2009: A Requiem for rHuEPOs—But Should We Nail Down the Coffin in 2010?

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The recombinant human erythropoietins and allied proteins (epoetin alfa, attempted copies and biosimilar variants of epoetin alfa, epoetin beta, epoetin delta, epoetin zeta, epoetin theta, epoetin omega, darbepoetin alfa, and methoxy-polyethylene glycol-epoetin beta) are among the most successful and earliest examples of biotechnologically manufactured products to be used in clinical medicine. This article charts a brief history of their use in clinical medicine, mainly dealing with chronic kidney disease, paying special attention to how these agents were introduced into clinical medicine and what has happened subsequently; in 2009, there were several developments that could be regarded as a “perfect storm” in terms of the long-term use of these compounds in chronic kidney disease and oncology and, likely, elsewhere. We are now very much at a “crossroads,” where mature reflection is required, because with the latest trials and meta-analyses, these therapies seem not only expensive but also very much a clinical tradeoff (increased risk of adverse effects versus a small gain in fatigue scores). How we arrived at this crossroads is a useful illustration of how easy it is, without properly designed randomized, controlled trials, to assume that clinical benefit must follow therapeutic interventions.


The recombinant human erythropoietins (rHuEPOs; epoetins) and allied proteins (epoetin alfa, attempted copies and biosimilar variants of epoetin alfa, epoetin beta, epoetin delta, epoetin zeta, epoetin theta, epoetin omega, darbepoetin alfa, and methoxy-polyethylene glycol-epoetin beta) are among the most successful and earliest examples of biotechnologically manufactured products to be used in clinical medicine (1). In the past two decades, they have been used in more than 1,000,000 patients, mainly in those with chronic kidney diseases (CKDs). The rate of expansion in the biopharmaceutical industries may have slowed with the recent global economic downturn but is still strongly positive (2), and many regard these expensive biotechnology products to be an important part of the future of medicine.

This article charts a brief history of their use in clinical medicine, mainly dealing with CKD, paying special attention to how these agents were introduced into clinical medicine and what has happened subsequently; in 2009, there were several developments that could be regarded as a “perfect storm” in terms of the long-term use of these compounds in CKD and oncology and, likely, elsewhere. We are now very much at a “crossroads,” where mature reflection is required, because with the latest trials and meta-analyses, these therapies seem not only expensive but also very much a clinical compromise. How we arrived at this crossroads is a useful illustration of how easy it is, without properly designed randomized, controlled trials (RCTs), to assume that clinical benefit must follow therapeutic interventions.

First-Generation rHuEPOs: Scientific Background

Erythropoiesis is a complex physiologic process through which homeostasis of oxygen (O2) levels in the body is maintained. It is primarily regulated by EPO, a 30-kD, 165–amino acid hematopoietic growth factor that is produced primarily by renal tubular and interstitial cells. Under normal conditions, endogenous EPO levels change with O2 tension. In the presence of EPO, bone marrow erythroid precursor cells proliferate and differentiate into red blood cells. In its absence, these cells undergo apoptosis (3). Binding of EPO causes conformational changes to the dimeric (two chains 64 kD) EPO receptor, transphosphorylation of associated JAK2 molecules, phosphorylation of tyrosine residues, and phosphorylation or activation of several signaling molecules. Phosphorylation of signal transducers and activators of transcription 5 transcription factor causes homodimerization, translocation to the nucleus, and activation of genes for antiapoptotic molecules (3).

The human EPO gene was first cloned in 1983. This was an essential step that led to clinical development of rHuEPO. Endogenous EPO and rHuEPO share the same amino acid sequence, with slight but functionally important differences in the sugar profile. In clinical practice, rHuEPO is typically administered as a bolus injection, and the dosage is titrated to give the desired effect (3).

