Anemia in conventional hemodialysis: Finding the optimal treatment balance

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Abstract
Renal anemia is a serious and common complication in hemodialysis (HD) patients. The introduction of erythropoiesis-stimulating agents (ESAs) has dramatically improved hemoglobin levels and outcomes. Several interventional studies reported that excessive correction of anemia and the massive use of ESA can trigger cardiovascular disease (CVD), and consequently may worsen the prognosis of patients undergoing HD. Therefore, it has been widely recognized that large doses of ESA should be used with caution. An effective use of iron preparations is required to yield the optimal effect of ESA. It is well-known that iron utilization is inhibited under pathological conditions, such as chronic inflammation, resulting in ESA resistance. It is postulated that a new class of therapeutic agents for renal anemia, hypoxia inducible factor prolyl hydroxylase (HIF-PH) inhibitors, will have beneficial treatment effects in patients on HD. HIF is induced by hypoxia and promotes erythropoietin production. In the absence of a hypoxic state, HIF is decomposed by the HIF catabolic enzyme. HIF-PH inhibitors inhibit this degrading enzyme and stimulate endogenous erythropoietin production via HIF induction. Additionally, HIF-PH inhibitors promote effective utilization of iron and raise erythropoietin to physiological concentrations. Accordingly, HIF-PH inhibitors improve anemia and iron metabolism. It appears that this effect persists irrespective of chronic inflammatory conditions. HIF-PH inhibitors do not overshoot erythropoietin above physiological concentrations like ESAs. Therefore, it is hypothesized that HIF-PH inhibitors would not increase the risk of CVD in patients undergoing HD.

1 INTRODUCTION

Erythropoiesis is regulated by erythropoietin produced in the stromal cells near the proximal renal tubule of the kidney. Renal anemia is caused by the relative deficiency of endogenous erythropoietin secretion1 and is the most frequent complication in chronic kidney disease (CKD) patients. Generally speaking, renal anemia occurs when the estimated glomerular filtration rate (eGFR) is less than 60 mL/min;2 it is reported that more than 90% of CKD patients with eGFRs less than 30 mL/min exhibit renal anemia.3 Until the 1980s, treatment for renal anemia was limited to the administration of an iron preparation, vitamins, and a protein anabolic hormone.
and red blood cell transfusions if these other treatments failed to achieve an adequate response. However, red blood cell transfusions have various complications, including the production of antierythrocyte antibodies, risk of infection such as viral hepatitis, iron overload, etc. Moreover, due to the limited supply of red blood cells for transfusions, low hemoglobin levels, around 7 g/dL, were deemed clinically acceptable, to some extent, for the treatment of renal anemia.

The development and clinical application of erythropoiesis-stimulating agents (ESA) dramatically improved the management of renal anemia in CKD patients, even in hemodialysis (HD) patients, in whom renal anemia has become a treatable complication. Human recombinant erythropoietins (rHuEPO), epoetin alfa and beta, were developed at the end of the 1980s, and both darbepoetin alfa and epoetin beta pegol, which are long-acting erythropoietin receptor activators with longer half-lives than rHuEPO, were developed in the late 2000s. Endogenous production of erythropoietin is induced by a decline in oxygen transport accompanied by anemia. Hypoxia inducible factor prolyl hydroxylase (HIF-PH) regulates the expression of erythropoietin. Recently, a new class of therapeutic drugs for renal anemia, HIF-PH inhibitors that directly stimulate HIF, has been developed and they are currently in clinical trials worldwide.

To date, there still remain questions concerning the appropriate target hemoglobin level, proper utilization of iron preparations, and ESA hyporesponsiveness, among others. In this article, we describe the trends in renal anemia management in HD patients, and discuss the progress and challenges of treatment for renal anemia in patients undergoing conventional HD. We also include a future perspective on novel therapeutic approaches, including HIF-PH inhibitors, for renal anemia in this patient population.

