Recombinant Human Factor VIIa for Alveolar Hemorrhage Following Allogeneic Stem Cell Transplantation


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ABSTRACT

The mortality rate of alveolar hemorrhage (AH) after allogeneic hematopoietic stem cell transplantation is greater than 60% with supportive care and high-dose steroid therapy. We performed a retrospective cohort analysis to assess the benefits and risks of recombinant human factor VIIa (rFVIIa) as a therapeutic adjunct for AH. Between 2005 and 2012, 57 episodes of AH occurred in 37 patients. Fourteen episodes (in 14 patients) were treated with steroids alone, and 43 episodes (in 23 patients) were treated with steroids and rFVIIa. The median steroid dose was 1.9 mg/kg/d (interquartile range [IQR], 0.8 to 3.5 mg/kg/d; methylprednisolone equivalents) and did not differ statistically between the 2 groups. The median rFVIIa dose was 41 μg/kg (IQR, 39 to 62 μg/kg), and a median of 3 doses (IQR, 2 to 17) was administered per episode. Concurrent infection was diagnosed in 65% of the episodes. Patients had moderately severe hypoxia (median PaO$_2$/FiO$_2$, 193 [IQR, 141 to 262]); 72% required mechanical ventilation, and 42% survived to extubation. The addition of rFVIIa did not alter time to resolution of AH (P = .50), duration of mechanical ventilation (P = .89), duration of oxygen supplementation (P = .55), or hospital mortality (P = .27). Four possible thrombotic events (9% of 43 episodes) occurred with rFVIIa. rFVIIa in combination with corticosteroids did not confer clear clinical advantages compared with corticosteroids alone. In patients with AH following hematopoietic stem cell transplantation, clinical factors (ie, worsening infection, multiple organ failure, or recrudescence of primary disease) may be more important than the benefit of enhanced hemostasis from rFVIIa.

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INTRODUCTION

Alveolar hemorrhage (AH) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT) that occurs in 2% to 14% of recipients [1]. AH may account for up to one-third of cases of acute respiratory failure requiring mechanical ventilation after HSCT and has a mortality rate of >60% [2-7]. Factors contributing to the development of AH include graft-versus-host disease (GVHD) and pulmonary endothelial and epithelial cell injury.
due to chemotherapy, conditioning agents, or total body irradiation [8–10]. In addition to supportive care (eg, blood product administration, oxygen therapy, mechanical ventilation), high-dose corticosteroids have been routinely used to treat AH after HSCT [11–13].

Recent studies have noted similarities in the clinical presentation, management, and high mortality of AH after HSCT in the presence and absence of infection (infection-associated AH [IAH] and diffuse alveolar hemorrhage [DAH], respectively) [5,6]. The difficulty in clinically distinguishing DAH from IAH raises the concern that high-dose corticosteroids may increase the risk of infection and cause harm. Three agents have been used as adjunctive therapies to enhance pulmonary hemostasis and to decrease the dose and duration of corticosteroid therapy: aminocaproic acid [14], tranexamic acid [15], and recombinant human factor VIIa (rFVIIa). Aminocaproic acid and tranexamic acid both inhibit plasmin, thereby impeding fibrinolysis. rFVIIa promotes hemostasis via both a tissue factor-dependent pathway at sites of endothelial injury and a tissue factor–dependent mechanism, directly activating factors IX and X on the surface of activated platelets [16,17]. Although rFVIIa was originally approved in the United States for use in patients with hemophilia and inhibitors to factors VIII or IX [18], off-label indications account for the vast majority of its use [19–25]. Safety concerns regarding the risk of venous and arterial thromboembolic events and an apparent lack of clinical efficacy in patients without hemophilia have been noted [26–30].

Limited data are available regarding the off-label use of rFVIIa in HSCT recipients [31]. A phase II study evaluating rFVIIa for the treatment of hemorrhage after HSCT (including 7 patients with AH) did not demonstrate any overall beneficial effects [32]. Case reports of i.v. and i.p. rFVIIa have suggested clinical improvement in HSCT recipients with AH (Table S1); however, in a large case series of AH after HSCT (reported as an abstract), rFVIIa did not improve outcomes from respiratory failure or overall survival [33]. Thus, the utility of adjunctive rFVIIa therapy for AH post-HSCT remains uncertain.

Here we report the use of rFVIIa therapy for AH in a large cohort of HSCT recipients. We evaluated the clinical factors associated with rFVIIa administration, including dose, timing, outcome, and thromboembolic events. The characteristics and outcomes were compared in a cohort of rFVIIa recipients and a contemporaneous cohort of patients with AH treated with corticosteroids alone.

