3. Kindmark CO, Sjolin J, Nordlinder H, et al. Aplastic anaemia in a case of hepatitis B with a high titer of hepatitis B antigen. *Acta Med Scand.* 1984;214:89–92.
4. McSweeney PA, Carter JM, Green GJ, Romeril KR. Fatal aplastic anemia associated with hepatitis B viral infection. *Am J Med.* 1988;85:255–256.
5. Romet-Lemonne JL, McLane MF, Elfassi E, et al. Hepatitis B virus infection in cultured human lymphoblastoid cells. *Science.* 1983;221:667–669.
6. Zeldis JB, Mugishima H, Steinberg HN, et al. In vitro hepatitis B virus infection of human bone marrow cells. *J Clin Invest.* 1986;78:411–417.
7. Galun E, Ilan Y, Livni N, et al. Hepatitis B virus infection associated with hematopoietic tumors. *Am J Pathol.* 1994;145:1001–1007.
8. Pontisso P, Locasciulli A, Schiavon E, et al. Detection of hepatitis B virus DNA sequences in bone marrow of children with leukemia. *Cancer.* 1987;59:292–296.
9. Gentile G, Mele A, Monarco B, et al. Hepatitis B and C viruses, human T-cell lymphotropic virus types I and II, and leukemias: a case-control study. The Italian Leukemia Study Group. *Cancer Epidemiol Biomarkers Prev.* 1996;5:227–230.
10. Tooze JA, Marsh JC, Gordon-Smith EC. Clonal evolution of aplastic anaemia to myelodysplasia/acute myeloid leukemia and parosysmal nocturnal haemoglobinuria. *Leuk Lymphoma.* 1999;33:231–241.

CONTROL OF LIFE-THREATENING PULMONARY BLEEDING WITH ACTIVATED RECOMBINANT FACTOR VII

To the Editor:

Massive pulmonary hemorrhage is a serious and life-threatening complication that is associated with high (10% to 40%) mortality (1). Current treatment involves the infusion of fresh frozen plasma, packed cells, and, when bleeding persists, embolization of the bleeding vessel or surgical treatment (2). Despite this therapy, bleeding may continue. We report the successful use of activated recombinant factor VII (rFVIIa) (Novoseven, Novo Nordisk, Copenhagen, Denmark) in life-threatening pulmonary bleeding that was uncontrollable with standard treatment.

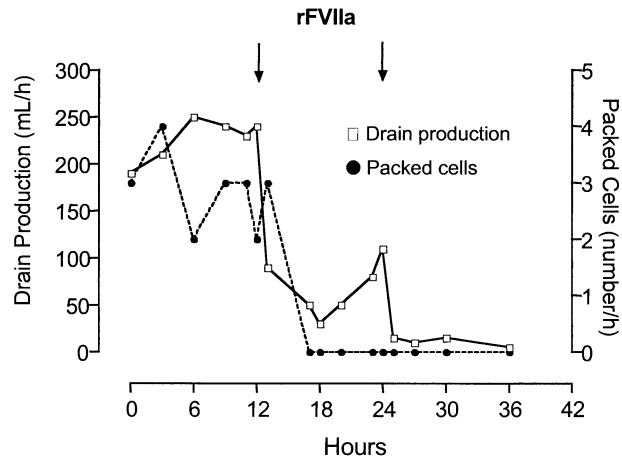

Figure. Drain production and transfusion requirements. Administration of activated recombinant factor VII is indicated by vertical arrows. rFVIIa = activated recombinant factor VII ; T = 0: start of the thoracic drain production.

A 44-year-old man was hit by a train while attempting suicide. At the site of the accident, his right leg was amputated, and the profound bleeding at the stump was stopped with bandages and compression. The patient underwent tracheal intubation, and a chest drain was inserted in the right side because of a suspected pneumothorax. On admission, the patient was hemodynamically unstable. Hemoglobin level was 3.0 mmol/L (normal, >8.4 mmol/L), platelet count was 104 x 10^9/L (normal, >150 x 10^9/L), activated partial thromboplastin time was 89.8 seconds (normal, <40 seconds), and prothrombin time was 22.2 seconds (normal, <14 seconds). A chest radiograph revealed contusion of both lungs, without fractures of the rib, and there were fractures of the pelvis (stabilized with an external fixator), and acetabulum. Profuse bleeding in a ruptured right iliac artery was successfully embolized, and the patient was transferred to the intensive care unit.

Two hours later, heavy bleeding from the thoracic drain began at a rate of 200 mL/h. The patient became hemodynamically unstable, with signs of multiorgan failure. The hemoglobin level decreased from 5.7 mmol/L to 3.1 mmol/L, and treatment with rapid infusion of fluids (packed cells, 32 units; fresh frozen plasma, 24 units; platelets; tranexamic acid; and desmopressin) was started over 12 hours. Chest radiograph revealed a right-sided hemothorax. Despite improved coagulation parameters (platelet count, 105 x 10^9/L; prothrombin time, 14.9 seconds; activated partial thromboplastin time, 51.8 seconds), drain production increased to 250 mL/h. During thoracotomy, several adherent clots were found in the right lung, without localized bleeding, which were controlled surgically. After insertion of a second drain, the chest was closed. The patient continued to bleed heavily and seemed likely to have a fatal outcome. He was treated with 60 μmg/kg of intravenous rFVIIa, which led to a decrease in the drain production to 30 mL/h, as well as in transfusion of packed cells to 4 units in the following 48 hours (Figure). Twelve hours later, drain production increased to 110 mL/h and a second 60-μmg/kg dose of intravenous rFVIIa was given, after which no further bleeding occurred. Two days later, chest radiograph showed resolution of the hemothorax. The patient recovered fully.