2 | TIME COURSE OF RENAL ANEMIA TREATMENT IN PATIENTS UNDERGOING HD

Several clinical guidelines for renal anemia management in HD patients have been proposed and updated with new findings, resulting in various target values for the anemia management index. In 2004, the distribution of target hemoglobin level by country was reported cross-sectionally in the Dialysis Outcomes and Practice Patterns Study (DOPPS). DOPPS is an internationally representative, prospective, cohort study of randomly selected, prevalent HD patients, aged 18 years or older, from facilities across the world. In Japan, the mean hemoglobin levels of incident and prevalent HD patients were 8 and 10 g/dL, respectively, compared to 10 g/dL and 11 to 12 g/dL for the other participating countries.

Subsequent trends in renal anemia management in HD patients were also reported from the DOPPS data. In a 2010 study, the trends of hemoglobin levels and ESA doses were described in each country for DOPPS phases 1 through 3 (1996-2008). Hemoglobin levels increased significantly in all DOPPS countries except Sweden, which had the highest proportion of hemoglobin levels above 12 g/dL in HD patients of the DOPPS phase 2 countries. ESA dosage increased significantly in all DOPPS participating countries with the exception of Belgium. The increases in the rate of ESA dosage ranged from Japan (9.6%) to France (106.6%), between DOPPS phases 1 to 3. During this period, various clinical guidelines, including the Kidney Disease Outcomes Quality Initiative (KDOQI), recommended relatively high hemoglobin target levels (11.0-13.0 g/dL). Consequently, it was suggested that hemoglobin and ESA dose levels were both increasing.

In 2006, Japan’s health insurance system instituted a bundling policy including ESA treatment in outpatients undergoing HD. We examined the effect of this ESA bundling policy on renal anemia management in HD patients using the Japan DOPPS cohort. After this policy change, the mean dose of ESA significantly decreased by 11.8% (from 5266 to 4645 units/week). Conversely, the percentage of patients prescribed intravenous (IV) iron significantly increased (from 31.8 to 41.2%), but the mean dose of IV iron did not change. As a result, there was no change in the mean hemoglobin level (10.39 vs 10.38 g/dL) and the ESA administration rate (81.9 vs 82.2%) before and after the introduction of the ESA bundling policy.

ESA dosage among patients on HD was initially much higher in the United States than in either European countries or Japan. Fuller et al estimated and compared the trends in ESA dosage and hemoglobin levels in patients undergoing HD across the DOPPS participating countries. They found that mean ESA dosage among HD patients in the United States rose steadily from 2002 to 2010, and then sharply declined from 2010 to 2013 in response to changes in the reimbursement and regulatory policies for ESA in 2011 (Figure 1A), and subsequently continued to gradually decline from 2013 to 2016 (Unpublished DOPPS data). On the other hand, the mean ESA dosage in Europe rose from 2002 to 2005 and reached a plateau between 2006 and 2012 (Figure 1A). In Japan, the mean ESA dosage declined between 2002 and 2006, but then, increased slightly through 2013 irrespective of the ESA-bundling policy introduced in 2006 (Figure 1A).

Mean hemoglobin levels among ESA-treated HD patients in the United States and Europe reached their peaks, of around 11.5 g/dL in 2005 and 2006, respectively, and then, declined gradually in both regions, reaching equivalency in 2010 and 2011 (Figure 1B). Then in the United States, it sharply dropped to below 11 g/dL in 2017 after the reimbursement and regulatory policies for ESA in 2011 (Unpublished DOPPS data). Hemoglobin levels in Japan increased steadily from 2002 to 2012, irrespective of the ESA-bundling policy in 2006, reached equivalency with the United States in 2013 (Figure 1B), and then overtook the United States in 2016 (Unpublished DOPPS data).

