Erythropoiesis-Stimulating Agents: Continued Challenges

The interest of the public, elected representatives, and payers in the use of erythropoiesis-stimulating agents (ESAs) has grown in recent times. In May of this year, the *New York Times* published an article critical of physicians' use of ESAs, and attempts to link at least some of this use to rebates received by physicians from the manufacturers.¹ In addition, within the last several months, data published or released in preliminary form prompted the US Food and Drug Administration (FDA) to take several actions. In March, the FDA revised both the epoetin alfa and darbepoetin alfa product labels, with new "black box" warnings and expanded information on safety, tumor progression, and survival. Additionally, the new warning states that ESAs are not indicated for patients with active malignant disease receiving neither chemotherapy nor radiotherapy. After these FDA revisions to the product labels, one of the compendia accepted by the Centers for Medicare and Medicaid Services (CMS) for use in coverage decisions revised its indications for epoetin and darbepoetin alfa, removing the treatment of anemia of cancer (ie, not associated with treatment) from its "accepted" list. Some private payers have followed the CMS's lead and are now restricting their own coverage of ESAs.

This article will provide context for this recent activity. We will discuss the introduction of ESAs as a treatment for anemia, review key Oncologic Drug Advisory Committee (ODAC) meetings in 2004 and 2007, discuss recent actions by the CMS, and examine the current controversies.

History

Epoetin alfa (Epogen; Amgen, Thousand Oaks, CA; Procrit; Ortho Biotech, Bridgewater, NJ) and darbepoetin alfa (Aranesp; Amgen) are approved for marketing in the United States for a variety of indications. Most important to oncologists, these agents are approved for use to avoid blood transfusions in patients with cancer receiving chemotherapy. "Off-label" use in other settings, particularly in patients with myelodysplastic syndromes, has also become an important use.

Before the approval of ESAs for clinical use, patients with cancer who were suffering from anemia due to chemotherapy

had only the option of blood transfusion for correction of the anemia. Blood transfusions carry with them their own well-known risks, and the approval of ESAs gave patients and their physicians a potential alternative. Although blood transfusions have become much safer with regards to known infectious agents during the years since the initial approval of ESAs, transfusions still carry risks, including iron overload, transfusion reactions or anaphylaxis, and transfusion-related acute lung injury.

Epoetin alfa was the first ESA to be approved in 1989, and at that time, it was indicated only for the treatment of anemia associated with chronic renal failure. In 1993, the indication was expanded to include the treatment of anemia associated with cancer chemotherapy, based on studies that showed a reduction in the proportion of patients receiving transfusion during chemotherapy with epoetin alfa use. Similarly to epoetin, darbepoetin alfa was approved in 2001 for the treatment of anemia associated with chronic renal failure, and then in 2002, the indication was expanded to include the treatment of anemia associated with cancer chemotherapy. Darbepoetin alfa approval for the latter indication was also based on a study showing a reduction in the proportion of patients receiving transfusions during chemotherapy. It should be noted that both the US FDA and CMS consider all

Reporting of Anemia Quality Indicators

On July 2, 2007, the CMS released its notice of proposed changes in the Medicare physician fee schedule for 2008. The proposal would implement recent legislation requiring that claims submitted to Medicare for the treatment of anemia in connection with patients undergoing cancer treatment must include information on the patient's hemoglobin or hematocrit levels, beginning in 2008. CMS states that it will use this information to help determine the prevalence and severity of anemia associated with cancer therapy, the clinical and hematologic responses to antianemia therapy, and the outcomes associated with various doses of antianemia therapy.

Drug Discounts and Rebates

The controversies surrounding ESAs have also prompted interest in the issue of drug rebates. Rebates from manufacturers to physicians who purchase drugs are discounts in the price that the physician pays for the drugs. These discounts are made in the form of rebates rather than invoice discounts because of the structure of the drug distribution system. Generally, physicians purchase drugs from wholesalers and specialty distributors, not directly from manufacturers. If a manufacturer wants to offer a price discount to selected end-users of their product (such as high-volume physician purchasers), the discount must be provided indirectly rather than in the form of a reduced invoice price. Rebate agreements are one way for manufacturers to provide these discounts to physicians. The discount is provided periodically (generally quarterly or annually) in the form of rebates based on the volume of purchases previously made.

