Erythropoiesis-stimulating agents

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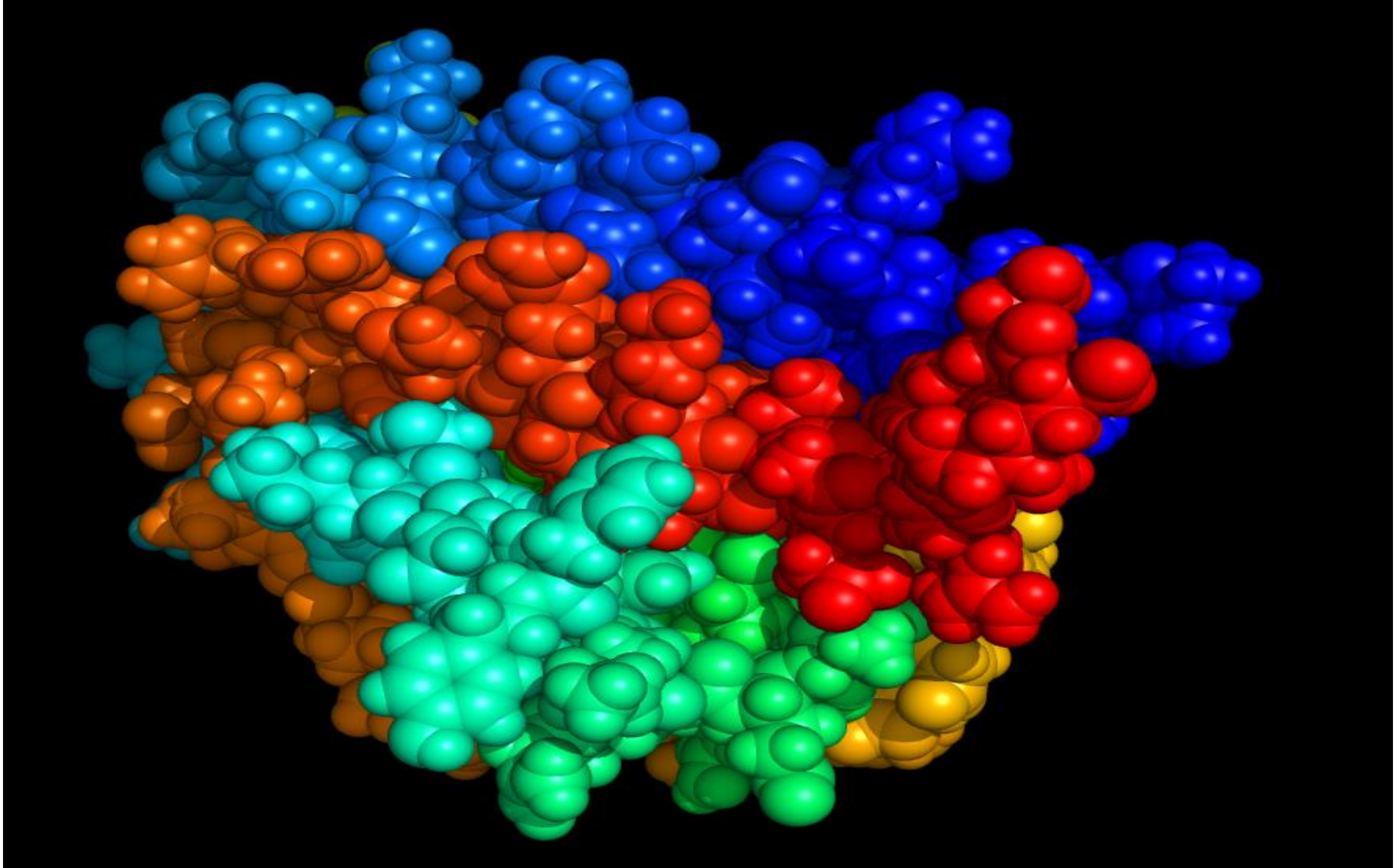
Erythropoiesis-stimulating agents (**ESA**) are medications which stimulate the bone marrow to make red blood cells. They are used to treat anemia due to end stage kidney disease, chemotherapy, major surgery, or certain treatments in HIV/AIDS. In these situations they decrease the need for blood transfusions. The different agents are more or less equivalent. They are given by injection. **Common side effects may include joint pain, rash, vomiting, and headache. Serious side effects may include heart attacks, stroke, increased cancer growth, or pure red cell aplasia**. It is unclear if use is safe during pregnancy. They work similar to naturally occurring erythropoietin.

