, social function and mental health domains. However, none of the changes would be considered clinically significant as targeting Hb levels of >12.0 g/dl resulted in small, yet not clinically meaningful, improvements in QOL. Although many RCTs concluded that ESA treatments can improve QOL, end points of QOL are different depending on RCTs. Although there is a possibility that targeting Hb levels of >12.0 g/dl improves QOL in physical functioning more significantly than in low-Hb group, clinical significance may remain obscure.

High Doses of ESA Targeting High Hb

The important questions include whether high Hb levels per se are detrimental in CKD patients or whether other factors associated with achieving high Hb levels contribute to adverse outcomes. Analysis of the prospective, observational Dialysis Outcomes and Practice Patterns Study showed that naturally occurring Hb concentration of >12 g/dl does not associate with increased mortality among hemodialysis patients, suggesting that high Hb levels per se are not bad in CKD patients [15]. However, it is likely that high doses of ESA to achieve the target of high Hb may increase the risk of ESRD and cardiovascular events. In the secondary analysis of the CHOIR trial, high-dose epoetin-alpha was associated with a significant increased hazard of a primary end point [16]. We do not recommend high doses of ESA to achieve the target Hb because it might lead to increase in the risk of CVD although maintaining a high Hb of >12 g/dl without ESA is not harmful for CKD patients.

Dialysis Patients

There are several RCTs regarding how we should target Hb in dialysis patients. Besarab et al. [17] performed RCT with 1,233 patients who had clinical evidence of CHF or ischemic heart disease undergoing hemodialysis. Six hundred and eighteen patients were assigned to receive epoetin to achieve and maintain a hematocrit of 42%, and 614 patients were assigned to receive doses of epoetin to maintain a hematocrit of 30% throughout the

study. As a result, the study was halted although the difference in event-free survival between the 2 groups did not reach the statistical stopping boundary because there were more deaths and non-fatal myocardial infarctions among patients in the normal-hematocrit group than those in the low-hematocrit group (table 1).

Recent analysis of the Japan Dialysis Outcomes and Practice Patterns Study cohort found interaction between ages stratified by the age of 75 years and Hb values ($p = 0.045$) with use of Cox's proportional hazard model. The non-elderly population had poorer prognosis with Hb <10 g/dl, while the elderly population with only Hb <9 g/dl. For both Hb strata <9, ≥ 9 and <10 g/dl, interactions between age and Hb were significant [18]. Thus, the elderly population might tolerate low Hb levels, and target Hb levels may differ based on the ages of patients. We think that achieving higher Hb levels in the elderly patients who are older than 75 years may be associated with the decreased survival rates or the increased rates of occurrence for CVD. Excessive low levels of Hb may affect survival rates in the elderly dialysis patients (Hb <9.0 g/dl) and non-elderly dialysis patients (Hb <10 g/dl). We suggest that it is desirable to determine the target Hb in dialysis patients depending on their ages.

ESA Resistant Renal Anemia

Definition of ESA Resistance and Its Possible Causes

ESA resistance is generally defined as lack of responses to exogenous ESA administration. However, there is no clear definition of the ESA resistance. In the European Renal Best Practice Guidelines, ESA hypo-responsiveness was defined as the weekly 300 U/kg (20,000 U/week) or inability of darbepoetin alfa at 1.5 $\mu\text{g}/\text{kg}$ (100 $\mu\text{g}/\text{week}$) to achieve the target Hb (11.0–12.0 g/dl) [2]. In the Kidney Disease Outcomes Quality Initiative (KDOQI) 2006 guideline, ESA resistance was defined as Hb <11.0 g/dl despite Epo administration of 500 U/kg [19]. In the revised version of KDOQI 2012, it was defined as lack of Hb elevation in spite of ESA administration for >1 month [20].

There are several causes of ESA resistance such as gastrointestinal hemorrhage, inflammation, infection to blood access and others, insufficiency of dialysis, malignant tumors, iron deficiency, folic acid or vitamin B12 deficiency and hematological disorders such as multiple myeloma. Uremic solutes, such as indoxyl sulfate (IS), also appear to contribute to ESA resistance. IS induces endoplasmic reticulum stress [21–23], suppresses Epo expression and leads to the progression of CKD. Recent

Table 1. Summary of representative RCTs for the target Hb in CKD patients. This is the list of representative RCTs for renal anemia

