**Erythropoiesis-Stimulating Agents in a Meta-Stable State: Guidelines, Economics, and Policy in Flux**

Interview (Part 2) with Samuel M. Silver, MD, PhD

Medicare coverage of erythropoiesis-stimulating agents is a complex issue with implications for a variety of healthcare stakeholders. In the first part of the interview (see *AHDB*, May 2008), Samuel M. Silver, MD, PhD, examined the evolution and clinical implications of the Medicare coverage decisions and the eventual shift in clinical practice away from the approved indication to situations involving quality-of-life issues. In this second part, Dr Silver discusses with F. Randy Vogenberg, RPh, PhD, the clinical implications of the Medicare coverage decision regarding erythropoiesis-stimulating agents, pointing out the noneconomic reasons why transfusions can be risky to cancer patients, and how such policy decisions can have profound implications for patients. Dr Silver calls for new studies to be initiated, which would be funded by the 2 major manufacturers of these drugs, to investigate the concerns regarding tumor progression and thromboembolic events that are potentially associated with these expensive and potentially toxic medications. The discussion resumes where Dr Silver explains why it would be good to compare claims data of cancer patients who are receiving these medications and their transfusion requirements. [ADHB. 2008;1(9):14-18.]

**F. Randy Vogenberg:** There have been attempts to look at large claim databases (eg, WellPoint’s) of patients receiving erythropoiesis-stimulating agents (ESAs). News about the cutback on ESA use was accompanied by reports about the rise in the number of transfusions. At the same time, articles published in pharmacy and hospital journals were advocating the use of ESAs to avoid transfusions. So, the message is mixed. What people are doing in an inventory environment is not the same as what they are doing in an institutional inpatient environment. And hospitals may continue to use ESAs to avoid the more costly transfusion, a purely cost consideration. Is this how you see it?

**Samuel Silver:** I think this may be true. But the issue of transfusion is beyond cost, especially in the outpatient setting today, where 85% of cancer patient care occurs in the community and not in academic medical centers.

The first issue is that giving transfusions at centers such as the University of Michigan is relatively simple, and our facilities are well prepared to administer them.

We have a good blood bank on site and plenty of chairs for transfusions, so we can get people set up, and we have blood irradiators (see below). But in the community, physicians by and large don’t give transfusions in their offices because of the administrative and procedural hassle. Rather, they send patients to their hospital outpatient infusion area, which is usually very small, where they can run out of transfusion chairs relatively rapidly, so that we now have a group of patients either requiring admission for transfusion or experiencing a significant delay waiting for an outpatient chair. And these are not patients with shortness of breath who require admission but rather it’s a quality-of-life (QOL) matter, because of the requirement of an inpatient stay.

The second issue is that the typical Medicare beneficiary has many comorbid conditions (eg, heart failure) in addition to cancer. Thus, we are no longer talking only about potential infectious complications of transfusion but also about issues of fluid overload that would not occur when using an ESA.

The third concern is that many patients receiving chemotherapy, especially those with hematologic malignancies, are immunosuppressed. They require irradiated blood products to avoid transfusion-associated graft-versus-host disease. Irradiating blood is very easy; any university blood bank will have a blood irra-

---

Dr Silver is Professor of Internal Medicine, Director, Cancer Center Network, Division of Hematology/Oncology, and Assistant Dean for Research, University of Michigan Health Systems, Ann Arbor, MI.
diator. It does not require much time, but it will add some expense. Nonetheless, it is well worth it. However, if the patient is in a suburban or rural community, that patient may not have immediate access to irradiated blood and will have to wait a day or two to get it. So, all of a sudden something that would be simple for me at the University of Michigan becomes a process that takes several days for a patient that receives chemotherapy in a suburban or rural facility. These are some of the noneconomic, procedural issues that are involved in giving transfusions.

Vogenberg: The other side of this issue concerns younger populations. The 50- to 60-year-old patient may still have a commercial insurance and not Medicare. Thus, there are also direct economic costs to consider, such as absence from work, particularly when the patient may be tied up for a day or two, as you said. There are many repercussions for Medicare, which is the focus for the Centers for Medicare & Medicaid Services (CMS), and for commercial insurers and employers, who are paying the bills. This is not well understood; the tendency is to just look at the drug cost and the drug companies, and this is more emotional than rational.

