Erythropoiesis-stimulating agents: friends or foes?

Globally, it is estimated that one out of every four human beings is affected by anemia and many suffer from its dire consequences. The prevalence of anemia in hospitalized patients is even higher—whether present on admission or acquired (and exacerbated) during hospital stay—and the consequences are also potentially more dismal and alarming. Traditionally, existing anemia often remained recognized but rarely treated. If intervention was considered, clinicians usually relied on transfusion while concurrently overlooking both the underlying etiology and the more appropriate interventions to manage it.

For the first time in the early 1980s, the need for realignment of this approach became obvious with the advent of human immunodeficiency virus (HIV) in the blood supply. Attitudes toward allogeneic transfusion changed in both public and professional realms, and while transfusion rates decreased only transiently until reliable testing became standard, the vulnerability of the system became widely recognized, making the case for substantial changes in transfusion practices.

Although yet unnamed, the evolution of patient blood management (PBM) had begun. This patient-centered approach focuses not on donated blood and blood transfusion but rather on the patient and aims to optimize and manage the patient to achieve the best clinical outcomes while often minimizing the need for allogeneic blood transfusions. Not surprisingly, a key provision in PBM is optimization of the hemoglobin (Hb) level through prevention and timely treatment of anemia.

Introduction of recombinant erythropoietin (and the related drugs collectively called erythropoiesis-stimulating agents [ESAs]) into clinical practice in 1989 dramatically changed the life of many patients suffering from renal failure, cancer, and other diseases associated with chronic anemia, by helping to maintain a “reasonably” normal Hb level without repeated exposure to allogeneic transfusion. At an unprecedented rate, ESAs became one of the top-selling prescription medications both in the United States and abroad. The notion that ESA was essentially a naturally occurring glycoprotein with vital roles in human physiology sent the message that this agent has little risk. Pockets of complications such as red blood cell (RBC) aplasia, seizures, possible malignancy, hypertension, and occasional venous thrombosis were warning signs, yet users remained undeterred thanks to ESAs’ perceived benefits.

Over subsequent years, the often faulty principle of “if some was good then more is better” dominated the use of ESAs, ushering in an era of increasingly higher doses, longer durations of administration, and indiscriminate use, exemplified by the increase in the mean injection dose of ESAs in the United States from around 5000 units soon after its introduction to a maximum of above 20,000 in around 2004. This growth might have even led subjects in a handful of randomized controlled trials to the halls of harm, sadly not a new phenomenon in medicine. Whether attributable to greed or illusion, ESAs lost their luster, and attention swiftly turned to their “high” costs and risks. In response, the US Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services reacted by issuing warnings, revising labeling, and curbing reimbursement for the ESAs. These measures were deemed appropriate to some extent to ensure the safety of the patients in general, but at the same time, it can be debated that they also restricted the ability of those who adhered to evidence-based medicine to care for their patients with the appropriate prescription of ESAs. This action resulted in many patients losing the potential benefits of the drug. Within the first year of restriction and the accompanying negative press, prescriptions were reduced by 50%. Current regulations have frightened many physicians from using ESAs at all. In many cases, these restrictions resulted in the abandonment of an effective therapy, often in favor of allogeneic blood transfusions, perhaps to the detriment of the patients.

The story of the rise and fall of the ESAs is not unique or unprecedented. Another example is aprotinin, a once-promising medication used in PBM with demonstrated efficacy in reducing blood loss and transfusion rates, but later disgraced due to its troubled safety profile. In both these and many other similar cases, evidence of risks emerged (or gained publicity) long after the agent had been widely used, and the result was often a “knee jerk reaction” to pull the drug from the market or severely restrict its use. While such approaches do generally align with the primum non nocere doctrine of medicine, urgency of avoidance of harm to the general patient populations should not deprive the more needy subgroups of patients from the medications which may benefit them, to avoid even greater harm. Interestingly, evidence is emerging to support a renewed, though selective, role for aprotinin.

In the case of ESAs, the revised labeling proscribed their usage in patients undergoing cardiovascular surgery. The decision to exclude these patients was largely based on studies in patients undergoing coronary artery bypass surgery, with little if any consideration of the differences...
between these procedures and cardiac valve surgeries. Despite this, valve procedures were also excluded from the indications for ESAs, leaving these patients and their physicians more dependent on allogeneic blood transfusions with their known risks.18