Patents for epoetin alfa are held by Amgen and Kirin, which market epoetin alfa under the brand name Epogen and ESPO, respectively. Epoetin alfa is also marketed by licensee Johnson & Johnson in the United States as Procrit and in non-US terri-
tories as Eprex. Combined worldwide 2005 sales of epoetin alfa were US$6.163 billion. Epoetin alfa is indicated for the treatment of anemia associated with chronic renal failure, including patients who are and are not on dialysis (which holds true for the other epoetins). Epoetin alfa is also indicated for treatment of anemia in zidovudine-treated patients with HIV infection; patients who have cancer and are on chemotherapy; and patients who are scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusion. The European patent for epoetin alfa expired in 2004, and the US patent expired in 2004 for the gene and will expire in 2013 for the compound.

Patents for epoetin beta are held by Roche and Chugai, originating from the Genetics Institute. The companies market epoetin beta only in non-US territories under the brand name Neo-Recromon (Roche) and Epozin (Chugai), respectively. Consolidated epoetin beta sales in 2005 were US$1.726 billion. Approved indications for epoetin beta are basically the same as those for epoetin alfa. The European patent for epoetin beta expired in 2006.

Both epoetin alfa and epoetin beta (a more glycosylated protein that has a longer half-life in vivo) are produced in CHO cells, whereas epoetin omega is produced in baby hamster kidney cells. Baxter acquired epoetin omega from Elanex Pharmaceuticals. Epoetin omega is marketed in more than 15 countries outside the United States, but Baxter later abandoned the development of epoetin omega (also known as Epomax) in Europe.

Epoetin delta was developed by Transkaryotic and Aventis in Europe and obtained European Marketing Authorisation. Shire Pharmaceuticals, which acquired Transkaryotic Therapies, launched epoetin delta in 2007 (produced in a human cell line and therefore possessing glycosylations that are characteristic of human cells, not other mammalian cells as in all other recombinant epoetins); the marketing of this epoetin was then withdrawn 1 year later because of unfavorable market conditions.

Second-Generation EPO

Both major EPO manufacturers Amgen and Roche then developed next-generation EPO molecules with a longer duration of action, thereby reducing the frequency of administration (3). Amgen achieved this goal by glyco-engineering of EPO and obtained darbepoetin alfa (Aranesp, or KRN321; Kirin). Aranesp was already approved in 2001 and achieved sales of US$3.273 billion in 2005. Roche’s follow-up EPO product—involving a pegylation to achieve a molecule of approximately 60,000 Da and an extended half-life of approximately 137 hours, continuous erythropoietin receptor activator [CERA] (4)—was filed in 2007 in the United States and in the European Union for renal anemia but immediately caused Amgen to sue Roche (and win) over alleged violation of Epozen patents, preventing its further importation into or use in the United States.

And Beyond

After the approval of the first biosimilar versions of epoetin in the European Union (5)—including epoetins omega, zeta, and theta—and of the first next-generation, longer acting EPO-derived product (CERA [4]), the competitive situation in the pipeline of new erythropoiesis-stimulating agents (ESAs) has considerably changed in favor of next-generation ESAs with improved features compared with early rHuEPOs. A wide spectrum of biologics and of small molecules is now under development (3). At least seven next-generation ESAs are in clinical development, and approximately 25 are in preclinical research and development (3). As of 2010, manufacturing of rHuEPO in off-patent countries has become a commodity all over the globe from countries in Europe (e.g., Ireland, Ukraine, Croatia), South America (e.g., Argentina, Cuba, Brazil, Mexico), Africa and the Middle East (e.g., Egypt, Israel, Iran, South Africa), and Asia (e.g., India, Vietnam, Korea, China, Taiwan).

What Has Gone Wrong?

