

Recombinant Factor VIIa in Massive Haemoptysis Associated with Chronic Necrotising Aspergillosis

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ABSTRACT

The successful use of recombinant activated factor VII (rFVIIa), in treating massive, life-threatening haemoptysis in a 55-year-old male patient with chronic necrotising aspergillosis, is reported. Patient diagnosed with chronic necrotising aspergillosis three months ago was admitted to our department with massive haemoptysis. Patient was treated as outpatient with itraconazole. One day post-admission, two doses of rFVIIa (30 µg·kg⁻¹) were administered and the haemoptysis was successfully resolved. Two further doses of rFVIIa (30 µg·kg⁻¹) were given the following day, and after that there were no more recurrences of pulmonary haemorrhage. No thromboembolic or other adverse events were observed following rFVIIa therapy. Our findings suggest that use of rFVIIa may represent a safe and effective treatment choice for patients with haemoptysis due to aspergillosis.

Key words: haemoptysis, recombinant activated factor VII, pulmonary aspergillosis

Introduction

Aspergillus is a ubiquitous soil-dwelling fungus that can be transmitted to humans via inhalation of airborne spores¹. Chronic necrotising aspergillosis (CNA) describes a destructive process of the lung caused by *Aspergillus* spp. invasion, and is most prevalent among patients with chronic lung disease or mild immunosuppression¹.

The process is different from aspergilloma in that there is local invasion of the lung tissue, not needed pre-existing cavity, although the same can develop as a consequence of fungi destruction. In contrast to invasive aspergillosis, in CNA there is no vascular invasion or dissemination to other organs and the course of the disease is slowly over months to years.

Haemoptysis occurs in approximately 10% of patients with CNA¹, carrying a mortality rate of 2–14%². Bleeding usually occurs from bronchial blood vessels caused by local invasion of blood vessels, and/or endotoxins released by the fungus with hemolytic properties. In cases of mild haemoptysis, medical therapy involves bed rest, humidified oxygen, administration of cough suppressants and postural drainage. Surgical intervention can be considered in patients with massive haemoptysis, though the

surgical treatment of CNA remains hazardous and controversial³. Therefore, alternative haemostatic treatment strategies are clearly needed for CNA patients with haemoptysis who are unsuitable candidates for surgical intervention.

We report the successful use of recombinant activated factor VII (rFVIIa) to treat a case of massive, life-threatening haemoptysis in a patient with CNA.

Case Report

We report a 55-year-old man with a history of tuberculosis 20 years ago and subsequent residual fibrothorax and bilateral pleural adhesions. One year before his first admission to our centre, he was diagnosed as sarcoidosis with severe skin involvement which required continuous treatment with varying doses of corticosteroid (prednisolone). This treatment was discontinued 3 weeks before his first admission to our hospital with symptoms of lung infection: productive cough, fever, night sweats and progressive dyspnoea. The chest radiograph showed an infiltrative process in upper lobes with adjacent pleural

thickening. He received different antibiotic therapies but failed to respond to treatment. Aspergillosis was confirmed following isolation of *Aspergillus* spp. in cultures derived from the sputum and bronchoscopic samples. The patient was treated with Aphothericin B intravenously followed with prolonged oral itraconazole therapy on an outpatient basis.

Two months later, the patient was re-admitted to the hospital with coughing and massive, life-threatening haemoptysis, approximately 500 mL of blood during the first day. He was normotensive and tachycardic, with a normal full blood count and coagulation parameters (Table 1). A CT scan revealed bilateral retracted dysfunctional upper lobes and a thick, irregular-walled cavity in the right upper lobe (with no coincidental aspergilloma), chronic active inflammation and alveolar haemorrhage (Figure 1).

