Trends-in-Medicine

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by Lynne Peterson

SUMMARY

An FDA Advisory Committee voted that ESAs should remain available to cancer patients with chemotherapy-induced anemia but that patients receiving potentially curative treatments (such as adjuvant breast cancer patients) should not take them. The panel favored stronger *written* informed consent, but rejected the idea of a restricted distribution system. The panel was divided on whether ESA use should be restricted to small cell lung cancer patients only and on whether patients with metastatic breast and/or head & neck cancer should take ESAs. Some panel members favored using hemoglobin ≤10 for ESA initiation in asymptomatic patients without co-morbidities, but others wanted more physician discretion.

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FDA Advisory Committee Recommends Keeping Anemia Drugs on The Market but with New Limits

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The FDA's Oncologic Drugs Advisory Committee (ODAC) voted overwhelmingly that erythropoiesis-stimulating agents (ESAs) should remain available to oncologists to treat the chemotherapy-induced anemia. However, panel members also told the FDA they should narrow the indications for use of the drugs – epoetin alfa (manufactured by Amgen, and marketed by Amgen as Epogen and by Johnson & Johnson/Ortho Biotech Products as Procrit/Eprex) and darbepoetin alfa (Amgen's Aranesp).

ESAs were first approved to treat anemia in patients with chronic kidney failure, but they also gained FDA approval to treat cancer patients whose anemia is caused by chemotherapy. Epogen and Procrit are also approved for patients scheduled for major surgery to reduce potential blood transfusions and for the treatment of anemia for certain HIV patients. ESAs have been widely used off-label to treat patients with anemia of cancer not on chemotherapy and patients with chronic kidney disease not on dialysis. ODAC focused only on the use of ESAs for cancer patients receiving chemotherapy. The FDA's Cardio-Renal advisory committee will meet in early autumn on ESAs in patients with chronic renal failure.

The ODAC panel opened with presentations by Amgen and J&J in defense of ESAs. Interestingly, there was no opening statement from FDA officials. Amgen and J&J officials attempted to convince panel members that there is ***no proof*** that ESAs promote tumor progression and that adverse events can be managed with new labeling and a risk management program. The companies also surprised the FDA and panel members with new proposals for hemoglobin levels and a safety study.

The bottom line from the panel – and the view of FDA officials after the panel meeting – was:

- **ESAs should stay on the market for present cancer indications, by a vote of 12 Yes, 1 No, 1 Abstention.** Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER), said, "There was a clear signal that the class of drugs should continue to have an oncology indication – for chemotherapy-induced anemia…One other message we got was based on further label modifications. Here we need to look at specifics to the label, but I think there was near unanimous agreement on continuing to market ESAs." Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, added, "I think we got a clear message that the drugs should still be available, at least in certain

oncology patients…but we also got a clear sense that they are concerned about the risk from the data available, but the risk is not entirely clear…We still need more data… We don't have perfect data at this point."

- **The panel was divided on whether ESA use should be restricted to small cell lung cancer patients only, with a vote of 8 against restricting, 6 in favor of restricting.** Dr. Pazdur called this a "draw," adding, "Here we need more internal discussions. A close vote like this requires us to discuss it internally, and then when we formulate our opinion on a restriction, if there were one, then that would be discussed with the company."

- **ESA use is *not* indicated for patients receiving potentially curative treatments** (e.g., adjuvant setting breast cancer), **by a vote of 11 Yes, 2 No, 1 Abstention.**

- **The panel was mixed on whether ESAs should be indicated in patients with metastatic breast and/or head & neck cancer, 9 voting they shouldn't and 5 they should.** Asked why the panel felt ESAs shouldn't be used in metastatic breast cancer but are all right to use in other metastatic cancer, Dr. Patricia Keegan, director of the FDA's Division of Biologic Oncology Products, CDER, said, "I would say that there seemed to be a strong feeling that it (an ESA) should be used in metastatic cancers for which there is not the potential for a cure… And there was less unanimity whether it should be restricted in metastatic breast cancer or head & neck cancer. So, I think this is an issue we need to go back and consider the sense of the committee." Dr. Pazdur said there were data in breast cancer and head & neck cancer that "heightened the obvious risk that may be there." Dr. Jenkins added, "If you have a patient where you expect you can cure the cancer, given the risks identified for ESAs, is it appropriate to use ESAs in that setting where you might subvert the value of the curative treatment vs. other settings in cancer where you are not expecting to cure the patient but to delay progression or decrease symptoms?"

- **Some panel members favored a hemoglobin (Hb) level for ESA initiation of ≤10 in asymptomatic patients without co-morbidities, but others wanted more physician discretion.** There was no vote on this. Dr. Pazdur said, "The company (Amgen) had proposed Hb ≤10 g/dL…but some of the committee really advocated for some flexibility here and for clinical judgment on when it should be used. Our current labeling says the lowest dose to avoid transfusions." In fact, Amgen's suggestion of an initiation target of ≤10 g/dL was not presented to the FDA before the panel meeting; that was news to FDA officials.

