

negative predictive value.<sup>1</sup> It should be noted that plasma levels of imatinib in patients given high doses of the drug exceed those of the no-effect level in the study of rat fertility. We also disagree with the specific reservations expressed by the correspondents. The time relationship was reasonable, with oligomenorrhea occurring a few months after the increase in the dose of imatinib. There were no other exposures, and no alternative causes were found on routine investigation of amenorrhea. Finally, the hypothesis of an etiologic link between imatinib and ovarian insufficiency is biologically plausible, since pathways involving kinases targeted by imatinib appear to play critical roles in the survival and maturation of follicles and oocytes.<sup>2-4</sup>

Constantinos Christopoulos, M.D., Ph.D.

Vasiliki Dimakopoulou, M.D.

Evangelos Rotas, M.D.

Amalia Fleming General Hospital  
15127 Athens, Greece  
cgchristopoulos@yahoo.gr

1. García-Cortés M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of Naranjo Adverse Drug Reactions Probability Scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008;27:780-9.
2. Hutt KJ, McLaughlin EA, Holland MK. Kit ligand and c-Kit have diverse roles during mammalian oogenesis and folliculogenesis. *Mol Hum Reprod* 2006;12:61-9.
3. Nilsson EE, Detzel C, Skinner MK. Platelet-derived growth factor modulates the primordial to primary follicle transition. *Reproduction* 2006;131:1007-15.
4. Carlsson IB, Laitinen MP, Scott JE, et al. Kit ligand and c-Kit are expressed during early human ovarian follicular development and their interaction is required for the survival of follicles in long-term culture. *Reproduction* 2006;131:641-9.

## Propranolol for Severe Hemangiomas of Infancy

**TO THE EDITOR:** Despite their self-limited course, infantile capillary hemangiomas can impair vital or sensory functions or cause disfigurement. Corticosteroids are the first line of treatment for problematic infantile capillary hemangiomas<sup>1,2</sup>; other options include interferon alfa<sup>3</sup> and vincristine.<sup>4</sup> We have observed that propranolol can inhibit the growth of these hemangiomas. Our preliminary data from 11 children are summarized in Table 1 in the Supplementary Appendix, available with the full text of this letter at [www.nejm.org](http://www.nejm.org).

The first child had a nasal capillary hemangioma. Despite corticosteroid treatment, the lesion was stabilized but obstructive hypertrophic myocardiopathy developed, so the patient was treated with propranolol. The day after the initiation of treatment, the hemangioma changed from intense red to purple, and it softened. The corticosteroids were tapered, but the hemangioma continued to improve. When the corticosteroids were discontinued, no regrowth of the hemangioma was noted. When the child was 14 months of age, the hemangioma was completely flat.

The second child had a plaque-like infantile capillary hemangioma involving the entire right upper limb and part of the face (Fig. 1). At 1 month of age, a subcutaneous component developed, and despite corticosteroid treatment, the hemangioma continued to enlarge. Magnetic resonance imaging revealed intraconal and extra-

conal orbital involvement, as well as an intracervical mass causing compression and tracheal and esophageal deviation (see the Supplementary Appendix). Ultrasonography showed increased cardiac output, and treatment with propranolol, at a dose of 2 mg per kilogram of body weight per day, was initiated. Seven days later, the child was able to open his eye spontaneously, and the mass near the parotid gland was considerably reduced in size. Prednisolone was discontinued at 4 months of age, without any regrowth of the hemangioma; at 9 months of age, the eye opening was satisfactory, and no major visual impairment was noted.

After written informed consent had been obtained from the parents, propranolol was given to nine additional children who had severe or disfiguring infantile capillary hemangiomas (see Table 1 in the Supplementary Appendix). In all patients, 24 hours after the initiation of treatment, we observed a change in the hemangioma from intense red to purple; this change was associated with a palpable softening of the lesion. After these initial changes, the hemangiomas continued to improve until they were nearly flat, with residual skin telangiectasias. Ultrasound examinations in five patients showed an objective regression in thickness associated with an increase in the resistive index of vascularization of the hemangioma (Table 1 in the Supplementary Appendix).