METHODS

An expanded Methods section is available in the online supplement.

Patient Identification

Our hospital’s Institutional Review Board approved this study (11-CC-N228) and granted a waiver of informed consent for its conduct. Three of our hospital databases were queried to identify patients who developed AH following HSCT performed between August 2004 and November 2012.

Diagnosis of AH

For this study, AH was defined as the acute onset of signs and/or symptoms of respiratory compromise with evidence of a new or worsening diffuse alveolar pattern on chest radiography or computer tomography (CT) scan. The diagnosis was established by either increasingly bloody return during bronchoalveolar lavage and/or the presence of >20% hemosiderin-laden macrophages, or clinical evidence of respiratory compromise with new or worsening pulmonary infiltrates and hemoptysis (n = 2), blood from an artificial airway (n = 5), or histological evidence of AH at autopsy (n = 1). Three patients had experienced at least 1 episode of AH documented by bronchoscopy within the previous 14 days. Alternative diagnoses, such as fluid overload or congestive heart failure, were excluded. The onset of AH was determined retrospectively based on a thorough review of the medical record and was defined as the earliest date when either evidence of respiratory compromise was noted or new widespread alveolar infiltrates were detected. A recurrent episode of AH was defined as new or worsening hypoxemia requiring increasing supplemental oxygen or the need for mechanical ventilation, evidence of new or worsening alveolar infiltrates on chest radiography, and clinical deterioration resulting in directed therapy for AH (ie, starting or increasing corticosteroids and/or resuming rFVIIa treatment). Patients meeting criteria for AH were classified as having either DAH or IAH based on either the absence or presence of a concomitant lower respiratory tract or bloodstream infection, respectively.

Patient Characteristics

Patient demographic data evaluated included underlying disease, premeditated conditions, and transplantation-specific factors, including conditioning regimens and GVHD prophylaxis. Laboratory and microbiological data and clinical outcomes, including organ failures during AH episodes, were reviewed.

CT Analysis

Chest CT scans completed 24 hours before or within 72 hours from the onset of AH were analyzed with computer-aided diagnosis (CAD) techniques to determine the extent and severity of hemorrhage in each patient group. Quantitative metrics of the abnormal lung imaging patterns, including the volume of pathological lung regions and the ratio of pathological lung volume to total lung volume, were analyzed.

Therapy for AH

Conventional therapy was defined as corticosteroids and supportive care (eg, supplemental oxygen and ventilatory support, transfusion of blood products, antimicrobial therapy). Corticosteroid and/or rFVIIa dose and duration of therapy were at the discretion of the treating physicians. Patients received platelet transfusions in an attempt to achieve a level >50,000/µL, fresh-frozen plasma to normalize prothrombin time and activated partial thromboplastin time, and cryoprecipitate to achieve a fibrinogen level >100 mg/dL. The use of any other prohemostatic therapy before or during an episode of AH was recorded.

To examine the effect of rFVIIa on episodes of AH, we compared 4 separate outcomes with patients treated with corticosteroids alone: (1) intensive care unit (ICU) length of stay in all patients admitted specifically for respiratory failure due to AH (rFVIIa, 23 patients; conventional therapy, 8 patients), (2) duration of mechanical ventilation for respiratory failure due to AH (rFVIIa, 25 episodes; conventional therapy, 7 episodes), (3) time to clinical resolution of AH (rFVIIa, 30 episodes; conventional therapy, 10 episodes), and (4) duration of supplemental oxygen use from onset of the initial episode of AH (all initial episodes included from each group). For the first 3 comparisons, the onset of the AH episode was defined as either the date of initiation of mechanical ventilation for AH or the date of admission to the ICU for AH in those who did not require mechanical ventilation. The resolution of an AH episode was defined as either successful extubation or discharge from the ICU for patients not requiring mechanical ventilation. In some patients, duration of bleeding could not be accurately ascertained—for example, a patient intubated for a reason other than AH who then developed AH while receiving mechanical ventilation. In patients who were transferred to the ICU and intubated for AH, time to extubation served as an indication of bleeding resolution. Duration of supplemental oxygen use was defined as the time from the onset of the initial AH episode to 24 hours after cessation of oxygen or death.

For each episode of AH, the total dose, daily mean dose, and maximum daily dose (converted to methylprednisolone equivalents per kilogram) were recorded. In 41 of 57 episodes, the duration of steroid therapy per AH episode was calculated as the time from the onset of AH to either resolution (ie, date of extubation or discharge from the ICU, as defined above) or death. In the 16 remaining episodes, the duration was determined based on a review of the patient’s medical record. In patients treated with rFVIIa, the total daily dose per kilogram, the number of doses administered per day during an episode, the number of total doses given per episode and the mean daily dose per kilogram (ie, total dose divided by the number of administrations per day) were recorded. Adverse events related to rFVIIa therapy were noted, and any thrombotic complications occurring within 7 days of rFVIIa administration were recorded.

