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REVIEW

Benefits and risks of erythrocyte-stimulating agents

Daisuke Katagiri, Fumihiko Hinoshita

Daisuke Katagiri, Division of Nephrology and Endocrinology, The University of Tokyo, Tokyo 162-8655, Japan
Fumihiko Hinoshita, Department of Nephrology, National Center for Global Health and Medicine, Tokyo 162-8655, Japan
Author contributions: Katagiri D and Hinoshita F contributed to this paper.
Correspondence to: Fumihiko Hinoshita, MD, PhD, Department of Nephrology, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan. fhinoshi@hosp.ncgm.go.jp
Telephone: +81-3-32027181 Fax: +81-3-32071038
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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.

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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.

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 hy-

Table 1 Risks associated with blood transfusions[11]

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.

potension 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 *et al*[10] first purified human EPO in an amount sufficient for chemical characterization. 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 m^2] 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 m^2 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 trial[24], 603 CKD 3-5 patients (GFR < 59 mL/min per 1.73 m^2) 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 patients (GFR, 15-59 mL/min per 1.73 m^2) were studied in the Correction of Hemoglobin and Outcomes in Renal Insufficiency 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 erythrocyte-stimulating agents (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],

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

Initial ESA hyporesponsiveness
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
In patients with ESA hyporesponsiveness, avoid repeated escalations of the ESA dose beyond double the initial weight-based dose
Subsequent ESA hyporesponsiveness
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
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
Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response
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 agent; 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
Check adherence	If poor, attempt to improve (if self-injection)
Reticulocyte count	If > 130000/μL, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
Serum vitamin B_{12}, 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
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

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

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:
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
Normal platelet and white cell counts
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.

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 and 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; and (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 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 *et al*[50] reported the first case of a patient with PRCA caused by rHu-EPO who recovered after the discontinuation of ESA therapy. 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 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? and (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.

REFERENCES

1 **Drüeke TB**, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s). *Kidney Int* 2012; **82**: 952-960 [PMID: 22854645 DOI: 10.1038/ki.2012.270]

2 **Okonko DO**, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011; **58**: 1241-1251 [PMID: 21903058 DOI: 10.1016/j.jacc.2011.04.040]

3 **Klip IT**, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013; **165**: 575-582.e3 [PMID: 23537975 DOI: 10.1016/j.ahj.2013.01.017]

4 **Bailie GR**, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant* 2005; **20**: 1443-1449 [PMID: 15855210 DOI: 10.1093/ndt/gfh820]

5 **Fletes R**, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis* 2001; **37**: 743-749 [PMID: 11273874]

6 **Brookhart MA**, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol* 2013; **24**: 1151-1158 [PMID: 23787911 DOI: 10.1681/asn.2012121164]

7 **Litton E**, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. *BMJ* 2013; **347**: f4822 [PMID: 23950195 DOI: 10.1136/bmj.f4822]

8 **Walker EM**, Walker SM. Effects of iron overload on the immune system. *Ann Clin Lab Sci* 2000; **30**: 354-365 [PMID: 11045759]

9 **Bernhardt WM**, Wiesener MS, Scigalla P, Chou J, Schmieder RE, Günzler V, Eckardt KU. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol* 2010; **21**: 2151-2156 [PMID: 21115615 DOI: 10.1681/asn.2010010116]

10 **Miyake T**, Kung CK, Goldwasser E. Purification of human erythropoietin. *J Biol Chem* 1977; **252**: 5558-5564 [PMID: 18467]

11 **Zhu X**, Perazella MA. Nonhematologic complications of erythropoietin therapy. *Semin Dial* 2006; **19**: 279-284 [PMID: 16893404 DOI: 10.1111/j.1525-139X.2006.00173.x]

12 **Delano BG**. Improvements in quality of life following treatment with r-HuEPO in anemic hemodialysis patients. *Am J Kidney Dis* 1989; **14**: 14-18 [PMID: 2757025]

13 **Revicki DA**, Brown RE, Feeny DH, Henry D, Teehan BP, Rudnick MR, Benz RL. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis* 1995; **25**: 548-554 [PMID: 7702049]

14 **Marsh JT**, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, Nissenson AR. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int* 1991; **39**: 155-163 [PMID: 2002629]

15 **Macdougall IC**, Lewis NP, Saunders MJ, Cochlin DL, Davies ME, Hutton RD, Fox KA, Coles GA, Williams JD. Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. *Lancet* 1990; **335**: 489-493 [PMID: 1968526]

16 **Evans RW**, Rader B, Manninen DL. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group. *JAMA* 1990; **263**: 825-830 [PMID: 2404150]

17 **Eschbach JW**, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987; **316**: 73-78 [PMID: 3537801 DOI: 10.1056/nejm198701083160203]