To understand what has gone wrong, it is necessary to travel back in time to the 1980s and to the first reports of the human use of rHuEPO (6). It is worth reproducing the abstract from this seminal article, because this provides a nice description of the primary benefit of the intervention—transfusion avoidance (with the attendant risks from transfusion—infusion, iron overload, and allosensitization—all largely thereby abrogated)—pitted against hypertension and thrombosis as treatment-associated adverse effects:

“Ten patients with end-stage renal failure and anaemia (mean haemoglobin 6.1 g/dl, range 4.6–8.8 g/dl) on thrice-weekly haemodialysis were treated with human erythropoietin derived from recombinant DNA (rHuEPO). This was given as an intravenous bolus after each dialysis in rising doses within the range 3–192 IU/kg. All patients showed increases in reticulocyte numbers and haemoglobin concentration and after the first week of treatment none of the four previously transfusion-dependent patients needed further transfusions. In nine patients treated for 12 weeks haemoglobin rose to a mean of 10.3 g/dl, range 9.5 to 12.8 g/dl. Thereafter the dose of erythropoietin was adjusted to avoid a further rise in haemoglobin. During treatment one patient had an episode of hypertensive encephalopathy and two had clotting in their arteriovenous fistulas (complete in one). rHuEPO is an effective treatment for the anaemia of end-stage renal failure but longer-term observations are needed on the consequences of increasing the haematocrit. . .”

Even at this earliest stage, the administration of rHuEPOs was seen as a compromise, something that in 2010, 24 years later, is still very plain to see (7).

Three years later, in 1989, in an elegant and largely prescient review of the still nascent topic of rHuEPOs, Winearls (8) (again) concluded,

“Should all patients with renal anaemia receive erythropoietin?—“approximately one-quarter of haemodialysis patients are severely anaemic, requiring intermittent if not absolutely regular transfusions, and a further one half cope with haemoglobin of 7 to 9 g/dl. The case for treating patients is very strong. The decision to treat less severely anaemic patients, including those with chronic renal failure not yet established on dialysis, will be influenced not only by cost, but by objective

These comments were made in 1989, in the middle of the rHuEPO era. It is worth remembering that at that time, the use of rHuEPO was not widespread, and that many patients were still dependent on regular transfusions. The decision to treat patients with rHuEPO was therefore a significant one, and the benefits of treatment were clear.
assessments of the effect of treatment on symptoms and exercise tolerance and BP and the rate of progression of renal failure.”

The issue then was a simple one: No one at the time really appreciated the importance of mortality as a primary outcome of therapy. The focus was on the dramatic, palpable improvement in quality of life and functional capacity (physical and mental) of patients who previously had had terrible anemia, symptomatically so, with only potentially hazardous transfusions to support them. The benefit was “obvious” to all, to patients in particular. The battle indeed was then to try to afford this precious and expensive new drug therapy in the context of a long-term, expensive medical device treatment paradigm—renal dialysis—rather than to ration it (9).

As this battle was fought, a crucial opportunity was let slip, too. This was exemplified in the studies of the effect that rHuEPOs had on the heart. Cardiovascular disease takes a terrible toll on patients with CKD. Further work on rHuEPO showed that cardiac (and other physiologic) changes occurred with the correction or amelioration of anemia (10): Regression of left ventricular hypertrophy (LVH; driven originally largely but not exclusively by profound anemia). LVH of course is well appreciated as a malign influence on patient survival and is more frequent as kidney function declines and with each 1-g/dl reduction of hemoglobin (Hb). It was therefore assumed that with the reduction in LVH seen with rHuEPO would be a survival benefit, but proving this outcome formally was never undertaken using clinical trials. London et al. (11) showed in a miniscule trial of just 11 hemodialysis patients, over no more than 6 months of rHuEPO, that partial correction of severe anemia led to reduced LV cavity volume, left atrial volume, and LV mass index, using primitive (by today’s standards) echocardiographic techniques. MacDougall et al. (12) studied just 10 hemodialysis patients, albeit more comprehensively, and for longer (12 months), and, again, with substantial but incomplete correction of profound anemia, there were salutary changes in many cardiorespiratory parameters.