- **A *written* informed consent/patient agreement should be required, by a vote of 8 Yes, 5 No, 1 Abstention.** *Asked how an informed consent procedure would get implemented and how would it work*, Dr. Pazdur said, "The exact implementation of that has to be worked out...We have to go back and see how it would be implemented." Dr. Jenkins said, "We do have a few programs with informed consent as part of their RiskMAP. There are not very many. You have to look at the logistics. They (the panel) voted for informed consent but against a restricted distribution system. The places we have informed consent are generally in concert with a restricted distribution system…So, we have to consider that…We heard from some committee members that oncologists give drugs every day that are far more toxic, and those don't require a separate, individual informed consent…but others felt that it is very important to be sure the patient is very well informed about the risk to make informed decisions."

- **A restricted distribution system was not recommended, by a vote of 11 No, 1 Yes, 2 Abstentions.**

TIMELINE

This ODAC panel represents only the latest in a series of actions – and the third FDA Advisory Committee meeting – the FDA has taken since the safety of ESA became an issue. Some of the key time points have been:

March 2008: Just days before a second ODAC panel meeting on ESAs, the FDA further strengthened ESA labels with a new safety warning that "ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin (Hb) 12 g/dL." This was the sixth label revision since Epogen was first approved.

November 2007: The FDA strengthened the boxed warnings for ESAs and made other safety labeling changes to the drugs. The FDA also issued an advisory that there is **no proven quality of life benefit** to ESAs in cancer or HIV patients, and no proven benefit on fatigue, the symptoms of anemia, or overall patient well-being. Any reference to ESAs affecting happiness and well-being were deleted. The FDA also announced that a **Medication Guide** (MedGuide) was being prepared that pharmacists would give to every patient with every prescription. The FDA had not figured out how patients in the hospital or in doctors' offices would get the MedGuide.

September 2007: The FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC), in a joint meeting with the Drug Safety and Risk Management Advisory Committee (DSaRM), rejected an FDA staff proposal to establish a Hb ceiling "not to exceed ~11 g/dL," largely because panel members did not like the "not to exceed" language. However, the FDA's take-away message from the panel was that the labeling language could be improved.

July 2007: The Centers for Medicare and Medicaid Services (CMS) issued a national coverage decision (NCD) on ESAs

that restricted use somewhat. The NCD provided coverage for ESAs, with some restrictions, for the treatment of anemia secondary to myelosuppressive anticancer chemotherapy in certain cancer conditions, such as solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia. Among the restrictions were Hb <10 g/dL for initiation of therapy, limiting ESA treatment duration to a maximum of 8 weeks after a chemotherapy session ends, limiting the starting dose to the FDA recommended starting dose, and limiting dose escalation levels.

May 2007: ODAC, citing concerns about safety, voted 15-2 that the FDA should impose additional restrictions on use of ESAs. The panel also voted unanimously that additional safety trials are needed. Panel members expressed dismay at the dearth of valid data from any trials and expressed concern at the evidence that showed ESAs decrease survival and, in fact, may promote tumor growth.

March 2007: The FDA ordered a "black box" warning on ESAs, asking doctors to use the lowest dose possible to avoid the risk of heart attack and stroke.

THE INDUSTRY PERSPECTIVE

Dr. Paul Eisenberg, director of global regulatory affairs and safety at Amgen, broadly defended ESAs, "We believe that in aggregate the data while raising concerns and indicating the need for appropriate use do not justify further actions or restrictions at the levels that have been suggested. He pointed out that the ESA labels have been revised to include strong warnings on off-label use and that there was new guidance on dosing in nephrology.

Dr. Eisenberg said Amgen, Roche, and J&J are proposing "conservative" initiation of ESAs at hemoglobin levels of 10 g/dL. He added, "An important message from ODAC last year was that more data were needed. This recommendation appropriately reflected concerns with existing studies, even though these concerns occurred in (off-label) use…Two studies since the 2007 ODAC meeting (the GOG-0191 trial in cervical cancer and the PREPARE trial in breast cancer) do not change the benefit:risk profile."

Dr. Eisenberg insisted that ESA risks can be identified and managed. He emphasized that there is no clear evidence of ESA-stimulated tumor progression, and a "plausible and unifying explanation for the mortality signal is TVE (thrombovascular event)."

He also noted that Amgen is committed to pharmacovigilance and a risk minimization plan. He said the companies do not plan any broadcast advertising of ESAs. However, he didn't rule out print advertising except to say that the future focus of advertising would be to inform patients of the risks and benefits of ESAs.

