Individualizing Decision-Making—Resurrecting the Doctor-Patient Relationship in the Anemia Debate

Rajiv Agarwal
Indiana University School of Medicine and Roudebush VA Medical Center, Indianapolis, Indiana

Among patients with chronic kidney disease (CKD), erythropoiesis-stimulating agents (ESAs) are approved for avoiding transfusions, a risk that increases when hemoglobin (Hgb) falls to <10 g/dl. Transfusions increase sensitization, prolong the waiting time to and the likelihood of transplantation, and when transplantation is performed worsen graft survival. Accordingly, the risk of transfusion among those expecting transplantation is comparable to that of cardiovascular events. Nonetheless, targeting Hgb to >13 g/dl is associated with increased cardiovascular events. Paradoxically, if this level is achieved mortality is lower. The anemia paradox—higher cardiovascular events when targeting higher Hgb but lower events when patients achieve these targets—appears to be at least partially attributable to a hyporeponse to ESAs. Whether it is the ESAs or conditions that lead to the increased ESA dose that provokes morbidity cannot be answered definitively at present. The lowest ESA dose to achieve the desired level of anemia correction appears to be a safer strategy. In acute illnesses, reducing the dose of ESAs or stopping it altogether may aggravate anemia, but this may be permissible. The rate of rise in Hgb >1 g/dl in any 2-week period is associated with an increase in blood pressure (BP) and poor outcomes. Accordingly, while initiating and maintaining ESA therapy, monitoring BP at home twice daily is warranted. The clinical decision-making process in managing anemia should consider the risks of transfusion; kidney transplant potential; presence of cancer; and the risks of stroke, heart failure, and possibly death. Above all, clinical decision-making should incorporate patient preference.

In the registration trials, transfusion requirements decreased within weeks after the initiation of therapy. The prestudy transfusion requirements of 0.52 units/patient per month were reduced to 0.1 units/patient per month after the first 4 weeks on epoetin therapy, and to ≤0.04 units/patient per month through 14 months of study (11).

Reduction in transfusion needs seen in registration trials was replicated in clinical practice (12). In the years preceding introduction of erythropoietin, in any given quarter of the calendar year, between 10% and 20% of the patients on hemodialysis were transfused as outpatients. In the first quarter of 1989, 15% of the patients required transfusions; by the fourth quarter of 1989 the transfusion rate dropped to 5%. A steady decline in transfusion rate as outpatients has been observed since then. At present, in any given quarter, <2% of the patients require outpatient transfusions. There is little doubt that with epoetin alpha use transfusions have been avoided.

The Risk of Transfusion Is Not Trivial

Transfusions among patients on dialysis or those progressing to ESRD are of concern because they can cause sensitization to HLAs, leading to production of panel reactive antibodies (PRAs). The number of HLA molecules contributed by the red cells is comparable to that of the leukocytes; depletion of leukocytes and platelets selected from donors with low amounts of red-cell HLA is not beneficial for reducing sensitization (13). Leukoreduction of red blood cell transfusions does not confer any protection against transfusion-associated allosensitization for potential kidney transplant candidates (14). The risk of...
sensitization is substantial and important. For example, compared with patients who have never received a transfusion, patients who receive more than ten transfusions have odds of having PRA >50% of approximately 4 (15). Even with one to five transfusions, the odds are doubled. The risk of broad sensitization with transfusion is disproportionately borne by patients with previous failed transplantation or multiparous women (16). Increased titers of PRAs increase the median time to transplantation and may completely preclude transplantation. For example, compared with those with PRAs <10%, patients with PRAs >10% had a median waiting time to receive a kidney transplant that was twice as long; the median time at which 50% of the patients receive a deceased donor transplant continues to increase and for those listed in 2003 was 2.8 years (12). Over the years, these patients with high PRA levels represent a disproportionately large share of the waitlisted patients. Currently, the percent of patients with PRAs >20% is 15.7%; those >80% represent 5.1% of the waitlisted patients (12). Furthermore, even when transplanted, compared with those with no PRAs, the graft of patients with higher PRAs may not survive as long (17). Introduction of epoetin has resulted in a significant decrease in the requirements for blood transfusion among patients awaiting transplantation and is associated with a significant reduction in transfusion-related sensitization and mean waiting time for transplantation (18). Epoetin has not changed sensitization associated with pregnancy (18).