Silver: True. And the next thing we know, we are talking about Medicare Part B, and we begin to reach out to Medicare Part A, when we start admitting people to the hospital. Apparently those involved in Medicare Part B decisions don’t see this, but we certainly see this as citizens and on the private side. And the employers see this. So the US Food and Drug Administration (FDA) has issued new warnings, which essentially reflect the concerns about potential tumor progression, venous thromboembolism, and keeping the hemoglobin level at <12 g/dL (although this cut-off measure was dropped by the FDA from the most recent ESA labeling).

The FDA reiterated this in its most recent statement. That is where we are from the point of view of the FDA and CMS. And the Senate passed a nonbinding resolution about it, since the Senate has a sense that the National Coverage Decision (NCD) has no weight and should be changed.

Vogenberg: This NCD issue probably comes at a good time for CMS, because the current Congress is deadlockened on many issues. So nothing is going to happen. There are no repercussions against CMS’s decision about ESAs, and it can come back and say it has saved a lot of money, while preventing further harm to their beneficiaries. It is really almost a neutral situation from a public policy perspective.

Silver: In the meantime, Representatives Peter Stark and Henry Waxman are saying they are protecting the patients from this “miracle grow for tumors.” And because we have no quality-of-life (QOL) data, there are no improvements in QOL issues. Now what do we do? We definitely require more data.

The next thing we know, we are talking about Medicare Part B, and we begin to reach out to Medicare Part A, when we start admitting people to the hospital.

Silver: CMS is not transparent at all. When you read the NCD, their background materials have been tightened up a bit. But the intellectual basis to bridge between the final coverage decision background material and the rules is missing.

Vogenberg: How transparent is CMS regarding its data?

Vogenberg: This is very typical of what you would see in almost any insurance company. You get caught up in this dynamic of economics and cost, and you are trying to provide just enough access so that people are happy, but at the same time less attention is paid to QOL than to the science, so it really is about economics. For CMS, it appears to be about money. They had to stay within a budget, and they
knew the ESA coverage was a budget buster and a high-expenditure category, as it is for any employer. This is the perfect moment to come up with a Solomon-like decision. CMS is not required to disclose as much as the FDA. This makes it easier for the commercial carriers to follow suit.

Medicare is not supposed to talk about costs or to consider it in its decisions, but of course it is the underlying context.

Silver: In addition, CMS will identify 10 more questions that should be answered, as they did 1 year ago, even though many of these questions are unanswerable, because the data don’t exist, and CMS knows it; a true Catch-22.

Vogenberg: This points to an interesting dichotomy between what the Agency for Healthcare Research and Quality is doing and Medicare Part D initiatives and the general Medicare initiatives about quality issues in hospitals, such as pay-for-performance. On one hand, CMS is saying it is going to pay for improved performance and outcomes in the hospitals, which, based on the current literature, suggests they would be using ESAs; these drugs lead to better results and reduce complications and readmissions, which are the criteria for quality. But on the other hand, Medicare coverage decision, which was based on an outpatient basis, prevents clinicians from using these drugs.

Silver: That brings up an interesting point. In CMS's Physicians' Quality Reporting Initiative, one of the early reporting initiatives dealt with the use of ESAs in myelodysplastic syndrome (MDS). It was necessary to make sure patients had sufficient iron stores, which was a quality point. Yet, the payment for MDS associated with ESAs was denied at that time, as we discussed in the first part of this interview (AHDB. May 2008;1[4]:46-50).

Vogenberg: And then it could be argued that the cost of these medications is too high?

Silver: Actually, Medicare is not supposed to talk about costs or to consider it in its decisions, but of course it is the underlying context.

Vogenberg: And what is the Veterans Administration (VA) doing with the coverage?

Silver: I do not have the answer to that. The VA has an excellent electronic medical records system; however, in the past few months the VA was unable to use any of their data for Health Services Research purposes because of confidentiality and HIPAA (Health Insurance Portability and Accountability Act) issues.