3 | OPTIMAL TARGET HEMOGLOBIN LEVEL IN PATIENTS UNDERGOING HD

It had been reported that low hemoglobin levels in HD patients is associated with left ventricular hypertrophy, a lower quality of life.
between the 2 groups using the Cox proportional hazard model, and the other with ages ≥75. We examined the risk of death in HD patients differed between the elderly and nonelderly.20 This study compared both the survival and (RCT), enrolled 1233 HD patients with congestive heart failure and the optimal target hemoglobin level for the benefit of HD patients.21 In this study, 3341 maintenance Japan-DOPPS cohort patients.23 In this study, 3341 maintenance of death in HD patients differed between the elderly and nonelderly.20 We showed that the relationship between hemoglobin level and risk of death in HD patients differed between the elderly and nonelderly.20 We showed similar findings in regional DOPPS study in Japan.21

The differences between the findings of the Normal Hematocrit Study and the DOPPS studies are problematic. Another DOPPS study enrolled 29 796 HD patients and compared the survival of 545 patients (1.8%) who had maintained hemoglobin levels >12 g/dL without using ESA to that of the other patients. They found that there was no difference for mortality risk between the 2 groups (relative risk 0.98, 95% CI 0.80-1.19).22 Therefore, it was suggested that the poor survival of the HD patients was caused by therapeutic normalization of hemoglobin and was not due to the high level of hemoglobin itself. There are uncertainties for therapeutic interventions such as if aiming for lower hemoglobin target level would result in different risk/benefit and if non-ESA therapies would result in different outcomes.

Recently, the aging of the HD population has been remarkable. We showed that the relationship between hemoglobin level and risk of death in HD patients differed between the elderly and nonelderly Japan-DOPPS cohort patients.23 In this study, 3341 maintenance HD patients were classified into 2 groups, one with ages less than 75 and the other with ages ≥75. We examined the risk of death between the 2 groups using the Cox proportional hazard model, considering hemoglobin levels as time-dependent variables. Using hemoglobin levels between 10-11 g/dL as a reference, the hemoglobin levels less than 10 g/dL were associated with a higher mortality risk in the group aged <75 years (HR 1.46, 95% CI 1.07-2.00), but in the group aged ≥75 years, an increased risk of death was only observed with hemoglobin levels less than 9 g/dL (HR 1.90, 95% CI 1.31-2.75). There was an interaction between age and hemoglobin level with a statistically significant difference as well. From these results, we concluded that the relationship between hemoglobin level and risk of death may differ by age in HD patients, which highlights the necessity of the individualization of renal anemia management. However, these findings came from observational study design, it remains unclear whether or not interventions for renal anemia should be applied differently to the elderly patients.

Predialysis hemoglobin levels are commonly assessed in the management of renal anemia in patients undergoing HD. Several dialysis facilities also measure the postdialysis hemoglobin levels. However, the evidence for clinical interpretation of postdialysis hemoglobin levels is limited. Therefore, we conducted a case crossover study to investigate the association between postdialysis hemoglobin levels and vascular access failure among patients undergoing HD in Japanese facilities.24 We postulated that the excess homoconcentration occurring with dialysis that raises hemoglobin levels might also initiate access thrombosis. We showed that postdialysis hemoglobin levels above 11.8 g/dL had a progressively greater risk for vascular access failure. Postdialysis hemoglobin levels and odds ratios (ORs) (95% CI) for vascular access failure were hemoglobin 12.0 g/dL, 1.1 (1.0-1.1); 14.0 g/dL, 1.4 (1.0-2.0); and 16.0 g/dL, 2.1 (1.1-4.3) respectively, relative to the reference value (hemoglobin 11.8 g/dL). It remains unclear how to incorporate postdialysis hemoglobin level in therapeutic algorithms in part because these results are based on an observational study.

4 | ESA HYPORESPONSIVENESS IN PATIENTS UNDERGOING HD

ESA hyporesponsiveness has not been well defined, although there are various proposed definitions. In 2004, revised European Best Practice Guidelines (EBPG) for the management of anemia in
patients with chronic renal failure advocated that ESA hyporesponsiveness should be suspected when a patient either fails to attain the target hemoglobin concentration (11-12 g/dL) while receiving >300 IU/kg/week (>20 000 IU/week) of epoetin or 1.5 µg/kg of darbepoetin alfa (>100 µg/week), or has a continued need for such high dosages to maintain their target hemoglobin levels. The KDOQI clinical practice guidelines and clinical practice recommendations for anemia in CKD in adults, defined ESA hyporesponsiveness as a failure to increase the hemoglobin level to greater than 11 g/dL, despite an ESA dose equivalent to epoetin >500 IU/kg/week. The 2008 Japanese Society for Dialysis Therapy guidelines for renal anemia in CKD provided the opinion that hyporesponsiveness to ESA therapy is defined as a failure to achieve anemia correction and the target hemoglobin level despite the use of 9000 IU/week of epoetin or 60 µg/week of darbepoetin alfa in HD patients. The revised Japanese guideline released in 2015 mentioned that patients are possibly hyporesponsive to ESA if their hemoglobin level does not increase, or the target hemoglobin level is not maintained with the regimen or dose approved under the health insurance system in Japan, making defining ESA hyporesponsiveness with numerical values difficult.

