

Chapter 3: Use of ESAs and other agents* to treat anemia in CKD

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ESA INITIATION

BACKGROUND

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980s was a major breakthrough in the treatment of the anemia of patients with CKD. The development of rHuEPO was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. It remains unclear whether the main cause of anemia is a loss of kidney EPO production capacity or a derangement in oxygen sensing, as proposed more recently.¹⁰⁵

In the early years, rHuEPO administration was regarded by the nephrology community as a beneficial therapy for long-term dialysis patients whose Hb values fell to extremely low levels, making them transfusion-dependent. The immediate benefit of rHuEPO in CKD patients with severe anemia and anemia-related signs and symptoms was clear. In addition, the reduction in the need for regular blood transfusions was another major benefit, resulting in less frequent transmission of blood-borne viral diseases, such as hepatitis B and C, less allosensitization, predisposing to prolonged wait times or failure to receive a kidney transplant, transplant rejection, and less transfusional hemosiderosis.^{106–109}

After introduction of rHuEPO into clinical practice its administration was limited to dialysis patients with the most severe forms of anemia. Progressively, its use was extended to the majority of dialysis patients with renal anemia, and subsequently also to anemic patients with CKD 4–5 in countries in which the high cost of rHuEPO did not limit the number of patients eligible for this treatment.

Hb targets also increased progressively, often into the range of normal values. The idea that anemia should be corrected completely was based on pathophysiologic considerations and the demonstration by numerous observational studies of an inverse association between Hb concentrations up into the normal range and intermediate outcomes such as left ventricular hypertrophy,¹¹⁰ as well as hard patient outcomes such as cardiovascular events,^{111–113} hospital admission,¹¹⁴ and death.^{115,116} Of note, a recent study also showed that CKD 5D patients with naturally occurring Hb concentrations greater than 12 g/dl (120 g/l) were not at increased mortality risk.¹¹⁷ However, the suggestion drawn from epidemiological studies that anemia

should be completely corrected in patients with CKD was not supported by the Normal Hematocrit Study in CKD 5D patients¹¹⁸ and several recent randomized controlled trials (RCTs) performed in large CKD patient cohorts (Supplementary Table 7 online).

In CKD 5D patients Hb concentrations often fall below 8 g/dl (80 g/l) if anemia is untreated, whereas in CKD ND patients higher Hb concentrations are usual, unless patients are close to dialysis or have another contributing cause. The decision to prescribe ESAs should be based on evidence accrued from RCTs. However substantial heterogeneity exists in RCTs performed to evaluate ESA therapy, particularly in relation to classification of patients, research design, baseline Hb, target Hb, clinical outcome measures, and definitions of clinically meaningful improvements.

Outcomes of interest in RCTs of ESAs include mortality, cardiovascular and kidney endpoints, safety, quality of life (QoL), blood transfusions and cost. QoL outcomes are particularly important for CKD 5D patients and for some may be more important than cardiovascular events or mortality, since they have relatively short life expectancy and the symptoms attributable to anemia (e.g., low energy, fatigue, decreased physical function, and low exercise capacity) occur frequently and can be disabling.¹¹⁹ However, QoL is extremely difficult to quantify as is the clinical importance of changes measured. Furthermore, unless assessed under rigorous double-blind conditions, the validity of QoL measurements is questionable. Avoidance of transfusions is important, as mentioned above.

The guidelines to treat or not to treat the anemia of CKD are also valid for CKD 4–5T patients. Of note, blood transfusions may increase the risk of alloreactivity and rejection episodes after kidney transplantation.¹²⁰ In addition a recent randomized trial has shown that early post-kidney transplant anemia correction by ESAs reduces the progression of allograft nephropathy, although its effect on hard outcomes in this patient population remains unknown.¹²¹

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded*)

RATIONALE

After diagnosing anemia in a patient with CKD all correctable causes should be treated before considering ESA therapy. Above all, this recommendation is based on the observation that iron supplementation given to CKD patients with

*Excluding iron which is discussed in Chapter 2.

proven iron deficiency or impaired iron availability ('functional iron deficiency') generally leads to an increase in Hb (See Chapter 2). However, the correction of other deficiency states also may ameliorate anemia. In patients with inflammatory diseases, including bacterial and viral infections, the attenuation of the inflammatory status is often followed by an improvement of Hb.

There are several reasons why correctable causes other than erythropoietin deficiency should be actively sought. As in any disease state, pathological conditions which can be cured should be corrected first. As examples, ESA treatment is unlikely to be fully effective in raising Hb concentrations until either severe systemic bacterial infections or severe secondary hyperparathyroidism are appropriately treated (Supplementary Table 8 online). When several different factors are thought to contribute to the anemia of CKD, even though the main underlying cause is impaired kidney EPO synthesis, appropriate medical care dictates treating all underlying causes.

3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)

RATIONALE

Treatment of severe anemia

Objective evidence to support treatment of Hb concentrations below 9 g/dl (90 g/l) is quite strong because the transfusion benefits are substantial and the QoL improvements are clinically important. However the safety of ESAs in treating severe anemia has not been evaluated in large placebo controlled trials.

The Canadian Erythropoietin Study Group reported a double-blind RCT of 118 CKD 5HD patients in 1990. ESA was utilized in patients with Hb concentrations <9 g/dl (<90 g/l), and three randomly allocated groups were followed (placebo, target Hb 9.5–11 g/dl [95–110 g/l], high target Hb >11 g/dl [>110 g/l]).¹²² Baseline Hb was 7.0 g/dl (70 g/l) and the mean transfusion requirement was 7 transfusions per year. After 8 weeks, 58% (N=23/40) in the placebo group were transfused and only 2.5% (N=1/40) was transfused in the group with target Hb of 9.5–11 g/dl (95–110 g/l) and 2.6% (N=1/38) in the group with target Hb >11 g/dl (>110 g/l). After 6 months, significant improvements in fatigue, physical function, and 6 minute walking tests were reported for the low Hb group compared to placebo, but no improvement was observed comparing low vs high Hb group. In an open-label RCT of only 83 CKD ND patients with Hb <10 g/dl (<100 g/l), significant improvements in energy and physical function were also reported.¹²³

Treatment of moderate anemia

There are several large RCTs of ESA therapy where baseline Hb is >10 g/dl (>100 g/l).^{118,124–128} The intervention being

tested in these trials is complete correction of anemia with ESAs, compared to partial correction with ESAs in five RCTs^{118,124–126,128} and to placebo in one.¹²⁷ A double-blind design is necessary to accurately assess subjective or clinician-driven endpoints particularly QoL, starting dialysis, and giving transfusions. Notably, only 3 of the 6 trials were double-blind – the Normal Hematocrit Study reported in 1998,¹¹⁸ the Canada-Europe Study reported in 2005,¹²⁶ and TREAT reported in 2009.¹²⁷ The Scandinavian Study,¹²⁵ CREATE¹²⁴ and CHOIR¹²⁸ trials were open label.

