Recombinant Activated Factor VII for Massive Hemoptysis in Patients With Cystic Fibrosis

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Massive hemoptysis is a common complication in patients with cystic fibrosis (CF) and is associated with significant morbidity and mortality. Conventional treatment with antibiotic therapy and early bronchial artery embolization (BAE) is usually successful in achieving hemostasis in the majority of patients. Recombinant activated factor VII (rFVIIa), originally developed for use in patients with hemophilia, has emerged as a general hemostatic agent that is potentially useful in the management of many life-threatening bleeding conditions. In this article, we present four patients with CF lung disease and massive hemoptysis who were treated successfully with rFVIIa. We suggest that in patients with CF who present with massive hemoptysis, the use of rFVIIa can be considered in patients with refractory hemoptysis despite conventional therapy or as a temporizing therapy when BAE is not immediately available.
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Abbreviations: BAE = bronchial artery embolization; CF = cystic fibrosis; rFVIIa = recombinant activated factor VII; TF = tissue factor

Hemoptysis is a common complication of cystic fibrosis (CF). In the majority of patients, bleeding is usually minor, but 4 to 6% of patients experience at least one episode of massive hemoptysis (defined as > 240 mL/d or recurrent bleeding of > 100 mL/d over several days), with a recurrence rate of up to 26%.[1,2] Bleeding is more common in older patients and those with more severe lung disease. Major bleeds are life-threatening due to asphyxiation, airflow obstruction, and circulatory collapse. Chronic infection, persistent inflammation, and subsequent vascular growth result in hypervascularization of the bronchial circulation, and erosion of these abnormal bronchial vessels is believed to be the mechanism responsible for hemoptysis.

The current available therapeutic options are conservative medical therapy, bronchial artery embolization (BAE), and surgery. The severity of the bleeding usually determines the therapeutic approach. BAE has been accepted as a safe and effective method in controlling hemoptysis,[3–6] although its efficacy has never been demonstrated in controlled trials.

Recombinant activated factor VII (rFVIIa) was originally developed for the promotion of hemostasis in patients with hemophilia who have an antibody to coagulation factors VIII or IX. However, it has been used increasingly as an off-label general hemostatic agent in a variety of clinical settings such as intracranial hemorrhage, trauma, surgery, and GI and obstetric bleeding.[7,8] In this article, we report our experience at Royal Prince Alfred Hospital (Sydney, NSW, Australia) from 2004 to 2008 with the use of rFVIIa for the treatment of massive hemoptysis in patients with CF.

Materials and Methods

All patients were managed at the adult CF center at Royal Prince Alfred Hospital. Four patients with five episodes of massive hemoptysis in whom rFVIIa had been used therapeutically were identified from a review of medical records from 2004 to 2008. Table 1 summarizes the demographic data, clinical characteristics, and baseline lung function of patients. The best lung function in the past 12 months prior to the episode of massive hemoptysis was recorded. Table 2 summarizes the laboratory, radiology, and sputum microbiology findings. No patients underwent CT scanning or bronchoscopy. The cumulative volume of hemoptysis and the bronchial angiography findings are shown in Table 3. Case summaries of the patients are described next.

Patient 1

A 33-year-old man with a background of moderately severe CF lung disease, pancreatic insufficiency, and CF-related diabetes presented in June 2004 with hemoptysis in the context of a pulmonary exacerbation. The patient was from England and was vacationing in Australia. He had previously undergone three BAEs for hemoptysis (August 2000, January 2001, and August 2001). He had coughed up 260 mL of fresh blood mixed with clots on the day of hospital admission. He was started with IV meropenem and tobramycin. On hospital days 2 and 3, he had ongoing hemoptysis of 100 to 150 mL/d. He remained hemodynamically stable despite ongoing bleeding. On hospital day 4, he underwent BAE to abnormally dilated vessels in the right and left bronchial arteries, and systemic collaterals from the right internal mammary and left internal mammary arteries. Despite BAE, he experienced fresh bleeding of 270 mL in the 24-h period after undergoing BAE. On hospital day 5, the patient was given a single dose of rFVIIa, 90 μg/kg, with subsequent cessation of bleeding. The patient was discharged on hospital day 16 and returned to England 1 month later.

Patient 2

A 22-year-old man developed massive hemoptysis 4 months after undergoing orthotopic liver transplantation for severe CF-

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Table 1—*Clinical Characteristics of Patients*

Patient No.	Age, yr/Sex	FEV_1* (% Predicted)	BMI, kg/m^2	Previous BAE	Comorbid Conditions
1	33/M	1.63 L (44)	20.0	August 2000, January 2001, August 2001	Pancreatic exocrine insufficiency; CF-related diabetes
2	23/M	3.02 L (80)	19.5	March 2004	Pancreatic exocrine insufficiency; severe CF-related liver disease with portal hypertension; orthotopic liver transplantation
3	23/F	0.95 L (28)	19.3	July 2003, December 2003	Pancreatic exocrine insufficiency; osteopenia; epilepsy; listed for double lung transplantation
4	27/M	2.12 L (55)	22.8	No	Pancreatic exocrine insufficiency; CF-related diabetes; severe CF-related liver disease with portal hypertension