Patients	Authors	Year	Study name	Patients number	ESAs	Objectives	Group (targeted Hb)	Follow-up period	Primary endpoint	Results	Journal
Pre-dialysis	Drüeke et al. [20]	2012	CREATE	603	Epoetin beta (5,000 IU/patient)	GFR 15–35 ml/min/body weight with Hb mild to moderated anemia (11.0–12.5 g/dl)	Group 1: Hb normal 13–15 g/dl Group 2: Hb subnormal (10.5–11.5 g/dl)	3 years	Composite of 8 cardiovascular events	Complete correction of anemia did not affect a first cardiovascular event. Dialysis was required more in group 1	N Engl J Med
	Singh et al. [10]	2006	CHOIR	1,432	Epoetin alfa	CKD stages 3 and 4G	Group 1: targeted Hb 13.5 g/dl Group 2: targeted Hb 11.3 g/dl	16 months	Composite of death myocardial infarction, hospitalization for CHF	Target Hb level of 13.5 g/dl was associated with increased risk	N Engl J Med
	Pfeffer et al. [11]	2009	TREAT	4,038	Darbepoetin alfa	Patients with diabetes, CKD and anemia	Group 1: targeted Hb 13 g/dl Group 2: placebo, rescue with ESA when Hb <9.0 g/dl	4 years	Composite outcomes of death or a cardiovascular event, CHF, stroke, hospitalization for myocardial ischemia and death or ESRD	The use of darbepoetin alfa did not reduce the risk of death or cardiovascular event and increased risk of myocardial ischemia stroke	N Engl J Med
	Akizawa et al. [13]	2011		321	Darbepoetin alfa	Hb <10 g/dl, serum creatinine of 2.0–6.0 mg/dl	Group 1: targeted Hb 11.0–13.0 g/dl Group 2: targeted Hb 9.0–11.0 g/dl	48 weeks		Quality of life scores improved in the high Hb. Left ventricular mass index decreased significantly in the high Hb group	Ther Apher Dial
On dialysis	Besarab et al. [17]	1998	Normal hematocrit cardiac trial	1,233	Epoetin	CHF or ischemic heart disease	Group 1: targeted hematocrit 30% Group 2: targeted hematocrit 42%	14 months	Death of a first non-fatal myocardial infarction	The study was halted because the targeting normal hematocrit group had more deaths and non-fatal myocardial infarctions	N Engl J Med

studies by Wu et al. [24] showed improvement of anemia in pre-dialysis CKD patients by treatment with AST-120, oral adsorbent to reduce serum IS levels. However, as AST-120 treatment was associated with preservation of renal functions in this study, it remains unknown whether improvement of anemia in these patients was due to removal of uremic toxins or secondary to preserving better renal functions.

Results of RCTs

The most striking problem of ESA resistance is that patients with ESA resistance have poor prognosis [25, 26]. It is not clear whether ESA resistance itself is a risk or whether administration of high dose of ESA may result in poor prognosis. Kilpatrick et al. [27] analyzed the data from 321 patients randomized to the hematocrit normalization arm of the Normal Hematocrit Cardiac trial. The results showed that highest versus lowest responsiveness was associated with a hazards ratio of 0.41 (95% CI 0.20–0.87) after adjusting for baseline prognostic indicators. They concluded that lower Epo responsiveness is a strong predictor of mortality risk. Solomon et al. [28] also assessed the initial Hb responses to darbepoetin alfa as a second-order analysis of the TREAT trial. They defined a poor initial response to darbepoetin alfa as the lowest quartile of percent change in Hb level (<2%). The results showed that patients with poor initial response had a lower average Hb levels than patients with a better Hb response despite receiving higher doses of darbepoetin alfa. Patients with a poor response had higher risks of composite CVD or death [28]. Analysis of the data from Japan's dialysis registry also showed that ESA hyporesponsiveness based on a combination of ESA dosage and Hb levels was an important risk factor for all-cause and cardiovascular mortalities [29]. ESA resistance index (ERI) is also suggested by Panichi et al. [26]. ERI is defined as the weekly ESA doses per kilograms of body weight divided by Hb (g/dl). On the basis of the ERI values, non-dialysis patients were divided into 4 quartiles and patients belonging to quartile IV were defined as hyporesponders. ERI as ESA resistance value was correlated with all-cause mortality and fatal/non-fatal CVD. ERI is also reported to be associated with malnutrition inflammation complex [30].

We suggest that we should start ESA treatment from the early phase of renal anemia because ESA hyporesponsiveness itself is a poor prognostic factor. Studies to establish an equation to estimate ESA hyporesponsiveness that predicts poor outcome accurately are required.

Iron Deficiency and Replacement Therapy

It is recommended that CKD patients, whether they are receiving dialysis or not, should be evaluated for iron deficiency because iron is generally deficient in this population [31–33]. Iron status, such as serum ferritin and transferrin saturation (TSAT), should be checked at least once a month in patients receiving iron replacement therapy, and once per 3 months in those without. If serum ferritin becomes <100 ng/ml without iron replacement therapy, we should consider iron replacement therapy before ESA administration [34]. In the Kidney Disease Improving Global Outcomes (KDIGO) guideline 2012, ESA should be considered under the conditions of serum ferritin <500 ng/ml and TSAT <30% [20]. Rationale behind the guideline is that excessive serum ferritin has a possibility of leading to iron deposition to organs of the reticuloendothelial system [35–37] and increasing complications such as CVD [38, 39] and infections [40, 41]. Patients receiving enough amounts of ESA should be for considered iron replacement therapy when serum ferritin becomes <100 ng/ml or TSAT becomes <20%. However, it remains unclear whether long-term treatments of iron replacement therapy is safe. Careful monitoring of the iron status is warranted in these populations, both in order to initiate timely iron supplementation therapy and to avoid excessive iron administration.