Contrast these early findings with the largest and most recent and complex examination of the effect of partial correction of anemia on the heart, a study of 603 patients: 451 (baseline) echocardiograms performed patients who had CKD and were not on dialysis, with repeated echocardiography at annual intervals (155 having echocardiograms at year 3). This trial was performed in a crucial respect, namely the comparison was between modest and more vigorous anemia correction (not correction versus no correction, or using the patients as their own historical controls). In that article (13), the effect of LVH on survival was abundantly clear, whereas the effect of anemia correction (to different Hb targets) on LV mass was very difficult to discern, although in the relatively few patients (approximately 20%) who started with “eccentric” LVH, there was a suggestion that this pattern of LV structure was poorly served by more complete anemia correction (reduction in survival, \( P = 0.034 \), but uncorrected for several other important confounders). It is likely that partially correcting severe anemia does improve cardiac structure and function, as shown 20 or more years ago, but also that a more complete correction of milder anemia seems not to confer as much or possibly any structural or functional benefit, let alone improve patient survival.

Crucially and explaining why “controlled” trials were not performed, in the interim, guidelines groups (Kidney Disease Outcomes Quality Initiative [KDOQI]), spurred on by clear epidemiologic associations, favorable small reports, and intermediate/surrogate end point optimism, had recommended the routine use of rHuEPOs to achieve Hb targets of 11 to 12 g/dl (14,15). The latest KDOQI revised guidelines statement (15) has nicely reviewed the history of rHuEPO trials (Figure 1), and this clearly shows that once the first set of guidelines had been issued in 1997 (14), there were no RCTs involving placebo arms (until the Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT] [7], reported in 2009). In the 20 years between 1989 and 2009, a lot happened “on the ground” with the routine treatment of patients. rHuEPO use gradually became ubiquitous for dialysis patients whose spontaneous Hb was <11 g/dl (driven by repeated guideline statements [14,15] and by repeated international dialysis and therapy practice comparison exercises [e.g., Dialysis Outcomes and Practice Patterns Study [DOPPS]] (16)). Both of these parallel and self-referencing influences then led to a marked increased in both the rHuEPO dosage (and hence cost) and final achieved Hb concentrations in dialysis patients, with a marked trend also to include patients who had CKD with lesser degrees of renal dysfunction. It was a one-way system—pointing upward.

This made it practically impossible to contemplate using a placebo arm in future trials; therefore, more than a decade followed from the first guideline position in 1997, after which, despite the obvious and challenging expense of the intervention, there was an innate assumption that the use of rHuEPOs must be favorable and that failing to deploy them was a marker of poor clinical practice (16). This rose-tinted view of the correction of anemia being primarily ESA based was reinforced by studies that attempted to quantify and track quality-of-life improvements (8). But the battle was fought in the context of a long-term, expensive medical device treatment paradigm—renal dialysis—rather than to ration it (9).

![Image](Image)

Figure 1. RCTs comparing lower and higher Hb target levels before the TREAT (see references [7,24]). Data are represented as target Hb (whiskers), achieved mean Hb for patients who were assigned to lower (○) or upper (○) Hb targets, and placebo or untreated control subjects (△). Study size (N) is indicated by the bars on the left (15).
changes with rHuEPOs (for a more detailed account see references [17,18]). By the early part of this new millennium, at a stage that in retrospect will be seen to be a “high Hb mark” for rHuEPOs, there were calls from guidelines groups (19) for more complete correction (which becomes, with each 1 g/dl of attempted correction, noticeably more expensive and more difficult to achieve).