Statistical Analysis

Categorical patient characteristics were compared using either Pearson’s chi-square test or Fisher’s exact test, as appropriate. Continuous patient characteristics were compared between 2 groups using Welch’s t-test. Episode-level variables were compared using linear mixed models with
random subject effects to account for the correlation within each subject. Standard residual diagnostics were used to check model assumptions. Log-transformation was applied when necessary. The log-rank test was used to compare survival times from the date of transplantation and the onset of AH in the 2 treatment groups. Survival times from the onset of AH were also compared in the 2 treatment groups between patients with DAH and those with IAH. Propensity scores (generated using logistic regression) were used to adjust for key baseline differences between the 2 groups by stratification and regression adjustment. Analyses were conducted using either R version 2.15.1 (http://www.R-project.org) or SAS version 9.4 (SAS Institute, Cary, NC). All P values are 2-tailed and are considered significant at P ≤ .05.

RESULTS

Patient Characteristics

Between 2005 and 2012, 648 patients underwent allogeneic HSCT at the National Institute’s of Health Clinical Center, of whom 37 (5.7%) developed AH. Baseline patient and transplantation characteristics were similar in the rFVIIa and conventional treatment groups (Table 1). Twenty-nine of these 37 patients (78%) underwent HSCT after a reduced-dose HSCT protocol. Propensity scores (generated using logistic regression) were used to adjust for key baseline differences between the 2 groups by stratification and regression adjustment. Analyses were conducted using either R version 2.15.1 (http://www.R-project.org) or SAS version 9.4 (SAS Institute, Cary, NC). All P values are 2-tailed and are considered significant at P ≤ .05.

AH

Fifty-seven episodes of AH occurred in the 37 patients. Forty-four episodes of AH occurring in 14 patients were treated with conventional therapy. The remaining 43 episodes, occurring in 23 patients, were treated with rFVIIa in addition to conventional therapy. Episodes occurred as early as 5 days post-HSCT and as late as almost 7 years post-HSCT (Figure S1). AH was confirmed by bronchoscopy in 86% of the episodes (35 in the rFVIIa group and all 14 in the conventional therapy group). Fifty-six episodes were treated in the ICU (98%). Ten of the 23 patients (10 of 23) in the rFVIIa group experienced 2 or more discrete AH episodes, separated by a median of 17 days (interquartile range [IQR], 11 to 41 days) (Table 2 and Figure S1). None of the patients treated with conventional therapy alone developed recurrent AH.

GVHD prophylaxis given at the onset of each AH episode was similar in the 2 groups, as was the addition of adjunctive immunosuppression at any time during an AH episode (Table 2 and Table S2) and the degree of thrombocytopenia during the first 3 days of an episode (Table 2 and Figure S2). Prolonged prothrombin time and activated partial thromboplastin time at the onset of AH was seen in both groups.

The majority of the patients in both groups had moderately severe hypoxemia, with a median PaO₂/FiO₂ ratio of 193 (IQR, 141 to 262), and more than two-thirds required mechanical ventilatory support (Table 2) [34].

Hospital mortality, as well as 30-, 60-, and 180-day survival rates, did not differ significantly between the 2 groups (Table 2). Median overall survival after the onset of the initial AH episode was 80 days in the conventional therapy group and 49 days in the rFVIIa group (P = .97) (Figure 1; Figure S3 presents long-term survival curves). To adjust for important baseline differences between the 2 groups, we generated propensity scores using the following variables from the first episode of AH: maximum Sequential Organ Failure Assessment (SOFA) score [35], need for vasoressor support, need for renal replacement therapy, lower respiratory tract infection, and bloodstream infection. Despite adjustment based on the propensity score using either stratification

(\(P = .24\)) or regression (\(P = .79\)) there was no difference in hospital mortality between the 2 treatment groups.

Twenty-seven of the 37 patients with AH underwent at least 1 CT scan during the study period (40 total scans). The median ratio of pathological lung parenchyma (consolidation and ground-glass opacities) at the onset of AH was similar in the 2 groups (16.4% [IQR, 12.7% to 28.9%] in the conventional therapy group and 23.8% [IQR, 17.9% to 32.5%] in the rFVIIa group; \(P = .37\)) (Figure S4). Results were similar when accounting for pleural fluid volume (data not shown). Representative images showing increasing amounts of parenchymal involvement are shown in Figure 2A-E. Images demonstrating the distinction between parenchymal infiltrates and pleural effusion and showing changes in parenchymal and pleural abnormalities over time in patients with recurrent AH episodes are presented in Figure S5 and Video S3. In patients who experienced multiple AH episodes, parenchymal infiltrates recurred in a similar radiographic distribution as seen in their initial episode (Video S3).