The US Normal Hematocrit Trial by Besarab *et al.*¹¹⁸ was the first of a series of RCTs which cast serious doubt on the assumption that full anemia correction should be achieved in the majority of dialysis patients. A cohort of 1233 prevalent CKD 5HD patients with symptomatic heart failure or ischemic heart disease were allocated to either partial treatment of anemia or full anemia correction, using epoetin-alfa. The eventually achieved hematocrit values were 31% and 40%, respectively. In the normal hematocrit group treated with epoetin there were 183 deaths and 19 myocardial infarcts, producing 202 primary events, compared to 164 events (150 deaths, 14 myocardial infarcts) in the group in which anemia was partially corrected with epoetin. The risk ratio for the primary endpoint was 1.3 (95% CI 0.9–1.9) which did not satisfy the pre-specified criterion for statistical significance (even though the nominal p value was 0.03) after adjusting for interim analyses. The trial was stopped early in a situation where the primary hypothesis was unlikely to be proven and the intervention being tested caused harm: 39% had vascular access clotting in the intervention arm and 29% in the control arm ($P=0.001$).

The double-blind Canada-Europe trial by Parfrey *et al.*¹²⁶ of 596 incident CKD 5HD patients without symptomatic heart disease (18% with diabetic nephropathy) examined the question whether full anemia correction by epoetin-alfa in the group randomized to a Hb target of 13.5–14.5 g/dl (135–145 g/l), as compared to partial treatment of anemia in the group randomized to a Hb target of 9.5–11.5 g/dl (95–115 g/l), had a beneficial effect on left ventricular volume and mass index. The eventually achieved Hb values were 13.1 and 10.8 g/dl (131 and 108 g/l), respectively. There was no difference in left ventricular volume index or mass index between the two groups during this 96-week study. Of note, patients in the full anemia correction group had a significantly higher stroke incidence (secondary endpoint) than patients in the partial treatment correction group. However, the absolute numbers of patients with stroke were very small. As one might expect, the high Hb group received significantly fewer transfusions than the low Hb group, but extent of the benefit was modest: although 9% in the high Hb arm received at least one transfusion compared to 19% in the low Hb arm ($P=0.004$) during the 96-week study, the transfusions per patient per year was 0.3 in the high Hb arm and 0.7 in the low Hb arm ($P<0.0001$).¹²⁹ In addition significant improvements in QoL were reported for the *a priori* selected domains of vitality and of fatigue.^{126,130}

The goal of the CREATE study by Drueke *et al.*¹²⁴ was to show superiority of full anemia correction in terms of cardiovascular events, as compared to partial correction of anemia, when starting ESA therapy at an earlier stage than end-stage renal disease (ESRD). In this trial, 603 CKD 3–5 patients (26% with diabetes) were randomly allocated to either a Hb target of 13.0–15.0 g/dl (130–150 g/l) or a Hb target of 10.5–11.5 g/dl (105–115 g/l) using epoetin-beta. The eventually achieved Hb values were 13.5 and 11.6 g/dl (135 and 116 g/l), respectively. Dialysis was required in significantly more patients in the high Hb group than in the low Hb group. However the rate of fall of GFR in the two groups during the 3 year study was similar. Statistically significant improvements in some domains of QoL, including physical function and vitality, were observed in the high Hb group, although these must be interpreted cautiously because the study was open-label.

The US CHOIR study by Singh *et al.*¹²⁸ similarly aimed to show superiority of full anemia correction by ESA administration in terms of cardiovascular events and death, as compared to partial treatment of anemia, in patients with CKD not yet on dialysis. In this trial, 1432 CKD 3–4 patients (49% with diabetes) were randomized to Hb targets of 13.5 g/dl (135 g/l) and 11.3 g/dl (113 g/l) using epoetin-alfa. Withdrawal rate was high: 17% due to renal replacement therapy and 21% for other reasons. The study was prematurely stopped after an interim analysis with a median study duration of 16 months. The achieved Hb values were 12.6 and 11.3 g/dl (126 and 113 g/l), respectively. At this time point, 125 patients in the complete anemia correction group but only 97 patients in the standard correction group had reached the primary combined cardiovascular endpoint ($P=0.03$). No differences in QoL were observed comparing the two groups although, again, this finding must be interpreted cautiously because the study was open-label.

Finally, the international trial of darbepoetin-alfa in type 2 diabetes and CKD (TREAT) by Pfeffer *et al.*¹²⁷ examined cardiovascular and kidney outcomes in 4038 CKD 3–4 patients. Of note, this is by far the largest ESA trial, and has the best research design, as it was placebo controlled and double-blinded. Patients received either darbepoetin-alfa to achieve a Hb target of 13.0 g/dl (130 g/l) or placebo with rescue darbepoetin-alfa when the Hb concentration was <9.0 g/dl (<90 g/l). The achieved Hb values were 12.5 and 10.6 g/dl (125 and 106 g/l), respectively. The median follow-up duration of the study was 29 months. There were no differences in the two primary endpoints, which were the composite outcomes of death or a cardiovascular event (first primary endpoint) and death or ESRD (second primary endpoint). The hazard ratio for death/composite cardiovascular event was 1.05 (95% CI 0.94–1.17), and for death or ESRD it was 1.06 (95% CI 0.96–1.19). However there was a substantial increased risk of stroke (HR 1.92; 95% CI 1.38–2.68), although the absolute risk of stroke overall was modest: 5.0% of the high Hb group had a stroke compared to 2.6% in the placebo group ($P<0.001$). The relative increase

in risk of stroke was similar in patients with and without a past history of stroke. As a result, the absolute risk of stroke was substantial in the 11% of subjects with a prior history of stroke; 12% in the darbepoetin group compared to 4% in the placebo group. Venous thrombo-embolic events occurred significantly more frequently in the high Hb arm (2.0%) compared to the placebo arm (1.1%, $P=0.02$). A signal that normalization of Hb with darbepoetin may be harmful in patients with a history of malignancy was reported following a post-hoc analysis: 14/188 (7.4%) of those with a history of malignancy at baseline died from cancer in the darbepoetin arm compared to 1/160 (0.6%) ($P=0.002$) in the placebo arm. A statistically significant improvement in Functional Assessment of Cancer Therapy-Fatigue (FACT-fatigue) scores was reported at week 26 favoring the darbepoetin group, but the clinical significance of this was modest, as 55% of the high Hb group had a clinically important improvement in fatigue score compared to 50% of the placebo group. Transfusions were prescribed relatively frequently, and more often in the placebo arm (25%) compared to the high Hb arm (15%). The harm:benefit trade-off in TREAT was 1 stroke for 5 transfusions prevented by the high Hb target¹³¹ (Supplementary Tables 9–19 online). In a large subset of the TREAT patients QoL was assessed using FACT-fatigue, SF-36, and EQ-5D through 97 weeks. Compared to placebo, darbepoetin conferred a consistent, but small improvement over 97 weeks in fatigue and overall QoL, but none in energy and physical function. Interim stroke had a substantial negative impact on fatigue and physical function.¹³²

