Medicare Coverage for Erythropoiesis-Stimulating Agents: The Perfect Storm

Interview (Part 1) with Samuel M. Silver, MD, PhD

Medicare policy changes have an immediate impact on health plans with regard to setting payment policy for providers. So when Medicare tightened payment guidelines for a lucrative class of anemia drugs—erythropoiesis-stimulating agents—an ambitious set of rules was put into effect. Health plans often follow suit in short order, enforcing public guidelines on private payors, even when saving money is not a consideration. However, when Medicare takes an unreasonably hard line, plans tend to focus on members and physicians more fervently, attempting to soften the hard line. In this first part of the interview, Dr Silver examines the coverage decisions set by the Centers for Medicare & Medicaid Services for the use of erythropoiesis-stimulating agents and discusses the issues surrounding their adoption, indications versus off-label use, as well as lingering questions about their role in tumor progression and other risk factors. [AHDB. 2008;1(4):46-50.]

Robert Henry: Medicare’s recommendations for erythropoiesis-stimulating agents (ESAs) revolves around several key stakeholders with diverse agendas—those of the US Food and Drug Administration (FDA), the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and pharmaceutical companies. What are the coverage issues for these various stakeholders?

Sam Silver: This is a very sensitive issue. Articles published in the New York Times were quite negative with regard to perverse economic incentives for physicians’ prescribing of ESAs. Oncologists are seeking flexibility in determining how to use the ESA medications based on a hemoglobin level cut-off of less than 12 g/dL. Professional medical societies value evidence-based findings. Practicing oncologists can be made to look like the “bad guys” interested only in profit margins and not in the patient; but this issue is far more complicated than that. Physicians do try to do the best for their patients, and yet financial incentives can be an inappropriate driver.

Henry: Dr Randy Vogenberg will be leading the discussion to explore the issue from the different stakeholders’ perspectives.

F. Randy Vogenberg: I am a pharmacist by training, with a PhD in healthcare administration, and I have been involved in employer-related benefit issues. I also work with pharmacy benefit managers, health plans, benefit consultants, and brokers, so I see this issue from a variety of perspectives in terms of the financial and clinical implications in the marketplace.

Silver: During my 10 years of being the director of Bone Marrow Transplantation at the University of Michigan, I got interested in reimbursement issues for clinical trials, especially with regard to bone marrow transplantation.
transplantations for breast cancer in the 1990s. I eventually became active at ASH and chaired several committees, including their Reimbursement Subcommittee, and I am finishing my term on their Executive Committee. I was also a member of the Board of the American Society of Blood and Marrow Transplantation and currently serve on several committees of ASCO. In addition, I am still practicing hematology/oncology, while remaining involved in reimbursement.

Hematologists and oncologists have been looking for the Holy Grail—how to avoid transfusions—for quite some time, and thought they had found it in ESAs. We all had concerns about blood products since the arrival of HIV, particularly in the hemophilic population. Red blood cell transfusions are fraught with possible complications, including hepatitis and other side effects, such as transfusion-associated lung injury. Consequently, we allowed patients to run low hemoglobin counts secondary to their underlying malignancies and chemotherapy, but this negatively affected their quality of life (QOL). Today many of us use transfusions as needed, without a particular target in mind, and we tend to focus on symptomatology rather than on any target hemoglobin level that signals the need for transfusion.

**Vogenberg:** Could you discuss the evolution of the uses and concerns regarding ESAs?

**Silver:** When ESAs came on the market, they were well embraced. The FDA-labeled indication was to decrease the number of transfusions or avoid them altogether, but in time, studies implied that increasing hemoglobin levels also improved patients’ QOL. The pharmaceutical industry embraced and publicized these studies to physicians and through direct marketing to patients. And so, years after the original FDA indication, these agents became associated with QOL issues. With all the off-label uses common today, we forgot that these drugs were actually indicated to avoid transfusions, and the focus shifted to QOL.

Around 2004, it became apparent that patients with end-stage renal disease (ESRD) and chemotherapy-induced anemia were having thromboembolic events as a result of treatment with ESAs, especially in patients whose hemoglobin levels were driven to more than 12 g/dL. The Oncology Drug Advisory Committee (ODAC) noted that appropriate studies were not being conducted to examine the effects of these drugs on ESRD patients or on tumor progression. Rather, existing studies examined transfusion-avoidance and QOL issues associated with hemoglobin levels higher than 12 g/dL.