Treatment of AH

Corticosteroid therapy was administered in 95% of the AH episodes overall (14 of 14 episodes in the conventional therapy group and 40 of 43 episodes in the rFVIIa group; Table 3). The corticosteroid dose was not increased above the pre-AH dose in 29% of the episodes (4 of 14) in the conventional therapy group (median pre-AH methylprednisolone dose, 70 mg/d) and in 14% of the episodes (6 of 43) in the rFVIIa group (median pre-AH methylprednisolone dose, 55 mg/d). In 3 episodes occurring in 2 patients in the rFVIIa group, corticosteroids were not given. The total dose, daily mean dose, and highest daily dose was similar in the 2 groups (Table 3).

All patients who received rFVIIa during their initial AH episode were treated with rFVIIa during each subsequent episode. The first rFVIIa dose was given within the first 48 hours after the onset of AH in 70% of the episodes (30 of 43), and 53% of the episodes (23 of 43) were treated on day 0, suggesting that the majority of patients were treated early rather than as a rescue therapy. The median rFVIIa dose was 41 μg/kg (IQR, 39 to 62 μg/kg), and patients received a mean of 3 doses (IQR, 2 to 17 doses) (Table 1). The mean daily dose of rFVIIa per patient decreased over time (\(P = .007\); Figure S6A) and the total daily dose of rFVIIa paralleled this decrease (\(P = .08\); Figure S6B). ICU length of stay, duration of mechanical ventilation, time to resolution of bleeding, and duration of oxygen supplementation were similar in the 2 treatment groups (Figure 3).

Incidence and Types of Infection Concurrent with AH

DAH occurred in 5 of 14 episodes treated with conventional therapy and in 15 of 43 episodes treated with rFVIIa. In the rFVIIa group, 3 patients accounted for 12 of the 15 episodes of DAH. IAH was present in 64% of the episodes (9 of 14) treated with conventional therapy and in 65% of the episodes (28 of 43) treated with rFVIIa (Figure S1). A lower respiratory tract infection was detected in 47% of the total AH episodes (27 of 57; conventional therapy group, 6 episodes in 6 patients; rFVIIa group, 21 episodes in 15 patients) (Table S3). Ten episodes of IAH were associated with concomitant bacteremia (conventional group, 3 episodes in 3 patients; rFVIIa group, 5 episodes in 4 patients) or fungemia (rFVIIa group, 2 episodes in 1 patient) in the absence of a lower respiratory tract infection (Table S4). Survival from the onset of the first AH episode was similar in the 2 treatment
groups in patients with DAH (P = .35; Figure 4A) and those with IAH (P = .56; Figure 4B).

Incidence of Thrombotic Events in Patients Treated with rFVIIa

Thrombotic complications possibly related to rFVIIa therapy were noted in 9% (4 of 43) of AH episodes, occurring between less than 1 hour and up to 4 days after rFVIIa administration. These included a blood clot obstructing an endotracheal tube, a basilic vein thrombosis associated with a peripherally inserted central catheter, and 2 cases of disseminated intravascular coagulation (DIC) before death, 1 resulting in the loss of pulses in 2 extremities (occurring 2 days after rFVIIa administration) and the other associated