This history leads to a simple question: Do two wrongs make a right? The misuse of ESAs shares similarities with the well-documented overuse and variability seen in transfusion practices.19 When benefit to a patient cannot be demonstrated clearly for a specific treatment, what we often emphasize is the potential for harm, an important concern for many allogeneic blood transfusions. Our understanding of the benefits of ESAs is much better than transfusion, which gives an edge to the ESAs, considering that ESAs and RBC transfusions play on the same medical field and are used primarily to optimize Hb level. Nonetheless, the difference in the way these two treatments are utilized in practice is quite enlightening. RBC transfusion continues to stand as a default decision and readily available option in treating hospitalized anemic patients whereas the use of ESAs requires planning. To use transfusion, clinicians are not required to determine the etiology of anemia per se; they simply order transfusion based on how low a patient’s Hb is (or quite often as is the case in prophylactic transfusions, how low Hb is anticipated to be). There are no regulatory or “labeling” restrictions on the transfusion of allogeneic RBCs. The use of an ESA, on the other hand, requires a specific diagnosis and is restricted to on-label use in specific populations. In the outpatient setting, unlike RBC transfusion, the use of ESAs often requires preapproval from insurance carriers.

Instead of reinforcing these principles of evidence-based care and promoting sensible use of ESAs tailored to the specific patient’s needs, which could help us in reducing potentially harmful transfusions,20 we acted as we often do in cases of crisis where it is necessary to rapidly face the consequences of saving some and neglecting others. Yet it is debatable whether such crisis existed with ESAs. During the HIV and hepatitis C virus “epidemics,” a true crisis in health care, voluntary reductions in transfusion were evident, yet no regulatory restrictions on blood use were ever imposed. Since then, we have managed to largely reduce the risk of transmitting infections through transfusions (though still not completely eliminate it as demonstrated by the emergence of new transfusion-transmissible viral and prion agents),21 but it is becoming evident that the noninfectious risks of allogeneic blood are far more common and significant and much harder to eliminate.22 Despite the marred safety profile and the debated benefits of allogeneic blood, more often than not, we still find ourselves practically debating over allogeneic blood versus ESAs.

PBM as defined by the Society for the Advancement of Blood Management (SABM) is “the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome (Society for the Advancement of Blood Management [SABM]: http://www.sabm.org).” The concept is patient centered and addresses the patient’s underlying condition with the intent on modifying and reducing risks while ultimately improving clinical outcomes. Given the central role of anemia management and the increasing adoption of PBM,23,24 the downward trend in the cost of ESAs (likely to continue with the expiration of the patent on the recombinant ESAs and availability of biosimilars), and growing understanding of the risk: benefit ratio of ESAs in specific populations, a new look at the current prescribing regulation and restrictions of ESAs is in order. This, as well as applying new reasonable guidelines, will not only confer onto these medications their rightful place in the therapy of anemia, but more importantly give many patients who are currently denied ESA the benefits of a better quality of life and improved outcomes.25

In this issue of TRANSFUSION, Doodeman and colleagues26 present their findings on one aspect of PBM—identifying and treating anemia preoperatively with the hope of reducing allogeneic transfusions. In their observational time-series study, Doodeman and colleagues compared the allogeneic transfusion rate of 4568 patients undergoing total hip arthroplasty before and after introduction of a preoperative ESA protocol with up to four weekly injections of an ESA as part of a multimodality PBM program in a period spanning over 10 years at a single hospital. They observed an overall reduction of 17% (25% in patients with preoperative Hb of 10-13 g/dL) in the transfusion rate before and after the introduction of the protocol. They also found that in the postintroduction period, transfusion rate was significantly lower in patients who received ESAs compared with those who did not.26 These results are without doubt noteworthy.

Although the study’s main end point was achieved, we raise several issues with this study. Missing from this data set is an enhanced description of the studied patient population. It would be both useful and important to understand what the causes of anemia were, particularly in patients with Hb levels of 10 to 13 g/dL, since the appropriate choice of preoperative ESA versus iron, particularly parenteral iron, and other anemia treatments would depend on the cause of anemia.27 The authors stated that the studied patients were managed under a PBM initiative; however, some patients with Hb levels below 9 g/dL proceeded with elective surgery. Even though they were excluded from the analysis, this raises red flags on the level of commitment and organization of the PBM initiative during the study period. Additionally, the authors described a number of other PBM strategies such as transfusion guidelines that were
sporadically implemented, but they acknowledged that the effects that any of these measures had on the use of transfusion were unaccounted. The confounding role of other PBM measures going on during the study period complicates assessment of the net impact of the ESA protocol.

Another important point is the choice of type of iron administered as well as the chosen route of administration. It is stated that oral iron was used in the studied population, even though it is well known that oral iron is poorly absorbed in patients with inflammation, and it is also well documented that compliance with oral iron regimens is poor. Intravenous (IV) iron formulations are generally more effective.28 IV iron has been put forward as a potential alternative to ESAs (or to reduce the needed dose of ESAs) in the face of the restrictions imposed on ESAs, and their use should be considered as part of PBM strategies.29

Last and most importantly, while oftentimes the implementation of an institutional PBM program has a secondary effect on reducing total transfusion usage,30 the primary goal by definition is improved patient outcomes.5 Unfortunately the study by Doodeman and colleagues has missed a great opportunity in this regard by omitting the safety measures and clinical outcomes other than the length of stay. While the benefits of ESAs are persuasive, the main debate remains their safety, and the net impact on the outcomes of the patients, and this study has little to offer to this important debate. Most of the PBM studies using ESAs are underpowered to compare the safety profile compared to ESA use for other chronic conditions.