Such price discounts, whether in the form of invoice discounts or rebate agreements, are legal, and are common in the hospital purchasing setting, but unusual in the physician office setting. The federal antikickback statute and the implementing regulations issued by the Health and Human Services Office of Inspector General allow price reductions, whether in the form of on-invoice discounts or rebates.

Since 2005, the Medicare program has based drug payment amounts on 106% of the manufacturer's average sales price (ASP) for the drug. Rebates and other discounts lower the ASP and therefore the reimbursement amount. Physicians as a group do not benefit under the Medicare program from rebates since they receive 106% of the manufacturer's ASP after rebates and discounts are figured into the ASP calculation.

The rebate issue is complicated by the fact that one manufacturer provides rebates only when physicians purchase a "bundle" of two drugs. The CMS proposed rule for the Medicare physician fee schedule for 2008 addresses this issue for the first time. In this proposal, CMS issued instructions to drug manufacturers on how to calculate ASP in the case of "bundled" pricing arrangements. CMS is proposing that the total amount of price concessions should be allocated to the various products involved in proportion to the sales of each drug sold under the bundled arrangement.

of the currently available ESAs to be interchangeable in terms of their safety and effectiveness profiles, and thus consider them as one class for purposes of safety, efficacy, and coverage. (This includes other ESAs approved for use in other countries [eg, epoetin beta].)

As early as the initial approval of epoetin alfa in patients with cancer, the US FDA expressed concern that it might be a potential growth factor for tumors. The sponsor of Procrit agreed to conduct a postmarketing study (N93-004) designed to rule out a decrement in response rate with epoetin use in patients with small-cell lung cancer.

After these agents were approved for clinical use, they continued to be tested in subsequent trials for different indications in cancer. Almost all of these trials were conducted either in a nonindicated patient population (eg, patients with cancer not receiving chemotherapy or receiving radiotherapy alone), or set hemoglobin targets higher than what was used in standard practice—primarily to test the hypothesis that increased oxygen delivery to tumors could improve anticancer effect. Published reports of some of these trials showed negative effects on either survival or tumor progression, and in 2004, the US FDA convened a public meeting of its external advisors, the ODAC, to reassess the safety of ESAs.

ODAC 2004

At this meeting, the results of Study N93-004 (the agreed-on postmarketing study), the BEST study,² and the ENHANCE study³ were discussed. Study N93-004, conducted in patients with small-cell lung cancer undergoing treatment with chemotherapy and radiotherapy, was terminated early by the sponsor, due to slow accrual rates. With 224 of a planned 400 enrolled, the study did meet its end point, which was to show noninferiority in overall response rates. Both the BEST and ENHANCE studies, however, showed decreased survival in patients with cancer receiving ESAs, and in addition the ENHANCE study showed decreased locoregional progression-free survival and a shorter time to locoregional progression in patients treated with an ESA.

The BEST study² was a randomized study, conducted outside of the United States, of epoetin alfa in 939 women with metastatic breast cancer. Patients were receiving first-line chemotherapy, and patients in the epoetin arm were given epoetin if their baseline hemoglobin was ≤ 13 g/dL, or if the hemoglobin went below 13 g/dL while patients were on study. The study targeted hemoglobin levels of 12 g/dL to 14 g/dL, and study participants received epoetin alfa for 12 months. The study was terminated early due to the decreased survival seen in patients treated with epoetin. A final analysis

of the 1-year overall survival rate continued to show decreased survival in the epoetin-treated patients.

The ENHANCE³ study was also a randomized trial, conducted in 351 patients with advanced head and neck cancer receiving radiotherapy without chemotherapy. Patients randomly assigned to the epoetin beta arm received epoetin during radiotherapy, to a target hemoglobin of 14.5 g/dL (women) or 15 g/dL (men). In addition to shorter overall survival in patients randomly assigned to the epoetin arm, this study also showed shorter locoregional progression-free survival and shorter time to locoregional progression.

Also discussed at the 2004 ODAC meeting were several studies that were terminated early, due to increases in risk of thrombotic and cardiovascular events (EPO-CAN-15, PR00-03-006, GOG 191).⁴ After review of these and additional data presented at the 2004 ODAC meeting, the members made several recommendations for necessary design features in future clinical trials examining ESAs. In addition, the “Warnings and Precautions” section of the product label for Procrit/Epogen was revised in May 2004 to include information on epoetin effects on response rates, time to progression, and overall survival in patients with solid tumors. In December 2004, the “Warnings and Precautions” section of the Aranesp label was also revised, with the addition of information on thrombotic events and tumor promotion.