18 **Roth D**, Smith RD, Schulman G, Steinman TI, Hatch FE, Rudnick MR, Sloand JA, Freedman BI, Williams WW, Shadur CA. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis* 1994; **24**: 777-784 [PMID: 7977319]

19 **Kilpatrick RD**, Critchlow CW, Fishbane S, Besarab A, Stehman-Breen C, Krishnan M, Bradbury BD. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; **3**: 1077-1083 [PMID: 18417744 DOI: 10.2215/cjn.04601007]

20 **KDIGO**. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Supplements* 2012; **2**: 279-335

21 **Fishbane S**, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 2005; **68**: 1337-1343 [PMID: 16105069 DOI: 10.1111/j.1523-1755.2005.00532.x]

22 **Yang W**, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI. Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol* 2007; **18**: 3164-3170 [PMID: 18003781 DOI: 10.1681/asn.2007010058]

23 **Eckardt KU**, Kim J, Kronenberg F, Aljama P, Anker SD, Canaud B, Molemans B, Stenvinkel P, Schernthaner G, Ireland E, Fouqueray B, Macdougall IC. Hemoglobin variability does not predict mortality in European hemodialysis patients. *J Am Soc Nephrol* 2010; **21**: 1765-1775 [PMID: 20798262 DOI: 10.1681/asn.2009101017]

24 **Drüeke TB**, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**: 2071-2084 [PMID: 17108342 DOI: 10.1056/NEJMoa062276]

25 **Singh AK**, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085-2098 [PMID: 17108343 DOI: 10.1056/NEJMoa065485]

26 **Solomon SD**, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zeeuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* 2010; **363**: 1146-1155 [PMID: 20843249 DOI: 10.1056/NEJMoa1005109]

27 **Szczech LA**, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 2008; **74**: 791-798 [PMID: 18596733 DOI: 10.1038/ki.2008.295]

28 **Brookhart MA**, Schneeweiss S, Avorn J, Bradbury BD, Liu J, Winkelmayer WC. Comparative mortality risk of anemia management practices in incident hemodialysis patients. *JAMA* 2010; **303**: 857-864 [PMID: 20197532 DOI: 10.1001/jama.2010.206]

29 **Schaefer RM**, Leschke M, Strauer BE, Heidland A. Blood rheology and hypertension in hemodialysis patients treated with erythropoietin. *Am J Nephrol* 1988; **8**: 449-453 [PMID: 3218658]

30 **Abraham PA**, Macres MG. Blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. *J Am Soc Nephrol* 1991; **2**: 927-936 [PMID: 1751794]

31 **Raine AE**, Roger SD. Effects of erythropoietin on blood pressure. *Am J Kidney Dis* 1991; **18**: 76-83 [PMID: 1928084]

32 **Lebel M**, Kingma I, Grose JH, Langlois S. Hemodynamic and hormonal changes during erythropoietin therapy in he-

