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ORIGINAL ARTICLE

A study of 65 patients with acquired hemophilia A in Taiwan

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Background/Purpose: Acquired hemophilia A (AHA) is a rare disorder that has not been comprehensively reported in the Chinese population. Treatment-related fatal sepsis (TRS), other than hemorrhage, is the leading cause of death in patients with AHA. However, researchers have not systematically evaluated salient parameters, to determine their association with the risk of TRS in this rare disorder. This study reports the salient features of AHA in Chinese patients and presents possible factors associated with TRS.

Methods: Sixty-five Chinese patients with AHA, including 42 men and 23 women, were studied retrospectively.

Results: The median age was 64 years (range = 18–94 years). The features, laboratory findings, and outcomes of various therapies designed to arrest acute bleeding and eliminate autoantibodies against the factor VIII coagulant protein (VIIIi) were comparable to those previously reported. The complete response (CR) rate was 60%, and the median time to CR was 16 weeks. Ten patients (15%) died of bleeding related to FVIIIi by the end of the median follow-up period of 115 months. The estimated 1- and 5-year hemorrhage-related mortality rates were 15% and 22%, respectively. The absence of CR to therapy was the only independent factor associated with shorter survival. The rate of TRS was 20%, and the use of a rituximab-based (Rb) regimen (odds ratio = 8.0, 95% CI, 1.1–68.2) and platelet $< 1.5 \times 10^{11}$/L at diagnosis (odds ratio = 38.5, 95% CI, 1.3–1107.6) were the two significantly independent factors associated with TRS.

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Conclusion: The salient features of AHA and treatment outcomes of the patients in this study are similar to those of other patients. Two independent factors (the use of a Rb regimen and platelet $< 1.5 \times 10^{11}$/L) were significantly associated with TRS.

Introduction

Acquired hemophilia A (AHA) is a rare disorder caused by the spontaneous development of autoantibodies against the FVIII coagulant protein (FVIIIi) in the nonhemophiliac population. The incidence of AHA is approximately 1—4 per million per year, and increases with age until 70—80 years. There are no sex differences in AHA distribution at any age except 20—40 years, when the preponderance of AHA in women is pregnancy-related.[1,2]

Because FVIIIi-related hemorrhages are associated with high morbidity and mortality, aggressive treatment of AHA is recommended.[3] The main goals of AHA therapy are to arrest bleeding and eliminate FVIIIi. There are two main options for controlling acute bleeding in patients with AHA; the use of bypassing agents and raising FVIII levels.[1—4] Researchers have proposed the use of long-term conventional immunosuppressive (IS) therapy, consisting of corticosteroids alone or combined with cytotoxic agents (CTAs), such as cyclophosphamide, azathioprine, cyclosporine, or tacrolimus, to eliminate FVIIIi.[1,4,5] Several emerging treatments [e.g., anti-CD20 antibody (rituximab),[6—8] or immune tolerance treatment (ITT)[9,10]] can efficiently eliminate FVIIIi. However, no comparative studies have been performed to evaluate the efficacy and safety of these treatments, because the number of available patients is relatively small.[1]

Treatment-related fatal sepsis (TRS), in addition to hemorrhage, is also a leading cause of death in patients with AHA.[2—4] A recent study, using a retrospective review of death certificates, analyzed the deaths of 121 patients with AHA and determined that hemorrhagic shock and infectious events related to IS treatment were the most frequent causes of death.[11] Therefore, IS therapy should be strictly tailored to patient characteristics (i.e., age, sex, and general health status) to minimize adverse treatment-related effects.[2] Some prophylactic strategies may also be required, particularly for infectious processes in AHA patients during the treatment, to eradicate FVIIIi. To date, no salient parameters have been systemically evaluated to determine the risk of TRS in this rare disorder. Therefore, this study retrospectively examines the clinical characteristics and treatment outcomes of a relatively sizable cohort of Chinese patients with AHA, and surveys any parameter associated with TRS.

Patients and methods

Patients

This study retrospectively investigates 65 Chinese patients with AHA in the hemophilia centers of two institutes, between September 1987 and April 2010.