For most patients with ESRD, it is widely accepted that a successful transplantation is the renal replacement therapy of choice. Not being transplanted or having to wait longer for transplantation is risky because in reduces survival (19). This is because the biggest risk of dialysis is being on dialysis. Not being transplanted is therefore a grave risk for an otherwise eligible dialysis patient (20). Kidney transplantation is a life-saving, life-prolonging, and a life-transforming procedure. The risk of sensitization is therefore not trivial. Given the nontrivial nature of this risk, the level of Hgb at which the risk increases may offer some guidance for the lower limit that we set for the Hgb target.

**Relationship Between Hgb Level and the Risk for Transfusion**

Studies suggest that the risk of transfusion increases substantially when Hgb falls to <10 g/dl. Randomized trials and observational studies can inform us of these risks. For instance, in the randomized normal hematocrit trial, compared with a reference Hgb level of 10 to 11 g/dl, the hazard ratio for transfusion doubled when Hgb was between 9 and 10 g/dl (6). This hazard ratio at Hgb <9 g/dl was 5. In the Trial to Reduce Cardiovascular Endpoints with Aranesp Therapy (TREAT) study, the hazard ratio of transfusion was 0.54 (95% confidence interval 0.49 to 0.65) among patients in the higher group (Hgb ≥13 g/dl) compared with those assigned to rescue therapy (9).

**Cardiovascular Risk of Targeting Hgb to ≥13 g/dl**

In the post-epoetin era, observational studies revealed the importance of anemia as a cardiovascular risk factor. These studies demonstrated that Hgb was associated with several benefits: reduced hospitalization, reduced heart failure, and even improved survival (1–5). Among those with CKD, anemia was determined to be a novel nontraditional cardiovascular risk factor. Those caring for these patients questioned whether patients should have just partial correction of anemia. Therefore, studies were designed to attempt complete correction of anemia. Four major trials have been performed to correct anemia completely or to near normal levels (summarized in Table 1). All of these studies targeted Hgb to ≥13 g/dl. All of these studies show that attempting to correct anemia to near complete levels is associated with increased cardiovascular morbidity and mortality.

**Table 1a. Trials with hard outcomes targeting Hgb >13 g/dl: Normal Hematocrit Trial**

<table>
<thead>
<tr>
<th>Normal Hematocrit Trial 1998</th>
<th>Target</th>
<th>Hemodialysis with Clinically Evident CHF or Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (30% [Hgb 10 ± 1])</td>
<td>High (42% [Hgb 14 ± 1])</td>
</tr>
<tr>
<td>Number</td>
<td>631</td>
<td>634</td>
</tr>
<tr>
<td>Death</td>
<td>185 (29%)</td>
<td>221 (35%)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>16 (2.5%)</td>
<td>20 (3.2%)</td>
</tr>
<tr>
<td>Either (primary end point)</td>
<td>201 (32%)</td>
<td>241 (38%)</td>
</tr>
</tbody>
</table>

The event rates are those based on the FDA’s analyses and not those reported in the published report. MI, myocardial infarction; CHF, congestive heart failure; CI, confidence interval.
However, when correction of anemia was achieved even within the high target arms, there was a lower observed risk of mortality (Figure 1). Like the observational studies, these randomized trials demonstrated that a higher achieved Hgb, even in the higher stratum, was associated with better outcomes (Figure 1); patients who did not achieve the target Hgb had the worst outcomes. This was the anemia paradox: a higher target Hgb increased cardiovascular events; a higher achieved Hgb was associated with fewer cardiovascular events.

### Explaining the Paradox

It is clear from the above that achieved Hgb does not appear to be associated with increased cardiovascular risk. Only when Hgb is targeted to be high and this target is not achieved is the increased cardiovascular risk seen. This is the paradox. Understanding this paradox will allow physicians to more wisely use erythropoiesis-stimulating agents (ESAs).

The disparity in cardiovascular event rate between achieved and target Hgb needs explanation. Patients who were targeted to near normal levels of Hgb often did not achieve the target and therefore were given more ESAs to achieve these targets. These patients were hyporesponsive to erythropoietin. This hyporesponsiveness carried with it an increased cardiovascular risk. What underlies this risk is unclear, but two culprits are evident: ESAs themselves or conditions that conferred hyporesponsiveness. Which of the two is the culprit cannot be an-

### Table 1b. Trials with hard outcomes targeting Hgb >13 g/dl: CHOIR 2006

<table>
<thead>
<tr>
<th>CHOIR 2006</th>
<th>Target</th>
<th>CKD, Hgb &lt;11, No Epoetin Past 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (Hgb 11.3 g/dl)</td>
<td>High (Hgb 13.5 g/dl)</td>
</tr>
<tr>
<td>Number</td>
<td>717</td>
<td>715</td>
</tr>
<tr>
<td>Death</td>
<td>39 (5.5%)</td>
<td>26 (3.6%)</td>
</tr>
<tr>
<td>CHF hospitalization</td>
<td>59 (8.3%)</td>
<td>42 (5.9%)</td>
</tr>
<tr>
<td>MI</td>
<td>12 (1.7%)</td>
<td>13 (1.8%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (1.7%)</td>
<td>11 (1.5%)</td>
</tr>
<tr>
<td>Either (primary end point)</td>
<td>125 (17.5%)</td>
<td>97 (13.5%)</td>
</tr>
</tbody>
</table>

The event rates are those based on the FDA’s analyses and not those reported in the published report.