Meta-analyses

Assessment of ESAs in CKD using meta-analysis is problematic because of the heterogeneity of patients entered, the different quality and research designs of the RCTs performed, and differences in definitions of endpoints. In addition abstraction of aggregate data from the reports of RCTs to populate the meta-analysis data base is also a limitation, as individual patient data would be preferable. The most recent meta-analysis¹³³ concluded that higher Hb concentrations in CKD increases risk for stroke (relative risk [RR] 1.51, 95% CI 1.03–2.21), hypertension (RR 1.67, 95% CI 1.31–2.12), and vascular access thrombosis (RR 1.33; 95% CI 1.16–1.53), and may perhaps increase risk for death (RR 1.09; 95% CI 0.99–1.20), serious cardiovascular events (RR 1.15, 95% CI 0.98–1.33) or ESRD (RR 1.08; 95% CI 0.97–1.20). In our opinion, because of the heterogeneity of patients and interventions across studies in the meta-analysis greater credence should be given to the results of the very large, placebo controlled, double-blind trial, TREAT, than to the meta-analyses, in areas where the results differ: TREAT found no difference between the higher Hb, darbepoetin, group and the lower Hb, placebo, group for the two primary composite outcomes (either death or a cardiovascular event, or death or a renal event).¹²⁷

The existing meta-analyses of QoL outcomes are further complicated by inclusion of data from open label studies,

different instruments to measure QoL, differences in research design across RCTs, incomplete reporting as some trials chose (*a priori*) specific domains as trial outcomes, and differences in the definition of clinically meaningful improvement in QoL domains.¹¹⁹ Results from two systematic reviews published recently^{134,135} suggest that improvements in QoL are maximized in the 10–12 g/dl (100–120 g/l) range. In CKD ND patients the review focused on energy and physical function¹³⁴ and in CKD 5D patients the review focused on physical function and the meta-analysis on exercise tolerance.¹³⁵

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy (2C).

RATIONALE

The joint guideline from the American Society of Clinical Oncology¹³⁶ and the American Society of Hematology¹³⁷ recommend using ESA therapy with great caution in patients with active malignancy, particularly when cure is the anticipated outcome. This advice is supported in CKD patients by the post-hoc analysis in TREAT which demonstrated a significantly higher death rate from cancer in the darbepoetin arm in patients with a history of a malignant condition at baseline as compared with the placebo arm.¹²⁷

The relative risk of stroke in patients in the darbepoetin arm of TREAT was the same in those with and without a history of stroke (i.e., approximately doubled). However the absolute risk of stroke was much higher in subjects with a history of stroke (in both study arms) and the absolute risk of stroke attributable to high Hb/darbepoetin was particularly high, 8% in those with a history of stroke vs 1% in those without a history of stroke over 29 months.¹³⁸ Consequently the Work Group concluded that ESAs should be used with great caution in those with a prior history of stroke.

3.4.1: For adult CKD ND patients with Hb concentration ≥ 10.0 g/dl (≥ 100 g/l), we suggest that ESA therapy not be initiated. (2D)

3.4.2: For adult CKD ND patients with Hb concentration < 10.0 g/dl (< 100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (2C)

3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (2B)

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (Not Graded)

3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D)

RATIONALE

In adult CKD-ND patients TREAT demonstrated that the high Hb darbepoetin arm was associated with harm. In the patients on placebo with rescue treatment allowed when Hb fell to below 9.0 g/dl (90 g/l) the achieved median Hb value was as high as 10.6 g/dl (106 g/l), despite the majority of patients receiving no or little darbepoetin¹²⁷ (Supplementary Tables 15–19 online).

There is no convincing evidence that the active increase of Hb towards concentrations in the normal range leads to demonstrable benefit in adult patients with CKD stages 3–5. Moreover, when Hb falls below 10 g/dl (100 g/l) in these patients the Work Group were unconvinced that all patients should have an ESA initiated, particularly as the rate of Hb fall may be slow. It was suggested that the decision to initiate ESA therapy in CKD-ND when Hb is > 9.0 and < 10.0 g/dl (> 90 and < 100 g/l) should be individualized based on risk of requiring transfusions and on the presence of symptoms attributable to anemia, particularly as some patients may be at higher risk of requiring red-cell transfusions, and some patients are more prone to developing symptoms and signs associated with anemia (Supplementary Tables 15–19 online).

In adult hemodialysis patients the rate of fall of Hb is faster than in ND patients, and if untreated Hb will frequently fall below 8 g/dl (80 g/l).¹²² As the risk of transfusions is high in those HD patients whose Hb falls below 9 g/dl (90 g/l) the Work Group suggested that ESA therapy should be used to prevent the Hb concentration from falling below 9.0 g/dl (90 g/l), which in practice means that the Hb concentration at which ESA should be initiated should be between 9.0 and 10.0 g/dl [90 and 100 g/l] (Supplementary Tables 9–14 online).

However, there may be subgroups of adult CKD stage 3–5 and 5D patients in whom it may not be wise to let Hb values descend below 10 g/dl (100 g/l), particularly in elderly patients who are more prone to developing symptoms and signs associated with anemia, and those who are prone to requiring red-cell transfusions.

Moreover, physical and mental performances and QoL may be seriously compromised in adult CKD patients with severe anemia. RCTs supporting registration of epoetin-alfa for the treatment of anemia in dialysis patients demonstrated that ESA treatment of subjects with a Hb of < 10 g/dl (< 100 g/l) to a Hb target of approximately 10–12 g/dl

(100–120 g/l) improved patient-reported physical functioning.^{134,135} The question of the Hb value above which there is no further improvement in these parameters remains unsolved, especially for CKD-ND patients without diabetes and CKD-5D patients with or without diabetes.