Life-threatening bleeding due to lung or airway injury can be treated with supportive care, bronchial artery embolization, or surgical resection (2), which may not always be success-

ful. In such instances, treatment with rFVIIa may be an option. Activated recombinant factor VII is a new hemostatic agent that forms tissue factor:factor VIIa complexes at the site of vessel injury, where the endothelium is damaged and tissue factor expression is increased. This leads to thrombin generation and stable local clot formation (3). Activated recombinant factor VII may be effective in bleeding associated with use of inhibitors in patients with hemophilia (4), thrombocytopenia (5), severe abdominal bleeding (6), and hemoptysis due to invasive aspergillosis (7). We believe that this new treatment has a potential role in severe pulmonary bleeding that does not respond to conventional therapy.

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1. Lee TW, Wan S, Choy DKL, Chan M, et al. Management of massive hemoptysis: a single institution experience. *Ann Thorac Cardiovasc Surg.* 2000;4:232–235.
2. Fernando HC, Stein M, Benfield JR, et al. Role of bronchial artery embolization in the management of hemoptysis. *Arch Surg.* 1998;133:862–866.
3. Ten Cate H, Bauer KA, Levi M, et al. The activation of factor X and prothrombin by recombinant factor VIIa in vivo is mediated by tissue factor. *J Clin Invest.* 1993;92:1207–1212.
4. Hedner U, Glazer S, Pingel K, et al. Successful use of recombinant factor VIIa in a patient with severe hemophilia A during synovectomy. *Lancet.* 1988;2:1193.
5. Meijer K, Sieders E, Slooff MJH, et al. Effective treatment of severe bleeding due to acquired thrombocytopenia by single dose administration of activated recombinant factor VII. *Thromb Haemost.* 1998;80:204–205.
6. Vlot AJ, Ton E, Mackaay AJC, et al. Treatment of a severely bleeding patient without preexisting coagulopathy with activated recombinant factor VII. *Am J Med.* 2000;108:421–422.
7. Meijer K, de Graaff WE, Daenen SMGJ, et al. Successful treatment of massive hemoptysis in acute leukemia with recombinant activated factor VII. *Arch Intern Med.* 2000;160:2216.

INHALED FLUTICASONE AND ZAFIRLUKAST IN PERSISTENT ASTHMA

To the Editor:

The article by Nathan et al. (1) is very important in that it demonstrates that even very low doses of inhaled steroids (176 μg of fluticasone administered daily) provide an average benefit in excess to that found with zafirlukast in patients with mild, persistent asthma. However, our experience and that of the existing literature suggest that leukotriene modifiers are most active in various subgroups of patients with asthma, such as those with the aspirin sensitivity-nasal polyps-asthma triad (2). Its role may not be universal in all patients with asthma, but may be applicable in selected patients. With this in mind, it is surprising that the authors presented only their mean data, omitting all data, for instance, which would demonstrate which portion of the zafirlukast group exceeded the mean fluticasone response. Hopefully, they can provide this information.

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1. Nathan RA, Bleecker ER, Kalberg C. A comparison of short-term treatment with inhaled fluticasone propionate and zafirlukast for patients with persistent asthma. *Am J Med.* 2001;111:195–202.
2. Barnes PJ. Airway pharmacology. Murray JF, Nadel JA, eds. *Textbook of Respiratory Medicine.* Philadelphia, Pennsylvania: W. B. Saunders; 2000:285.

The Reply:

Mean data were presented since means are an easily calculable and conventional method for summarizing data in a large clinical study. We sought to show that in a population of "all comers," the mean response to fluticasone exceeded the mean response to zafirlukast. The mean data clearly indicate that, similar to studies of longer duration, a low dose of fluticasone was more effective in treating "all comers" compared with a leukotriene receptor antagonist (1,2). Regarding Dr. Aelony's point about patient subgroups, we computed the percentage of patients receiving fluticasone whose response exceeded the mean zafirlukast response by 5% or greater at endpoint. We found that for forced expiratory volume in 1 second (FEV_1), 63% of patients who received fluticasone exceeded the mean response for zafirlukast; for morning peak expiratory flow (PEF), 68% of patients; for percentage of symptom-free days, 76%; and for use of rescue albuterol, 84% of patients. However, our study was not designed to test the effects of leukotriene-modifying drugs in patient subgroups such as those previously reported (3–5); therefore, it is difficult to draw any clear conclusions for these post hoc analyses.

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1. Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol.* 2001;107:461–468.
2. Bleecker ER, Welch MJ, Weinstein SF, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol.* 2000;105:1123–1129.
3. Hasday JD, Meltzer SS, Moore WC, et al. Anti-inflammatory effects of zileuton in a subpopulation of allergic asthmatics. *Am J Respir Crit Care Med.* 2000;161:1229–1236.
4. Stevenson D, Simon RA, Mathison DA, Christiansen SC. Montelukast is only partially effective in inhibiting aspirin responses in aspirin-sensitive asthmatics. *Ann Allergy Asthma Immunol.* 2000;85:477–482.
5. Drazen JM, Yandava CN, Dube L, et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nat Genet.* 1999;22:168–170.