### Table 1c. Trials with hard outcomes targeting Hgb >13 g/dl: CREATE 2006

<table>
<thead>
<tr>
<th>CREATE 2006</th>
<th>Target</th>
<th>CKD, Hgb 11 to 12.5 g/dl, No Epoietin. Epoietin Begun in Subnormal Group Once Hgb &lt;10.5 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (Hgb 11 to 12.5 g/dl)</td>
<td>High (Hgb 13 to 15 g/dl)</td>
</tr>
<tr>
<td>Number</td>
<td>301</td>
<td>302</td>
</tr>
<tr>
<td>Primary end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58 (19.3%)</td>
<td>47 (15.6%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Primary end point in CREATE: sudden death, MI, acute heart failure, stroke, transient ischemic attack, angina requiring hospitalization, peripheral vascular disease complication, or cardiac arrhythmias requiring hospitalization.

<sup>b</sup>Hazard ratio is that of lower target versus higher target.

### Table 1d. Trials with hard outcomes targeting Hgb >13 g/dl: TREAT 2009

<table>
<thead>
<tr>
<th>TREAT 2009</th>
<th>Target</th>
<th>CKD, Diabetes Mellitus, Not on Dialysis, Hgb &lt;11 g/dl, Darbepoietin for Rescue for Hgb &lt;9 g/dl. Double Blind</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (Hgb &gt;9 g/dl)</td>
<td>High (Hgb 13 g/dl)</td>
</tr>
<tr>
<td>Number</td>
<td>2026</td>
<td>2012</td>
</tr>
<tr>
<td>Death</td>
<td>395 (19.5%)</td>
<td>412 (20.5%)</td>
</tr>
<tr>
<td>CHF hospitalization</td>
<td>229 (11.3%)</td>
<td>205 (10.2%)</td>
</tr>
<tr>
<td>MI</td>
<td>129 (6.4%)</td>
<td>124 (6.2%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>53 (2.6%)</td>
<td>101 (5.0%)</td>
</tr>
<tr>
<td>Either (primary end point)</td>
<td>602</td>
<td>632</td>
</tr>
</tbody>
</table>
answered by the present data. Although conditions that confer hyporesponse may be the culprit, for now, for the sake of safety, the minimum dose of ESAs to achieve the clinical goal should be used. Not all adverse effects of ESAs are attributable to hyporesponsiveness. The rate of rise of Hgb and blood pressure (BP) are discussed below. Another situation that may reflect the “off-target” effect of ESAs deserves special mention. ESA use among patients with cancers can lead to metastasis and worsened survival. Accordingly, among these patients, the use of ESAs has been restricted by the FDA (21).

**Defining Hyporesponse**

The maximum doses that have been used in clinical trials have varied considerably. In response to the safety signals observed in the clinical trials, the FDA had the manufacturers of ESAs modify their package insert to address hyporesponsiveness. According to the package insert, the initial starting dose of 50 to 100 IU/kg given 3 times a week can be increased at four weekly intervals by 25%, but if a target Hgb of 10 g/dl is not achieved over 3 months, then the dose should not be increased further. Thus, 156 IU/kg of epoetin should, according to the label, be a ceiling dose. When given subcutaneously, the dose of epoetin can be reduced by approximately one-third (22). Thus, in my opinion, 100 IU/kg epoetin given subcutaneously 3 times a week should be the ceiling dose. Above this dose, the patient should be considered hyporesponsive.

It should be noted that the state of ESA responsiveness will vary over time in individual patients. This is borne out by the FDA analysis of the Normal Hematocrit Trial data (23). The initial response to a protocol-mandated increase in ESA dose of 50% to achieve a normal hematocrit allowed estimations of quintiles of response. No relationship emerged between these quintiles and subsequent mortality. No relationship emerged between the initial response to ESAs and the subsequently achieved Hgb. Therefore, ESA hyporesponse is dynamic and must be evaluated on an ongoing basis. One study found that an acute-phase reactant, serum albumin concentration, tracks closely with ESA response (24). Larger studies are needed to determine whether serum albumin and change in serum albumin can be used to track ESA responsiveness and individualize therapy.

