

area, with the maintenance dose adjusted according to the therapeutic response and the plasma drug level.

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1. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;360:544-6.
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**THE AUTHOR REPLIES:** Since eculizumab has not been studied in children, our initial dose was chosen on the basis of extrapolation from pharmacokinetic modeling in adults,<sup>1-3</sup> which showed variable clearance rates not related to weight. In clinical trials of eculizumab in patients with paroxysmal nocturnal hemoglobinuria, standard dosing was associated with breakthrough of terminal complement activation, and dose adjustment was required in approximately 10% of patients.<sup>1,3</sup> Therefore, to prevent further renal damage from thrombotic microangiopathy,<sup>4</sup> real-time pharmacokinetic and pharmacodynamic monitoring was done to ensure complete, sustained complement blockade. Four weekly infusion doses of 300 mg,

followed by doses of 600 mg every 14 days, were associated with therapeutic serum drug levels and complete inhibition of serum hemolytic capacity, effects that are similar to those observed in adults.<sup>1-3</sup> We are currently cautiously attempting to reduce the eculizumab dose, with close pharmacokinetic monitoring. We share the concern about the potential for severe infections, but the risk of infection is related to C5 blockade, which is complete at a serum drug level of 35  $\mu\text{g}$  per milliliter or more.<sup>1</sup> An increase in the risk of infection is not expected above this level. Trials of eculizumab in children are required for additional dosing guidance.

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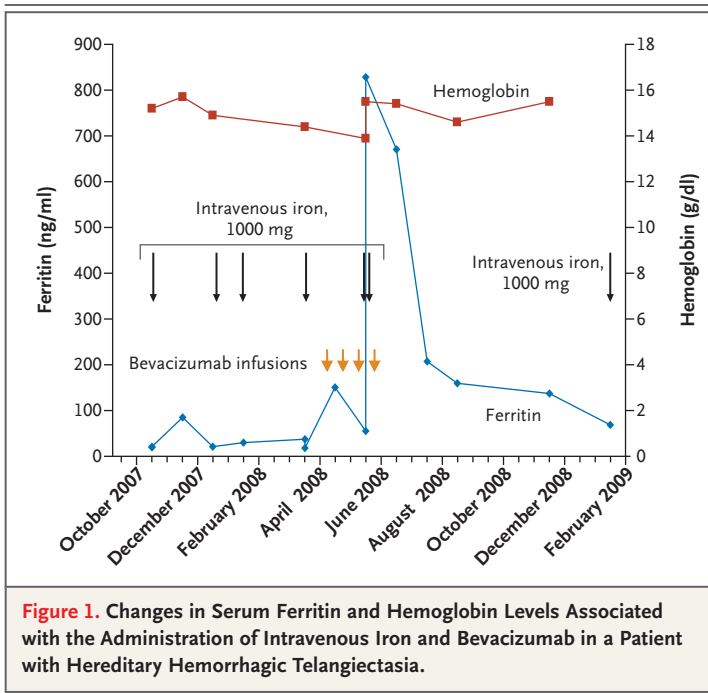
## Bevacizumab in Hereditary Hemorrhagic Telangiectasia

**TO THE EDITOR:** Hereditary hemorrhagic telangiectasia (HHT) (also known as the Osler-Weber-Rendu syndrome) is an inherited vascular dysplasia whose main features are mucocutaneous telangiectasias, epistaxis, gastrointestinal bleeding, and iron-deficiency anemia.<sup>1</sup> It is a disorder of unbalanced angiogenesis.<sup>2</sup> Patients have elevated plasma concentrations and tissue expression of vascular endothelial growth factor (VEGF) and transforming growth factor  $\beta$  (TGF- $\beta$ ).<sup>3</sup> TGF- $\beta$  stimulates the production of VEGF, which plays a key role in angiogenesis. We report on a patient with HHT<sup>1</sup> who had an impressive response to an anti-VEGF antibody, bevacizumab.

A 42-year-old man presented with long-standing epistaxis, hemoptysis, and a hemoglobin level of 6 g per deciliter. He had a three-generation family history of HHT. The physical examination revealed mucocutaneous telangiectasias. Screening

for arteriovenous malformations disclosed two pulmonary malformations. The findings on echocardiography were consistent with an intrapulmonary shunt.

Treatment with oral iron failed to raise the hemoglobin level. The patient subsequently received 4000 mg of intravenous iron during a 6-month period, with the goal of maintaining a serum ferritin level of more than 100 ng per milliliter and a hemoglobin level of more than 12 g per deciliter (Fig. 1). After treatment with intravenous iron, he received four cycles of bevacizumab, administered every 2 weeks; the dose was 10 mg per kilogram of body weight during the first two cycles and 5 mg per kilogram for the next two cycles. The serum ferritin level increased from a mean of 33 ng per milliliter in the 6 months before the initiation of bevacizumab therapy to a mean of 315 ng per milliliter in the 9 months after



the initiation of bevacizumab therapy. The patient received only 2000 mg of intravenous iron during the latter period. The second infusion of iron (in May 2008) was given before the ferritin level had been checked. In January 2009, intravenous iron was administered again, because the ferritin level had dropped to 69 ng per milliliter.

The patient's epistaxis improved, with a reduction from three to four episodes daily before the initiation of bevacizumab therapy to one or two episodes per week for 12 weeks after the initiation of bevacizumab therapy. Thereafter, the number of episodes increased to one or two per day, with each episode lasting approximately 10 minutes, as compared with 30 to 45 minutes before

treatment with bevacizumab. The appearance of the minimally visible telangiectasias on the patient's lips, chest, and hands did not change. The hemoglobin level remained stable, at 14 to 15 g per deciliter without red-cell transfusion.

In other cases, a patient with HHT who was receiving bevacizumab for malignant mesothelioma had a dramatic reduction in gastrointestinal bleeding from arteriovenous malformations.<sup>4</sup> A patient with severe hepatic HHT who received six courses of bevacizumab no longer required liver transplantation and was well 6 months after completing treatment.<sup>5</sup> The 1-year follow-up of our patient suggests that the effect of bevacizumab in HHT is not permanent and that maintenance therapy may be required.

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