In November 2007, the FDA strengthened its “black box” warning for the use of ESAs, because of increased evidence of tumor progression and reduced survival. In March 2008, the Oncology Drug Advisory Committee recommended limiting the use of these agents in the cancer setting to circumstances where chemotherapy is not given for curative purposes, and not to exclude their use in patients with head and neck cancer or breast cancer.

**KEY POINTS**

- ESAs are indicated for treating patients as a way to avoid transfusions, but the focus in practice has since shifted to off-label use for quality-of-life concerns.
- Safety issues have become a serious concern with ESAs, as findings of early death, tumor progression, and serious cardiovascular events linger.
- In 2007, ESAs had the highest drug expenditures in Medicare Part B.
- In November 2007, the FDA strengthened its “black box” warning for the use of ESAs, because of increased evidence of tumor progression and reduced survival.
- In March 2008, the Oncology Drug Advisory Committee recommended limiting the use of these agents in the cancer setting to circumstances where chemotherapy is not given for curative purposes, and not to exclude their use in patients with head and neck cancer or breast cancer.
Finally, there was an Amgen study conducted in Eastern Europe. It was conducted on patients with multiple types of cancer who had not received chemotherapy or radiation. These patients were randomized to receive transfusions alone or ESAs. Survival was shortened in patients who were not receiving chemotherapy. This finding caused particular concern at the FDA, because this use of ESAs was completely off-label: This was not chemotherapy-induced anemia but rather it was the anemia associated with cancer itself. We do not know whether the shorter survival was from the tumor progression or whether it was related to the thromboembolic events, but there certainly appeared to be a shortened survival in the ESA arm of the study.

The findings from these studies led to the first black box warning for ESAs, issued by the FDA in March 2007. The FDA announced that physicians should only use the lowest dose of an ESA necessary to avoid the need for blood transfusions caused by anemia. Based on the Henke study, the FDA also noted that there was a reduced time to tumor progression in patients with advanced head and neck cancer with the use of these agents. This study, as well as the European study which showed a decreased survival in patients with cancer-related anemia who received ESAs, led the FDA to determine that ESAs are not indicated in patients whose hemoglobin levels are more than 12 g/dL or in patients who are not receiving chemotherapy or radiation.

In May 2007, the New York Times published a front-page story titled, “Doctors Reaping Millions for Use of Anemia Drugs.” The article described how 2 of the world’s largest drug companies are paying hundreds of millions of dollars to doctors every year in return for giving their patients “anemia medications” and in doses that regulators now say may be unsafe. It was noted that the doses were legal, but that very few people apart from the doctors were aware of the high doses used. Critics, including prominent cancer and renal experts, said that the payments gave physicians an incentive to prescribe the medications at levels that may increase patients’ risks of heart attacks or strokes. We thus have what I call, “ESAs—the perfect storm.”

The ESAs are supportive-care drugs, but providing them in doses higher than indicated by the FDA appears to result in an increased incidence of thromboembolic events, early death, and possibly tumor progression.

Vogenberg: Was there a marketing issue surrounding all this?

Silver: When ASH/ASCO issued their guidelines in 2003, they reviewed QOL issues in the literature and were not impressed by the evidence. Apparently there was a very high dropout rate of patients in the involved studies. The scales used in the studies did not make clear what a clinically significant benefit meant from a QOL point of view. Perhaps if they had compared differences in QOL in patients with hemoglobin levels of 8 g/dL versus 11 g/dL (instead of higher levels), the QOL issues could have been clearer.

The marketing issue revolved around the QOL issue. If one could show conclusively that QOL increased when hemoglobin levels increased above the indicated level, it would have provided sufficient evidence to raise hemoglobin levels.

Vogenberg: There are many issues surrounding QOL from a payor perspective, including a strong bias against it. I think that might have contributed to this perfect storm situation.

Silver: True. But, as you know, marketing and research go hand in hand. This is nothing new, but it certainly is an issue, especially when dealing with QOL and survival.

The day after the New York Times article appeared, ODAC reviewed the clinical trials data. The companies released a lot of data on QOL, which did not convince ODAC. The companies did agree that there was an increased incidence of thromboembolic events, but they tried to dismiss the issue of tumor progression. I think the issue of tumor progression is something we really do not understand, and it has not been well demonstrated. In December 2007, the National Cancer Institute convened a meeting of investigators who concluded that there were compelling in vitro data to continue investigations on ESAs and tumor progression.
The ODAC review indicated that the FDA should consider adding to the product labeling further restrictions on the use of ESAs in patients with the types of tumors implicated in available trials, which the FDA did in November 2007.\textsuperscript{10} Because the issue of tumor progression had not been sorted out, it was suggested that additional trials should be conducted.