The patient was treated with oxygen, antitussive drugs and sedatives, but with poor response. Bronchoscopy revealed a great amount of fresh blood in the trachea and both main bronchi, but surgical resection or other invasive procedures were not possible owing to scarring, pleural adhesions, diffuse bilateral disease and high risk of further bleeding and spreading of infection. On the day after admission, the patient therefore received two bolus doses of rFVIIa ($30 \mu\text{g}\cdot\text{kg}^{-1}$) 2 hours apart, with immediate resolution of haemoptysis. Re-bleeding occurred the next day, so two further doses of rFVIIa were given, with similarly successful results. No thromboembolic or other adverse events occurred, and no further pulmonary haemorrhage was observed. The patient's coagulation status before and after treatment with rFVIIa is shown in Table 1.

Following treatment with rFVIIa, computed tomography revealed the presence of chronic bronchopulmonary lesions associated with CNA, with no evident disease dynamics (Figure 2). The patient was discharged on the 14th day post-admission following successful resolution of symptoms and satisfactory radiographic findings. Pa-

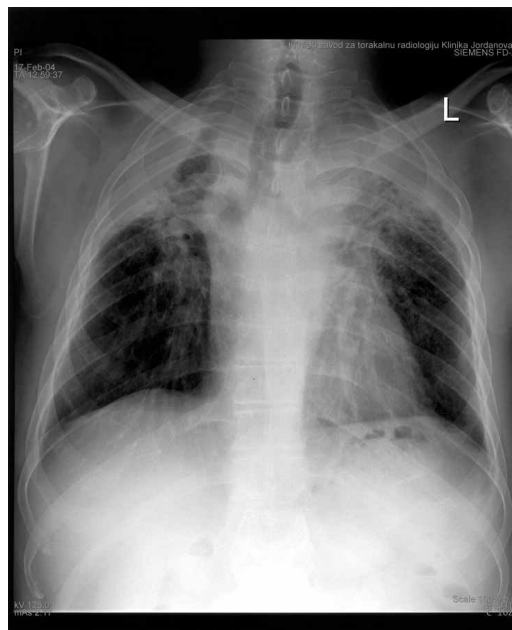


Fig. 1. Chest radiograph: bilateral retracted dysfunctional upper lobes with thick, irregular-walled cavity on right upper lobe.

teint was later followed for one year without recurrent bleeding.

Discussion

Recombinant FVIIa is licensed for the treatment of bleeding in patients with haemophilia A or B and inhibitors. It has recently been approved in Europe for the treatment of haemorrhage in FVII deficiency and Glanzmann's thrombasthenia, and increasing evidence suggests that rFVIIa may have an additional haemostatic role in previously non-coagulopathic patients in a variety of bleeding situations⁴⁻⁶. The agent has also shown efficacy in treating pulmonary haemorrhage of various

TABLE 1
COAGULATION STATUS BEFORE AND AFTER RECOMBINANT ACTIVATED FACTOR VII (rFVIIa) ADMINISTRATION

Parameter	Admission	Treatment with rFVIIa			
	Day 1	Day 2	Day 3	Day 7	Day 14
Haemoglobin ($\text{g}\cdot\text{L}^{-1}$)*	125	115	106	104	94
Platelets ($\times 10^9\cdot\text{L}^{-1}$)	229	220	212	345	293
PT (%)†	75	99	99	100	82
INR‡	1.27	1.0	1.0	1.0	1.2
APTT (s)§	25.1	26.4	24.5	26.0	28.1
Fibrinogen ($\text{g}\cdot\text{L}^{-1}$) ^{dd}	5.1	5.4	5.5	4.4	5.00
D-dimers ($\text{mg}\cdot\text{L}^{-1}$) ¶	–	0.25	–	–	0.36
Factor VIII**	–	–	–	–	2.53

PT – prothrombin time; INR – international normalized ratio; APTT – activated partial thromboplastin time.
 *Normal range 140–180 $\text{g}\cdot\text{L}^{-1}$, †Normal range 70–140%, ‡Therapeutic range 2–4, §Normal range 24–35s, ^{dd}Normal range 1.7–3.9 $\text{g}\cdot\text{L}^{-1}$,
 ¶Normal range <0.25 $\text{mg}\cdot\text{L}^{-1}$, **Normal range 0.6–1.8.



