Anemia develops in most persons with progressive chronic kidney disease. When it becomes severe, the administration of erythropoiesis-stimulating agents (ESAs) is generally required, along with the repletion of iron stores and the correction of other causes of anemia. The introduction of ESAs 30 years ago markedly improved the lives of many patients with chronic kidney disease, who until then had severe, often transfusion-dependent anemia.¹

Two types of recombinant human erythropoietin (epoetin alfa and epoetin beta) have been available since ESAs first came into use; both types are highly effective but short-acting (approved for dosing three times a week). Subsequently, two second-generation ESAs with an extended duration of action were developed — darbepoetin alfa, which has an altered glycosylation pattern, and a continuous erythropoietin-receptor activator called methoxy polyethylene glycol-epoetin beta (PEG-EPO) (Mircera, Hoffmann–La Roche), which contains a polyethylene-glycol moiety. Darbepoetin alfa is approved for dosing every 2 weeks worldwide, and PEG-EPO for dosing once a month in Europe. In all cases, the production of first- and second-generation ESAs involves the use of complex recombinant DNA technology and mammalian cell lines. The Kidney Disease: Improving Global Outcomes (KDIGO) work group recently suggested that only ESAs that have been formally approved by an independent regulatory agency (level of evidence 2D) should be prescribed, a recommendation created to avoid potentially serious and unanticipated adverse events.²

On the basis of observational studies conducted during the early days of erythropoietin usage, clinicians aimed to normalize hemoglobin levels in patients with chronic kidney disease. However, randomized, controlled trials later showed that partial correction of anemia was preferable to complete correction, a practice aimed at reducing the risk of cardiovascular events and other potential adverse events. Subsequently, KDIGO suggested that in general, ESAs should not be used to maintain hemoglobin levels above 11.5 g per deciliter in adult patients with chronic kidney disease (level of evidence 2C).² However, it is unclear whether the negative effects of the complete correction of anemia are due primarily to high hemoglobin levels per se, to excessive ESA doses, or to both.³

In the past decade, several new approaches to the correction of anemia have been tried, including erythropoietin gene therapy,⁴ the stabilization of hypoxia-inducible factor,⁵ and peptide-based erythropoietic agents, such as the dimeric pegylated peptide, peginesatide.⁶ Such peptide-based erythropoietic agents are not homologous with erythropoietin and therefore exhibit no antibody cross-activity. This means that patients with transfusion-dependent chronic kidney disease with antibody-mediated pure red-cell aplasia may be “rescued” upon treatment with drugs of this class.⁷

In this issue of the Journal, Macdougall et al.⁸ and Fishbane et al.⁹ report the results of four event-driven, randomized, controlled, open-label trials that compared the efficacy and safety of peginesatide with standard ESA therapy. In one pair of studies, PEARL 1 and 2 (Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating...
Agents), anemic patients with chronic kidney disease stages 3, 4, or 5 who were not yet receiving hemodialysis were treated with peginesatide once per month or darbepoetin alfa once every 2 weeks. In the other pair of studies, EMERALD 1 and 2 (Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin), patients with anemia who had been undergoing hemodialysis received either peginesatide once per month or epoetin alfa one to three times per week. In both articles, peginesatide is shown to be noninferior to standard ESAs in increasing and maintaining hemoglobin levels within a target range of 11 to 12 g per deciliter (the PEARL studies) or 10 to 12 g per deciliter (the EMERALD studies). However, although the cardiovascular composite safety end points for the groups receiving peginesatide and the groups receiving standard ESAs were similar in the patients receiving hemodialysis, the hazard ratio with peginesatide for the patients not receiving hemodialysis was 1.32 (95% confidence interval, 0.97 to 1.81), and there was also an increased incidence of sudden death, unstable angina, and arrhythmia among these patients. Moreover, the rate of acute kidney failure and back pain of unknown mechanism was twice as high among the patients receiving peginesatide and not undergoing hemodialysis.