They were first approved for medical use in the United States in 1989. It is on the World Health Organization's List of Essential Medicines. Commercially available agents include epoetin alfa and darbepoetin alfa, and biosimilars. Use among athletes is prohibited by the World Anti-Doping Agency.

- epoetin alfa:
  - Darbepoetin (Aranesp)[14][15]
  - Darbecept (Celon labs)
  - Epocept (Lupin pharma)
  - Nanokine (Nanogen Pharmaceutical biotechnology, Vietnam)
  - Epofit (Intas pharma)
  - Epogen, made by Amgen
  - Epogin
  - Eprex, made by Janssen-Cilag
  - Binocrit, made by Sandoz[16]
  - PDpoetin, made by pooyeshdarou biopharmaceutical company IRAN
  - Procrit[17]
  - Bioyetin, made by Probiomed[18]
  - Abseamed (Medice Arzneimittel Pütter GmbH Co. KG) [19]
- epoetin beta:
  - NeoRecormon, made by Hoffmann–La Roche
  - Recormon
  - Methoxy polyethylene glycol-epoetin beta (Mircera) by Roche[20]
- epoetin delta:
  - Dynepo trademark name for an erythropoiesis stimulating protein, by Shire plc[21]
- epoetin omega:
  - Epomax
- epoetin zeta (biosimilar forms for epoetin alpha):
  - Silapo (STADA Arzneimittel AG)[22]
  - Retacrit (Hospira, Pfizer Europe MA EEIG)[23]
- Miscellaneous:
  - Epocept, made by Lupin Pharmaceuticals
  - EPOTrust, made by Panacea Biotec Ltd
  - Erypro Safe, made by Biocon Ltd.
  - Repoitin, made by Serum Institute of India Limited
  - Vintor, made by Emcure Pharmaceuticals
  - Epofit, made by Intas pharma
  - Erykine, made by Intas Biopharmaceutica
  - Wepox, made by Wockhardt Biotech
  - Espogen, made by LG life sciences.
  - ReliPoietin, made by Reliance Life Sciences
  - Shanpoietin, made by Shantha Biotechnics Ltd
  - Zyrop, made by Cadila Healthcare Ltd.
  - EPIAO (rHuEPO), made by Shenyang Sunshine Pharmaceutical Co.. LTD. China
  - Cinnapoietin, made by CinnaGen biopharmaceutical Iran.



Erythropoiesis-stimulating agents

Indications and contraindications —

Most CKD patients who have a hemoglobin (Hb) <10 g/dL, providing the transferrin saturation (TSAT) is >25 percent and ferritin >200 ng/mL.

An important exception is among patients with active malignancy or a recent history of malignancy, particularly those in whom cure is anticipated, or who have had a stroke since such patients may be at higher risk for adverse effects from ESAs.

To patients with TSAT ≤25 percent and ferritin ≤500 ng/mL, we usually administer iron before giving an ESA since they may respond to iron with an increase in Hb.

The administration of ESAs has substantially reduced the need for red cell transfusions (with an attendant decrease in and/or risk for transfusion-related complications)

However, the Hb concentration at which to initiate ESAs is not known with certainty, and the safety of ESAs in treating even severe anemia has not been evaluated in large, placebo-controlled trials. 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines that the
Potential benefits of reducing blood transfusions and anemia-related symptoms should be balanced against the harm in individual patients (such as stroke, vascular access loss, and hypertension).

Route of administration

For CKD patients, an ESA,

whether epoetin or darbepoetin, be administered subcutaneously.

Studies have shown that the subcutaneous dose of epoetin required to achieve a target Hb is approximately 30 percent less than that required with intravenous administration .

Intravenous and subcutaneous administration of darbepoetin are of similar efficacy.

For nondialysis CKD patients, subcutaneous administration is more convenient for the patient as it allows self-administration.

The avoidance of intravenous administration also allows the better preservation of veins for future hemodialysis access.

However, IV administration is often favored for hemodialysis patients because subcutaneous administration is associated with significantly greater discomfort and IV access is available for the dialysis treatment.

In the United States, over 90 percent of hemodialysis patients received ESAs intravenously in a report published in 2004. Subcutaneous administration used to be more commonly used outside the United States.