In anemic children with CKD there are no RCTs examining the effects of ESA administration on hard outcomes. Therefore, any suggestion for Hb targets in this subgroup of CKD patients has to rely on results obtained in the adult CKD patient population and on clinical experience in the pediatric setting. The upper and lower Hb targets are opinion-based, in keeping with the lack of pediatric specific evidence. There are a number of factors unique to children that make exclusive reliance on evidence in adults inappropriate such as age-specific variation of normal Hb concentrations as well as QoL, growth, developmental, and psychological differences between children and adults.⁵⁸ Limited data suggest that children with CKD and a Hb less than 9.9 g/dl (99 g/l) are at increased risk for mortality,¹³⁹ left ventricular hypertrophy,^{140,141} and/or decreased exercise capacity¹⁴² compared to those with a Hb greater than 9.9 g/dl (99 g/l). When evaluated as a continuous variable, hematocrit (Hct) was linked directly to measures of improved health and physical functioning in a health based QoL questionnaire administered to a pediatric CKD population.¹⁴³

ESA MAINTENANCE THERAPY

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (2C)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (Not Graded)

RATIONALE

The suggestion to set the upper Hb target in general to values ≤ 11.5 g/dl (≤ 115 g/l) in adult CKD patients is based on the interpretation of the combined results of the recent major RCTs that there may be more harm than benefit at higher Hb concentrations. Of note, the update of the 2006 KDOQI anemia guideline in 2007 had already led to the recommendation to limit the upper Hb target to 12 g/dl (120 g/l), not to exceed 13 g/dl (130 g/l).⁵¹ The present suggestion not to exceed in general a Hb limit of 11.5 g/dl (115 g/l) has been influenced by the fact that the upper boundary of the Hb concentration in the control group of the major ESA RCTs usually did not exceed 11.5 g/dl (115 g/l); no data exist on the benefits of Hb targets between 11.5 and 13.0 g/dl (115 and 130 g/l); and high Hb targets are associated with adverse outcomes.

The Work Group recognized that some patients experience an improvement in QoL when the Hb value is above 11.5 g/dl (115 g/l). This opinion is supported by the heterogeneity of QoL outcomes in the major RCTs: in the double-blind Canada-Europe Study and in open label

CREATE study statistically significant improvements in some QoL domains that may be clinically important were reported with higher Hb values.^{124,126,130} In the double-blind TREAT study the QoL benefits of higher Hb were modest^{127,132} and in open label CHOIR study no benefits were observed¹²⁸ (Supplementary Tables 9–19 online).

As all CKD patients in TREAT study also had type 2 diabetes, it is possible that improvements in QoL may be more difficult to achieve in this subgroup of patients than in those not suffering from diabetes.

An increase of Hb above 11.5 g/dl (115 g/l) towards 13 g/dl (130 g/l) may also be justified in individual patients with a high bleeding tendency since this results in lower transfusion needs, as shown by 8 RCTs.¹³³

Obviously, increasing Hb above 11.5 g/dl (115 g/l) up to 13 g/dl (130 g/l) has to be weighed against the probability of increased harm. This perspective needs to be clearly explained to each patient who wishes to examine the possible benefits of more complete anemia correction.

3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (1A)

RATIONALE

The strong recommendation not to aim for Hb increases to concentrations > 13 g/dl (> 130 g/l) is based on the interpretation of the combined results of the recent major RCTs showing more harm than benefit with higher Hb targets, as compared to lower Hb targets, including increased risks for stroke,^{126,127} hypertension,¹³³ and vascular access thrombosis (in hemodialysis patients).¹¹⁸ TREAT did not demonstrate significant differences for serious cardiovascular or kidney events comparing correction of anemia with darbepoetin to the placebo group.¹²⁷ Thus the increased risk of kidney events reported in CREATE¹²⁴ and of cardiovascular events reported in CHOIR¹²⁸ were not substantiated in the much larger TREAT trial.¹²⁷ However, a recent meta-analysis point estimate indicated increased mortality at higher Hb target¹³³ (Supplementary Tables 9–19 online).

An exception to the recommendation to avoid Hb increases to concentrations > 13 g/dl (> 130 g/l) might however be made for patients with comorbidities that are normally associated with elevated Hb levels (e.g., cyanotic heart disease).

3.7: In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (2D)

RATIONALE

As mentioned above, in children with CKD observational data associates high Hb with better survival¹³⁹ and/or increased exercise capacity.¹⁴² Moreover, a recent North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) retrospective analysis done on pediatric CKD

patients found an increased risk of hospitalization in children with low Hb compared to those with normal Hb.¹⁴⁴ However, based on recent experience with the adult CKD patient population, caution is warranted with any extrapolation from observational treatment studies to conclusions on hard outcomes. This being said, direct extrapolation of the results from adult trials to pediatric patients is not appropriate given the differences in causes of CKD, contributions of age to growth and development, and impact of comorbidities on outcomes.

ESA DOSING

- 3.8.1: We recommend determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (1D)**
- 3.8.2: We recommend that ESA dose adjustments be made based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (1B)**
- 3.8.3: We suggest decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (2C)**
- 3.8.4: Re-evaluate ESA dose if (*Not Graded*):**
- The patient suffers an ESA-related adverse event
 - The patient has an acute or progressive illness that may cause ESA hyporesponsiveness (see Recommendations 3.13.1–3.13.2)

RATIONALE

The initiation of ESA therapy, ESA dose adjustments and rates of changes have remained similar to those outlined in the 2006 KDOQI Anemia Guideline.⁵⁰ In general, the objective of initial ESA therapy is a rate of increase in Hb concentrations of 1.0 to 2.0 g/dl (10 to 20 g/l) per month. This is consistent with the findings in ESA trials of CKD-associated anemia where the mean initial rates of Hb concentration increase were of 0.7 to 2.5 g/dl (7 to 25 g/l) in the first 4 weeks. However, a rise in Hb of greater than 2.0 g/dl (20 g/l) over a 4-week period should be avoided.

The rate of increase varies greatly as a function of individual ESA responsiveness. Poor responders are more likely to be female, to have a history of cardiovascular disease (CVD), to have signs of iron deficiency and inflammation, and to be overweight.¹⁴⁵ The response also depends on initial dose, dosing frequency, and route of administration. The dependence on dosing frequency and route of administration concerns epoetin-alfa, epoetin-beta, and darbepoetin but not CERA (continuous erythropoietin receptor activator [methoxy polyethylene glycol-epoetin-beta]). When ESAs were introduced into clinical practice over 20 years ago, hypertension was frequently noted in the first 3 months after initiating therapy in severely anemic patients, and seizures in rare instances. It is possible, although not proven, that these events were related to a too rapid rate of increase in Hb concentrations.