modialysis patients. *J Am Soc Nephrol* 1998; **9**: 97-104 [PMID: 9440093]
33 **Mayer G**, Hörl WH. Cardiovascular effects of increasing hemoglobin in chronic renal failure. *Am J Nephrol* 1996; **16**: 263-267 [PMID: 8739276]
34 **Palmer SC**, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, Pellegrini F, Ravani P, Jardine M, Perkovic V, Graziano G, McGee R, Nicolucci A, Tognoni G, Strippoli GF. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010; **153**: 23-33 [PMID: 20439566 DOI: 10.7326/0003-4819-153-1-201007060-00252]
35 **Tang YD**, Hasan F, Giordano FJ, Pfau S, Rinder HM, Katz SD. Effects of recombinant human erythropoietin on platelet activation in acute myocardial infarction: results of a double-blind, placebo-controlled, randomized trial. *Am Heart J* 2009; **158**: 941-947 [PMID: 19958860 DOI: 10.1016/j.ahj.2009.06.032]
36 **Churchill DN**, Muirhead N, Goldstein M, Posen G, Fay W, Beecroft ML, Gorman J, Taylor DW. Probability of thrombosis of vascular access among hemodialysis patients treated with recombinant human erythropoietin. *J Am Soc Nephrol* 1994; **4**: 1809-1813 [PMID: 8068879]
37 **Tang IY**, Vrahnos D, Valaitis D, Lau AH. Vascular access thrombosis during recombinant human erythropoietin therapy. *ASAIO J* 1992; **38**: M528-M531 [PMID: 1457917]
38 **Casadevall N**, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, Michaud P, Papo T, Ugo V, Teyssandier I, Varet B, Mayeux P. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; **346**: 469-475 [PMID: 11844847 DOI: 10.1056/NEJMoa011931]
39 **Weber G**, Gross J, Kromminga A, Loew HH, Eckardt KU. Allergic skin and systemic reactions in a patient with pure red cell aplasia and anti-erythropoietin antibodies challenged with different epoetins. *J Am Soc Nephrol* 2002; **13**: 2381-2383 [PMID: 12191983]
40 **Rossert J**, Casadevall N, Eckardt KU. Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004; **15**: 398-406 [PMID: 14747386]
41 **Casadevall N**, Cournoyer D, Marsh J, Messner H, Pallister C, Parker-Williams J, Rossert J. Recommendations on haematological criteria for the diagnosis of epoetin-induced pure red cell aplasia. *Eur J Haematol* 2004; **73**: 389-396 [PMID: 15522059 DOI: 10.1111/j.1600-0609.2004.00348.x]
42 **Shinohara K**, Mitani N, Miyazaki M, Sakuragi S, Matsuda K, Ogawara S, Saito T, Kaneoka H, Ooji T. Pure red-cell aplasia caused by the antibody to recombinant erythropoietin, epoetin-beta, in a Japanese patient with chronic renal failure. *Am J Hematol* 2005; **78**: 15-20 [PMID: 15609276 DOI: 10.1002/ajh.20245]
43 **Katagiri D**, Shibata M, Katsuki T, Masumoto S, Katsuma A, Minami E, Hoshino T, Inoue T, Tada M, Hinoshita F. Anti-epoetin antibody-related pure red cell aplasia: successful remission with cessation of recombinant erythropoietin alone. *Clin Exp Nephrol* 2010; **14**: 501-505 [PMID: 20652821 DOI: 10.1007/s10157-010-0318-8]
44 **Rossert J**. Erythropoietin-induced, antibody-mediated pure red cell aplasia. *Eur J Clin Invest* 2005; **35** Suppl 3: 95-99 [PMID: 16281965 DOI: 10.1111/j.1365-2362.2005.01536.x]
45 **Verhelst D**, Rossert J, Casadevall N, Krüger A, Eckardt KU, Macdougall IC. Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet* 2004; **363**: 1768-1771 [PMID: 15172775 DOI: 10.1016/s0140-6736(04)16302-2]
46 **Bennett CL**, Cournoyer D, Carson KR, Rossert J, Luminari S, Evens AM, Locatelli F, Belknap SM, McKoy JM, Lyons EA, Kim B, Sharma R, Costello S, Toffelmire EB, Wells GA, Messner HA, Yarnold PR, Trifilio SM, Raisch DW, Kuzel TM, Nissenson A, Lim LC, Tallman MS, Casadevall N. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. *Blood* 2005; **106**: 3343-3347 [PMID: 16099877 DOI: 10.1182/blood-2005-02-0508]
47 **Fisch P**, Handgretinger R, Schaefer HE. Pure red cell aplasia. *Br J Haematol* 2000; **111**: 1010-1022 [PMID: 11167735]
48 **Zecca M**, De Stefano P, Nobili B, Locatelli F. Anti-CD20 monoclonal antibody for the treatment of severe, immune-mediated, pure red cell aplasia and hemolytic anemia. *Blood* 2001; **97**: 3995-3997 [PMID: 11389047]
49 **Willis F**, Marsh JC, Bevan DH, Killick SB, Lucas G, Griffiths R, Ouwehand W, Hale G, Waldmann H, Gordon-Smith EC. The effect of treatment with Campath-1H in patients with autoimmune cytopenias. *Br J Haematol* 2001; **114**: 891-898 [PMID: 11564082]
50 **Prabhakar SS**, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997; **47**: 331-335 [PMID: 9181281]
51 **Casadevall N**, Dupuy E, Molho-Sabatier P, Tobelem G, Varet B, Mayeux P. Autoantibodies against erythropoietin in a patient with pure red-cell aplasia. *N Engl J Med* 1996; **334**: 630-633 [PMID: 8592526 DOI: 10.1056/nejm199603073341004]
52 **Stead RB**, Lambert J, Wessels D, Iwashita JS, Leuther KK, Woodburn KW, Schatz PJ, Okamoto DM, Naso R, Duliege AM. Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood* 2006; **108**: 1830-1834 [PMID: 16720830 DOI: 10.1182/blood-2006-04-015818]
53 **Macdougall IC**, Rossert J, Casadevall N, Stead RB, Duliege AM, Froissart M, Eckardt KU. A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med* 2009; **361**: 1848-1855 [PMID: 19890127 DOI: 10.1056/NEJMoa074037]
54 **Kaushik T**, Yaqoob MM. Lessons learned from peginesatide in the treatment of anemia associated with chronic kidney disease in patients on dialysis. *Biologics* 2013; **7**: 243-246 [PMID: 24348017 DOI: 10.2147/btt.s34935]
55 **Sato Y**, Yanagita M. Renal anemia: from incurable to curable. *Am J Physiol Renal Physiol* 2013; **305**: F1239-F1248 [PMID: 23884144 DOI: 10.1152/ajprenal.00233.2013]

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