Dr. William Hait from J&J/Ortho Biotech R&D insisted that "the available data allow us to recognize and manage the use of ESAs…The totality of the data and the weight of the evidence indicates ESAs have a favorable benefit:risk in labeled indications." He cited several points on which he believes there is general agreement:

- Anemia in cancer patients is multifactorial.
- ESAs decrease transfusions in chemotherapy patients. "~50% of anemic chemotherapy patients require transfusions in the absence of ESAs. Transfusions have transient benefit and are associated with known and unknown risks…Is it logical to assume that avoiding transfusions is beneficial?"
- ESAs increase the risk of TVEs in CIA, CRF, and surgery.
- Unexplained increased mortality has been observed with ESA use in investigational settings. However, he argued, "We do not agree that the data point to tumor progression as the mechanism for increased mortality." He pointed out that the mortality risk in 59 controlled ESA studies of 15,249 patients showed "some studies trend in favor of ESA, some favor the control arm, and some are neutral," and many of the negative studies were investigational studies.
- Data from >12,000 patients in controlled studies are available to inform benefit:risk.
- The most rigorous study to date (20010145) did not demonstrate increased mortality or tumor progression.
- A relationship between Epo-R expression and tumor proliferation has not been established.

Dr. Tom Lillie, Amgen global R&D, pointed out that safety concerns have been included in the ESA labels since the May 2004 ODAC meeting. He, again, pointed out that "statistically significant increases in tumor progression have not been observed" in chemotherapy studies, "Twenty studies measured disease progression as an endpoint, using heterogeneous measures, with inconsistent outcomes. None were statistically significant."

Dr. Lillie proposed several label changes to ESAs:

- Initiation at hemoglobin ≤10 g/dL.
- Limiting dose escalation.
- Discontinuing ESA for non-responders. (~2/3 of patients respond to ESA, and non-responders tend to receive higher doses.)

Dr. Lillie characterized several ESA trials:

- PREPARE breast cancer trial of Aranesp (darbepoetin alfa) as showing no difference in tumor progression with ESA use. He updated the data provided to the panel in the FDA briefing book with new data.

J&J Analysis of PREPARE Trial

Measurement	Control n=377	Aranesp n=356	p-value
Mean Hb	12.61 g/dL	13.59 g/dL	---
Relapse-free survival	78%	72%	Nss, p=0.06
Overall survival	89%	85%	Nss, p=0.16

- 20010145 as showing no increased tumor progression with ESA use.
- BEST as showing no difference in time to tumor progression with epoetin (57%) vs. placebo (59%), but lower time to death with control (p=0.012). "Thus, while there is a mortality signal, it is far from clear in this study that tumor progression is the underlying cause."
- 2 head & neck cancer studies as showing reduced loco-regional control with ESA use, but he pointed out that the hemoglobin target was higher (14-15 g/dL), the failure was not distant, patients received radiotherapy alone (no chemotherapy), so "the suggestion is that high hemoglobin interferes with radiotherapy efficacy."
- The randomized, open-label, multicenter GOG-0191 trial in cervical cancer – showed no statistically significant difference in progression-free survival and overall survival in patients on an ESA vs. no ESA. He said the FDA has not yet had time to analyze the data Amgen provided to the FDA from this trial. "On PFS, there was a small number of excess events (2), and on overall survival, there was also a slight excess with ESA."
- AGO/NOGGO, a cervical cancer trial, which showed a decreased number of events in the ESA arm.

Dr. Lillie concluded:

- Cancer patients are at increased risk of TVE, and ESAs increase this risk. "TVE could underlie observed mortality signals."
- The role of Epo-R in tumor biology is unclear.
- Tumor progression (with ESAs) has not been established in the chemotherapy setting.
- Reduced loco-regional control in head & neck cancer may reflect interference with the efficacy of radiotherapy.

In a study-level meta-analysis, he said there does not appear to be a signal of worsened mortality with ESAs, "We do not see a consistent signal within all studies when we place them together…All three manufacturers have submitted their data for an independent, patient-level meta-analysis, and the results will be available later this year."

The manufacturers are conducting numerous post-marketing studies that they believe will further inform use, and Amgen is *proposing* another non-inferiority study (20070782) to assess patient survival in a rigorous manner. The primary endpoint is overall survival, the secondary endpoint is PFS, but there are also other safety and efficacy endpoints. This will be a 6,186-patient study of Aranesp vs. placebo.

Dr. Adrian Thomas, global safety and benefit:risk management at J&J Pharmaceutical Group, reviewed the manufacturers plans for risk management. He said, "We will propose tools that are evidence-based and that allow appropriate product access…We want to be sure we don't put undue burdens on the clinical settings." Elements of the proposed RiskMAP for mitigation in chemotherapy-induced anemia include:

1. High Hb (labeled boxed warning)
2. Anemia of cancer with radiotherapy only (labeled boxed warning)
3. TVE risk (labeled boxed warning)
4. Non-responders (Label – proposed dose modification).

The plans are for:

- A RiskMAP in chemotherapy-induced anemia.
- Targeted education and outreach with Dear Healthcare letters, patient package inserts, a medication guide (MedGuide), a patient start-up kit, and continuing education.
- Reminder systems with a healthcare provider/patient document discussing the benefit:risk of ESAs, documenting of patient receipt of the MedGuide, and a prescribing checklist.
- Controlled oncology distribution, with pharmacies and distributors distributing only to enrolled sites and enrolled provider sites agreeing to comply with the RiskMAP.