Epoetin-alfa or epoetin-beta dosing usually starts at 20 to 50 IU/kg body weight three times a week. Darbepoetin-alfa dosing usually starts at 0.45 µg/kg body weight once weekly by subcutaneous (SC) or IV administration, or 0.75 µg/kg body weight once every 2 weeks by SC administration. CERA dosing starts at 0.6 µg/kg body weight once every 2 weeks by SC or IV administration for CKD ND and CKD 5D patients, respectively, or 1.2 µg/kg body weight once every 4 weeks by SC administration for CKD ND patients. Higher baseline Hb concentrations require lower initial ESA doses, except for CERA for which there is no initial dose change. In patients with a history of CVD, thrombo-embolism or seizures, or in those with high blood pressure, the initial doses should be in the lower range. Epoetin-alfa or epoetin-beta dosage may subsequently be increased every 4 weeks by a weekly dose of 3×20 IU/kg if the increase of Hb is not adequate. Increases in dose should not be made more frequently than once a month. If the Hb is increasing and approaching 11.5 g/dl (115 g/l), the dose should be reduced by approximately 25%. If the Hb continues to increase, doses should be temporarily withheld until the Hb begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. Alternatively, one could simply repeat the Hb determination again in a shorter interval (e.g., weekly) and interpret any further rise, in particular in light of reticulocyte counts and their direction, before considering holding the dose. If the Hb increases by more than 1.0 g/dl (10 g/l) in any 2-week period, the dose should be decreased by approximately 25%. See Recommendations 3.13.1 to 3.15.2 regarding ESA hyporesponsiveness and loss of ESA response (Supplementary Table 20 online).

Dose adjustments may be necessary once the Hb target range has been reached. Note that in clinical practice, achieved Hb values may easily rise above or fall below the optimal Hb limits. Therefore, cautious dose adaptations are required. In general, ESA dose adjustments are made only after the first 4 weeks after ESA initiation. The frequency of ESA dose adjustment should be determined by the rate of increase in Hb concentrations during initial ESA therapy, the stability of Hb concentrations during maintenance ESA therapy, and the frequency of Hb testing. The minimum interval between ESA dose adjustments in the outpatient setting generally is 2 weeks because the effect of most dose changes will not be seen within a shorter interval. ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb concentration is needed. Withholding ESA doses, particularly for long periods, may lead to a delayed decrease in Hb concentrations to less than target range. Such a decrease may initiate periodic cycling of Hb concentrations at greater than and less than the target Hb range.¹⁴⁶ Hb variability has been found to be an independent predictor of mortality in a large US CKD 5HD patient population¹⁴⁷ although this observation could not be confirmed in a large European CKD 5HD patient cohort.¹⁴⁸

Each time a patient with CKD is hospitalized the treating clinician should evaluate or reevaluate the patient's ESA

requirements. Disease states such as severe infections or post-surgery may modify the ESA responsiveness profoundly. In case of profound anemia and markedly impaired ESA response a red cell transfusion may be preferred to administering ESAs or increasing ESA dose.

ESA ADMINISTRATION

3.9.1: For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (2C)

3.9.2: For CKD ND and CKD 5PD patients, we suggest subcutaneous administration of ESA. (2C)

RATIONALE

As outlined in the 2006 KDOQI guideline,⁵⁰ the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA used. Among CKD 5D patients undergoing intermittent hemodialysis or hemofiltration therapy, either SC or IV administration is possible. In the outpatient setting, SC administration is the only routinely feasible route of administration for patients with CKD 3–5 or on peritoneal dialysis treatment. Among short-acting ESAs, efficacy of SC administration in patients with CKD 5HD may be superior to that of IV administration, as shown by a large multicenter RCT in hemodialysis patients.¹⁴⁹ However, another RCT of much smaller sample size did not find an advantage of SC over IV administration in CKD 5HD patients.¹⁵⁰ Among long-acting ESAs, efficacy of SC compared with IV administration appears to be equivalent at examined dosing frequencies.^{151–153} Furthermore, CKD 5HD patients in general prefer IV to SC administration of ESAs because SC administration may be painful (Supplementary Tables 21–24 online).

Frequency of administration

3.10: We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (2C)

RATIONALE

The frequency of ESA administration depends on considerations of efficacy, convenience and comfort. Maximum efficacy occurs within dosing intervals that are ESA class specific. For example, in patients on hemodialysis treatment receiving SC or IV short-acting ESA therapy, epoetin-alfa efficacy decreases when the dosing is extended from 3 times weekly to once-weekly administration,¹⁵⁴ and even more so when the dosing intervals are extended to every other week administration.¹⁵⁵ Among long-acting ESAs, darbepoetin-alfa appears to have maximum efficacy when administered every 2 weeks, and methoxy polyethylene glycol-epoetin-beta (CERA) every 4 weeks.¹⁵⁶ When converting short-acting

ESAs to long-acting ESAs, differences in drug half-life need to be considered. For the sake of comparison, 3 times weekly administered epoetin-alfa to darbepoetin-alfa given only once monthly resulted in a decreased frequency of injections needed to maintain Hb concentrations of CKD patients within an accepted target range¹⁵⁷ (Supplementary Tables 25–28 online).

When converting a patient from one ESA to another the pharmacokinetic and pharmacodynamic characteristics of the new ESA need to be taken into consideration. The manufacturers have provided conversions from epoetin-alfa or epoetin-beta to darbepoetin-alfa or CERA. Note that the conversion ratios from epoetin to darbepoetin are non-linear.

When using different types of approved ESAs (biosimilars that have received approval by official regulatory bodies such as FDA and European Medicines Agency [EMA]), license information provided by companies should also be taken into account.

TYPE OF ESA

3.11.1: We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (1D)

3.11.2: We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically for ‘copy’ versions of ESAs, true biosimilar products should be used. (2D)

RATIONALE

As outlined above, the choice of short-acting or long-acting ESAs needs to take into account a number of different aspects, encompassing patient-oriented issues and country-specific considerations. At present, there is no evidence that any given ESA brand is superior to another in terms of patient outcomes, with the historical exception of the temporary increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) about 10–20 years ago, which was associated with SC administration of an epoetin-alfa formulation available in Europe, but not in the United States.^{158,159} It is the considered opinion of the Work Group that the likelihood of differences in clinical outcomes among ESA brands is low, although there is no robust evidence supporting this assumption (Supplementary Tables 29–32 online).

At present, a number of different types of short-acting or long-acting ESAs are available worldwide, including original formulations, biosimilars, and ‘copy’ ESAs which have not been exposed to the rigor of scientific evaluation as mandated by the regulatory agencies prior to approval. Their accessibility and costs vary from country to country. True biosimilars, as defined by the EMA, are not identical to the originator products, but they have undergone a minimum number of regulatory ‘equivalence’ or ‘non-inferiority’ studies to gain marketing authorization in Europe. In other countries outside Europe, some ‘copy’ ESA products have

been marketed that may not have undergone the same rigorous testing.¹⁶⁰ Since patient safety is one of the most important drug treatment issues, only biosimilars approved by an independent regulatory agency should be used.

EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HEMOGLOBIN CONCENTRATION

Frequency of monitoring

- 3.12.1: During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (*Not Graded*)
- 3.12.2: For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (*Not Graded*)
- 3.12.3: For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (*Not Graded*)

RATIONALE

ESA initiation phase. The suggestion to monitor Hb values at least monthly in patients in whom ESA therapy is started is intended to provide sufficient surveillance information to assist in achieving and maintaining desired Hb concentrations safely and follows common practice.⁵⁰ The minimum interval between ESA dose adjustments is 2 weeks because the effect of most dose changes will not be seen within a shorter interval. Consideration of an ESA dose adjustment is based on the next projected Hb concentration. Because the accuracy of projection (extrapolation) increases with the number of contributing data points, the frequency of Hb monitoring is likely to be an important determinant of the accuracy of ESA dose adjustment. However, evidence to support this line of reasoning is indirect. Several RCTs have randomized CKD 5HD patients with target-range Hb concentrations to a change in frequency of ESA administration, a change in ESA class, or both. RCTs that have monitored Hb values weekly and adjusted ESA doses as frequently as every 2 weeks have achieved stable Hb concentrations early after randomization.^{152,161,162} In contrast, an RCT that monitored Hb concentrations and considered ESA dose adjustment monthly required 6 to 9 months to stabilize Hb concentrations after randomization,¹⁶³ but mean Hb concentration remained within the target range for that trial.

ESA maintenance phase. Within the recommended ranges for monitoring and dose adjustment, unstable Hb concentration, inappropriate high or low Hb concentration, and hemodialysis favor shorter intervals of ESA administration, whereas stable Hb concentration, within target Hb concentration, peritoneal dialysis, CKD 3–5, and minimizing laboratory resource utilization favor longer intervals for long-acting ESAs such as darbepoetin. The frequency of ESA dose adjustment is unaffected by length of action: during an 8-week period with weekly Hb monitoring, about equal

numbers of patients receiving either short-acting ESA thrice weekly or darbepoetin once weekly required dose adjustments (44% and 49%, respectively).¹⁶²

Initial ESA hyporesponsiveness

- 3.13.1: 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. (*Not Graded*)
- 3.13.2: In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (*2D*)

Subsequent ESA hyporesponsiveness

- 3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 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. (*Not Graded*)
- 3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (*2D*)

Management of poor ESA responsiveness

- 3.15.1: Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (*Not Graded*)
- 3.15.2: For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):
- decline in Hb concentration
 - continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and
 - blood transfusions

RATIONALE

Relative resistance to the effect of ESAs is a common problem in managing the anemia of patients with CKD and remains the subject of intense interest, all the more since ESA hyporesponsiveness has been found to be among the most powerful predictors of the risk of cardiovascular events and mortality.¹⁶⁴ Recently a report from TREAT assessed the initial Hb response to darbepoetin after two weight-based doses at 2 weekly intervals, in 1872 patients with CKD and diabetes.¹⁴⁵ Patients with a poor response, (the lowest quartile, who had <2% change in Hb concentration after 1 month), had higher rates of the composite cardiovascular events (adjusted HR 1.31, 95% CI 1.09–1.59), compared to those with a better response. Although this differential effect may be related to comorbidity in hyporesponsive patients, nonetheless it is possible that the high ESA doses used in

hypo-responsive patients may be toxic. Though not empirically tested, *per se*, the definition of initial hypo-responsiveness agreed upon by the Work Group is derived from the secondary analysis of the TREAT study.¹⁴⁵ Since a <2% increase in the Hb concentration is likely to be within the variability range of Hb values in individual patients, this value is considered as "no increase." The definition of initial hypo-responsiveness relies on presently accepted ESA starting doses, as indicated in the Rationale under 3.8.1–3.8.4. Of note, weight-based doses for darbepoetin do not differ for IV or SC routes, but do differ for epoetin-alfa.

If lower initial dosages than those used in TREAT are chosen, the diagnosis of hypo-responsiveness must take this into account. For example, in the USA the label for darbepoetin now recommends a starting dose of 0.45 µg per kg per four weeks, much lower than the dose used in TREAT or in Europe (i.e., 0.45 µg per kg per week or 0.75 µg per kg per two weeks). If such lower starting doses are used, repeated escalations in ESA dose should be allowed to reach double the weight-based dose used in TREAT.

Although the distinction between initial ESA hypo-responsiveness and acquired partial or complete loss of ESA responsiveness in a patient with already treated, stable anemia is somewhat artificial, it is useful in our opinion for clinical practice.

In the Normal Hematocrit Study both the high Hb and the low Hb groups revealed an inverse relationship between achieved Hb and the primary outcome (death or myocardial infarction).¹¹⁸ This is consistent with the idea that those patients who failed to achieve the target Hb were unable to do so because comorbid condition(s) existed that prevented achievement of this target. Thus, hypo-responsiveness may just have been a marker for adverse outcomes, although the possibility that high ESA doses used in hypo-responsive patients are toxic in themselves cannot be excluded. Dose-targeting bias has been reported by the Kidney Disease Clinical Studies Initiative Hemodialysis Study (HEMO) investigators.¹⁶⁵ In this RCT ESRD patients, randomly allocated to either high or low quantity of dialysis, as measured by Kt/V, demonstrated an inverse relationship between achieved Kt/V and mortality. The interpretation was that patients with comorbid conditions were unable to achieve higher Kt/V and that comorbidity predisposed these patients to earlier death.

The same principle as used with defining hypo-responsiveness to darbepoetin could be applied to the early response to other short-acting ESAs but cannot be applied to longer acting ESAs such as CERA. In that case, evaluating the Hb response after a time period of 2 months appears to be appropriate. Early ESA hypo-responsiveness or the subsequent occurrence of hypo-responsiveness in CKD patients with previously stable Hb values should lead to an intensive search for potentially correctable factors which might be causally involved. Unfortunately, besides iron deficiency, there are only few other easily reversible factors that contribute to ESA hypo-responsiveness, as shown in Table 3. If other such factors are identified they should be treated as well. Although most

Table 3 | Potentially correctable versus non correctable factors involved in the anemia of CKD, in addition to ESA deficiency

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency	Infection/ inflammation	Hemoglobinopathies
Vitamin B ₁₂ /folate deficiency	Underdialysis	Bone marrow disorders
Hypothyroidism	Hemolysis	
ACEi/ARB	Bleeding	
Non-adherence	Hyperparathyroidism	
	PRCA	
	Malignancy	
	Malnutrition	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; PRCA, pure red cell aplasia.

disorders associated with hypo-responsiveness are readily apparent, hypo-responsive patients should be evaluated for coexisting oncological or hematologic disorders. They include hematological and non-hematological malignancies as well as such diverse hematological conditions as thalassemia, sickle cell disease or the anemia associated with other chronic diseases. Myelodysplastic syndromes are a particular case. If at all ESA responsive, the anemia in patients with myelodysplastic syndrome responds more slowly. Therefore, 1 month may be too short to define hypo-responsiveness in this and several other conditions. Moreover, patients with myelodysplastic syndromes may need higher ESA doses. Finally, a rare disorder, PRCA, deserves special consideration (see 3.17.1–3.17.3). The estimation of loss of ESA response also may require a longer observation time in some patients. Note that poor ESA response, either in the initial correction phase or subsequently, is most often a transient condition. Complete loss of response is exceptional. Poor responders should periodically be re-tested for responsiveness, including after the correction of treatable causes of hypo-responsiveness.