A “Perfect Storm”

Apart from the clear descriptions of adverse effects and potential harm seen with the administration of rHuEPOs, well described in the 1980s and 1990s, the first serious safety and mortality concerns came with the Normal Hematocrit study by Besarab et al. (20) in 1998. Much has been written about this seminal study, but, in essence, a clear safety signal was sent whereby near-complete correction was attempted in a large cohort of cardiovascularly compromised hemodialysis patients (compared not with placebo but with incomplete, milder Hb correction). Despite this setback, recommendations became more, not less, liberal (19). Concerns became much more sharply focused in 2006, when two additional studies, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) (21) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (22), both in nondialysis cohorts with CKD, and, again, not using placebo-controlled subjects but treating to two different target Hb ranges, reported no benefit (CREATE) and possible cardiovascular harm (CHOIR)—in both cases, the primary end points were composite death and cardiovascular events. This time, more action ensued, with the Food and Drug Administration putting out a black-box warning for rHuEPOs (23). The different response was also in part because of another trend: In a sustained, never-ending search for different rHuEPO therapy indications, rHuEPO use was now increasingly to be found in patients with diabetes, in chronic heart failure, and cancer. Much, if not all, of the seminal research into the indications for and use of rHuEPOs (for a more detailed account see reference [27]) has now reached a new level of understanding. The impact of anemia associated with renal transplantation was. The results were revelatory: There were more significant anemia. The results were revelatory: There were more

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This has now has reached a new level of understanding. The TREAT (7) (reviewed in depth in reference [24]) showed, with, importantly, a placebo/rescue design, that there was no patient event-free survival benefit to having an Hb level of 12.5 g/dl (which was the achieved Hb level; the trial target was 13 g/dl) versus placebo 1.05; 95% confidence interval [CI] 0.94 to 1.17; P = 0.41). Death or ESRD occurred in 652 patients who were assigned to darbepoetin-alfa and 618 patients who were assigned to placebo (HR 1.06; 95% CI 0.95 to 1.19; P = 0.29). Fatal or nonfatal stroke occurred in 101 patients who were assigned to darbepoetin alfa and 53 patients who were assigned to placebo (HR 1.92; 95% CI 1.38 to 2.68; P < 0.001), and venous and arterial thromboses were more common. Red cell transfusions were administered to 297 patients who were assigned to darbepoetin alfa and 496 patients who were assigned to placebo (P < 0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group. It would have been only too easy for this study to have been cancelled after CREATE and CHOIR—there was much criticism of its design (lower Hb target unethically low as judged by some and the upper target unethically high, after CREATE and CHOIR, as judged by others), but wiser counsel prevailed, and the trial was allowed to be completed.

At the same time (in the same year, 2009), two large meta-analyses of the use of rHuEPOs in patients with cancer (a potentially very “lucrative” anemia market) both highlighted limited symptomatic benefit offset by safety and mortality concerns (cancer is known to be a state in which increased coagulability potentiates thrombosis [25,26]). A total of 13,933 patients with cancer from 53 trials were analyzed; 1530 patients died during study and 4993 died overall. rHuEPOs increased on-study mortality (combined HR [cHR] 1.17; 95% CI 1.06 to 1.30) and worsened overall survival (cHR 1.06; 95% CI 1.00 to 1.12), with little heterogeneity between trials (I² = 0% [P = 0.87] and I² = 7.1% [P = 0.33], respectively). Thirty-eight trials enrolled 10,441 patients who were receiving chemotherapy. The cHR for on-study mortality was 1.10 (95% CI 0.98 to 1.24) and 1.04 (95% CI 0.97 to 1.11) for overall survival.

We can also add to the mix another negative aspect of anemia correction by rHuEPOs. Heinze et al. (27) used an extensive Austrian registry of transplant recipients to ask the what the impact of anemia associated with renal transplantation was. There was a graded relationship between worse anemia and patient survival—itself not so surprising—but also a worrying increase in mortality seen in rHuEPO-treated patients with Hb values >14 g/dl (26).