The Kidney Disease: Improving Global Outcome clinical practice guideline for anemia in CKD was released in 2012. KDIGO guidelines classify patients as having ESA hyporesponsiveness if they have no increase in hemoglobin concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. This definition came from the secondary analysis results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), in which ESA hyporesponsiveness was associated with subsequent poor prognosis in CKD patients not requiring dialysis, with type 2 diabetes mellitus. Similar results were reported in the secondary analysis of the Normal Hematocrit Study, a RCT in HD patients. Meta-analysis of RCTs in HD patients subsequently revealed that a higher ESA dose was associated with an approximately twofold increase in mortality risk, independent of hemoglobin level. It was considered that abnormally higher ESA concentrations were induced by using greater ESA doses, resulting in a poor prognosis.

The Japanese Renal Data Registry (JRDR) cohort data showed that mortality in patients undergoing HD was affected by ESA hyporesponsiveness irrespective of the interactive effects of ESA dose and hemoglobin level. We also revealed that ESA hyporesponsiveness was associated with higher mortality among incident HD patients using a multicenter, prospective, observational study cohort. A recent multicenter observational propensity-score matched study in incident HD patients revealed that an ESA dose of >8000 IU/week was associated with an increased risk of mortality, even when adjusted for cohort characteristics including hemoglobin levels. Therefore, it has been suggested that the poor survival of HD patients caused by the normalization of hemoglobin was due to high ESA doses, rather than high hemoglobin levels themselves. It is assumed that increased blood pressure and/or elevated risk of thromboembolic events initiated by higher ESA doses may result in these poorer outcomes.

Modifiable or potentially modifiable factors involved in ESA hyporesponsiveness are as follows: iron deficiency, vitamin B12/folate deficiency, hypothyroidism, hyperparathyroidism, under-dialysis, the use of renin angiotensin aldosterone system inhibitors (RAASIs), and various sources of inflammation. Iron deficiency is the most important and common cause of ESA hyporesponsiveness, and we discuss this issue in detail in the next section. Other interventions for improving hyporesponsiveness to ESA treatment have been proposed. A systematic review suggested that a vitamin E-coated dialyzer may reduce ESA resistance. Recently, we examined if statin prescriptions would improve ESA hyporesponsiveness using the Japan DOPPS cohort, and suggested that statins may slightly reduce ESA hyporesponsiveness in patients undergoing HD.

5 PROPER UTILIZATION OF IRON PREPARATION IN PATIENTS UNDERGOING HD

In the treatment of renal anemia among HD patients, iron supplementation necessary for hematopoiesis is very important, in addition to the adequate administration of ESA. However, there are differences in opinions on iron supplementation for patients undergoing HD in each guideline. The KDIGO guideline, announced in 2012, proposed the initiation of iron therapy for HD patients with a transferrin saturation (TSAT) of 30% or less and a serum ferritin level of 500 ng/mL or less. EBPG set the iron treatment start standard values of TSAT and serum ferritin levels lower than the KDIGO guideline, which suggest a trial with iron therapy for dialysis patients not on ESA if TSAT <25%, and for those on ESA if TSAT <30%. The serum ferritin level is targeted between 300 and 500 ng/mL in the EBPG guidelines. In the JSDT guidelines, the TSAT and serum ferritin levels are set to the lowest levels for both the starting and stopping of the iron preparations. The JSDT guidelines, far more conservative, suggest iron therapy, if the serum ferritin level is <50 ng/mL for patients not on ESA, and when the TSAT is <20% and the serum ferritin level is <100 ng/mL for those on ESA. They do not recommend iron preparation targeting of serum ferritin levels >300 ng/mL.