It is important to note that the dosing requirements may differ substantially between children and adults. Registry data from NAPRTCS showed that young children require higher doses of ESA than adults, ranging from 275 U/kg/week to 350 U/kg/week for infants and 200–250 U/kg/week for older children.¹⁶⁶ Another retrospective analysis among patients on chronic hemodialysis found that children and adolescents required higher absolute doses of ESA than adults to maintain target hemoglobin levels, despite the lower mean body weight of the children.¹⁶⁷ Unfortunately, there are no RCTs that establish the appropriate dosing of ESA in children. Future research to establish pediatric ESA dosing guidelines is needed, especially for infants and younger children.

There may be toxicity from high doses of ESA, as suggested, though not proven, by recent post-hoc analyses of major ESA RCTs,^{145,168} especially in conjunction with the achievement of high Hb levels.¹⁶⁹ Therefore, in general ESA dose escalation should be avoided. The Work Group suggestions for initial and acquired hypo-responsiveness imply that maximal doses should be no greater than four times initial weight-based appropriate doses.

Table 4 | Practical approach in presence of ESA hyporesponsiveness

Tests	Finding and action
1. Check adherence	If poor, attempt to improve (if self-injection)
2. Reticulocyte count	If >130,000/ μ l, 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
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.

In practice, Tables 3 and 4 can guide to diagnose and correct ESA hyporesponsiveness. In patients in whom all correctable causes have been maximally treated but who remain hyporesponsive, ESA therapy may be continued cautiously at doses up to 4 times the initial dose to prevent a further decline in Hb concentration. Red cell transfusions can be used to prevent or treat anemia-related symptoms and signs. The treatment strategy needs to take into account each patient's anemia tolerance and potential benefits and risks linked to increases in Hb values solely obtained by high ESA dosing.

Given the disproportionate burden of morbidity and mortality that the hyporesponsive patient population bears and the ESA expense that hyporesponsiveness engenders, further research is necessary on the causes and management of hyporesponsiveness.

ADJUVANT THERAPIES

3.16.1: We recommend not using androgens as an adjuvant to ESA treatment. (1B)

3.16.2: We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (2D)

RATIONALE

Several adjuvant treatments have been proposed, either with the goal of limiting the use of more expensive ESA therapy or to improve ESA responsiveness.

Androgens. The use of androgens for treatment of anemia was suggested long before rHuEPO became available in clinical practice. Androgens were used regularly in many centers in the treatment of anemia in dialysis patients despite the need for intramuscular (IM) injection and a variety of adverse events, including acne, virilization, priapism, liver dysfunction, injection-site pain, and risk for

peliosis hepatis and hepatocellular carcinoma. The three RCTs that tested androgens in combination with ESA therapy in CKD 5HD patients were all small short-term studies. Currently recommended Hb concentrations were not achieved, and in two of them the ESA doses used were lower than current practice.^{170–172} The studies did not enroll patients with ESA hyporesponsiveness, so the effect of androgens on hyporesponsiveness is unknown. The risks of androgen therapy and their uncertain benefit on Hb concentration or clinical outcomes argue against their use as an ESA adjuvant.

Vitamin C. Vitamin C has been reported to increase the release of iron from ferritin and the reticuloendothelial system and increase iron utilization during heme synthesis.^{173,174} A recent meta-analysis of vitamin C use in CKD 5HD¹⁷⁵ and a more recent small RCT¹⁷⁶ concluded that vitamin C may result in larger increases in Hb and may limit the use of ESAs. In seven trials, patients generally had functional iron deficiency and in three studies they had EPO hyporesponsiveness (variously defined).^{176–178} However, the number of patients studied was insufficient to address the safety of this intervention. Thus the long-term safety of IV ascorbic acid in HD patients remains undefined, and whether secondary oxalosis should be a concern.

Convincing data do not exist for other potential adjuvants including vitamin D, vitamin E, folic acid, L-carnitine and pentoxifylline. Several anecdotal reports, small case series, and nonrandomized studies, primarily in CKD 5HD patients, have been published, but do not provide sufficient evidence upon which to base a recommendation. Future RCTs are clearly needed for ESA adjuvants.

EVALUATION FOR PURE RED CELL APLASIA (PRCA)

3.17.1: Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (Not Graded):

- 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, AND
- Normal platelet and white cell counts, AND
- Absolute reticulocyte count less than 10,000/ μ l

3.17.2: We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (1A)

3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (1B)

RATIONALE

Rarely, patients undergoing ESA therapy develop antibodies that neutralize both ESA and endogenous erythropoietin. The resulting syndrome, antibody-mediated PRCA, is characterized by the sudden development of severe transfusion-dependent anemia. Rapid recognition, appropriate

evaluation, and prompt intervention can be effective in limiting the consequences of this life-threatening condition. Antibody-mediated PRCA, although rare in patients administered ESAs, received urgent attention after 1998. Between 1989 and 1998, three reports described the development of PRCA in only a small number of patients with CKD administered ESAs. Reports of PRCA increased sharply in 1998 and reached a peak in 2002.^{159,179} These reports were associated with SC administration of an epoetin-alfa formulation not available in the United States. After removal of this formulation from the market, by 2004, the incidence of new antibody-mediated PRCA had decreased to pre-1998 levels. Isolated cases of PRCA have been observed in association with the use of other ESAs.^{159,179,180} Outside this historical episode the incidence rate of PRCA with SC use of all other forms of SC-administered ESA is estimated to be 0.5 cases/10,000 patient-years.¹⁵⁸ Antibody-associated PRCA stemming from IV administration of ESAs is rare and has only been reported anecdotally.¹⁸¹

Recommendations based on expert opinions have been published to guide the workup and therapy of patients suspected to have antibody-mediated PRCA.^{179,182–184} The two main distinguishing features of antibody-mediated PRCA are the associated decline in blood Hb concentration of approximately 4 g/dl (40 g/l) per month, and a decrease in the number of circulating reticulocytes to <10,000/ μ l of blood.¹⁸⁵ Bone marrow biopsy characteristically shows reduced numbers or absence of erythroblasts. The definitive diagnosis is dependent upon demonstration of the presence of neutralizing antibodies against erythropoietin. Evidence for parvovirus infection as an alternative cause of PRCA should be sought and excluded.