Fig. 2. Computed tomographic scan revealing pleural thickening of bilateral upper lobes.

aetiologies^{7–12} when given in doses of 90 $\mu\text{g}\cdot\text{kg}^{-1}$; this is in line with the dose recommended for the treatment of bleeding in haemophilia patients (90–120 $\mu\text{g}\cdot\text{kg}^{-1}$). In contrast, we achieved successful haemostasis in our patient using four bolus doses of 30 $\mu\text{g}\cdot\text{kg}^{-1}$ over a two day period. This case showed that in patients with acute lung bleeding due to chronic necrotising aspergillosis could be successfully stopped with Recombinant FVIIa, even in a dose smaller than recommended for haemophilia.

Surgery was not considered to be a feasible option for our patient due to the presence of bilateral lesions, pleural adhesions and chronic changes in the lower parts of the lungs. Bronchial artery embolisation should be con-

sidered as a temporary procedure in these patients, although it rarely results in control of haemoptysis because of the massive collateral vessels and high incidence of recurrent bleeding. Furthermore, we were unable to perform bronchial artery embolisation as both main bronchial passageways were filled with blood and the exact location of the massive bleeding could not be determined. Following unsuccessful use of conventional therapies, the decision was made to administer two doses of rFVIIa (30 $\mu\text{g}\cdot\text{kg}^{-1}$). Haemoptysis was immediately resolved, and rebleeding the following day was also treated successfully with two further bolus doses.

No thromboembolic or other adverse events were observed in our patient. To date, rFVIIa has demonstrated a highly favourable efficacy and safety profile across a variety of indications and a wide range of doses^{13–15}, an observation that may be explained by the agent's mode of action. Recent theories suggest that rFVIIa may act by binding weakly to activated platelets and thus improving thrombin formation independently of tissue factor¹⁶. Such localisation of rFVIIa activity explains its haemostatic efficacy and ensures that systemic activation of coagulation – and subsequent risk of thrombotic events – is reduced¹⁶.

Only few randomised trials proved efficacy and safety of recombinant FVIIa^{17,18}, none of them in acute lung bleeding.

Nonetheless, we suggest that rFVIIa may play an important role as «universal» haemostatic agent in managing severe, life-threatening haemoptysis in non-coagulopathic patients with pulmonary aspergillosis, particularly when surgical intervention is contraindicated. Further information on clinical application of this agent is needed.

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AKTIVIRANI REKOMBINANTNI ČIMBENIK VII U BOLESNIKA S MASIVNIM HEMOPTIZAMA KAO POSLJEDICOM KRONIČNE NEKROTIZIRAJUĆE ASPERGILOZE

S A Ž E T A K

U radu je prikazana uspješna uporaba aktiviranog rekombinantnog čimbenika VIIa (rfVIIa), u liječenju 55-godišnjeg bolesnika, sa masivnim, po život ugrožavajućim hemoptizama kao posljedicom kronične nekrotizirajuće aspergiloze. Bolesnik, kojem je tri mjeseca pred prijem postavljena dijagnoza kronične nekrotizirajuće aspergiloze, primljen je putem hitne službe zbog masivnih hemoptiza. Ambulantno je do tada liječen itrakonazolom. Dan nakon prijema, bolesnik je dobio dvije doze rfVIIa ($30 \mu\text{g}\cdot\text{kg}^{-1}$) nakon čega je došlo do zaustavljanja krvarenja. Dvije dodatne doze rfVIIa ($30 \mu\text{g}\cdot\text{kg}^{-1}$) bolesnik je dobio slijedeći dan, te potom više nije bilo znakova krvarenja. Nije primijećeno tromboembolijskih incidenata, niti ostalih nuspojava. Ovaj slučaj ukazuje da je primjena rfVIIa u bolesnika s krvarenjem iz pluća zbog kronične nekrotizirajuće aspergiloze sigurna i učinkovita, te predstavlja dodatnu terapijsku opciju u bolesnika sa masivnim hemoptizama u bolesnika sa aspergilozom pluća.