International trends in IV iron use among HD patients have been reported using DOPPS data. There were increases in IV iron use and serum ferritin levels in all DOPPS participating countries, from 1999 to 2011. In 2010, the prevalence of IV iron use was 36% in Japan, but ranged from 70% to 90% in other countries. In the latest report, the proportion of IV iron use in Japan was still the lowest among the DOPPS countries (Japan 41%, United States 83%). Some countries, such as the United States, had an increase in serum ferritin levels over time, with the mean serum ferritin levels reaching around 800 ng/mL in 2016 (Unpublished DOPPS data). On the other hand, serum ferritin levels in Japan remained around 100 ng/mL. A recent paper from the JSDT also showed that approximately 80% of HD patients in Japan had serum ferritin levels less than 300 ng/mL, which is overwhelmingly lower compared to other countries.
Several observational studies have reported an association between high serum ferritin levels and mortality in maintenance HD patients. The JSDT cohort study showed that the highest serum ferritin decile (496 ng/mL or more) had an increased mortality risk compared to the lowest decile (21 ng/mL or less) (HR 1.54, 95% CI 1.31-1.81). However, high ferritin levels may be in part a result of underlying inflammation or liver disease; hence, these studies are insufficient to prove a deleterious effect of iron therapy. Bailie et al. evaluated the associations between IV iron dose and mortality risk using the DOPPS cohort data. They reported that higher mortality risk was associated with IV iron doses between 300-399 mg/month (HR 1.13, 95% CI 1.00-1.27) and ≥400 mg/month (HR 1.18, 1.07-1.30) compared with IV iron doses between 100-199 mg/month (the most common dose range). Although each of these reports is based on observational research, it is suggested that excessive iron load may increase the risk of death in HD patients.

The latest systematic review and meta-analysis from 7 RCTs and 15 observational studies showed that greater IV iron doses (≥400 mg/month and 200 mg/month in RCTs and observational studies, respectively) were not associated with increased risk of mortality, infection, or CVD. Charytan et al. cautioned in their review that there are not sufficient clinical evidences for defining optimal iron utilization in dialysis-dependent patients.

The Proactive IV Iron Therapy in Dialysis Patients (PIVOTAL) trial is currently ongoing. The PIVOTAL trial is the first RCT to assess the long-term safety and efficacy of IV iron use comparing proactive (400 mg/month IV iron unless their ferritin is >700 µg/L, TSAT >20%) or reactive (IV iron if ferritin <200 µg/L, TSAT <20%) arms in incident HD patients. The findings of future research, including the PIVOTAL trial, are expected to help achieve the goal of safe iron therapies. Recently, several novel phosphate binders containing iron have become available for HD patients. An observational study using the US Renal Data System suggested the association of intravenous iron administration, particularly in short-term continuous and high doses, with the risk of infection among HD patients. The Randomized Trial to Evaluate IV and Oral Iron in Chronic Kidney Disease (REVOKE) trial that included patients with nondialyzed CKD, compared the clinical outcomes between oral and IV iron supplementation groups. This RCT was terminated early because of the greater incidence of cardiovascular and infectious complications in the IV iron supplementation group. In contrast, there is no safety concern in terms of cardiovascular and infectious complications in the other larger and multicenter RCT, the Ferinject Assessment in Patients with Iron Deficiency Anemia (FIND-CKD) trial. The FIND-CKD trial also evaluated the efficacy of oral or IV iron in patients with nondialyzed CKD and iron deficiency anemia. No difference was found in the incidence of cardiovascular and infectious complications in the FIND-CKD trial.

There is a debate over the safety of IV iron use reflecting the discrepancy in the safety data from these trials. It is expected that novel phosphate binders containing iron, a new tool for iron supplementation in dialysis patients, may offer an alternative but their long-term safety, including the issue of iron overload, needs to be examined through future research.