Following a diagnosis of antibody-mediated PRCA, patients should stop treatment with the incriminated ESA immediately and not resume treatment with the same or another EPO-derived ESA.¹⁸⁴ Immunosuppressive therapy may hasten the disappearance of circulating antibodies in patients with EPO-induced PRCA, and allow endogenous erythropoiesis to recover to pre-treatment levels. In a retrospective study of 47 patients who developed PRCA during EPO therapy (primarily epoetin brand 'Eprex[®]' in Europe), 29 of 37 patients (78%) who received immunosuppressive therapy recovered, whereas none of the nine patients who did not receive immunosuppressive therapy recovered.¹⁸⁵ Red cell production recovered only when patients received immunosuppressive treatment. Re-exposure to epoetins or darbepoetin-alfa can re-induce the formation of antibodies.¹⁸⁶ Anaphylactoid reactions after repeated injections of epoetin- or darbepoetin-alfa have been reported in a patient with pure red-cell aplasia.¹⁸⁷ A novel approach to the treatment of this condition using a synthetic, peptide-based erythropoietin-receptor agonist (peginesatide) has generated optimistic results,¹⁸⁸ and has the advantage of avoiding immunosuppressive therapy.

The recognition of antibody-mediated PRCA in patients treated with recombinant epoetins has underscored the need

for full clinical documentation and post-marketing surveillance with newer ESAs and biosimilar products, as well as therapeutic recombinant proteins in general.¹⁸⁹

If a decision to treat with peginesatide is taken, it can be initiated at a dose of 0.05 to 0.075 mg/kg body weight by subcutaneous injection every 4 weeks. Subsequently, the dose needs to be adjusted to reach the desired target Hb value.

RESEARCH RECOMMENDATIONS

The following research questions have arisen during the deliberations of the Work Group, and further research will be necessary to answer them.

- In cohort studies moderate anemia is associated with an increased incidence of cardiovascular events. Is anemia really a risk factor for these events or is it a marker for some other cardiovascular risk factor(s)?
- There is uncertainty about optimal Hb targets for ESA therapy. What is the risk-benefit ratio of low Hb targets <10.0 g/dl (<100 g/l) or high targets of 11.5–13.0 g/dl (115–130 g/l), compared to conventional targets of 10.0–11.5 g/dl (100–115 g/l)?
- These guidelines have stressed individualization of anemia therapy. Should the objective of anemia therapy be improvement in clinical outcomes (provided Hb concentration is <13.0 g/dl [<130 g/l]) rather than achievement of a specified Hb target range? Should these outcomes include improvements in QoL, and if so, what defines clinically important improvements?
- As the relationship between ESA responsiveness and hard patient outcomes may be the result of co-morbidity or of high ESA dose, what is the impact of high vs low dose on clinical outcomes in ESA hyporesponsive patients?
- Is the risk-benefit ratio of anemia correction similar in non-diabetic and diabetic CKD patients?
- Is there a difference in adverse clinical outcomes comparing IV and SC routes of administration?
- Are the risk-benefit ratios for biosimilars comparable to current ESAs?
- What is the pathogenesis of cerebrovascular and vascular toxicity associated with normalization of Hb using ESAs?
- Are CKD patients with cancer or a cancer history who are receiving ESA therapy at higher cardiovascular risk than non-CKD patients with cancer or a cancer history?
- What is the effect of vitamin C administration in functional iron deficiency and what is the clinical impact of increased oxalate levels?
- There appears to be differences in anemia treatment outcomes between different geographic regions. What are the reasons for this?
- What are the risks and benefits of ESA administration on outcomes in anemic children with CKD?
- What are the appropriate, weight-based, dosing regimens for the younger pediatric patients, especially those under the age of two years?

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SUPPLEMENTARY MATERIAL

Supplemental Table 7: Association between anemia severity (prior to erythropoietin use) and clinical outcome in multivariable analyses.

Supplemental Table 8: Association between hyperparathyroidism and ESA responsiveness in multivariable analyses.

Supplemental Table 9: Evidence profile of RCTs comparing higher vs. lower Hb targets/ESA doses in the HD-CKD and PD-CKD populations.

Supplemental Table 10: Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the HD-CKD and PD-CKD populations.

Supplemental Table 11: Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the HD-CKD and PD-CKD populations.

Supplemental Table 12: Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the HD-CKD and PD-CKD populations.

Supplemental Table 13: Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the HD-CKD and PD-CKD populations.

Supplemental Table 14: Summary table of RCTs comparing different Hb targets/ESA doses on exercise capacity in the HD-CKD and PD-CKD populations.

Supplemental Table 15: Evidence profile of RCTs comparing different higher vs. lower Hb targets/ESA doses in the ND-CKD populations.

Supplemental Table 16: Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the ND-CKD population.

Supplemental Table 17: Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the ND-CKD population.

Supplemental Table 18: Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the ND-CKD population.

Supplemental Table 19: Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the ND-CKD population.

Supplemental Table 20: ESA protocols from the major trials in CKD populations.

Supplemental Table 21: Evidence profile of RCTs examining IV vs. SC EPO in CKD patients with anemia.

Supplemental Table 22: Summary table of RCTs examining IV vs. SC ESA in CKD patients with anemia (categorical outcomes).

Supplemental Table 23: Summary table of RCTs examining IV vs. SC ESA in CKD patients with anemia (continuous outcomes).

Supplemental Table 24: Summary table of adverse events in RCTs examining IV vs. SC EPO in CKD patients with anemia.

Supplemental Table 25: Evidence profile of RCTs examining different dosing schedules in CKD patients with anemia.

Supplemental Table 26: Summary table of RCTs examining different dosing schedules in CKD patients with anemia (categorical outcomes).

Supplemental Table 27: Summary table of RCTs examining different dosing schedules in CKD patients with anemia (continuous outcomes).

Supplemental Table 28: Summary table of adverse events in RCTs examining different dosing schedules in CKD patients with anemia.

Supplemental Table 29: Evidence profile of RCTs examining ESA vs. ESA in CKD patients with anemia.

Supplemental Table 30: Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes).

Supplemental Table 31: Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (continuous outcomes).

Supplemental Table 32: Summary table of adverse events in RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php