In conclusion, Amgen's Dr. Eisenberg said, "There is a concern with TVEs, and we think that can be managed…We do believe comprehensive patient-level analysis is important, and we are delighted that the Cochran group has agreed to do that with data from all the manufacturers…We do not believe the data support further restrictions based on tumor type or withdrawal of the indication…We strongly feel, and both sponsors agree, that third-party oversight and monitoring are important."

THE FDA PERSPECTIVE

Dr. Vinni Juneja, a medical officer in the FDA's Division of Biologic Oncology Products, provided a summary overview of the risks and benefits of ESAs. Among the points he made were:

- At best 30% of patients (1 in 3) benefit from an ESA through avoidance of transfusion.
- Unproven perceptions of ESA "benefits" include:
  - Improved quality of life, fatigue, and other symptoms associated with anemia have ***not*** been established in randomized, double-blind, placebo-controlled trials.

- Improved survival or improved tumor control has ***not*** been established.

➢ No trial has collected data on transfusion risks to assess the impact of ESAs on the reduction of transfusion risks in patients with cancer.

➢ Many of the trials that have been done were never reviewed in advance by the FDA and do not adequately address the safety of ESAs.

FDA View of ESA Post-Approval Trials

Trial	Number of patients	Primary endpoint	ESA adverse outcome
Chemotherapy			
BEST (breast)	939	12-month OS	Decreased 12-month OS
161 (lymphoid)	344	Change in Hb	Decreased OS
PREPARE (breast)	733	RFS, OS	Decreased RFS, decreased OS
GOG-0191 (cervical)	114	PFS	Decreased OS
Radiotherapy			
ENHANCE (head/neck)	351	Loco-regional PFS	Decreased LR PFS, decreased OS
DAHANCA (head/neck)	522	Loco-regional control	Decreased loco-regional control, decreased OS
No chemotherapy or radiotherapy			
CAN-20 (NSCLC)	70	Quality of life	Decreased OS
103 (heter-ogeneous)	989	Transfusion	Decreased OS

➢ The risks of ESAs include:

- TVEs, with increased morbidity and potentially increased mortality.
- Decreased survival.
- Increased tumor promotion – both decreased loco-regional control and decreased PFS. "Six studies have shown statistically significant evidence of increased tumor promotion and/or decreased survival…And two studies have shown trends of increased tumor promotion and/or decreased survival."

Dr. Juneja reviewed the two newest trials the panel is considering:

➢ **PREPARE in neoadjuvant breast cancer**, where, with 3 year median follow-up, overall survival was 86% ESA vs. 90% control (HR 1.42), and relapse-free survival was 72% ESA vs. 78% control (HR 1.33). Dr. Juneja said this trial showed a trend to decreased survival with ESA and a trend to decreased relapse-free survival with ESA.

➢ **GOG-0191 in cervical cancer**, which was terminated early due to increased TVE (19% vs. 9%) in the ESA arm. Dr. Juneja said this trial showed a trend to decreased overall survival with an ESA.

Dr. Juneja also offered some new FDA analyses:

- **Achieved vs. targeted hemoglobin.** He noted that data on *achieved* Hb was submitted to the FDA on 7 of 8 trials, and in 2 of those trials it was <12, "This leads to the question, 'Is the upper range for the target Hb of 12 g/dL safe?'...No adequately-designed studies have been concluded with target Hb <12, two studies where the achieved median Hb was <12 showed decreased survival, and the safety of target Hb <12 is not established."
- **Survival and tumor promotion by tumor histology.** He noted that there are statistically significant survival data showing a benefit to ESA in SCLC but not in any other tumor type. He added that there are no data on ESA adverse effects in "numerous" tumor types, including GU, ovarian, leukemia, CNS, melanoma, sarcoma, and more.

Since the last ODAC panel meeting in May 2007, the FDA initiated a MedGuide for ESAs in October 2007 and revised the ESA labels in November 2007 and again in March 2008. Dr. Juneja said there are examples of increased risk present across these factors and wondered, "Is there an oncology setting where ESAs do not have an increased risk?"

The latest boxed warning added new language that said: "ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of <12 g/dL.

Among Dr. Juneja's conclusions were:

- ESAs do ***not*** increase survival and may increase tumor growth.
- Reconsideration of the risk:benefit of ESAs is warranted. "ESAs are supportive agents, so establishing safety is necessary…Numerous studies in oncology and non-oncology have shown an increased TVE risk. There should be a reconsideration of the risk:benefit of ESAs in cancer patients."
- Results from adequately designed ongoing or proposed studies will not be available for several years.
- Meta-analyses are problematic to definitively rule out the risk of ESAs.
- The absence of evidence (in new data submitted to the FDA by the sponsors) of increased risk is ***not*** definitive evidence of absence.
- The sponsors' proposal for various forms of physician education will not adequately address the risk.