Thus, it was only in chronic heart failure (often but not invariably accompanied by mild CKD) that there was evidence of benefit (symptoms, cardiac biomarkers). Compared with placebo, rHuEPO therapy was associated with improvement in six cardiovascular parameters assessed by at least three of the analyzed trials, including increase in Hb levels (HR 2.35; 95% CI 1.76 to 2.93; P < 0.00001), increase in exercise duration (HR 0.91; 95% CI 0.89 to 1.73; P = 0.03), improvement in New York Heart Association functional class (HR 1.46; 95% CI −2.32 to −0.60; P = 0.0009), improvement in 6-minute walk test (HR 1.42; 95% CI 0.31 to 2.54; P = 0.01), decrease in B-type natriuretic peptide (HR 0.54; 95% CI 1.03 to −0.06; P = 0.03), and improvement in peak oxygen consumption (HR 0.93; 95% CI 0.52 to 1.34; P < 0.00001). These findings are promising and clearly in the direction of net clinical benefit, but as yet we have reports of only a few hundred patients who were administered rHuEPO over a relatively small period (typically <6 months.
Most recently, though, a striking finding that challenges the orthodoxy that only rHuEPO therapy confers quality-of-life improvements was reported in the Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Heart Failure (FAIR-HF; ClinicalTrials.gov identifier NCT00520780 [29]). Here, the long-term use of intravenous iron therapy improved symptoms, functional capacity, and quality of life, without any relation to the achieved Hb on treatment and with an acceptable adverse effect profile.

Clearly, it is fundamental to a mature contemporary understanding of these newer clinical indications for the use of rHuEPOs once again to allow large and long-duration studies to be undertaken to ascertain the true clinical picture using a placebo/control-arm design. Animal models, however seductive, can provide only really limited guidance [30] for long-term use in humans. It may well be that the majority of the apparent clinically noticeable benefit from rHuEPOs (once Hb has risen or if it starts from higher levels) will come from iron-based interventions; this must be prospectively tested in a logical sequence (using first intravenous iron and then, only if necessary, adding in rHuEPOs) in patients with heart failure and also in patients with CKD.

**Shorter Term Clinical Actions of rHuEPOs: The Jury Is Still Out**

Nonhematologic indications for the use of rHuEPOs (and allied molecules)—especially protection against ischemia-reperfusion injury (31)—remain a tantalizing further potential short-term use for these same molecules. Some years ago, there was a suggestion from a small clinical study that rHuEPOs could provide some modest neuroprotection in acute stroke. However, in the recently published double-blind, placebo-controlled, randomized German Multicenter EPO Stroke Trial (Phase II/III; ClinicalTrials.gov identifier NCT00604630) in which 522 patients with acute stroke involving the middle cerebral artery were enrolled and randomly assigned to received 40,000 IU of rHuEPO, not only was there no benefit—in fact the rate of thrombolysis was high—but there was a clear safety message: 16.4% of rHuEPO-treated patients died compared with 9% of control subjects (P < 0.01) (32). Another recent large clinical study that examined the use of rHuEPO in intensive care unit-related acute kidney injury reported negative results (33). No other convincing clinical studies have emerged, which sadly relegates this rHuEPO-promulgated "cytoprotection" to the brigades of therapies that have failed to make the transition from bench to bedside.

**New Drugs for Old**

Another important development with respect to future uses of rHuEPOs came in 2009 from a report of the use of a novel EPO-mimetic peptide (not a hyperglycosylated or pegylated variant of native EPO) that successfully induced a rise in Hb in patients with pure red cell aplasia (anti-EPO antibodies, cross-reacting and neutralizing), opening up the possibility of another way to achieve long-term elevation of Hb without using something that closely resembles the native hormone (i.e., rHuEPO) but using a cleverly engineered peptide that acts through the same receptor (34) and causes presumably identical intracellular events. That of the 14 patients who were treated one showed anti-Hematide antibodies, again cross-reacting and neutralizing, is a concern, but the true frequency of this important adverse effect (and any others) will become apparent only once several large Phase III trials have been reported later in 2010.

**Conclusions: Back to the Future?**

We are perhaps closer to being back in the 1980s than we might care to admit now. Severe anemia we know is unpleasant and most likely harmful to patients with CKD—we have known this about CKD for nearly five decades (8). Contrary to our hopes and expectations of a couple of decades ago, however, correcting anemia fully using rHuEPO seems to lack evidence to recommend it clinically, let alone pharmacoeconomically.