<p>| Table 1 Baseline Patient and Transplantation Characteristics |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>rFVIIa (n = 23)</th>
<th>Conventional Therapy (n = 14)</th>
<th>P Value</th>
</tr>
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<tr>
<td>Sex, males/females, n</td>
<td>13/10</td>
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<td>Age, median (range)</td>
<td>36 (9-66)</td>
<td>45 (13-59)</td>
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</tr>
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<td>Primary disease, n</td>
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<tr>
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<tr>
<td>Chronic lymphocytic leukemia</td>
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<td>Hodgkin disease</td>
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<td>1</td>
<td></td>
</tr>
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<td>Myelodysplastic syndrome</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
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<td>5</td>
<td></td>
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<tr>
<td>Severe aplastic anemia</td>
<td>6</td>
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<tr>
<td>Other</td>
<td>5</td>
<td>0</td>
<td></td>
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<td>Pulmonary function, median (IQR)</td>
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<td></td>
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<tr>
<td>FVC, L</td>
<td>3.30 (2.59-3.96)</td>
<td>3.72 (2.57-3.90)</td>
<td>.44</td>
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<tr>
<td>FVC, % predicted</td>
<td>90 (78-103)</td>
<td>82 (73-103)</td>
<td>.53</td>
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<td>FEV₁, L</td>
<td>2.60 (1.92-3.05)</td>
<td>3.02 (2.18-3.17)</td>
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<td>FEV₁, % predicted</td>
<td>95 (74-104)</td>
<td>87 (72-98)</td>
<td>.39</td>
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<tr>
<td>Diffusion capacity, % predicted</td>
<td>62 (55-78)</td>
<td>68 (66-78)</td>
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</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td>.71</td>
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<tr>
<td>Coronary artery disease</td>
<td>1 (4)</td>
<td>1 (7)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>2 (9)</td>
<td>2 (14)</td>
<td></td>
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<tr>
<td>Venous thromboembolism</td>
<td>3 (13)</td>
<td>3 (21)</td>
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<td>Conditioning regimens</td>
<td></td>
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<tr>
<td>Reduced-intensity conditioning, n (%)</td>
<td>19 (83)</td>
<td>10 (71)</td>
<td>.44</td>
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<tr>
<td>Fludarabine/cyclophosphamide</td>
<td>8 (35)</td>
<td>7 (50)</td>
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<tr>
<td>Fludarabine/cyclophosphamide and equine antithymocyte globulin</td>
<td>7 (30)</td>
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<tr>
<td>Other</td>
<td>4 (18)</td>
<td>3 (21)</td>
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<tr>
<td>Total body irradiation, n (%)</td>
<td>9 (39)</td>
<td>6 (43)</td>
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<td>Myeloablative regimen</td>
<td>3 (13)</td>
<td>4 (29)</td>
<td></td>
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<tr>
<td>Reduced-intensity regimen</td>
<td>6 (26)</td>
<td>2 (14)</td>
<td></td>
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<tr>
<td>Stem cell source, n (%)</td>
<td></td>
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<td>.14</td>
</tr>
<tr>
<td>Peripheral blood only</td>
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<td>13 (93)</td>
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<td>Bone marrow</td>
<td>0</td>
<td>1 (7)</td>
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<tr>
<td>Peripheral and cord blood</td>
<td>3 (13)</td>
<td>0</td>
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<td>Matched transplants, n (%)</td>
<td></td>
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<td>.69</td>
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<td>Related</td>
<td>11 (65)</td>
<td>10 (77)</td>
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<td>Unrelated</td>
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<td>3 (23)</td>
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<tr>
<td>Unrelated</td>
<td>5 (22)</td>
<td>4 (29)</td>
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<tr>
<td>Related and unrelated</td>
<td>3 (50)</td>
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<td>Post-transplantation course, n (%)</td>
<td></td>
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<tr>
<td>Time to engraftment, d, median (IQR)</td>
<td>15 (12-17)**</td>
<td>12 (10-15)</td>
<td>.50</td>
</tr>
<tr>
<td>Absolute lymphocyte count at day +30, cells /µL, median (IQR)</td>
<td>452 (206-789)**</td>
<td>520 (200-1107)**</td>
<td>.94</td>
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<tr>
<td>Cytomegalovirus reactivation, n (%)†</td>
<td>14 (61)</td>
<td>5 (36)</td>
<td>.37</td>
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<tr>
<td>Incidence of acute GVHD before AH, n (%)</td>
<td>11 (48)</td>
<td>8 (57)</td>
<td>.83</td>
</tr>
<tr>
<td>Incidence of chronic GVHD before AH, n (%)</td>
<td>8 (35)</td>
<td>4 (29)</td>
<td>1.00</td>
</tr>
<tr>
<td>Donor lymphocyte infusion, n (%) †</td>
<td>6 (26)</td>
<td>4 (29)</td>
<td>.83</td>
</tr>
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<td>Stem cell boost, n (%) ††</td>
<td>5 (22)</td>
<td>4 (29)</td>
<td>.70</td>
</tr>
</tbody>
</table>

FVC indicates forced vital capacity; FEV₁, forced expiratory volume in 1 second.

* Other includes multiple myeloma, sickle cell disease, chronic granulomatous disease, GATA2 deficiency, and thalassemia.

† All pulmonary function testing was done before transplantation except in 4 patients (3 in the rFVIIa group and 1 in the conventional group) in whom testing was done post-transplantation but before any episodes of AH. Pulmonary function testing data were not available for 2 patients in the conventional group.

‡ Comparison of the number of patients in each group with at least 1 comorbidity.

§ rFVIIa group: alemtuzumab, n = 2; alemtuzumab and busulfan, n = 1; EPOCH-F, n = 1; conventional therapy group: EPOCH-F, n = 2; pentostatin, n = 1.