ODAC 2007

Subsequently, in May 2007, FDA convened another ODAC meeting to reassess the safety and effectiveness of ESAs in patients with cancer. The data considered at this meeting included a mix of published studies, summary results from closed studies (provided to the US FDA by the sponsors or others), and primary data from closed studies (data provided to the US FDA by the sponsors). Of greatest concern to the US FDA were the studies showing decreased survival times (BEST, ENHANCE, 20010103, 20010161, EPO-CAN-20)^{2,3,5,6} and poorer locoregional control or progression-free survival (ENHANCE, DAHANCA-10/SE 2002–9001^{3,7}); (PE) the BEST and ENHANCE studies are discussed here previously, and a brief discussion of the remaining studies follows.

EPO-CAN-20⁶ was a randomized trial in patients with NSCLC unsuitable for curative therapy, designed with quality of life as the primary outcome. This trial was also closed early after accrual of 70 patients, after an unplanned safety analysis (prompted by reports of thrombotic events in other studies) showed decreased median survival in the ESA arm.

The DAHANCA 10 trial⁷ was a randomized trial of darbepoetin alfa use in head and neck patients with cancer receiving radiotherapy. The trial was temporarily stopped in October of 2006 due to unexpected adverse events; the

timing of this suspension coincided with a planned interim analysis (484 patients included), which showed increased locoregional failure in patients receiving darbepoetin alfa, but no decrease in overall survival.

Study 20010103 (FDA⁵) enrolled 989 patients with nonmyeloid malignancies who were not receiving chemotherapy. Target hemoglobin was 12 to 13 g/dL. Overall survival was poorer in the ESA arm than in the control arm; moreover, no difference was seen in the occurrence of blood transfusions between arms. Study 10010161 (FDA⁵) enrolled 344 patients with lymphoproliferative malignancies receiving chemotherapy. Target hemoglobin was greater than 15 g/dL (male patients) or greater than 14 g/dL (female patients). Overall survival was poorer in the ESA arm, but progression-free survival was no different between the two study arms. A summary of the studies demonstrating ESA effects on survival or tumor response is included as Table 1.

In addition to considering the evidence presented by the US FDA and the manufacturers, ODAC members heard from members of the public and patient advocacy groups. Many patients and patient advocates expressed outrage that ESAs had been marketed directly to consumers with the message that these agents could improve quality of life, when the US FDA had never accepted quality-of-life improvement as an indication for ESA use in patients with cancer. ODAC members issued several recommendations during their meeting for FDA consideration, including the following: the setting of a “baseline” hemoglobin level for ESA initiation; reassessment of anemia postchemotherapy regimen; restriction of use in certain malignancies; further restrictions to indications on the product label; and the conduct of further clinical trials designed to detect differences in survival and prospectively collect data on specific adverse events.

CMS Actions

Shortly after the ODAC meeting, in that same month, CMS proposed a “National Coverage Decision” on coverage of ESAs in nonrenal indications, and requested public comment. CMS proposed many new restrictions on ESA use, including considering coverage only in the context of a clinical trial. Proposed restrictions included setting a “baseline” hemoglobin level for initiation of ESAs; setting a maximum covered duration per calendar year; setting a maximum covered 4-week treatment dose; no coverage for use in anemia associated with myelodysplastic syndromes; no coverage for use with antiangiogenic agents or mono- or polyclonal antibodies directed against the epidermal growth factor receptor; and restrictions in treatment for hypo- or hyper-responders. (The CMS Proposed National Coverage Decision [NCD], with a complete listing of the proposed restrictions, can be found at <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp>; ASCO’s comments on the Proposed Decision Memo can be accessed at ascopubs.jp).

