

## Case report

# Treatment of diffuse alveolar hemorrhage after allogeneic bone marrow transplant with recombinant factor VIIa

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### Summary:

**Diffuse alveolar hemorrhage (DAH) is a potentially life-threatening pulmonary toxicity that occurs in 1–21% of patients following bone marrow transplantation. The syndrome is associated with a high mortality rate; and current treatment options are limited. Recombinant factor VIIa (rFVIIa, Novoseven) has recently been approved for the treatment of bleeding in patients with hemophilia A/B with inhibitors. A greater understanding of the mechanism by which rFVIIa restores hemostasis has recently become available; with *in vitro* evidence supporting that the thrombin burst achieved by rFVIIa is independent of the presence or binding to tissue factor. This insight has suggested a range of other potential clinical uses for the drug; including the setting of pulmonary hemorrhage. We review our experience with using rFVIIa for treatment of DAH in a patient with acute myelogenous leukemia following a matched unrelated donor bone marrow transplant. Boluses of 90 µg/kg rFVIIa were given every 3 h × 4 doses/day, concurrently with high-dose corticosteroids and maintenance of a platelet count >50 000/mm<sup>3</sup>. Rapid clinical and radiological improvement was noted within several doses of rFVIIa, with discontinuation of the drug after eight doses. However, the patient's clinical condition began to rapidly deteriorate following cessation of rFVIIa, resulting in reinstatement of therapy 24 h later. The patient again exhibited rapid clinical improvement; and rFVIIa was continued for an additional 16 doses with no further evidence of pulmonary hemorrhage noted. No toxicity or adverse events were observed with rFVIIa treatment. Our experience indicates that rFVIIa may be an effective treatment option for DAH post bone marrow transplant; although further clinical studies are needed before recommendations can be made regarding off label use of rFVIIa in this clinical setting.**

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Diffuse alveolar hemorrhage (DAH) is a noninfectious pulmonary complication of bone marrow transplantation (BMT) that is associated with high mortality. Published reports have estimated the incidence of DAH in the transplant population at 1–21% with an associated mortality of 60–100%.<sup>1–4</sup> Although the syndrome was first noted in autologous patients following transplant for solid tumors,<sup>2</sup> recent data have implicated DAH as an increasing cause of morbidity and mortality after all allogeneic transplants.<sup>1,4</sup> At our center, DAH was found to be the most frequently diagnosed non-infectious condition leading to bronchoscopy, occurring in 15/42 (35%) of diagnostic BAL specimens.<sup>5</sup> Diffuse alveolar hemorrhage is second only to pneumonia as the most common cause of respiratory failure requiring intubation and admission to the intensive care unit. In a recent report describing 26 patients with DAH (following BMT) that required mechanical ventilation, five patients survived the 30 day post-transplant period, but only one patient was alive at 6 months post BMT.<sup>6</sup> Current treatment options, which are centered on corticosteroids and aggressive transfusion parameters, are largely unsuccessful, with an overall mortality rate exceeding 50% in published reports.<sup>7–9</sup> The lack of treatment options and the low survival statistics both indicate that newer, more effective strategies are needed for the treatment of DAH after bone marrow transplant.

In March 1999, recombinant factor VIIa (rFVIIa), an activated form of plasma coagulation factor VII became commercially available for the treatment of bleeding in patients with hemophilia A/B and the presence of inhibitors. Factor VII is a vitamin K-dependent zymogen that when activated, binds to tissue factor (TF) and forms a complex (TF–VIIa). This complex then activates both factors IX and X, and catalyzes the auto-activation of more FVII. This chain of events is now known to be the primary pathway involved in hemostasis *in vivo*.<sup>10</sup> In the setting of hemophilia rFVIIa acts by forming a complex with tissue factor to activate factor X, bypassing factors VIII and XI.<sup>11</sup> Recently, other properties of rFVIIa have been discovered, leading to interest in the agent for other clinical indications. *In vitro* studies have found that rFVIIa also binds with low affinity to activate platelet surfaces, induces the thrombin burst needed for hemostasis, and at higher dosages enhances the generation of factor IIa – all of which are done independently of tissue factor.<sup>10</sup> Recent clinical data have also supported a correlation between both prothrombin time

(PT) and bleeding time with factor X activation in the absence of tissue factor<sup>12</sup> in patients with bleeding secondary to thrombocytopenia, surgical procedure or liver dysfunction.<sup>13–16</sup> Our preliminary experience with rFVIIa involved a patient with acute leukemia with DAH following a matched unrelated donor bone marrow transplant.