In the report cited above, IV administration was the major route in 11 of 12 countries. More recent information about administration practices in different countries is not available.

Dosing —

The initial epoetin dose is approximately 50 to 100 units/kg/week. However, the use of lower doses would also be reasonable, particularly in patients with pretreatment Hb levels near 10 g/dL.

In practice, most patients are dosed by unit dosing (eg, a vial), rather than on a strict unit/kg basis. Thus, we initiate therapy in most patients beginning at 4000 or 10,000 units subcutaneously once weekly or 10,000 to 20,000 units subcutaneously every other week.

Weekly or even less frequent dosing regimens have been shown to be effective and safe, although long-term studies are lacking.

A meta-analysis including seven randomized trials demonstrated no difference in Hb when epoetin was administered every two to four weeks compared with more frequent (weekly) dosing intervals.

The dose of ESA required to reach target Hb varies widely among hemodialysis patients. Generally, the dose is adjusted monthly in response to the Hb. The Hb increase should generally be in the range of 1 to 2 g/dL per month. The dose of ESA should be reduced in patients whose Hb rises above this threshold increase. Among those with an Hb increase greater than 2.5 to 3 g/dL per month, the ESA dose should be held or reduced by at least 50 percent.

Darbepoetin is typically initiated with doses of 60 to 200 mcg subcutaneously every two to four weeks. If necessary, subsequent adjustments are made in interval and/or dose.
We suggest that **the lowest effective ESA dose be used**.
Higher ESA doses (primarily epoetin doses greater than 10,000 units per week or equivalent darbepoetin doses) have been associated with increased mortality and cardiovascular events independent of Hb level.
Methoxy polyethylene glycol-epoetin beta has also been approved for use in patients with CKD with a recommended initial starting dose of 0.6 mcg/kg by intravenous (IV) or subcutaneous injection every two weeks and monthly dosing subsequently.
Epoetin alfa-epbx is the first epoetin "biosimilar" agent approved in the United States; as with other epoetins, the package insert recommends thrice-weekly dosing, which is impractical

Types

- Erythropoietin (Epo)
- Epoetin alfa (Procrit, Epogen)
- Epoetin beta (NeoRecormon)
- Epoetin zeta (Silapo, Retacrit)
- Darbepoetin alfa (Aranesp)
- Methoxy polyethylene glycol-epoetin beta (Mircera)

Target hemoglobin value

— For most nondialysis CKD patients who are treated with ESAs, we maintain **Hb levels between 10 and 11.5 g/dL using the lowest possible ESA dose**.

We individualize therapy in some patients who may have improvements in quality of life at Hb ≥11.5 g/dL and will be prepared to accept the possible risks associated with higher Hb targets.

The US Food and Drug Administration (FDA) boxed warning on ESAs states that, for nondialysis CKD patients, one should consider ESA treatment only when the Hb level is <10 g/dL and reduce or interrupt the ESA dose if the Hb level exceeds 10 g/dL.

Among both dialysis and nondialysis CKD patients, multiple studies have shown that Hb targets ≥13 g/dL are associated with adverse outcomes.

A number of randomized trials have compared Hb target levels for predialysis patients with CKD .

The best data are from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial, in which 4038 patients with type 2 diabetes and CKD (estimated glomerular filtration rate [eGFR] between 20 to 60 mL/min/1.73 m^2) were randomly assigned to receive darbepoetin alfa to achieve a target Hb level of 13 g/dL or to placebo, with darbepoetin administered if the Hb level was <9 g/dL .

The primary endpoints were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction [MI], heart failure, stroke, and hospitalization for myocardial ischemia) and death or end-stage renal disease (ESRD).

The mean achieved Hb level was 12.5 g/dL and 10.6 g/dL in the darbepoetin and placebo groups, respectively.

At a median follow-up of 29 months, both groups had similar risks of death or a cardiovascular event or ESRD. However, there was an increased risk of fatal or nonfatal stroke with darbepoetin alfa (101 versus 53 patients with placebo; hazard ratio [HR] 1.92, 95% CI 1.38-2.68), while red cell transfusions were significantly more common in the placebo group (496 versus 297 patients). Fatigue was only modestly less common with darbepoetin. There was also an increased risk of death due to malignancy in the darbepoetin group, primarily in patients with a past history of malignancy.