¶ In 6 of 7 patients, total body irradiation was given twice daily for 4 days as part of a myeloablative conditioning regimen. The total dose was 1200 cGy (eight 150-cGy fractions) with a 600-cGy mediastinal boost (eight 75-cGy fractions). One patient in the rFVIIa group received 400 cGy (eight 50-cGy fractions) of total body irradiation as part of a myeloablative regimen.

∥ The dose of total body irradiation therapy given as part of reduced-intensity conditioning regimens ranged from 200 cGy to 400 cGy.

* Three patients received a haploidentical (related mismatched) and cord blood (unrelated mismatched) transplant.

** Two patients had a total lymphocyte count of <50, and 1 patient died before day +30.

†† Number of patients who received 1 or more donor lymphocyte infusions or stem cell boosts ≤60 days before the initial episode of AH.
In the rFVIIa-treated group, 35% of the patients (8 of 23) survived to hospital discharge. One death was related to AH and respiratory failure due an angioinvasive mold infection. Three patients died due to progression of their underlying disease, 1 patient died of respiratory failure due to pneumonia, and 1 patient died of sepsis and multiorgan failure.

In the conventional therapy group, 57% of the patients (8 of 14) survived to hospital discharge. One death was related to AH and respiratory failure due an angioinvasive mold infection. Three patients died due to progression of their underlying disease, 1 patient died of respiratory failure due to pneumonia, and 1 patient died of sepsis and multiorgan failure.

The remaining 7 episodes were excluded in the main comparison (P = .23). In a secondary analysis, missing respiratory values were imputed using the lowest possible value in the rFVIIa group and the highest possible value in the conventional group to recalculate the median SOFA score: median, 12 (IQR, 9–16) and 11 (IQR, 9–14), respectively (P = .19).

### Causes of Death

In the conventional therapy group, 57% of the patients (8 of 14) survived to hospital discharge. One death was related to AH and respiratory failure due an angioinvasive mold infection. Three patients died due to progression of their underlying disease, 1 patient died of respiratory failure due to pneumonia, and 1 patient died of sepsis and multiorgan failure.

In the rFVIIa group, 35% of the patients (8 of 23) survived to hospital discharge. Four patients died from respiratory failure due to AH; 3 of these patients had a concurrent infection (1 each with *Acinetobacter baumannii* pneumonia, parainfluenza pneumonia, and *Pseudomonas aeruginosa* bacteremia). One death in the rFVIIa group was attributed to progression of underlying malignancy. The remaining deaths were attributed to multiorgan failure in the setting of disseminated fungal infection (n = 4), DIC (n = 2), carbapenem-resistant *Klebsiella pneumoniae* infection (n = 2), and multiple infections (n = 2).
One patient survived 4 AH episodes during an initial hospitalization. This patient was rehospitalized 3 years later and ultimately died of multiorgan failure in the setting of parainfluenza pneumonia and AH.

Postmortem Analysis of Lung Parenchyma

Autopsies were performed in 36% of the patients (5 of 14) in the conventional therapy group and in 30% of those (7 of 23) in the rFVIIa group. Histopathological findings included intra-alveolar hemorrhage with hemosiderin-laden macrophages with elements of diffuse alveolar damage, including type II pneumocyte hyperplasia, focal hyaline membranes, and fibrin accumulation. In addition, 8 autopsies demonstrated evidence of organizing pneumonia with inflammation (Table 4 and Figure 5A-D). C4d-positive staining was noted mainly in larger vessels and within fibrinous deposits and hyaline membranes, but was usually negative in small-caliber vessels and capillaries (Figure 5C and D).

DISCUSSION

In this retrospective cohort study, we assessed the benefits and risks of the off-label use of rFVIIa in patients with AH following HSCT. AH was associated with substantial use of blood products, pharmaceuticals, and intensive care resources. More than one-third of the patients had AH without evidence of lower respiratory tract or bloodstream infection, whereas the remaining patients had a concomitant infection associated with AH. The majority of AH episodes were associated with acute respiratory distress syndrome, requiring mechanical ventilatory support. The lung injury was characterized by intra-alveolar hemorrhage with diffuse alveolar damage and organizing pneumonia owing in part to...
therapy group. The solid line represents the rFVIIa group; the dashed line, the conventional therapy group. The survival curves depicting outcomes in the initial episode of AH in patients with DAH (A) and patients with IAH (B). The survival rates were comparable to or better than the rates previously reported for patients with AH occurring within the first 30 days post-transplantation [4-6,38]. Improvements in supportive care may have contributed to some of these differences in outcomes. In addition, previous chemotherapy and radiation exposure, presence of GVHD, and concurrent infections contributed to patient heterogeneity and likely affected the effectiveness of the new therapy in these patients.