Vogenberg: There must have been some kind of analyses done within the VA military review structure when all this was transpiring, because they are so cost and quality conscious. I wonder what the VA system is doing about TRICARE and the active military, which represents a large population?

Silver: This is a very important issue. The FDA has asked the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) to determine what studies should be done in the future. ASH has asked the American Association of Cancer Research (AACR) to participate in this initiative. We are trying to convene a meeting with representatives from the FDA, CMS, ASH, ASCO, and AACR to determine what trials are needed and who should be running them.

Vogenberg: Would they be doing a corresponding health economics analysis with clinical studies parameters?

Silver: That would be an important thing to look at as well, but the executive committee of ASH believes that the National Institutes of Health (NIH) should not be paying for such studies to help determine the best hemoglobin range for ESA use. The Executive Committee is concerned that this type of study costs a lot of money. And diverting NIH money for this clinical question would leave less money for important basic science research.

Vogenberg: That is a good point.

Silver: It would be important to engage both Johnson & Johnson and Amgen to design an open study that would be funded by an unrestricted grant from both drug manufacturers to examine the pathophysiology of ESA-associated thromboembolism. And maybe we should involve the NIH and the National Cancer Institute or the National Institute of Diabetes and Kidney Disease to address issues surrounding end-
We need to focus on 3 aspects of the drugs—tumor promotion, the biology of venous thromboembolism, and the relationship to ESRD, which can teach us a lot.
Stakeholder Perspective
The Clinical and Economic Complexity of Biologics

Payers/Patients: The inability to predict outcomes with erythropoiesis-stimulating agents (ESAs) or with other biologic agents is emerging as a key concern. Whether in rheumatoid arthritis, multiple sclerosis, or erythropoiesis, unintended or unknown effects from these new biologic medication technologies are gradually better detected and better understood, helping to determine the most appropriate uses. From the perspective of economic decision makers—patients, health plans, or employers—the easy clinical decision to use biologic medications has become muddier, while these same (typically elderly) patients are rethinking their need for a wider variety of end-of-life therapies that have focused more on quality-of-life issues than on changing the lifespan.

ESAs provide an interesting insight into the complexity of clinical use of biologics and their economic impacts on all payers, as well as the types of clinical service providers. Given that many patients who are using biologics are covered under a Medicare drug plan but also have multiple comorbidities, this further illustrates the dilemma of finding a technological advancement end point where costs become more predictable. As Dr. Silver points out in the interview, several concerns involving patients who receive ESA therapy go beyond a single decision point.

Because of the paucity of data to clearly guide the multipoint clinical and coverage decisions, the Centers for Medicare & Medicaid Services (CMS) and private insurers are erring on the side of limited coverage, following the evidence-based medicine (EBM) model. Although in itself not sideling with any coverage position, EBM can conveniently be used for any stakeholder’s position, whether economic or clinical. In the case of ESAs, there seems to be a clinical and an economic dilemma foreboding of the bigger and more expansive decisions our society faces through the lens of healthcare insurance coverage for the growing pipeline of biologic-based technologies.

The role of regulators (CMS, US Food and Drug Administration) and system researchers (Association for Healthcare Research and Quality, quality improvement organizations) should be determined by Congress to better align incentives, along with a clearer direction for the use of new technologies (diagnostic or therapeutic). Mixed messages and misalignment of incentives has long been an albatross around the US healthcare system that has fed many debates and articles arguing the myriad of issues relevant to each of the stakeholders. This has been good for academics, consultants, and special interest lobbyists, but not for frontline patients and healthcare professionals, or those paying the bills for care.

Based on reports from the recent presidential campaign and from groups such as the Kaiser Foundation or the Wall Street Journal, neither party nor either of the candidates has had the single obvious solution to our looming healthcare crisis in the next decade. Perhaps our economic distress will aid patients, as reflective of our society, in establishing new parameters around life-and-death decisions that will help our healthcare system seek a new balance in harnessing technologies for the most appropriate use, which will then determine its hierarchical cost in our economy.

F. Randy Vogenberg, RPh, PhD
Chief Strategy Officer
Employer-based Pharmaceutical Strategies, LLC
Senior Scholar, Department of Health Policy
Thomas Jefferson University, Jefferson Medical School