**Vogenberg:** Have there been any data regarding the long-term use of ESAs in patients?

**Silver:** There is a wealth of data that show that using ESAs in inpatients with low-grade myelodysplastic syndrome (MDS) could lower their transfusion requirements. MDS is a chronic disease, and thus therapy may be required for many years. Using ESAs in cancer chemotherapy is very short-term—6 to 9 months at most. But this discussion is premature, because there is no FDA indication for its use in MDS, and it is unlikely that an indication would be added soon, given the current atmosphere.

The Centers for Medicare & Medicaid Services (CMS) recently issued a National Coverage Determination (NCD) on ESAs for non–renal disease indications. CMS remains mute on the use of ESAs for the treatment of anemia associated with myelodysplasia, since they stated it was a premalignant condition, and the Medicare NCD was for the chemotherapy-induced anemia in cancer patients. This is a major issue for me as a hematologist, because there are good data for the use of ESAs in low-grade MDS. Based on this NCD, Medicare has now placed its coverage of ESAs for MDS at the hands of Part B carrier medical directors and Part A fiscal intermediaries.

But the NCD stated that CMS still did not think that ESAs work for MDS, which could bias local carriers against it. CMS remained silent on differentiating types of tumors, but from the point of view of ASH, one of the things we considered most onerous in the NCD was that the trigger point was defined as a hemoglobin level of 10 g/dL. If a patient’s level was above 10 g/dL, you were to avoid ESA therapy.

So, initiation of therapy was at a hemoglobin level of less than 10 g/dL, and maintenance was also at less than 10 g/dL. This is a serious paradigm shift from how ESAs had been used, and yet there was no evidence to support it.

**Vogenberg:** As a clinician, how do you determine how to proceed, because it may take a couple of days before you see a response?

**Silver:** That’s very true. It remains to be seen how this will affect transfusions. I have suggested to CMS and to members of Congress that we should use claim-based data to look retrospectively and prospectively at the transfusion requirements of Medicare beneficiaries who are and those who are not receiving ESAs for chemotherapy-induced anemia, to determine transfusion use before and after the new NCD. It may now be more difficult to compare these time periods with claim-based data, because physicians will allow hemoglobin levels to get lower than they have allowed in the past.

**Disclosure Statement**

Dr Silver is a consultant to Bear Stearns, Lehman Brothers, and the Gerson Lehrman Group, and receives grant/research support from Blue Cross Blue Shield of New Jersey.

**References**


**AHDB Stakeholder Perspective**

**UnitedHealthcare’s Response to the ESA Debate**

**PAYORS:** It is important to remember why UnitedHealthcare became interested in the issue of the erythropoiesis-stimulating agents (ESAs). Following the US Food and Drug Administration (FDA) warning about potential problems with ESAs, UnitedHealthcare launched a pilot study in New York, New Jersey, and Connecticut, requiring precertification for any ESA injection. We used the guidelines issued by professional cancer societies to set our maximum hemoglobin coverage limit at 12 g/dL. Higher hemoglobin levels were not covered. This 6-month pilot study revealed a 35% reduction in the use of ESAs, indicating that 1 of 3 doses that were being administered could have potentially harmed the patient.

Physicians and patients have become confused about the purpose of these medications. As Dr Silver states in his article, ESAs were originally created to avoid transfusions—a dangerous procedure even with current sophisticated screening. The quality-of-life (QOL) marketing, misaligned economic incentives, and the erroneously perceived safety profile made it easy to become lax about the actual FDA indications for this therapy. Even now, the ESA problem is still not resolved.

Every therapy has a potential for toxicity. Transfusion medicine has improved substantially since the emergence of the HIV epidemic in the 1970s, but Dr Silver aptly summarizes the significant risks that still exist. If oncologists use transfusion for QOL reasons rather than for physiologic problems, such as angina, orthostatic hypotension, or resting dyspnea, we will simply be trading one set of problems for another.

**RESEARCH:** We can expect a rush of studies that will examine rates of transfusions before and as a result of the recent coverage changes for ESAs, but if these studies do not examine the hemoglobin levels and the medical indications for those transfusions, these studies will be worthless. The unanswered question that needs to be examined is: Is it worth any toxicity at all to treat patients with a hemoglobin level above 10 g/dL?

**HEALTH PLANS:** So while that debate goes on, UnitedHealthcare will continue its present policy of simply asking professionals to adhere to their own guidelines.

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**Correction**

In Table 2 in the article “Not waiting for Godot: the evolution of health promotion at PPG industries” (April 2008, page 31), STD indicates short-term disability, not sexually transmitted disease, as is incorrectly noted there.