In early studies, the most frequent causes of death in HSCT recipients with AH were sepsis and multiorgan failure [1,4,12], whereas refractory hypoxicemic respiratory failure has been reported in more recent studies [3,6]. Studies on the contribution of infection to outcome after AH have yielded conflicting results [5,6]. In the present study, death due to refractory hypoxemia and respiratory failure was uncommon, and most of the patients had active infection detected in proximity to an episode of AH. Compared with previous studies [5,6,38], our cohort had a higher incidence of lower respiratory tract and bloodstream infections with gram-negative bacilli, molds, and fungi. These infections might have contributed directly to pulmonary endothelial and epithelial injury or indirectly by promoting a pro-inflammatory state and the development of GVHD [39]. Furthermore, the preponderance of infection-related deaths in this patient population underscores the difficulty of accurately determining the efficacy of adjunctive rFVIIa for AH, because any potential benefit from enhanced hemostasis is unlikely to affect outcome in patients who ultimately die of sepsis and multiorgan system failure.

Recurrent AH episodes occurred in almost one-half of the patients treated with rFVIIa, but in none of the patients receiving conventional therapy alone. Recurrent AH alone may reflect a more severely immunocompromised patient population. In this setting, rFVIIa might have had a temporizing effect on the clinical course pending the effects of more definitive anti-inflammatory and antimicrobial therapy. The high rate of recurrence noted only in the patients treated with rFVIIa may suggest a detrimental effect of rFVIIa in the setting of AH. Hyaline membrane formation was more common in postmortem histopathology in the rFVIIa group, possibly reflecting more severe lung injury or a consequence of the earlier timing of autopsy after AH. rFVIIa administration in healthy adults modestly increases plasma IL-6 and IL-8 levels, an effect that may be potentiated in critically ill patients.

GVHD-related immunologic mechanisms and the direct and indirect effects of infection [36,37]. As such, anti-inflammatory and antimicrobial therapies were the cornerstones of therapy.

Our findings indicate that rFVIIa can be a useful adjuvant therapy along with corticosteroids and supportive care in the treatment of AH. However, the resulting enhanced coagulation from rFVIIa administration does not confer a survival advantage compared with corticosteroid therapy alone. Other factors, such as worsening infection, multiorgan failure, or recrudescence of primary disease, may outweigh any survival benefit of enhanced hemostasis in HSCT recipients with AH.

Previous reports suggest better outcomes associated with AH episodes occurring during the periengraftment period and within the first 30 days after HSCT compared with episodes occurring at later time points post-transplant [3,5]. The AH episodes in our series occurred later after HSCT than those in previous reports, and 27% of our patients experienced 2 or more episodes of AH. The 30-, 60- and 180-day survival rates were comparable to or better than the rates previously reported for patients with AH occurring within the first 30 days post-transplantation [4-6,38]. Improvements in supportive care may have contributed to some of these differences in outcomes. In addition, previous chemotherapy and radiation exposure, presence of GVHD, and concurrent infections contributed to patient heterogeneity and likely affected the effectiveness of the new therapy in these patients.

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patients. The mechanism of rFVIIa-induced proinflammatory cytokine production is likely multifactorial, related to thrombin generation [40,41], activated factor X production [42], or a direct effect of rFVIIa [43]. The relevance of these mechanisms to the inflammatory state that exists after HSCT is unknown; however, in a recent meta-analysis of its off-label use for intracranial hemorrhage, cardiac surgery, body trauma, brain trauma, and liver transplantation, rFVIIa therapy was not associated with increased mortality in any of these groups [29]. In contrast, rFVIIa therapy was associated with a decreased risk of acute respiratory distress syndrome in body trauma [29].

Recent systematic reviews and meta-analyses have highlighted the increased risk of arterial thromboembolic events with rFVIIa use in patients without hemophilia [27-30]. The relative risk of arterial thrombotic complications was associated with advanced age at cardiac surgery [28] and with rFVIIa doses >40 µg/kg in patients with intracranial hemorrhage [29], conditions that typically affect an elderly patient population. In contrast, no increased risk of arterial thromboembolic events was detected in a younger cohort of patients with body trauma [29]. HSCT recipients represented a minority of the patients included in these studies, however, and thus the applicability of these findings to these patients is uncertain. The dearth of adverse events data from randomized, controlled trials of rFVIIa use in HSCT recipients and/or patients with hematologic malignancies underscores the fact that risk factors for thrombotic events in this population are unknown and may differ significantly from those in patients included in larger systematic reviews and meta-analyses [28,31,44]. In the only randomized, placebo-controlled trial of rFVIIa for bleeding after HSCT reported to date, the median patient age was 37 years, and there was no evidence of increased thromboembolic events with rFVIIa.