**Managing Hyporesponse**

Increasing the dose of ESAs is not how hyporesponse should be treated. The underlying causes of hyporesponse often are readily apparent but at other times less obvious. There are numerous causes of hyporesponse of which iron deficiency still remains an important cause. Judicious use of iron and ESAs is generally associated with the best outcomes (25). Other treatable causes include missing dialysis, reducing the dialysis session length, volume overload, iron deficiency, hyperparathyroidism, infection, periodontal disease, diabetic foot, chronic allograft rejection, occult inflammation in a clotted access, aluminum intoxication, hemolysis, and rarely pure red cell aplasia (26). The breadth of causes that lead to hyporesponse suggests that the requirement of an increase in ESA need should alert the physician to an illness or condition that requires attention. The current focus of treating anemia in the U.S. dialysis unit through protocols has moved to simply achieving targets. Achieving targets has quite likely distanced the physician from investigating the cause of hyporesponse and the effect it has on the patient’s well being. The physician-patient relationship needs to be resurrected; the management of anemia is not about a target but about the well being of the patient.

**Individualizing Therapy—Incorporating Patient Preferences**

The current package insert has been revised to achieve a target Hgb between 10 and 12 g/dl. If the patient gradually achieves Hgb of 12.1 g/dl, is iron replete, has experienced a remarkable improvement in well being, and tells her physician not to cut the dose of epoetin alpha because it causes deterioration in the way she feels, should the physician heed her request? Suppose she receives epoetin alpha 15 IU/kg 3 times a week subcutaneously, should the physician cut the dose? Given the above scenario, there would be little reason not to heed the concerns of the patient. ESAs improve physical symp-
toms, performance, vitality, energy, sleep, cognitive functioning, and sexual functioning; social functioning and mental health show modest improvement, whereas emotional functioning and pain show very little improvement (27). On the other hand, if the patient was receiving 125 IU/kg, a high dose, the patient should likely have the dose reduced by 25%. They should be warned about the risks of targeting a higher level of Hgb.

There are several situations that deserve individual attention—children, pregnant women, and athletes. These patients have unique requirements and require individualized therapy. The objective should be to achieve a clinical goal mutually agreed on between the patient and their physician while minimizing the dose of ESAs: To dictate therapy by targeting Hgb to between 10 and 12 g/dl may not be appropriate for all patients. Consider as an example an athlete who complains of poor sports performance because of lack of energy and their Hgb is 12 g/dl. As an example, a professional basketball player, Alonzo Mourning, “was tired all of the time and was not able to even complete everyday tasks” when he was anemic (28). A meta-analysis among dialysis patients noted that ESA treatment has a consistent and positive effect on oxygen consumption per minute at the peak workload during the test (29). ESA treatment improved patient- and clinician-assessed physical functioning. Many patients, even when they are not athletes, do not feel that they have sufficient energy even when they have achieved Hgb of 12 g/dl. Patient preference and discussion of the risks and benefits should then guide therapy. In resolving the conundrum, the doctor patient relationship should take center stage—not guidelines, regulations, or financial considerations. No therapy is without risks. But physicians do not prescribe because a medication has risk; they prescribe for the benefits inherent to a drug. Balancing the risk and benefits should incorporate patient preferences.

Permissive Anemia

There are several situations in which the ESA dose may need to be capped. For instance, in a patient who has diabetic foot or an abscess, rather than ESA deficiency inflammation plays a more prominent role in the genesis of anemia. Some have even suggested that anemia is a protective response in these situations (30). Reducing ESA dose to the minimum or even stopping it altogether may lead to a further fall in Hgb. Fall in Hgb may be acceptable and physiologic. Trying to correct anemia at any dose of ESAs is probably not a wise strategy.

Borrowing from the term “permissive hypercapnia” often utilized to prevent barotrauma in patients with adult respiratory distress syndrome, permissive anemia should be explored as a treatment strategy among patients who have intercurrent illnesses. Permissive anemia may be transiently acceptable until the instigating event resolves. At present, patients with intercurrent illnesses often require very high doses of ESAs. These high doses of ESAs may have effects outside of the hemopoietic epoetin receptor and may instigate poor outcomes. Indeed, in a trial among medical, surgical, and trauma patients admitted to an intensive care unit, use of ESAs was associated with increased risk for thrombosis and no reduction in the need for transfusion (31). Allowing the Hgb to drift downward may be an acceptable strategy. How permissive we should be remains an unanswered question and needs to be explored in future randomized trials. The question is whether hyporesponsive patients would experience fewer cardiovascular events if the dose of ESAs was not increased further and lower Hgb was deemed permissible. Given the data at hand, it does not appear reasonable to achieve a target Hgb at any cost.