F = female; M = male; BMI = body mass index.
*Best FEV_1 in past 12 months.

related liver disease that was complicated by portal hypertension, variceal bleeding, hypersplenism, and progressive liver failure. He experienced chronic minor hemoptysis as well as a previous episode of major hemoptysis requiring bilateral BAE in March 2004. He underwent orthotopic liver transplantation in May 2004. He experienced intermittent minor hemoptysis that was managed conservatively during the immediate posttransplantation period. Allograft function was stable on standard immunosuppressive therapy with cyclosporine and prednisone. His posttransplantation course was complicated by severe respiratory failure secondary to recurrent chest sepsis. He required tracheostomy with prolonged ventilator weaning. On hospital day 136, he experienced a large-volume hemoptysis (approximately 200 mL of blood), with further hemoptysis totaling 150 mL the following day. On hospital day 137, he underwent bilateral BAE, which demonstrated a focal aneurysmal dilatation of a right upper lobe bronchial vessel, as well as abnormal clusters of vessels in the right and left bronchial circulations. These were successfully embolized with immediate control of bleeding. However, on hospital day 149 the patient had a recurrence of massive hemoptysis of approximately 300 mL of fresh blood. One single dose of rFVIIa, 90 μg/kg, was given after which the hemoptysis was resolved. He had further episodes of minor hemoptysis during the hospital admission without the need for intervention. Despite aggressive antibiotic treatment, the patient had recurrent chest sepsis that was difficult to control and remained dependent on noninvasive ventilation. After a 10-month hospital admission following his orthotopic liver transplantation and worsening respiratory failure, he made an informed decision for withdrawal of active treatment and died on hospital day 325.

Patient 3

A 23-year-old woman with severe CF lung disease and pancreatic exocrine insufficiency awaiting bilateral lung transplantation presented in July 2004 with a pulmonary exacerbation. This was her sixth hospital admission in the previous 12 months. She was started on IV ticarcillin/clavulanic acid and tobramycin. She had previously undergone right BAE in July 2003 and bilateral BAE in December 2003 for treatment of major hemoptysis. On hospital day 3, she coughed up 300 mL of fresh blood. She was given a dose of rFVIIa, 120 μg/kg, with a repeat dose 4 h later for ongoing bleeding. Hemoptysis settled after rFVIIa administration, and only episodes of minor hemoptysis (15 to 25 mL) of old blood occurred over the next 3 days. Unfortunately, the patient died from progressive respiratory failure in January 2005 without any recurrence of major hemoptysis.

Patient 4

A 27-year-old man with CF complicated by moderately severe suppurative lung disease, biliary cirrhosis, pancreatic exocrine insufficiency, and diabetes presented on three separate occasions with massive hemoptysis between 2007 and 2008. He had advanced liver disease with severe portal hypertension and previous variceal bleeds. He experienced chronic hemoptysis, particularly during periods of pulmonary exacerbations or high-intensity exercise. In October 2007, he presented with massive hemoptysis, expectorating > 500 mL of blood during the 6 hours prior to presentation. Hemodynamics revealed a systolic BP of 100 mm Hg and a pulse rate of 110 beats/min. He was given packed RBCs, fresh-frozen plasma, and platelet transfusions as needed to reverse his coagulopathy and thrombocytopenia. He was started on IV ticarcillin/clavulanic acid and tobramycin. Urgent BAE identified an enlarged left upper lobe bronchial circulation, which was embolized. The right bronchial circulation was not identified radiologically despite rigorous searching. Four hours postembolization, he experienced hemoptysis, expectorating a further 500 mL of fresh blood. He was given a single dose of rFVIIa, 90 μg/kg. Bleeding slowed, but the patient continued to have ongoing hemoptysis with approximate volumes of 100 mL/d over the next 3 days. On hospital day 5, a repeat BAE was performed. A slightly enlarged right bronchial artery that was not detected on previous examination was embolized. The repeat BAE achieved complete hemostasis with no further bleeding.

The patient presented again in May 2008 with massive hemoptysis. He underwent urgent BAE that again demonstrated enlarged bronchial arteries supplying the left upper lobe and right lower lobe, which had likely developed from recanalization or collateralization of the previously embolized vessels. Bilateral BAE was performed but was not successful in controlling his bleeding. rFVIIa, 90 μg/kg, was administered, with a repeat dose 6 h later due to ongoing bleeding. Complete hemostasis was achieved following a second dose of rFVIIa.

The patient experienced a recurrence of massive hemoptysis in December 2008. Abnormal clusters of vessels were once again visualized in the left upper lobe at bronchial angiography. Embolization of these vessels led to rapid control of the hemoptysis.

Discussion

To our knowledge, this is an original report of a case series on the use of rFVIIa in the treatment of massive hemoptysis in patients with CF. We believe that the administration of rFVIIa was successful in achieving con-