Even when we look from the epidemiologic clinical practice data (from DOPPS [16]), we see that the risk for mortality is the same from an Hb of 10.0 g/dl right up to 12.0 g/dl (Figure 2). Essentially, this is the same outcome as we see in TREAT (7), although TREAT, as an RCT, can also crucially inform us, in granular detail, about the "tradeoffs" in the clinical equipoise described. Although indeed in this same publication there is a "lower risk" with higher Hb (see Figure 2)—in the approximately 20% of the DOPPS population with an Hb >12.0 g/dl—this is not proof that pharmacologically manufacturing a higher Hb in someone who is starting with a lower one will confer the same benefit. Many of the patients in the "higher Hb" category will be there "spontaneously" or require minimal rHuEPO, reflecting better underlying health, fewer comorbidities, and possibly also better dialysis patterns. Put another way, resistance to the actions of rHuEPOs, which usually translates into higher rHuEPO dosages yet lower Hb values, may be a surrogate marker for many malign clinical factors that could be expected to skew survival.

Partial anemia correction may impart some modest (perhaps best also left for patients to adjudicate) quality-of-life gains—although probably measurable only up to a Hb level of approximately 12 g/dl (35) but potentially also at the cost of some adverse effects, potentially fatal ones in a few cases, with special concerns for those with a history of or present malignancy...
(7, 24, 25), in the context of renal transplantation (27) or patients with type 2 diabetes and significant but not yet dialysis-requiring kidney failure (7). The large clinical trials of short-term administration of rHuEPO to patients with acute stroke (32) or acute kidney injury (33) were "negative"—indeed, the stroke trial also raised significant thrombotic safety signals. All rHuEPO-based anemia therapy remains an expensive undertaking, especially when higher Hb targets are chased (36). It may now be more pragmatic and safer to suggest full repletion of iron using intravenous therapy followed by ESAs only if anemia remains moderate to severe (<10 g/dl) and the risk–benefit relationship would also favor intervention. This aspect, iron management followed by ESA only when, despite iron repletion, anemia remains significant or symptomatic needs urgently to be tested by RCTs and would be especially relevant to both nondialysis and dialysis CKD settings (where, in the latter case, long-term iron loss from repeated blood/iron loss on dialysis contributes to anemia, as does chronic inflammation and a host of other dialysis-related anemia risk factors). The upper Hb treatment level for correction is still not clear from the available evidence and might well vary among patient cohorts. It seems very hard now to justify ESA treatment to achieve Hb levels >12 g/dl in the majority of contemporary patients with CKD; others might even suggest a lower Hb treatment target of 11 g/dl (and none of these potential targets has been tested in a placebo-controlled RCTs).

One additional important unknown factor is whether in the mode of raising Hb—transfusion, slow steady correction using rHuEPOs, or soon-to-be available novel small molecules—we find that it is simply the eventual Hb achieved, as opposed to which intervention we choose to use to raise the Hb, that has the dominant effect on outcomes. Thus, the once "grand idea" of everyone being treated to a uniformly higher Hb now seems a clinical and financial misconception, based on optimism and extrapolated epidemiology, not on the rigor of randomized, placebo-controlled trials. The severe censure by Unger et al. (37) (from the Food and Drug Administration perspective) of the clinical and trial use of rHuEPOs is a serious challenge to all (from the Food and Drug Administration perspective) of the biomarkers for increased risk, and selective benefit, from the use of rHuEPO are now urgently required (and should have been nested as substudies in the several recent large investigational studies). One could say that these efforts are long overdue.

**Disclosures**

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**References**

11. London GM, Zins B, Pannier B, Naret C, Berthelot JM, Jacquot C, Safar M, Drueke TB: Vascular changes in hemo-

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**Figure 3.** Various potential mechanisms for rHuEPO toxicity in humans.