6 | NOVEL THERAPEUTIC APPROACH FOR RENAL ANEMIA IN PATIENTS UNDERGOING HD

Since the required ESA dose was lower in HD patients living at higher altitudes with low oxygen partial pressure, it has been speculated that HIF activation would be useful for the improvement of renal anemia. In recent years, a new class of therapeutic drugs, HIF-PH inhibitors, has been developed for renal anemia. These include roxadustat, molidustat, daprodustat, vadadustat, and JTZ-951. Hypoxia enhances the expression of erythropoietin via HIF. HIF-PH inhibitors are agents that attempt to improve renal anemia by increasing endogenous erythropoietin via HIF stabilization. Since HIF is a transcription factor that plays a central role in the adaptive response of cells to hypoxic stress, HIF is involved in the regulation of various physiological phenomena, not only endogenous erythropoietin production but also glucose, fat, and cholesterol metabolism, and angiogenesis. Therefore, the greatest concern with HIF-PH inhibitors use is the possibility of promoting tumor growth associated with angiogenesis. We reported that daprodustat presented dose-dependent increase in hemoglobin without changes in plasma vascular endothelial growth factor levels in patients on HD with anemia, in a 4-week, phase II, double-blind, placebo-controlled trial. HIF-PH inhibitors are orally administered pharmaceutical agents. It was reported that HIF-PH inhibitors increased endogenous erythropoietin but their concentrations remained within physiological range, without the extreme peaks seen during ESA administration. In addition, HIF-PH inhibitors promote endogenous erythropoietin production and, at the same time, suppress hepcidin expression, thereby promoting efficient use of iron, and inducing more effective hematopoiesis. HIF-PH inhibitors improved anemia efficiently in incident dialysis patients, regardless of iron repletion status, and C-reactive protein levels, and also reduced serum hepcidin levels. The hepcidin lowering effect by HIF-PH inhibitors could improve patient prognosis and ESA hyporesponsiveness. Furthermore, it has also been reported that HIF-PH inhibitors have a cholesterol lowering effect. However, the safety of HIF-PH inhibitors has not yet been established, and hence, long-term follow-up clinical studies will be important in the future.

Hepcidin is an acute phase reactant protein produced mainly in the liver and is increased by inflammation. Higher serum hepcidin levels limit iron availability. It was reported that serum hepcidin levels are very high in CKD patient populations, especially in dialyzed patients. Therefore, hepcidin plays a key role in iron homeostasis among patients undergoing HD with anemia. As noted above, HIF-PH inhibitors suppress hepcidin production.

Recent investigations have presented the effects of antihemoglobin agents, and phase 2 clinical trials are being conducted in patients...
receiving HD. Hitomi et al developed human-induced pluripotent stem (iPS) cells producing erythropoietin, and demonstrated that transplantation of these human iPS cells into mice with CKD improved hemoglobin levels to the normal range. In this experiment, erythropoietin concentrations sharply increased during the 4th week, but decreased after the 8th week and remained within the normal range. In other words, the automatic regulation system of erythropoietin production and hematopoiesis in the human body was reproduced in this treatment in murine models.

7 | CONCLUSIONS

The treatment of renal anemia in patients undergoing HD has made rapid strides over the past 30 years. ESA has played a central role in the management of renal anemia in this population. However, the target hemoglobin levels in the current therapeutic strategies for renal anemia in patients receiving HD are not in the physiological range. Is it inappropriate to set physiological hemoglobin levels as a therapeutic target for non-ESA therapies that may have fewer countervailing ill effects? To clarify these clinical issues for the optimal treatment balance for patients undergoing HD with renal anemia, future findings obtained from new therapeutic approaches are greatly anticipated.

CONFLICT OF INTEREST

TH has received consultant and lecture fees from Kyowa Hakko Kirin and received lecture fees from Chugai Pharmaceutical; FK has received speaker honoraria and a support grant from Kyowa Hakko Kirin, consultant fee from Kissei Pharmaceutical; TA has received consultant and lecture fees from Kyowa Hakko Kirin and Bayer, consultant fee from Astellas and Japan Tobacco, and lecture fee from Chugai Pharmaceutical and Kissei Pharmaceutical.

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