COMMITTEE QUESTIONS FOR THE FDA AND SPONSORS

The first few panel questions made it appear that the panel was favoring ESAs and negative to the FDA position, but it didn't take long before the same "friendly" voices turned negative. It was clear the panel believed ESAs are valuable, but they were

also troubled by safety concerns and a continuing lack of adequate safety data. Among the topics about which panel members questioned the FDA and the companies were:

Lack of statistical significance showing harm from ESAs. Dr. Michael Perry, an oncologist from the University of Missouri, quarreled with the FDA about the statistical significance of the ESA negative findings. He said, "We are making a great deal about studies without statistical significance. In previous ODAC meetings, when a sponsor was asked to produce data in favor of approving a drug, we declined if the data weren't statistically significant." The panel chair explained that the criteria are different for supportive drugs like ESAs, but Dr. Perry responded, "I want to be sure everyone is tried by the same judge and the same jury."

This prompted the FDA's Dr. Keegan to say, "We felt there were important public health issues to bring to the panel…The totality of the data appears to be consistent if not all equally statistically significant...And the level of evidence and the weight we put on an efficacy claim is different from the weight of evidence for safety…We use a different standard for safety, and we don't hold that to the same level of significance as we do for promotion claims."

Lack of transfusion data in ESA trials. A panel member was concerned that data on transfusions have not been collected in the ESA trials. An Amgen official responded that data on adverse events associated with transfusions have been very difficult to collect.

The feasibility of the new post-marketing safety trial (2007078) that Amgen is proposing. Asked when the results of this trial can be expected, an Amgen official said, "We anticipate an accrual period of five years…We are addressing this by making it a global study and allowing broader chemotherapy regimens, which we believe will improve accrual. There is 2:1 randomization (to ESA)…We are putting the full weight of the companies behind this to get it done as soon as possible…We do expect to seek an SPA (Special Protocol Assessment) from the FDA. Assuming that goes smoothly, we would hope to start (the trial) at the end of this year."

How distribution could be limited. An industry official said, "Our proposal is to target distribution by the provider side…at the hospital or community center level, making that the gate-keeper for prescriptions. It will be difficult in the retail pharmacy situation to differentiate between nephrology and oncology (use)…We agree that the restricted distribution used for some other drugs, given the large volumes in oncology, would be very difficult to enforce."

Whether Amgen's marketing practices – rebates and bundling of ESAs with Amgen's Neulasta (pegfilgrastim), a treatment for febrile neutropenia **– affect ESA use.** Dr. Perry spent some time trying to get Amgen to admit, yes or no, that it was doing bundling of ESA and Neulasta. It wasn't easy, but he finally got Amgen to admit it. The Amgen official tried very hard, though, to insist that there is no over-utilization of ESAs, saying that if there were, the following would be expected:

1. Large amounts of ESAs would be used to achieve higher Hb levels – but the official claimed that <5% of all ESAs are given with Hb >12.
2. High doses would be used – but he insisted this is not the case. "The mean weekly dose of Aranesp is ~20% less than the labeled dose."
3. Everyone would be treated if incentives were influencing utilization – but he said ~30% of patients with Hb <11 are not getting ESAs.
4. Differences in ESA patterns of care within different practice environments – but he said that has not happened.

The relationship between dose and adverse effects of ESAs. An Amgen official said, "We don't see an absolute relationship between the dose administered (and adverse events)…We randomized patients to higher dose vs. lower dose at initiation …and they did not show any difference in survival or TVE outcome."

The FDA's Dr. Richard Pazdur also had questions on ESA target ranges.

- *Is the CMS national coverage decision (NCD) consistent with the proposals industry is making?* Amgen's Dr. Eisenberg said, "We believe initiation <10 as is now reflected in the label – that will be implemented in Europe – is in the conservative range…We believe most clinicians in practice consider transfusion when Hb drops below 10 in otherwise healthy patients…We think it is a conservative approach…The difference with (CMS) NCD and the European label is that we believe the use of ESAs, if they are to be effective in avoiding transfusions and reducing exposure, need to be based on pharmacology…If someone's Hb rises above 10, all our data suggest that they will avoid transfusions…To wait for it to drop below 10, we don't think is a good decision."

- *Are the manufacturers suggesting a Hb level >10 is needed to avoid transfusion?* Dr. Eisenberg said, "Our data actually were best when, in clinical studies, initiation was <11…We believe that to have an abundance of caution the lowest dose to avoid transfusion is initiation <10…We don't advocate or think it is appropriate to target patients to a level higher than that needed to avoid transfusions."

- *Where should dosing be targeted? Dr.* Eisenberg said, "Initiation <10…If a patient is a good responder, the dose that achieved that response should be minimized to a dose needed to avoid transfusion…If a patient is at 10.5, I could even see reducing the dose…To keep the dose

between 10 and 11 we think would avoid transfusions…If it is a poor responder, we think it would be worth one more try…Certainly, if there is no response after 8 weeks, stop providing ESA…Our goals should be conservative management. We don't think we should be providing additional dosing to the high risk group…There are going to be some patients in whom the response will be quite brisk and may go >11, and we feel the dose should then be reduced…I think we can certainly provide label guidance that is quite specific."