It should be noted that, in the TREAT study and others comparing lower and higher Hb targets in patients with CKD, the mean age of study participants was typically in the 50- to 60-year range, and many patients had cardiovascular disease. Whether younger patients and those without other comorbid conditions are also at greater risk of complications when higher Hb levels are targeted remains to be studied.

The adverse effects associated with erythropoietin in predialysis patients are similar to those observed in hemodialysis patients.

Adverse effects of erythropoiesis-stimulating agents

Some adverse effects have only been described when ESAs are used to attain a normal Hb.
These include
1- increased mortality, 2- cardiovascular events, and 3- malignancy.
There is also an 4- increased risk of hemodialysis access thrombosis.
In the NHT trial, access thrombosis occurred in 39 percent in the 14 g/dL group compared with 29 percent in the 10 g/dL group.
5- Hypertension and seizure may be observed when ESAs are used to target lower Hb concentrations. The risk of hypertension appears to be independent of the target Hb.

There is little evidence of increased incidence of seizures in normotensive patients treated with an ESA.

It is not possible to predict in advance who will develop seizures with an ESA. Prodromal symptoms including persistent headache or visual disturbances that develop in the early weeks after institution of an ESA suggest the possibility that seizures will occur. The presence of other ESA-related reactions or side effects (such as exacerbated hypertension or a rapid rise in Hb) may suggest the possibility of seizures.

TRANSFUSION — Red blood cell (RBC) transfusions will immediately raise hemoglobin (Hb) levels.
However, they may be associated with significant complications that include transfusion-transmitted infection (very rare), immunologic sensitization, iron overload syndromes, volume overload, and/or transfusion reactions.
Transfusions are rarely administered in chronic dialysis facilities but are indicated for treatment of severe or symptomatic chronic anemia unresponsive to erythropoiesis-stimulating agent (ESA) and iron therapy.

ESA resistance, or hyporesponsiveness,

INTRODUCTION — Erythropoiesis-stimulating agents (ESAs) are commonly used to treat anemia associated with chronic kidney disease (CKD). **ESA resistance, or hyporesponsiveness, is a term used to describe patients who do not achieve the desired hemoglobin (Hb) concentration despite higher than usual doses of ESAs or who require increasingly higher ESA doses to maintain an Hb concentration.**

Failure:

ESAs may fail to achieve an adequate therapeutic response when one or more of the following is present:[13]

- Occult blood loss and/or iron deficiency
- Vitamin B_{12} or folate deficiency
- Infection and inflammation
- Inadequate dialysis
- Hyperparathyroidism
- Aluminum toxicity
- Patient adherence
- Hypothyroidism
- Primary disease activity
- Transplant rejection
- Malignancy
- Pure red cell aplasia

DEFINITION AND CRITERIA — As noted above, **ESA resistance is a term used to describe patients who do not achieve the desired hemoglobin (Hb) concentration despite higher than usual doses of ESAs or who require increasingly higher ESA doses to maintain a target Hb concentration.**

ESA resistance is generally relative rather than complete.

ESA resistance is also referred to as hyporesponsiveness.

Criteria for ESA resistance are not well defined. We use the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria of inability to achieve or maintain a desired Hb concentration using a maximum dose of 450 units/kg per week intravenous erythropoietin or 300 units/kg per week subcutaneous erythropoietin.

Other criteria have been suggested by European Best Practice Guidelines and Kidney Disease Improving Global Outcomes (KDIGO):

- Failure to attain or maintain desired Hb concentration with 300 units/kg per week of erythropoietin (approximately 20,000 units/week) and 1.5 mcg/kg per week of darbepoetin alfa(approximately 100 mcg/week).
- Having no increase in Hb concentration after the first month of appropriate weight-based dosing and/or requiring two increases in ESA doses up to 50 percent beyond the dose at which the patient had originally been stable.

A practical definition of an ESA-resistant patient is one who requires a dose that is greater than that given to 90 percent of patients in a given facility

EPIDEMIOLOGY — One contemporary, retrospective study identified ESA hyporesponsiveness, defined as two consecutive hemoglobin (Hb) levels <10 g/dL while receiving epoetin >7700 units per dose, in 12.5 percent of hemodialysis patients.

ESA resistance among patients on peritoneal dialysis has not been well studied but is likely much less common than among hemodialysis patients as peritoneal dialysis patients generally tend to have higher Hb levels and require lower ESA doses.