Transfusion Threshold

If ESAs are stopped or the dose of the drug is reduced during intercurrent illnesses, Hgb may drop substantially and some patients may require transfusions. Blood banking before elective surgery for autologous transfusion may be an attractive option for patients at all stages of CKD. The threshold of Hgb at which a patient should begin transfusion depends on the clinical situation. According to the recommendations of the American Society of Anesthesiologists Task Force, transfusion is always appropriate when the Hgb level is <6 g/dl; transfusion is rarely indicated when the Hgb level is >10 g/dl (32). When anemia is chronic, the level of 2,3-diphosphoglycerate is increased, shifts the oxygen dissociation curve, and improves oxygen delivery to the tissues. Thus, chronic anemia is better tolerated. Decisions to transfuse should be individualized and incorporate patient preference in decision-making.

Improving Safety—The Value of BP Monitoring

The FDA has recommended close monitoring of Hgb during ESA therapy. Specifically, the package insert calls for reducing the dose of the drug by approximately 25% if the Hgb increases by >1 g/dl in any 2-week period. The rate of rise in Hgb predicts future adverse events. Whereas intense monitoring of Hgb is possible among patients on chronic hemodialysis, this intensity of monitoring is less feasible when following outpatients with CKD. Although a cause and effect relationship between rate of change in Hgb and mortality has not been established, the rate of rise in Hgb is related to the rate of rise in BP.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) study noted more patients who experienced systolic hypertension in those randomized to a higher Hgb target (7). The TREAT study noted a 2-mmHg difference among patients randomized to Hgb >13 g/dl (P < 0.001) (9). It also noted a nearly doubling of stroke risk. There is a poor relationship between BP measurement in the clinic and those obtained outside (33). Sometimes large clinical trials have reported seemingly trivial changes in clinic BP (34). Yet when 24-hour ambulatory BP monitoring is performed large differences are found (35). The package insert notes hypertension as the most common adverse effect of epoetin alpha. Approximately 25% of the patients require initiation or escalation of antihypertensive therapy during epoetin therapy. Yet there appears to be complacency in monitoring this important cardiovascular risk factor that has been strongly associated with strokes and congestive heart failure (36). Having patients record their BP at home twice daily is a simple and effective
way to monitor this important cardiovascular risk factor; self-measured BP would also inform patients of the risk inherent in the use of this drug. Although there is substantial uncertainty whether a cause and effect relationship exists between hypertension and adverse cardiovascular outcomes, an increase over baseline in home BP of 10/5 mmHg should prompt measurement of Hgb and treatment of hypertension that may require lowering of ESA dose.

Conclusions

Transfusion risk is increased when Hgb falls to <10 g/dl. Transfusions increase sensitization, provoke PRAs, increase the waiting time to transplantation, reduce the likelihood of transplantation, and when transplantation is performed reduce the graft survival. Accordingly, the risk of transfusion is comparable to that of “hard” outcomes such as cardiovascular events and death. Targeting Hgb to >13 g/dl is dangerous. However, if this level is achieved with a relatively low dose of ESAs and the patient feels poorly at a lower Hgb, then incorporating patient preference in clinical decision-making appears reasonable. Many patients will not feel well when their Hgb falls below the upper limit of the target Hgb of 12 g/dl. In these patients, a low dose of ESAs appears to be an important therapy for the management of anemia. The upper dose of epoetin alpha is capped at 156 IU/kg administered 3 times weekly intravenously. If given subcutaneously, this dose can be cut by one-third to approximately 100 IU/kg so only a rare patient should receive an epoetin alpha dose of >10,000 IU 3 times weekly subcutaneously. In acute illnesses, reducing the dose of ESAs or stopping them altogether may aggravate anemia, but this may be permissible. Although the rate of rise of Hgb is associated with poor outcomes and monitoring Hgb twice weekly is recommended, for patients not on dialysis, this strategy is difficult to implement. The rate of rise in Hgb is associated with an increase in BP. Accordingly, while initiating and maintaining ESA therapy, monitoring BP at home twice daily is warranted. An increase over baseline in home BP of 10/5 mmHg should prompt measurement of Hgb and treatment of hypertension that may require lowering of ESA dose. The clinical decision-making process should consider the risks of transfusion; kidney transplant potential; presence of cancer; and the risks of stroke, heart failure, and possibly death. Above all, clinical decision-making should incorporate patient preference. The doctor-patient relationship should be guided, not governed, by guidelines. The focus should move from anemia targets to the patient.

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Disclosures

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