Infantile capillary hemangiomas are composed of a complex mixture of clonal endothelial cells associated with pericytes, dendritic cells, and mast cells.<sup>1</sup> Regulators of hemangioma growth and involution are poorly understood. During the growth phase, two major proangiogenic factors

are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)<sup>1</sup>; histologic studies have shown that both endothelial and interstitial cells are actively dividing in this phase. During the involution phase, apoptosis has been shown.<sup>1</sup> Potential explanations for

**Figure 1 (facing page). Photographs of Patient 2 before and after Treatment with Propranolol.**

Panel A shows the patient at 9 weeks of age, before treatment with propranolol, after 4 weeks of receiving systemic corticosteroids (at a dose of 3 mg per kilogram of body weight per day for 2 weeks and at a dose of 5 mg per kilogram per day for 2 weeks). Panel B shows the patient at 10 weeks of age, 7 days after the initiation of propranolol treatment at a dose of 2 mg per kilogram per day while prednisolone treatment was tapered to 3 mg per kilogram per day. Spontaneous opening of the eye was possible because of a reduction in the size of the subcutaneous component of the hemangioma. Panel C shows the patient at 6 months of age, while he was still receiving 2 mg of propranolol per kilogram per day. Systemic corticosteroids had been discontinued at 2 months of age. No subcutaneous component of the hemangioma was noted, and the cutaneous component had considerably faded. The child had no visual impairment. Panel D shows the child at 9 months of age. The hemangioma had continued to improve, and the propranolol treatment was discontinued.

the therapeutic effect of propranolol — a nonselective beta-blocker — on infantile capillary hemangiomas include vasoconstriction, which is immediately visible as a change in color, associated with a palpable softening of the hemangioma; decreased expression of *VEGF* and *bFGF* genes through the down-regulation of the RAF–mitogen-activated protein kinase pathway<sup>4</sup> (which explains the progressive improvement of the hemangioma); and the triggering of apoptosis of capillary endothelial cells.<sup>5</sup>

Christine Léauté-Labrèze, M.D.  
Eric Dumas de la Roque, M.D.  
Thomas Hubiche, M.D.  
Franck Boralevi, M.D., Ph.D.

Bordeaux Children's Hospital  
33 076 Bordeaux, France  
christine.labreze@chu-bordeaux.fr

Jean-Benoît Thambo, M.D.

Haut-Lévêque Heart Hospital  
33 600 Pessac, France

Alain Taïeb, M.D.

Bordeaux Children's Hospital  
33 076 Bordeaux, France

The authors report applying for a patent for the use of beta-blockers in infantile capillary hemangiomas. No other potential conflict of interest relevant to this letter was reported.

1. Frieden IJ, Haggstrom AN, Drolet BA, Mancini AJ, Friedlander SF, Boon L. Infantile hemangiomas: current knowledge, future directions: proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA. *Pediatr Dermatol* 2005;22:383-406.
2. Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. *Arch Dermatol* 2001;137:1208-13.
3. Ezekowitz RAB, Phil CBD, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *N Engl J Med* 1992;326:1456-63. [Errata, *N Engl J Med* 1994;330:300, 1995;333:595-6.]
4. D'Angelo G, Lee H, Weiner RI. cAMP-dependent protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation. *J Cell Biochem* 1997;67:353-66.
5. Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. *In Vitro Cell Dev Biol Anim* 2002;38:298-304.

Copyright © 2008 Massachusetts Medical Society.

## INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at <http://authors.nejm.org>. •A letter can have no more than five references and one figure or table. •A letter can be signed by no more than three authors. •Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the published articles.) •Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: <http://authors.nejm.org>

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.