Table 1. Studies Demonstrating ESA Effects on Survival or Tumor Response

Study	Design	Population (N), Therapy	Survival/Tumor Response	Comments
BEST	Epoetin alfa v placebo ESA given for 12 months Hgb target: 12-14 g/dL	Breast cancer, metastatic (N = 939); first-line chemotherapy; concurrent radiotherapy and hormonal therapy allowed	1-year OS: ESA, 70%; placebo, 76% (HR, 1.37, $P = .01$); no significant differences between ESA or placebo in objective response rates, TTP, or duration of PFS	Study terminated early due to higher mortality in epoetin arm
ENHANCE	Epoetin beta v placebo ESA given throughout duration of radiotherapy Hgb target: 14.5 g/dL (women) 15 g/dL (men)	Head and neck cancer, advanced (N = 351); radiotherapy (definitive or postoperative); no chemotherapy	In ESA-treated patients, significantly shorter OS (HR, 1.39; 95% CI, 1.05 to 1.84; $P = .02$); locoregional PFS (HR, 1.62; 95% CI, 1.22 to 2.14, $P = .0008$); time to locoregional progression (HR, 1.69; 95% CI, 1.16 to 2.47; $P = .007$)	
EPO-CAN-20	Epoetin alfa v placebo ESA given weekly for 12 weeks Hgb target: 12-14 g/dL	NSCLC unsuitable for curative therapy (N = 70) ± palliative radiotherapy; no chemotherapy	Significant difference in median survival in favor of the placebo arm (63 v 129 days; HR 1.84; 95% CI, 1.01 to 3.35; $P = .04$)	Study terminated early (planned sample size, N = 300); reports of thrombotic events in other trials led to an unplanned safety analysis (n = 66) after 70 patients randomly assigned
DAHANCA-10	Darbepoetin alfa v placebo Hgb target: not reported (baseline Hgb ≤ 14.5 g/dL)	Head and neck cancer (N = 522; 484 analyzed); radiotherapy; no chemotherapy	Planned interim analysis showed significantly poorer outcomes in the darbepoetin arm for primary end point of locoregional failure; no significant difference in OS	Study suspended 10/2006 due to unexpected adverse events occurred coincident to planned interim analysis
Study 20010103	Darbepoetin alfa v placebo Hgb target: 12-13 g/dL	Nonmyeloid malignancies (N = 989); no chemotherapy	OS poorer in the ESA v control arm (HR, 1.30; 95% CI, 1.07 to 1.57; $P = .008$)	Statistics based on FDA analysis of primary data submitted by study sponsor prior to May 2007 ODAC meeting
Study 10010161	Darbepoetin alfa v placebo Hgb target: > 14 (women), > 15 (men)	Lymphoproliferative malignancies (N = 344); chemotherapy	OS poorer in the ESA v control arm (HR, 1.37; 95% CI, 1.02 to 1.83, $P = .037$) PFS no different between the two study arms (HR 1.02; 95% CI, 0.80 to 1.30)	

Abbreviations: ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin; OS, overall survival; HR, hazard ratio; TTP, time-to-progression; PFS, progression-free survival; NSCLC, non-small-cell lung cancer; US FDA, US Food and Drug Administration; ODAC, US FDA Oncologic Drugs Advisory Committee.

org, and an explanation of the NCD process is in this month's Washington Consult.)

The Current Controversy

The current controversy can be separated into two separate yet related issues. First, there is the area of scientific uncertainty and disagreement. Complicating this is the second issue, regulatory in nature, whereby CMS is proposing restrictions on reimbursement for clinical use that are more stringent than current US FDA marketing approval for these agents. Layered over this uncertainty is the fact that the US FDA has yet to act on any of the ODAC's recommendations.

Therefore, any changes the US FDA may pursue are currently unknown, and it is likewise unknown if these eventual changes will concur with the proposed coverage restrictions, which are likely to be finalized by that time.

Within the scientific arena, one of the major points of contention rests in extrapolating the results of those studies showing poorer tumor control or overall survival to the use of ESAs as currently approved by the FDA. All of the studies, with the exception of 20010103, had a target hemoglobin above 12 g/dL, and all enrolled patients with a baseline mean or median hemoglobin above 10 g/dL (in studies that reported this criteria). Specifically, the

CMS Issues Final Decision on ESAs

On July 30, 2007, the CMS issued a final national Medicare coverage decision on the use of ESAs in cancer and related neoplastic conditions. Following is a brief synopsis of the key provisions in the final coverage determination as outlined by CMS.