There is no clear explanation for these unexpected adverse events. Baseline differences between the groups receiving hemodialysis and the groups not receiving hemodialysis included older age and more patients with a history of cardiovascular disease among the latter groups, although fewer patients in the latter groups had a history of diabetes and fewer were black. Probably more important are the facts that in the PEARL studies, which concerned patients not receiving hemodialysis, the groups treated with peginesatide were slightly older and had higher rates of diabetes and cardiovascular disease than the group treated with darbepoetin. Although the investigators adjusted for baseline differences and other covariates and performed sensitivity analyses, which reduced the hazard ratio, these adjustments did not fully account for the harmful effects. The target levels for hemoglobin and the dosage of peginesatide cannot be held responsible, since the target ranges were quite close and higher doses of peginesatide were used in the hemodialysis population, which was larger, without apparent harm. There also was no evidence of a difference in iron status or inflammatory state between the groups receiving hemodialysis and the groups not receiving hemodialysis. Although the ESA comparator was different — darbepoetin in the PEARL studies versus epoetin alfa in the EMERALD studies, there is no known difference in safety profile between these two compounds. Clearly, the underlying cause for the observed increase in composite safety end-point events requires further study, including examination of the potential for cardiovascular or systemic peginesatide toxicity in experimental models of chronic kidney failure.

Where do we go from here? Peginesatide can be used for anemia correction in patients undergoing hemodialysis, in which case its efficacy profile is similar to the profiles of established ESAs, but concerns remain about its safety in patients not receiving hemodialysis. Peginesatide has been recently approved in the United States for patients undergoing hemodialysis, but not for patients who are not receiving hemodialysis. Is there any advantage of using peginesatide rather than the existing ESAs? Less frequent dosing may be an advantage under certain circumstances. Peginesatide does not induce pure red-cell aplasia, but antibody development against this compound, although infrequent, may reduce its efficacy. As with any new class of drugs, prolonged experience and monitoring are necessary. Another important issue is cost. At a time when the prescription of much cheaper, biologically similar ESAs is steadily growing outside the United States,10 expensive new drugs will be competitive only if proven to result in better patient outcomes. Such outcomes remain to be demonstrated for peginesatide and other new types of ESAs that are in development.

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New Evidence That Cigarette Smoking Remains the Most Important Health Hazard

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Everyone knows cigarette smoking is bad for you. Most people in the United States assume that smoking is on its way out. But the grim reality is that smoking still exerts an enormous toll on the health of Americans, as documented in two articles in this issue of the Journal.1,2 Both articles review mortality trends over time for men and women according to smoking status, and both confirm that smoking remains a huge threat to the public’s health.

Jha et al. review data from the U.S. National Health Interview Survey, which involved 113,752 women and 88,496 men 25 years of age or older who were interviewed between 1997 and 2004. The investigators examined the rates and causes of death by the end of 2006.1 Within the age group 25 to 79 years, the mortality of current smokers of both sexes was three times that of participants who had never smoked. Diseases attributable to smoking accounted for about 60% of smokers’ deaths. The benefits of quitting smoking were dramatic for all age groups, with substantial gains in life expectancy, as compared with participants who had continued to smoke. Those who quit between the ages of 25 and 34 years lived 10 years longer; those who quit between ages 35 and 44 gained 9 years, those who quit between ages 45 and 54 gained 6 years, and those who quit between ages 55 and 64 gained 4 years. These differences persisted after adjustment for such potentially confounding variables as educational level, alcohol use, and adiposity.

These investigators also found that the prevalence of smoking is much lower among persons older than 45 years of age than among younger persons, a finding that reflects both successful efforts to quit and the earlier deaths among smokers. Those who continued to smoke rarely lived to the age of 85 years. It was surprising that many people began smoking after the age of 20 years, and 15% of women began smoking after age 25, which is later than is usually assumed and highlights the need to target young adults with appropriate nonsmoking messages.

The hazard ratios for lung-cancer mortality were staggering: 17.8 for female smokers and 14.6 for male smokers. Also, the risk of death for women who smoke is 50% higher than the estimates reported in the 1980s.

Thun et al. analyzed seven U.S. population surveys to determine whether death rates among female smokers — previously documented to be lower than those among male smokers — were converging with those for men.3 Indeed, women who smoke like men die like men who smoke. These investigators assessed mortality trends across three time periods in the United States (1959–1965, 1982–1988, and 2000–2010). During the 50-year survey span, mortality in the overall study population dropped by 50%, but female smokers received no benefit and male smokers showed only a 24% reduction. Relative risks for lung-cancer death among smokers were almost five times as high for men, as compared with women, in the 1959–1965 cohort, but in the 2000–2010 cohort the risks had equalized and had increased at 25 times as high for both men and women.

The study by Thun et al. spanned an era during which smoking habits were changing. Today, most smokers smoke filtered cigarettes that have less tar, and the habit of smoking is in-