The Ferinject assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease trial showed that intravenous ferric carboxymaltose targeting a ferritin level of 400–600 µg/l reached and maintained Hb level compared with oral iron [42]. On the other hand, Agarwal et al. [43] demonstrated that intravenous iron therapy is associated with an increased risk of serious adverse events among non-dialysis patients with CKD and iron deficiency anemia. They randomly assigned patients with stages 3 and 4 CKD and iron deficiency anemia to either open-label oral ferrous sulfate or intravenous iron sucrose. The primary outcome showed little chance of finding differences in the slopes of measures glomerular filtration rate but a higher risk of serious adverse events such as cardiovascular events in intravenous iron group.

Taken together, we should check serum ferritin and TSAT at least once a month to evaluate iron deficiency. We should start iron replacement therapy in pre-dialysis patients without ESA administration when serum ferritin level becomes <100 ng/ml before ESA administration. We should start iron replacement therapy when serum ferritin becomes <100 ng/ml or TSAT becomes <20% in the patients receiving enough amounts of ESA. Long-

Table 2. The Hb target for international guidelines. KDIGO 2012 and European Renal Best Practice guidelines indicate the target Hb for starting ESA and maintaining

Guidelines	Objectives	Target Hb for starting ESA	Target Hb for maintaining
KDIGO 2012	Pre-dialysis patients Dialysis patients	Under 10 g/dl 9.0–10.0 g/dl	10.0–11.5 g/dl* 10.0–11.5 g/dl*
European Renal Best Practice	CKD stages 3, 4 and 5	>11 g/dl (hematocrit 33%)	No clear evidence exists. No upper limit has been suggested. Hb >11 g/dl will need to be established**

* In all adult patients, ESAs should not be used intentionally to increase Hb concentration above 13 g/dl. ** Hb concentrations within the normal range are not recommended for patients with CVD. For these patients, 11–12 g/dl should be aimed for.

term administration of iron replacement therapy should be avoided because excessive iron intake may lead to increase in iron deposition in multiple organs. We should also pay attention to a risk of intravenous iron therapy with serious adverse events such as CVD.

Summary of Target Hb by Guidelines

There are several international guidelines referring to the target Hb (table 2). The KDIGO guidelines state that ESAs should not be used intentionally to increase Hb concentration above 13 g/dl in all adult patients. According to the KDIGO guideline 2012, ESA should be considered in the pre-dialysis patients with Hb levels below 10 g/dl and in dialysis patients with Hb between 9.0 and 10.0 g/dl. Target Hb for maintenance is 10–11.5 g/dl in all CKD patients [20]. On the other hand, the European Renal Best Practice guideline, the latest international guideline till date, indicates that Hb target for starting ESA is <11 g/dl in all the CKD patients. No clear evidence exists as to the Hb target levels [44]. Although no upper limit has been suggested, complete correction of renal anemia with ESA is not recommended for patients with CVD. Hb level of >11 g/dl should be aimed for all the CKD patients. All the international guidelines and our clinical experiences taken together, we should consider administration of ESA when the Hb level becomes <11 g/dl in pre-dialysis patients and 10 g/dl in dialysis patients. The target Hb we should achieve is >10 g/dl in dialysis patients and 11 g/dl in pre-dialysis patients. We recommend that the target Hb should not be >13 g/dl in all the CKD patients.

Future Challenges

Prolyl hydroxylase (PHD) inhibitors have recently emerged as a new therapy for renal anemia. Hypoxia inducible factor (HIF) is a master regulator of gene expressions under hypoxic condition. HIF receives hydroxylation of

proline residues by PHD under normoxia and receives degradation. Under hypoxic condition, PHD loses its activity and cannot hydroxylate HIF, which leads to HIF accumulation. PHD inhibitors inhibit PHD activity, block HIF degradation and upregulate the HIF and its downstream target gene expressions. It deserves attention whether the anemia treatments using PHD inhibitors affect long-term survival rates or prognosis in a different manner compared with ESA treatments using Epo derivatives.

Conclusions

The widespread use of ESA, particularly recombinant Epo, contributed greatly to improving the well-being of CKD patients. While undoubtedly beneficial, the target Hb levels that the ESA therapy should aim at is indeed ambiguous. As various kinds of large clinical studies have demonstrated that the targeted Hb should not be >13 g/dl because of an increased risk of CVD, we do not recommend high doses of ESA to achieve the target Hb although maintaining high Hb >12 g/dl without ESA is not harmful for CKD patients. It is desirable to determine the target Hb in dialysis patients depending on their ages. It is also a matter of debate whether correction of renal anemia with ESA might lead to better preservation of residual renal function, although studies achieving Hb differences of >2 g/dl between arms tend to report beneficial effects. It is also important that renal anemia should be monitored constantly to start ESA and iron replacement therapy at an appropriate time. It also remains to be discussed how to define ESA resistance: when to start and stop iron replacement therapy. Taken all our clinical experiences together, we should considering the administration of ESA when the Hb level becomes <11 g/dl in pre-dialysis patients and <10 g/dl in dialysis patients.

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