PUBLIC WITNESSES

ODAC heard from 16 public witnesses, and nearly all lobbied for continued access to ESAs, but a woman whose husband died after taking J&J's Procrit urged better informed consent. Comments included:

- **Christin Engelhart of the Aplastic Anemia and MDs International Foundation:** "ESAs are not appropriate for all patients…but for some patients they can reduce blood transfusions, and for some patients they are primary therapy."
- **Dan Cohen, senior vice president of fovernment relations public policy for U.S. Oncology,** the largest community oncology provider network in the U.S., who proposed using his network for a CMS demonstration project on ESAs that could include endpoints on transfusion frequency, progression-free survival, overall survival, and thrombovascular events.
- **Carlea Bauman, President of the Colorectal Cancer Coalition,** who suggested a patient registry program – as is done with Elan/Biogen's Tysabri (natalizumab).
- **Karen Pasqualetto, a colorectal cancer patient who has had both ESAs and blood transfusions.** She said, "I urge you to consider quality of life issues. For me to have an ESA allowed me to continue treatment, spend more time at home with my child, avoid prolong hospitalization, and 6-8 hours of infusion…ESAs worked very well for me in my stage of disease."
- **Dr. Peter Ellis of the University of Pittsburgh Cancer Centers:** "We believe the use of ESAs that drive Hb >12 clearly increase the risk of TVE and mortality…but we believe ESA use reduces transfusions and possibly improves quality of life…We do not believe that ESAs, as used in the NCD (CMS national coverage decision), have been shown to decrease patient safety…We do not see significant risk signals using these drugs (used appropriately)…We ask the committee to allow latitude for physician determination of the risk:benefit in consultation with the patient…and not impose overly restrictive rules."
- **Dr. Samuel Silver, a hematologist/oncologist from the University of Michigan, speaking on behalf of ASCO (the American Society of Clinical Oncology) and ASH (the American Society of Hematology):** "ASCO and ASH do not see significant evidence of harm to warrant cessation of use across all patients with malignancies… Furthermore, we believe there is compelling evidence for safe use in patients with low risk myelodysplastic syndrome (MDS)…Data suggest that ESA treatment may have a favorable survival impact in MDS…We realize that is not a labeled indication, but we believe access for these patients should remain available."
- **Dr. David Henry, a hematologist/oncologist from Pennsylvania Hospital:** "I believe that ESAs are appropriate to use in chemotherapy-induced cancer…I believe ESA use is safe when used responsibly."
- **Sharon Lenox, whose husband died 62 days before the panel meeting:** "He bled to death four hours after an injection of Procrit…We were never shown the black box warning…We have to sign HIPAA…McDonald's even tells you their coffee is hot…Would my husband still be alive if not given this drug or would his tumor have progressed? We don't know, but I think it should have been his choice."

FDA QUESTIONS TO THE COMMITTEE AND THE PANEL VOTES

The FDA prefaced its questions with the statement: "To obtain marketing approval for a drug or biologic product, an applicant must demonstrate that the product is safe and effective, when administered in accordance with product labeling. Specifically, there must be substantial evidence of clinical benefit (efficacy) demonstrated in adequate and well-controlled trial, and ***FDA must find*** that the risks of the product do not outweigh the benefits. The key issues we would like you to discuss are whether available data continue to demon-strate that there is a favorable benefit to risk relationship for ESA use for treatment of chemotherapy-induced anemia in patients with cancer and, if so, whether the current product labeling is sufficient to ensure safe and effective use."

1. **Considering all the available data on the benefits and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the currently approved oncologic indications?**

   12 Yes, 1 No, 1 Abstention.

The no vote was the patient advocate, and the abstention was Dr. Judith Kramer of Duke University. Comments included:

- *Helen Schiff, the patient advocate:* "How long do patients have to continue to be exposed to a drug we are not sure is safe? It seems to me we are conducting investigations while patients continue to receive this drug…We are terribly conflicted because it (an ESA) is so convenient, and even patients would prefer to get an injection in the doctor's office rather than come in for a transfusion, but if we are accelerating their mortality, have we been responsible?"

- *Dr. Wyndham Wilson, an oncologist with the National Cancer Institute (NCI):* "To me, other than convenience, there is not hard evidence (of the benefits of ESAs)."
- *Dr. Michael Perry, an oncologist from the University of Missouri:* "A transfusion is difficult and time-consuming, but it is also hazardous…So, it isn't as easy as saying we can simply stop giving ESAs and transfuse…Fewer and fewer people choose to donate (blood). If we stop using ESAs, it is likely we will encounter a shortage of red blood cells in the future…I am the only person on the panel who had both a transfusion and an ESA, and if you give me a choice, believe me I would rather have the ESA."
- *Dr. David Stroncek, a transfusion medicine expert from the National Institutes of Health (NIH):* "The transfusion trigger since this drug was approved has really decreased, and now for stable patients, most guidelines say the trigger is Hb 8 or even 7 g/dL…And I'm confident there will continue to be blood available."
- *The FDA's Dr. Keegan:* "We came to the conclusion that you can't make a judgment that there is an improvement in quality of life, primarily because of missing information and lack of information and how to handle that…We really can't say there is evidence of a quality of life (effect)…(Our) major concern is missing information… Last observation carried forward (LOCF) is one way of handling that, but we know in cancer trials that they are unlikely to be dropping out for a good reason, so to use LOCF is a major methodological issue for us."
- *Dr. David Harrington, a statistician from Dana-Farber Cancer Institute:* "Could this label be revised to say, 'Use in patients for whom a transfusion is not appropriate?'" The FDA's Dr. Pazdur responded that the FDA "could consider that later."
- *Dr. Anthony Murgo, an oncologist from NCI:* "I think the limited amount of data there is (on ESA safety) would have been sufficient for approval (if the panel had been voting on an initial application for ESA approval)."