### Case report

The patient was a 35-year-old female diagnosed in April 1999 with acute myeloid leukemia (M4 with inversion 16). She initially received CAT-G (cyclophosphamide, cytarabine, and topotecan with G-CSF support) induction and went into remission. Eight months later, she relapsed in the bone marrow and the central nervous system while receiving consolidation. She was then reinduced into second remission with fludarabine, cytarabine and intrathecal cytarabine, followed by matched unrelated allogeneic bone marrow transplantation on 3 March 2000. Her conditioning regimen included cyclophosphamide (60 mg/m<sup>2</sup> × 2 days), total body irradiation, and craniospinal radiation. Her initial post-transplant course was complicated by parainfluenza pneumonia, which responded to treatment with aerosolized ribavirin and antibiotics. On day +39, she was discharged from the hospital, no longer requiring platelet or red cell transfusions. Her blood counts at the time of discharge included a white blood cell count of 13.0, a platelet count of 140 000/mm<sup>3</sup> and a hemoglobin level of 12.4. She was treated in the outpatient setting over the next 2 weeks for a presumed fungal pneumonia, which was treated with liposomal amphotericin, as well as acute graft-versus-host disease of the skin that was controlled with steroids, tacrolimus and basiliximab. Blood counts during this time included a WBC of 8.1, hemoglobin of 13.6, and a platelet count that had decreased to 55 000/mm<sup>3</sup>. On the day of the current admission (day +54) the patient developed seizure activity at home and was transferred to the emergency room where a MRI as performed that demonstrated posterior ischemia with cerebral edema consistent with tacrolimus-induced leukoencephalopathy. The tacrolimus was withdrawn, and the patient improved with decadron and valproic acid, eventually allowing for the tacrolimus to be resumed at a lower dose. The patient remained seizure free throughout the remainder of her hospitalization, and follow-up MRI revealed near resolution of the brain abnormality.

Seven days after her admission to the hospital, the patient was found to have increasing shortness of breath, hypoxia and non-productive cough. ABG revealed pH 7.41, pCO<sub>2</sub> 32, and poO<sub>2</sub> of 78 while on 4 liters of oxygen support. A chest film and CT scan of the chest were performed demonstrating bilateral rapidly worsening air space disease suspicious of hemorrhage *vs* pneumonia. A ventilation-perfusion scan was negative for pulmonary embolus. The patient was pancultured repeatedly to look for an infectious explanation for the hypoxia, but all results remained negative. A bronchoscopy was performed which revealed bloody fluid, laden with a large number of hemosiderin-rich macrophages. No positive bacterial, fungal or viral organisms were identified. Due to progressively worsening hypoxemia and CO<sub>2</sub> retention, she was electively intubated

8 days after admission, and fresh blood was found in the endotracheal suction. ABG analysis revealed a pH of 7.4, pCO<sub>2</sub> of 41 and a paO<sub>2</sub> of 88 on 80% oxygen support. Chest X-ray (CXR) revealed rapid progression of bilateral air space disease. The presence of bloody secretions on bronchoscopy coupled with the rapidity of the radiographic and clinical deterioration of the patient in the absence of any other identifiable cause (ie pulmonary edema, congestive heart failure, infection) led to the eventual diagnosis of DAH. Once the diagnosis was determined, the patient was started on high-dose methylprednisolone (1000 mg i.v. every day × 3 days followed by slow taper), DDAVP, aminocaproic acid and aggressive transfusion support per our institution protocol. Complete blood counts were evaluated every 8 h, with platelets transfused to maintain a minimum level of 50 000 cells/mm<sup>3</sup> and packed red blood cells transfused to maintain a hemoglobin level of 8.5 g/dl or higher. Coagulation parameters were assessed daily, with fresh frozen plasma (FFP) utilized if the PT rose >16 despite vitamin K replacement. Baseline laboratory parameters at the initiation of DAH therapy included a WBC count of 20.1, hemoglobin level of 9.3, platelet level of 42 000 and a protime of 11.8. Factor VII levels are not routinely drawn at our institution and were not obtained in this case.

On day +9, due to the absence of clinical improvement, rFVIIa was initiated at 90 µg/kg i.v. every 3 h × 4 doses to promote hemostasis and assist in bleeding cessation. After the third administered infusion of rFVIIa, fresh blood was no longer noted in the patient's endotracheal tube secretions, and complete blood counts revealed a stabilization of the patient's hemoglobin level (ie no red cell transfusions were needed for 24 h following the third dose of rFVIIa). A reduction in prothrombin time from 12.0 s to 7.0 s was also noted after the first dose had been infused. Secondary to the patient's clinical improvement, we opted to continue rFVIIa treatment on day +10 at the same dosing regimen, with blood gas measurements demonstrating continued improvement in oxygenation and the chest films taken on day +11 revealing almost complete disappearance of pulmonary infiltrates consistent with resolving hemorrhage. Due to the marked clinical and radiographic improvement in the patient's condition, rFVIIa was discontinued after 2 days of treatment (day 11). However, on day 12 the patient's condition again worsened with increasing oxygen requirements and worsening consolidations seen on chest film. CBC at this time included a WBC of 12.9, a hemoglobin value of 7.7 and platelets of 84 000. Two units of red cells were transfused, and treatment with rFVIIa was resumed at 90 µg/kg i.v. now given every 6 h around the clock in order to prevent a window for rebleeding to occur. The patient rapidly improved within 24 h, with a decrease in her Fio<sub>2</sub> requirements from 60% to 40%, and a paO<sub>2</sub> value that increased from 64 to 94. She was successfully extubated on day +15 and was transferred out of the ICU to the BMT floor for further care. Treatment with recombinant FVIIa was continued for a total of 16 doses (days 12–16) and then was discontinued without any further evidence of hemorrhage noted. Unfortunately, the patient's overall condition continued to deteriorate over the next 2 weeks with the development of severe steroid-induced myopathy as well as a rapid weight loss of 8 kg over 7 days – both of