The criticism here should not undermine the valuable findings of the study by Doodeman and coworkers.26 ESAs can be marvelous tools to empower a patient’s own body to replenish RBCs and rectify anemia as demonstrated beyond reasonable doubt by many studies.20,31,32 The key here is how to balance that clear benefit with the risks and define practical criteria to identify those patients likely to benefit most from an ESA. For years, clinicians (falsely) felt secure and relied on allogeneic transfusion as their safety net, assuming that anemia can be “fixed” any time with relative ease and no need for further interventions or changes in their practice. Adverse consequences of such inappropriate transfusion practices are evident,33 and it is critical to avoid going down the same path with ESAs. Assuming that one can rush an anemic patient to the operating room for an elective procedure with “a little help” from ESAs, or taking anemia less seriously thinking that it can be quickly fixed with these agents is wrong, and not much different from the archaic liberal use of transfusions. Similarly, pursuing arbitrary Hb targets regardless of the patient’s response to the treatment, anticipated blood loss, and risk for transfusion is likely to cause more harm than good.

This brings us to the emerging and important issue of nonresponders to ESAs. In their pooled patient-level meta-analysis of data from six randomized controlled trials of an ESA (darbepoetin alfa) in treatment of chemotherapy-induced anemia, Ludwig and colleagues34 did not observe increased risk of death or cancer progression in patients who responded well to ESA therapy, despite achieving Hb levels in excess of 12 to 13 g/dL or experiencing Hb increases over 1 g/dL in 2 weeks or over 2 g/dL in 4 weeks. Similar results were noted in lung cancer patients.35 Hence, they speculated that the reported unfavorable patient outcomes in studies targeting high Hb levels with ESAs may be related to the patients who did not respond well to the treatment.34 In other words, it is likely that what is harming the patients is not necessarily achieving the higher Hb levels per se, but targeting the higher Hb level without consideration of the response rate, which in nonresponders could result in exposure to excessive doses of ESAs that do little other than harm.36 While more studies are needed to verify this, the prospect of identifying patients who are likely to benefit most from ESAs early on during their treatment is highly encouraging and likely to redefine the current indications and labeling of ESAs, shifting the focus from the Hb targets to the characteristics of the response of individual patients to ESAs.

Rather than being viewed as stand-alone agents, ESAs should be used wisely as one tool in the PBM arsenal as also portrayed in this study. The approach to an anemic patient scheduled for elective surgery cannot be centered on any single intervention or medication no matter how effective it is. Rather, a comprehensive, multimodality approach based on the etiology of the anemia and other specifics of the case is warranted. A patient scheduled for elective surgery should be screened for anemia early enough to allow timely management (and use of ESAs if needed as part of the protocol).27 This is the message that this study also conveys, even as it demonstrates the ESA’s action as part of a PBM strategy. We all know that there is no silver bullet in medicine, and ESAs are no exception.

Being among the first widely available drugs produced via recombinant DNA technology, ESAs have been in the forefront of pharmaceutical research and development: Other intriguing indications (e.g., promoting survival in ischemia)37 have been reported. Other potential approaches such as prophylactic use of antiplatelet therapy to mitigate the thromboembolic and hypertensive risks of ESAs have been proposed and could be effective in improving the safety of these agents pending further studies.38 New erythropoietic products designed and tailored with structural modifications to improve function and possibly reduce side effects are under investigation. Nonetheless, the case of peginesatide—a synthetic functional ESA analog—that was approved by FDA in 2012 but was recalled in early 2013 due to concerns over fatal anaphylactic reactions is just one example of the perils on the way.39,40
Any therapeutic intervention carries risks and the risk:benefit ratio in the context of each individual patient should drive the decision. Despite its high prevalence and considerable consequences, anemia remains surprisingly underrecognized and undertreated in many patient populations.\textsuperscript{41,42} This could be a result of a knowledge deficit by clinicians, underestimation of the risks of anemia, perceived high risk:benefit ratio of the available treatments, or a combination of all. In this era of heightened interest in patient safety and cost saving, efforts to choose the right therapy at the right dose for the right condition, the right patient, and the right time in the context of the right comprehensive PBM strategies are essential. More studies on PBM programs and modalities like the one by Doodeman and colleagues with increased focus on patient outcomes will help us better understand the benefits and risks of our treatment tools in battling anemia and helping our patients enjoy better clinical outcomes.

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**CONFLICT OF INTEREST**

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