2. If you recommend that the current indication should be retained, should FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.

2a. To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, NSCL, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. **Should the current indication be modified to restrict use only to patients with small cell lung cancer?** **8 No, 6 Yes.**

2b. The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk:benefit assessment is different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers. **Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments?** **11 Yes, 2 No, 1 Abstention.**

The two no votes were Dr. Bruce Redman, an oncologist from the University of Michigan, and Dr. Perry. Dr. Ruth Day, director of the Medical Cognition Laboratory at Duke University, abstained. Comments included:

- *Dr. Wilson:* "By going into a potentially curative group, we are significantly increasing the risk to patients…This group has a higher risk if an adverse event happens because you may convert someone from a curative to a non-curative patient, and this is a lifetime difference for them."
- *Dr. Joanne Mortimer, the panel chair and a breast cancer specialist from City of Hope Comprehensive Cancer Center in Duarte CA:* "We know women with early stage breast cancer accept a 1% risk to accept chemotherapy… If there is a signal (with ESAs) in advanced disease – and I think there are in the BEST neoadjuvant (breast cancer) trial – I think that it (an ESA) should not be used in the adjuvant setting."

2c. Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies – breast cancer and head and neck cancer. **Should the current indication be modified to include a statement that ESA use is not indicted for patients with metastatic breast and/or head & neck cancer?**

9 Yes, 5 No.

2d. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which WSA treatment should be initiated. **Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate. Should that be Hb ≤10 g/dL or higher?**

No vote. Some panel members thought ≤10 was a good target, and others wanted this left to physician discretion.

Comments included:

- *Dr. Wilson:* "I would say there is emerging evidence that the more EPO you give, the more risk to the patient…and Hb 7-8 g/dL is now the threshold for a transfusion, where it was higher in the past…so I would say you could go (let Hb fall) to 8 or 9 g/dL…This discussion sounds like (you think) most patients who get the drug at 10 g/dL will benefit…but we know only 1 in 3 will benefit. So, Hb 10 g/dL is not a very accurate number. I routinely treat patients with chemotherapy, and, at the end of the cycle, that can drop to 8 g/dL and then cycle back up. That is more common than sailing straight down…(But) there is a worrisome association between the amount of EPO given and toxicity."
- *Dr. Redman:* "Hb ≤10 gives the physician the ability to watch the patient…Hemoglobin in chemotherapy-induced anemia doesn't drop abruptly from 14 to 7…It might go 13, 11, 9.8, but if you can't use an ESA until 8, then you are taking away the window…The physician treating the patient is the best one to make the decision…We can't blanketly say 8 g/dL to start, but if the patient is between 8 and 10 g/dL, you can't use it."
- *Dr. Murgo:* "That was my concern…I think this has to depend on the individual patient, and this is where physician judgment has to come in…So, a cushion is very important…I think it really has to be physician judgment."
- *Patient advocate:* "You also have to look at the risk of treating patients who might never go that low…A lot of people stabilize at 9-10-11 g/dL and don't need anything."
- *Dr. Ronald Richardson, an oncologist from the Mayo Clinic:* "Most of the people I see are older folks with not only one co-morbidity but 10 co-morbidities, so the threshold for transfusion is a lot different than someone who is asymptomatic without co-morbidities."
- *Dr. Perry:* "I would hate to think that a committee of 14 people could take a hypothetical patient and therefore promulgate a regulation that affects millions of people. That is not good science. It may be good talk in the bar, but it is not the way you set levels…If you look where patients get the most improvement in hemoglobin, the most improvement in quality of life, it is between 10 and 11 g/dL, so I would prefer a level of 10 if I have to have an arbitrary number."

3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.

3a. An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physicians (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. **Should the FDA require the implementation of a *written* informed consent/patient agreement for the treatment of chemotherapy-induced anemia?**

8 Yes, 5 No, 1 Abstention.

3b. Examples of restricted distribution programs include STEPS [Celgene's Thalomid (thalidomide)], RevAssist [Celgene's Revlimid (lenalidomide)], and iPLEDGE [isotretinoin]. **Should FDA mandate a restricted distribution system for oncology patients receiving ESAs?**

11 No, 1 Yes, 2 Abstentions.

The Yes vote was the patient advocate, with Dr. Kramer and Dr. Michael Link of Stanford abstaining. Comments included:

- *Industry:* "(With a restricted distribution system) you would make nephrology patients prove they are not oncology patients…That is a significant burden being applied to a different indication."
- *Dr. Wilson:* "If the FDA changes the indications somewhat for this (ESAs), and there is an informed consent process, one could argue that to restrict access in the manner Revlimid is would probably be onerous for a drug like this. There are many drugs like this with toxicities that accrue if given wrong...which is one reason we go to medical school…I would argue that mandated restrictions like Revlimid would not be indicated with a drug like this."
- *Dr. Richardson:* "The sponsors should reduce physician incentives to use this drug because of the rebate at the end of the year…The use needs to be on evidence rather than some sort of financial interest."
- *Dr. Perry:* "I'd vote for this at the same time we restrict digoxin, which has probably killed more people in the U.S."

