BRIEF UPDATE

FDA Finalizes REMS Program for ESAs; Amgen Continues to Study Risks

By Vicki Brower

In February, the U.S. Food and Drug Administration announced a new program to restrict access to erythropoiesis-stimulating agents (ESAs) for patients with chemotherapy-induced anemia. This move—triggered by multiple clinical trials demonstrating an increased risk of tumor growth, heart attacks, blood clots, strokes, and death among patients taking ESAs—marks a new era in which patients can be prescribed ESAs only under a strict risk management program.

Known as a Risk Evaluation and Mitigation Strategy (REMS), the FDA program is designed to ensure that cancer patients are fully informed about the major risks of using the drugs. According to some, the strategy is a death knell for widespread use of ESAs in cancer, once taken by more than 50% of all cancer patients.

“The agency will not be revisiting this decision; it is final,” said FDA spokesperson Erica Jefferson.

But Amgen, which makes and distributes two ESAs, maintains that no definitive evidence on their risks exists and says it will continue to study the safety issues.

The hormone erythropoietin (EPO) controls the production of red blood cells by stimulating bone marrow to produce the cells. ESAs are approved in the U.S. to treat patients with chemotherapy-associated anemia, chronic kidney failure, and certain cases of human immunodeficiency virus, as well as to reduce the number of blood transfusions after some major surgeries. But over the past 8 years, clinical trials have shown that ESAs may shorten overall survival and increase the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. In 2008, the FDA required changing the labeling to reflect approval for use in patients receiving palliative care but not those being treated with curative intent.

“For patients receiving cancer treatment that has the potential for cure, ESAs’ risk may undermine this therapeutic goal,” said Richard Pazdur, M.D., head of the office of oncology drug products at the FDA, at a press meeting. “The risk–benefit balance is a delicate one and may be different for patients receiving palliative care.”

The new rules, which apply to Amgen’s Epogen and Procrit (both epoetin alfa) and to Aranesp (darbepoetin alfa), stipulate that the FDA will allow only physicians who register for the program, certify that they have received training, and sign off that they have discussed the risks with patients each time to prescribe and dispense ESAs. Physicians must reenroll every 3 years.

Patients must receive a medication guide explaining risks and benefits of the drugs and sign an informed-consent form.

“These rules are a long time coming, although REMS still rests in the hands of the manufacturer,” said Arthur Sytkowski, M.D., associate professor of medicine at Harvard Medical School–Beth Israel Deaconess Medical Center in Boston, whose research focused on EPO receptors until recently. Under the program, Amgen must monitor prescribers and hospitals to ensure complete compliance with the new regulations. Although the FDA has not yet determined penalties for not adhering to the REMS program, noncompliance could result in ESAs’ being pulled from the market, Pazdur said. Other REMS programs mandated by the agency involve opioids (see JNCI News 2009;101:1376–7).

Developing a risk management strategy for ESAs took time and carried with it...
certain unique challenges, Pazdur said at the press conference. For example, the field faces an inherent conflict of interest because, unlike most other drugs, physicians both prescribe and dispense ESAs, said FDA medical officer Jeff Summers, M.D. By limiting physicians’ ability to prescribe the drugs, the FDA hopes to combat this conflict of interest as well as restrict access to patients receiving palliative care.

ESA use has fallen markedly since late 2006–early 2007, when the FDA and the European Medicines Agency issued the first alerts. More declines are expected.

“This REMS is clearly going to decrease usage further, both by creating barriers for prescribers and by creating concern in patients, given the rather starkly worded consent forms,” said Leonard Saltz, M.D., attending physician at Memorial Sloan–Kettering Cancer Center in New York. Sytkowski said that “a number of oncologists at Beth Israel Medical Center [in Boston] with whom I have spoken say that they ‘can’t be bothered’ [to prescribe ESAs in light of new restrictions] and will simply transfuse patients now.”

**Dueling Studies**

With the FDA’s position on ESAs fully articulated and final, one might assume that any remaining debate would end. But Amgen still refutes the findings that ESAs shorten lifespans and induce cancer growth, and the company intends to prove so in clinical trials.

Amgen published two studies in the February issue of *Blood*, which, according to the company, demonstrate that no functional EPO receptors exist on four cell types and in human tumor cell lines. (The existence of such receptors, which other researchers have found, indicates a possible mechanism for ESAs to cause cancer growth.) “Based on a comprehensive analysis of the evidence in numerous preclinical and clinical studies, Amgen believes there is no definitive evidence of EPO receptor involvement in tumor progression, and no reliable evidence that functional EPO receptors are present on cancer cells or associated vasculature,” said an Amgen spokesperson in an e-mail.

Laurie Feldman, Ph.D., assistant professor of medicine at Harvard University, whose research, with Sytkowski’s, shows functional EPO receptors on ovarian, prostate, and breast cancer cells, believes that differences in the specificity of antibodies used to detect the receptors may partly explain the discrepancies. But she and others have not been able to access Amgen’s antibodies to independently verify its results.

“Amgen has also stated that its inability to demonstrate specific binding of radiolabeled EPO to cancer cells shows that there are no EPO receptors on these cells. But the big thing is why different labs see different things with the same cells,” Feldman said.

She observed that no standardized, commonly available reagents, assays, and cell lines exist that researchers use, a problem FDA flagged in 2007 and 2008 at the National Institutes of Health–sponsored workshops. But with no movement on that front, these questions probably will not be resolved to Amgen’s satisfaction. As for the FDA, the case in cancer is closed, and it has now moved on to investigating risks of ESAs in kidney failure.

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