1. CMS did not implement any restrictions on the use of ESAs in patients with myelodysplastic syndromes (MDS)
2. CMS determined that the use of ESAs is not reasonable and necessary for Medicare beneficiaries with the following conditions:
 - Any anemia in cancer or cancer treatment patients due to folate deficiency, vitamin B₁₂ deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
 - The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers
 - The anemia of cancer not related to cancer treatment
 - Any anemia associated only with radiotherapy
 - Prophylactic use to prevent chemotherapy-induced anemia
 - Prophylactic use to reduce tumor hypoxia
 - Patients with erythropoietin-type resistance due to neutralizing antibodies
 - Anemia due to cancer treatment if patients have uncontrolled hypertension
3. CMS determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia is only reasonable and necessary under the following conditions:
 - The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%)
 - The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alfa; equivalent doses may be given over other approved periods
 - Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is > 1 g/dL (hematocrit > 3%)
 - For patients whose hemoglobin rises < 1 g/dL (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10 g/dL after the 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%; continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1 g/dL (hematocrit rise < 3%) compared to pretreatment baseline by 8 weeks of treatment
 - Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dL (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%); continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose
 - ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen
4. CMS confirmed that local Medicare contractors may continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

This new national coverage decision became effective on July 30, 2007. CMS is developing instructions for its local contractors that process and review Medicare claims and anticipates that these changes will be implemented by September 30, 2007.

At press time, ASCO continues to review this coverage decision. Additional updates and resources are available as online supplements at ascopubs.jop.org.

ENHANCE and DAHANCA-10 studies enrolled patients receiving only radiotherapy without chemotherapy; 20010103 enrolled patients with active, nonmyeloid disease, receiving no therapy; and EPO-CAN-20 enrolled patients with NSCLC not receiving chemotherapy.

Because current guidelines (as well as the FDA label) do not recommend raising hemoglobin levels above 12 g/dL, starting ESAs above a hemoglobin of 10 g/dL, or using ESAs in the setting of anemia of cancer (with limited exceptions; eg, patients with MDS, these studies do not

necessarily shed light on the effect of ESAs in recommended settings.

As of the writing of this publication, although the FDA has yet to act on the ODAC recommendations stemming from the May 2007 meeting, CMS has proposed restrictions on reimbursement that are more stringent than the recommendations reached by the ODAC. Some private insurers have already adopted some of the more severe restrictions for their own payment systems than those proposed by CMS, before either the finalization of these proposals or further action by the FDA. While heated debate continues among health care providers, patients, insurers, federal agencies, and the manufacturers concerning the safety and possible over-use of these drugs, almost all involved agree that further research is needed in order to answer important outstanding questions. The major difficulty with the existing body of evidence showing harm with ESAs is that many of these trials were conducted in off-label settings (ie, in patient groups for whom ESAs are not indicated such as patients treated with radiation therapy only, and/or with hemoglobin targets higher than the currently recommended 12 g/dL). In earlier studies conducted in indicated populations and settings, the randomized trials were not adequately powered nor designed to detect differences in tumor progression or survival. Therefore, some argue that just because these earlier trials did not show a decrement in survival outcomes, this does not provide evidence of no harm ("absence of evidence is not evidence of absence"). Meta-analyses conducted by the drugs' manufacturers, and presented at both ODAC meetings, also did not indicate an adverse influence on tumor progression. Conversely, others argue that because the only

trials that have shown poorer outcomes in these end points have been in nonindicated settings, it is not possible to extrapolate these findings to settings where ESAs are used as indicated.

Because ESAs are already so widely used, there is concern that accruing patients to adequately powered trials designed to assess survival, tumor response, and safety as end points would be difficult, if not impossible. There is also concern that restrictions to ESA use could force many patients back into the transfusion setting, whether the anemia is due to acute conditions as in chemotherapy, or chronic conditions, as in MDS. As previously mentioned, while blood transfusions are safer now than they ever have been, risks still exist; moreover, there also exists the fear that sending potentially thousands of patients a year back into the transfusion setting would add a great strain to the nation's already over-taxed blood supply.

Regardless of the outcome of CMS's NCD process, the controversy over ESA safety is unlikely to be resolved in the near future. However, ASCO, in partnership with the American Society of Hematology (ASH), is in the process of updating their epoetin/darbepoetin alfa guidelines. It is hoped that these guidelines will provide a framework within which clinicians can carefully consider the risks and benefits of ESA use in their patients, and help prompt further research in areas where it is clearly needed.

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