

of registry data, there is no evidence that we should stop treating anemia.

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Dr. Locatelli reports serving on the advisory board of Amgen-Dompé, Roche, Affymax, Merck, and Johnson & Johnson and being a member of the safety monitoring board of Sandox. No other potential conflict of interest relevant to this letter was reported.

1. FDA strengthens boxed warnings, approves other safety labeling changes for erythropoiesis-stimulating agents. Silver Spring, MD: Food and Drug Administration, November 8, 2007. (Accessed January 28, 2010, at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109024.htm>.)

THE AUTHORS REPLY: We acknowledge the comment by Wright et al. that since women have lower normal hemoglobin values than men, targeting the same hemoglobin level could be considered relatively more intense for female patients. In reply to their requested analysis of the treatment: the sex interaction for stroke was not significant ($P=0.21$). The similar hazard ratios for women and men in the primary composite cardiovascular and renal outcomes in our trial also provide support for the lack of a differential influence of darbepoetin alfa according to sex.

In response to Minnerup and Schäbitz: in the TREAT study, nonhemorrhagic strokes were most common. Among the 101 strokes that occurred in patients in the darbepoetin alfa group, 74 were categorized as nonhemorrhagic, 13 were categorized as hemorrhagic, and 14 were unknown, whereas in the 53 strokes that occurred in patients assigned to placebo, 38 were categorized as nonhemorrhagic, 8 were categorized as hemorrhagic, and 7 were unknown. We cited the German trial of erythropoietin during acute ischemic stroke to highlight another disappointing recent finding with these compounds.¹

Regarding the comments of Hampl et al.: aside from the protocol-directed use of darbepoetin alfa, clinical care of the patients was individually managed by their physicians. Patients who were selected on a clinical basis for intravenous iron tended to have lower hemoglobin values throughout the study and, although highly confounded, more adverse cardiovascular and renal events. We agree that other strategies of addressing anemia warrant further investigation and underscore the importance of rigorous, double-blind, placebo-controlled clinical-event trials.

Locatelli and colleagues also raise concerns about the uneven clinical use of intravenous iron and red-cell transfusions after randomization. Consistent with clinical practice, the patients who received these additional treatments for anemia had lower hemoglobin levels during the trial. The intermittent treatment of patients in the placebo group for hemoglobin values of less than 9 g per deciliter resulted in a mean dose of 5 ± 11 μg in the placebo group and 225 ± 208 μg in the darbepoetin alfa group.

The most clinically relevant and important question posed was “Should we stop treating our patients?” Clearly, treatment decisions must be individualized. However, in this patient population, for this therapy that is not superior to placebo and is associated with risks, we respond: Why treat?

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Since publication of their article, the authors report no further potential conflict of interest.

1. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. *Stroke* 2009;40(12):e647-e656.

Vaccination against HPV-16 for Vulvar Intraepithelial Neoplasia

TO THE EDITOR: In the study by Kenter et al. (Nov. 5 issue)¹ regarding vaccination for the treatment of grade 3 vulvar intraepithelial neoplasia caused by type 16 human papillomavirus (HPV-16), it would have been interesting if the investigators

had included a placebo group. The authors state that the rate of spontaneous regression of such lesions is low, around 1.5%. These lesions include those associated with both Bowen's disease and Bowenoid papulosis. In Bowen's disease, sponta-

neous regression is never observed, whereas such regression occurs in of 35% of patients with bowenoid papulosis.²

One may wonder whether the complete regression of lesions that was observed in some patients in this clinical trial could be related to a spontaneous regression of multifocal lesions, particularly in very young women (e.g., Patient 11, who was 23 years of age) or in patients with a recent onset (<9 months) of the disease (Patients 11, 27, 29, and 30) or with very small lesions (Patients 11, 16, 27, 29, and 30, who had lesions ranging from 2 cm² to 8 cm²). Our clinical study involving six women who presented with bowenoid papulosis included a woman who was 23 years of age and who had multifocal lesions (measuring 10 cm²) that underwent spontaneous regression.³

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1. Kenter GG, Welters MJ, Valentijn AR, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. *N Engl J Med* 2009;361:1838-47.
2. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005;106:1319-26.
3. Bourgault Villada I, Moyal Barracco M, Zioli M, et al. Spontaneous regression of grade 3 vulvar intraepithelial neoplasia associated with human papillomavirus-16-specific CD4+ and CD8+ T-cell responses. *Cancer Res* 2004;64:8761-6.

THE AUTHORS REPLY: Bourgault Villada is correct that a randomized, placebo-controlled study is essential to compare the results of a new treatment with those of standard treatment, and such a study is currently under way. Although the terms “Bowen’s disease” and “bowenoid papulosis” were abandoned by the International Society for the Study of Vulvar Disease in 1989, the percentage of women who have a spontaneous regression of grade 3 vulvar intraepithelial neoplasia (according to the nomenclature of the World Health Organization) is not nearly as high as suggested. A systematic review of 3322 cases indicated a rate of spontaneous regression of only 1.5%.¹ Although one may always question the cause of observed regression of a lesion in one patient, the correlation with vaccine-induced immunity in our study should not be ignored.

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Since publication of their article, the authors report no further potential conflict of interest.

1. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005;97:645-51.

A Peptide-Based Erythropoietin-Receptor Agonist for Pure Red-Cell Aplasia

TO THE EDITOR: In their study of a peptide-based erythropoietin-receptor agonist (Hematide, Affymax) for pure red-cell aplasia, Macdougall et al. (Nov. 5 issue)¹ suggest that discontinuation of epoetin therapy and initiation of treatment with the peptide-based erythropoietin-receptor agonist can increase hemoglobin levels to target values; clearance of antierythropoietin autoantibodies occurred in at least 6 of 14 patients. Whether continued administration of the peptide-based erythropoietin-receptor agonist is required to maintain the hemoglobin value once target values have been reached remains unknown: the disappearance of antierythropoietin antibodies could eventually result in a sufficient level of endogenous erythropoietin to

maintain target hemoglobin levels in some patients. Since the trial did not assess serum erythropoietin levels, I suggest that a retrospective evaluation of serum samples should be performed to determine erythropoietin levels before discontinuation of the drug is considered in patients with undetectable autoantibodies. This point is crucial given both the high cost of long-term treatment with novel erythropoiesis-stimulating agents and the potential loss of response owing to the synthesis of neutralizing antibodies (as occurred in Patient 10 in the article by Macdougall et al.).

Since a limited course of corticosteroids plus low-dose cyclophosphamide can effectively treat erythropoietin-induced pure red-cell aplasia in up