POST-MEETING REACTION

FDA

FDA officials answered reporter questions about the panel votes.

What happens next? What is the timeframe for FDA action?

Dr. Keegan said, "We will have a follow-up communication with the company to talk about labeling changes. In the interim, if it is important to notify the public, we can issue a press release or an early communication, communicate with professional societies, and make other interim releases…We can communicate some information before we make a (deci-

sion)." Dr. Jenkins said, "We can't say. It isn't a drop of the pen decision...We need to consider it internally…(and) discuss with the company some of the issues we hear. Even if we wanted to set something up, it won't happen overnight…but we will work to get it done as quickly as we can."

How many patients would be affected by a recommendation to use ESAs only in the metastatic setting, not in the adjuvant setting?

Dr. Pazdur said, "I assume the majority of (ESA) use is in the advanced or metastatic disease setting…There are patients who get it in the adjuvant setting or when drugs are used to treat curative tumors. I assume that is a small portion of actual use."

Does the FDA still have to negotiate label changes or does the Food and Drug Administration Amendments Act of 2007 (FDAAA) allow the Agency to mandate changes?

Dr. Pazdur said, "The specifics of how we do that is still being reviewed by the Agency…I don't expect an issue in looking for a restriction in that area." Dr. Jenkins added, "The new authorities…become effective on March 25th, so they are not in place yet, but they will be in place in less than 2 weeks… and we are working through the process of understanding how we implement those...If we decide we need a RiskMAP, it will be required under the statute…The same on post-marketing studies on safety…We are still working on how safety labeling changes will operate, but we have already seen a signal from the company (Amgen) that they are eager to make the necessary changes in a timely manner."

What is the status of the MedGuide?

The FDA has been working with the companies on a MedGuide, but the details of that are still being worked out. Dr. Jenkins said, "The patient information that is required to be dispensed with every dosing of the product has not yet been approved…We need to see if the (proposed) MedGuide is sufficient or if we want true informed consent. The burden is usually on the sponsor to set up a system for informed consent …but that has been in a setting of restricted access, which the committee voted against."

What do the panel votes say about the CMS national coverage decision (NCD)?

Dr. Jenkins said, "We found the NCD to be consistent with what we had included in our labeling. We had included 'initiation should be the lowest dose to avoid transfusion,' and that was the rationale CMS used to put some parameters around that labeling language. We always felt the NCD was consistent with our labeling…We've been comfortable that their coverage decision was consistent with our understanding of the data."

Did the sponsors make a compelling case for the benefits (of ESAs), and what are those?

Dr. Keegan said, "The benefit upon which it was approved was reduction in patients who required red blood cell transfusion…and we think they have made a compelling case, and all the data continue to show it does reduce the number of patients who need to receive transfusions. The area where we have some disagreement is whether there are improvement in quality of life and in the patient sense of well being. We feel the companies have not made a compelling case for that at this time."

Amgen said it would seek an SPA (Special Protocol Assessment) for the ~6,000-patient post-marketing safety study. Aren't SPAs usually used for product approvals?

Dr. Pazdur said, "Having an agreement between the FDA and the companies on the design of the trial, on the statistical plan and eligibility, will help it answer an important question." Dr. Jenkins added, "Technically, the SPA program is set up for Phase III trials intended to support registration (approval). So, technically, the study may not be considered to qualify for an SPA, but we don't wholly stick to that…We clearly want to get to an agreement on such an important trial…and we will work with Amgen on that."

Had the RiskMAP that Amgen described to the panel been discussed in advance with the FDA?

Dr. Keegan said the RiskMAP presented to the panel was "somewhat different" from what Amgen had been discussing with the FDA prior to the panel meeting.

Johnson & Johnson

Shortly after the panel ended, J&J issued a press release. Among the comments in that were:

- "Ortho Biotech is concerned by the Advisory Committee's recommendations to restrict access to ESAs for chemotherapy-induced anemia in patients with metastatic breast and head & neck cancer, and patients treated with curative intent. The company believes that fully informed patients and their physicians should have the choice to use this important medication."
- "We hope the FDA will now take time to review this substantial body of (new) data (provided to the FDA over the past several months) before reaching its final decision."
- "The FDA has not yet reviewed new or follow-up survival data accounting for ~50% of the 7,444 patients in the company's database. The totality of available data support continuing (use in chemotherapy-induced anemia)."
- "The Cochran Collaboration…is about to generate important new analyses regarding the safety of ESA use in chemotherapy-induced cancer. The FDA should consider these analyses before making its final decision."

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