Table 4
Postmortem Histopathology after AH

<table>
<thead>
<tr>
<th>Time of autopsy relative to last dose of therapy for AH, d, median (IQR)</th>
<th>rFVIIa (n = 7)</th>
<th>Conventional Therapy (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death due to respiratory failure, n (%)</td>
<td>3 (2-3)</td>
<td>20 (7-26)</td>
</tr>
<tr>
<td>Histopathological findings, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated airspaces with intra-alveolar hemorrhage in different stages of organization with partial clot formation and fibrin accumulation</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hemosiderin laden-macrophages (alveoli and interstitium) *</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Focal hyaline membranes lining alveolar spaces</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Organizing pneumonia with inflammation</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Angioinvasive fungal infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Underlying hematologic malignancy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thromboemboli</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* One patient without hemosiderin laden macrophages died 1 day after recurrence of AH.
* Gray zone lymphoma.
* Epstein-Barr virus–associated lymphoproliferative disorder and nodular sclerosing Hodgkin lymphoma.

Figure 5. Autopsy sections of representative lung histopathology. (A) Hematoxylin and eosin staining showing accumulation of red blood cells, fibrin, and hemosiderin-laden macrophages in alveolar spaces. (Original magnification, 20×.) (B) Iron staining highlighting hemosiderin-laden macrophages within the alveolar and interstitial spaces. (Original magnification, 20×.) (C and D) C4d staining highlighting predominantly large-caliber vessels (C) and hyaline membranes (D). (Original magnification, 20×.)
therapy compared with placebo [32]. However, the concurrent use of prophylactic doses of heparin in 22% of patients may have mitigated the risk of thromboembolism in that study [32,45]. Similarly, a retrospective study reported no thrombotic complications in 24 patients treated with rFVIIa for AH post-HSCT [33]. Here we report 4 thrombotic events possibly related to rFVIIa, including a blood clot obstructing an endotracheal tube, an adverse event that has been reported previously [46]. All 4 of our patients were dependent on platelet transfusions at the time of rFVIIa administration, indicating that thrombocytopenia is not protective against thrombosis or DIC. We cannot suggest any screening tool to identify those patients who might develop thrombosis or DIC with the use of rFVIIa in this setting.

The minimum effective dose of rFVIIa for severe bleeding in patients without hemophilia is unknown. Doses used in clinical trials have varied greatly, from as low as 5 μg/kg up to 200 μg/kg given either as a single dose or multiple doses with varying frequencies [30]. Decisions regarding dose are particularly relevant to the risk of arterial thrombotic complications that appear to be dose-dependent [28]. In patients with intact mechanisms of thrombin generation, higher rFVIIa doses may augment thrombin production distant to the site of bleeding in a tissue factor–independent manner, producing thromboembolic complications without improved hemostatic effects [47]. In vitro data suggest that a low dose of rFVIIa (equivalent to 20 μg/kg) has similar efficacy as higher doses (100 to 200 μg/kg) as measured by thrombin generation [48]. Similarly, in moderate to severe thrombocytopenia, 50 μg/kg of rFVIIa was as effective as 100 μg/kg in decreasing the IVC bleeding time [49]. Compared with previous reports of rFVIIa therapy for AH after HSCT (Table S1), in our cohort the median dose per kilogram was lower and decreased over time, suggesting increased experience with this therapy with similar clinical effects.

Strengths of this study include the detailed data collection and analysis of each AH episode, an assessment of concurrent infections, long-term follow up of each patient, and inclusion of a contemporaneous comparator cohort treated with corticosteroids and supportive care alone. Nonetheless, several selection biases for and against the use of rFVIIa likely contributed to our inability to demonstrate any clear advantage or disadvantage of rFVIIa therapy for AH in this cohort. As a single-site retrospective study, selection and ascertainment bias, as well as unknown confounders, might have influenced our observations. In addition, our analysis is likely underpowered to assess some of the clinical variables (ie mortality, duration of mechanical ventilation, ICU length of stay, and resolution of AH) compared in the 2 treatment groups.

In conclusion, rFVIIa used in combination with corticosteroids did not confer a survival advantage compared with corticosteroids alone. Any putative advantage as adjunctive therapy with corticosteroids and supportive care will require a prospective randomized clinical trial. Further insight into the pathogenic mechanisms contributing to lung injury in individual patients with AH likely will inform therapeutic options and possibly provide the basis for improved therapies.

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Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.03.015.

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