which depict a 'failure to thrive' clinical presentation. Upon steroid taper from 250 mg to 100 mg (2 mg/kg), she developed new bilateral pneumothoraces on chest X-ray (day +29) and became increasingly hypercapnic. She was again transferred to the intensive care unit for management with initial stabilization of her respiratory function on nasal BiPap. Unfortunately, the patient's overall condition continued to decline, and the decision was made by the patient's family and medical team to withdraw respiratory support and institute comfort measures (day 43). The patient expired that day, 92 days post transplant.

## Discussion

Diffuse alveolar hemorrhage (DAH) is a life-threatening complication of high-dose chemotherapy and bone marrow stem cell transplantation. Although initially described to occur more commonly after autologous transplant, recent reports have suggested an increasingly frequency (up to 20%) of this complication after allogeneic transplantation; with rates up to 20% being reported.<sup>1,4,5</sup> In a recent review of 42 bronchoscopy specimens performed after BMT, DAH was the most common pulmonary complication ( $n = 15$ ) diagnosed, with 70% of these cases occurring after allogeneic transplant.<sup>5</sup> The cause of DAH is not fully understood. Radiation toxicity, drug toxicity, thrombocytopenia, infection (viral and fungal) and neutrophil influx into the lung have all been implicated in the pathogenesis of DAH.<sup>7,8</sup> More heavily pre-treated patients, concomitant viral or fungal infection in the setting of low platelets and rapid neutrophil recovery at the time of engraftment have also been correlated with an increased risk of DAH development.<sup>9</sup>

In the absence of a clear pathophysiology, treatment of DAH is empirical. Treatment with high-dose steroids may be beneficial when given early,<sup>9</sup> but overall mortality remains as high as 70–100%.<sup>1–4,8,9</sup> Steroid treatment is aimed at reducing a possible acute inflammatory response to hemorrhage; with successful treatment typically requiring very high doses (ie 1 g per day) and prolonged treatment duration. Prolonged steroid use, unfortunately, is well known to increase risk or the development of new opportunistic infections from fungal or atypical organisms. Therefore, new treatment modalities for DAH are desperately needed, not only to aid in the cessation of the acute bleeding episode, but also to 'steroid-spare' the patient from the long-term complications of steroid use. Recent studies have reported rFVIIa to be effective for the treatment of various bleeding disorders, including thrombocytopenia.<sup>10</sup> It has also been reported to be effective in treating/controlling pulmonary hemorrhage secondary to Aspergillus infection in two patients with leukemia.<sup>18,19</sup> These results demonstrate the successful use of rFVIIa treatment in patients with and without factor VII deficiency. In the patient with documented factor VII deficiency, successful outcome was attributed to the supraphysiological level of rFVIIa achieved with a dose of 90  $\mu\text{g}/\text{kg}$  (approximately 25 times normal). These very high factor VII levels combined with the abundant tissue factor exposed on subendothelial cells of the damaged vessels

results in the excess thrombin formation needed to induce stable clot formation.<sup>18</sup> The drug acts to enhance site-specific thrombin generation by enhancing tissue factor (TF):FVIIa assembly at the site of bleeding. Recombinant FVIIa along with aggressive platelet, corticosteroid and anti-fibrinolytic agent support was used to treat our patient for worsening hemorrhage. Our patient demonstrated rapid resolution of bleeding after two doses of 90  $\mu\text{g}/\text{kg}$  of rFVIIa, similar to previous case reports. In our case, however, DAH relapse occurred with rapid clinical deterioration and worsening CXR after stopping rFVIIa for 24 h. Upon reinstatement of rFVIIa, the patient again rapidly responded both clinically and radiographically; demonstrating that longer treatment courses may be needed in this setting. We continued rFVIIa for a total of 12 doses with continued improvement and successful extubation. Post extubation, rFVIIa was successfully withdrawn with no further bleeding episodes. This case indicates that rFVIIa may be an effective agent in life-threatening pulmonary hemorrhage post transplant, a condition for which alternative therapeutic options are minimal. Further clinical data are needed to evaluate use of recombinant activated factor VIIa (Novoseven) in this situation.

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