CAUSES — Iron deficiency and infection and/or inflammation are the two most common causes of ESA resistance. These and other causes are discussed below.

Iron deficiency — Iron deficiency is a common cause of ESA resistance. Iron deficiency may be absolute (which is often due to external blood losses) or functional (related to ESA administration or anemia of chronic disease). All patients with ESA resistance should be assessed for absolute and functional iron deficiency.

Infection or inflammation —
Chronic inflammation is common among hemodialysis patients and an important cause of ESA resistance.

1- Dialysis catheters are a common cause of chronic inflammation. Other causes include

2- skin or wound infections;

3- failed kidney transplant;

4- occult infection of an old,

5- nonfunctioning arteriovenous graft; and

6- human immunodeficiency virus (HIV) infection. The role of hepatitis C as a cause of ESA resistance has not been studied.

Inadequate dialysis —
Inadequate dialysis may cause ESA resistance.
In an old study of 20 stable hemodialysis patients who were modestly under-dialyzed (mean urea reduction ratio [URR] 60.7 percent), increasing the dialysis dose was associated with an increase in hematocrit despite a constant dose of ESA [14]. Differences in the dialysis membrane may have affected the ESA response since the increase in urea clearance was achieved by changing to a larger dialyzer with a different membrane. However, the dialyzer membrane has not been shown to affect the ESA response in other studies [16-18].

Other — Other conditions associated with ESA resistance include
1-severe hyperparathyroidism with osteitis fibrosis cystica,
2- bone aluminum accumulation (now very rare),
3- malignancy,
4- bone marrow disorders such as myelodysplastic syndrome and multiple myeloma, and hemoglobinopathies, such as sickle cell disease.
5- B12 and folate deficiencies have also been reported in ESA hyporesponsive patients.
6- Pure red cell aplasia, a condition of complete ESA resistance, has been associated with the subcutaneous administration of particular brands of ESA, which are no longer available.
6- Some reports suggest that the administration of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor antagonists may cause relative ESA resistance.

In patients with ESA resistance, the ESA can be stopped or continued at a low dose that helps to minimize transfusion requirements with use of transfusions as needed to manage anemia-related symptoms.

Results of a single, phase IIa, exploratory study indicated that the hypoxia-inducible factor prolyl hydroxylase inhibitor daprodustat increased hemoglobin (Hb) in two of seven hemodialysis patients who remained on treatment for 16 weeks [32]. Additional studies will be needed to assess the role of this newer class of ESAs in dialysis patients resistant to epoetins.

A number of noniron pharmacologic agents have been evaluated as adjuvants to ESAs. These agents include L-carnitine, ascorbic acid, androgens, pentoxifylline, statins, and others .

OUTCOMES

Mortality — ESA resistance is associated with increased mortality. one observational study of hemodialysis patients in the United States, patients who had hemoglobin (Hb) <9.5 g/dL and received larger ESA dose changes over an 11-month period had a higher mortality risk (hazard ratio [HR] 1.32).

In another study that used data from the Normal Hematocrit Cardiac Trial, a higher erythropoietin-responsiveness measure (defined as the ratio of the weekly hematocrit change per ESA dose increase) was associated with lower mortality (with an adjusted HR of 0.41 for highest versus lowest quartiles).

The increased mortality associated with ESA resistance is likely due to the underlying cause of ESA resistance. However, some studies have suggested that the increased mortality is related to the higher ESA doses that are used in these patients.

Progression of chronic kidney disease (CKD) — ESA resistance may be associated with more rapid progression to end-stage renal disease (ESRD). This was suggested by a study of 194 consecutive CKD patients who started ESAs between 2002 and 2006. Patients were classified as poor, intermediate, and good responders based upon their response to the first administered ESA dose. Responsiveness was calculated according to the formula: $(Hb_1\text{-}Hb_0)$/time/ESA dose where Hb_1 and Hb_0 correspond to Hb values at the first visit after ESA administration and at baseline, respectively; time refers to the period between visits; and ESA dose is the first weekly dose prescribed. ESA responsiveness was expressed as g/dL/month, standardized to 10 mcg/week. During a median follow-up of three years, poor responsiveness was associated with a higher risk of ESRD (HR 2.49, 95% CI 1.28-4.84). The mechanism underlying this possible association is not known.