Diagnosis and laboratory tests

The diagnosis of AHA required laboratory confirmation of FVIIIi levels in patients with no preexisting coagulopathy.[12] FVIIIi level was assayed using the Bethesda method,[13] and any plasma sample with an inhibitor level ≥ 0.6 Bethesda units (BUs) was considered positive. All blood sampling and laboratory procedures used in this study were described previously.[14]

Treatment and response

To arrest acute bleeding, patients were treated with one or more of the following agents: prothrombin complex concentrate (PCC) [Konyne-80 (Miles-Cutter, Berkeley, CA, USA), Proplex T, (Hyland Laboratories, Glendale, CA, USA)], activated prothrombin complex concentrate (APCC) (FEIBA; Baxter Immuno AG, Vienna, Austria), recombinant human activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark), hFVIII concentrate (Haemate P; Behringwerke, Marburg, Germany), and pFVIII (Hyate:C; Porton-Speywood, Ltd, Wrexham, UK). Plasma exchange was performed to remove approximately 3000 mL of plasma. Protein A sepharose columns were used for immunoabsorption. The relevant doses and schedules were similar to those described previously.[2,12] Acute bleeding was defined as new-onset bleeding requiring treatment. Severe bleeding was defined as bleeding from visceral organs, or the retroperitoneal compartment, or as life-threatening bleeding. The selection of agents or therapies depended on the patient's condition and agent/therapy availability. Control of acute bleeding was defined as hemostasis, no increase in hematoma size, and the absence of any new bleeding signs.

Thirty of the patients received prednisolone alone as the primary treatment, to eliminate FVIIIi for the first 6—8 weeks. Complete response (CR) was defined as a resolution of hemorrhagic signs, complete disappearance of FVIIIi, and the normalization of FVIII coagulant (FVIII:C). If the response was less than complete, CTA was added. Initial therapies included prednisolone and CTA simultaneously (PCTA) in 14 patients, CTA alone in two patients, immune tolerance therapy (ITT)[9] in three patients, and rituximab-based (Rb) regimens in seven patients (5 patients treated with concomitant prednisolone and/or CTA and 2 patients treated with rituximab alone). The doses and schedules of prednisolone, CTA and rituximab, and the IT regimen, were similar to those reported elsewhere.[2,3,12]

Statistical analysis

The Chi-square or Fisher's exact test was used for between-group comparisons of the discrete variables. A two-sample

t test was used for a between-group comparison of the means. The time to CR (TCR) was defined from the starting date of FVIIIi elimination therapy, to the date at which CR was documented. Bleeding specific mortality (BSM) was defined as death caused by FVIIIi-related bleeding. Event-free survival (EFS) was defined from the date of AHA diagnosis, to the date of BSM or the last follow-up. For EFS estimates, the patients who died because of other causes were considered alive and were lost to follow-up; thus, the patient status at the last follow-up was regarded as a censored event. Overall survival (OS) was calculated from the date of AHA diagnosis to the date of death for any reason, or to the last follow-up. This study uses Kaplan-Meier survival curves to estimate TCR, BSM, EFS, and OS, and compares the differences between groups using the log-rank test. Several clinical and laboratory variables at diagnosis were assessed to determine their impact on survival. These were sex, age, associated conditions, FVIII:C, titer of FVIIIi, levels of hemoglobin (Hb), white blood cell count (WBC), platelet count (PLA), albumin (Alb) level, lactate dehydrogenase (LDH) level, and activated partial thromboplastin time (APTT). As in previous reports,[4] the continuous variables were categorized on the basis of cut-off values as follows: age $>$ 65 years, FVIII:C $<$ 1%, low-titer FVIIIi $<$ 5 BU, intermediate-titer FVIIIi 5—10 BU, high-titer FVIIIi $>$ 10 BU $\leq$ 50 BU, very high-titer FVIIIi $>$ 50 BU, Hb $<$ 8 g/dL, WBC $< 4.0 \times 10^9$/L, PLA $< 1.5 \times 10^{11}$/L, Alb $<$ 3.5 g/dL, LDH $>$ 465 IU/L, and APTT $>$ 75 seconds. Factors identified as significant covariates by univariate analysis were tested using logistic or Cox regression multivariate analysis. All directional *p* values were two-tailed, with a *p* value $\leq$0.05 considered significant for all tests. All analyses were performed using SPSS 19.0 software (Chicago, IL, USA).

Results

Patients' clinical characteristics

The 65 patients in this study included 42 men and 23 women [median age at diagnosis = 64 years (range = 18—94 years)]. Peak incidence occurred at 71—80 years in both sexes, but also at 21—30 years in women and 51—60 years in men (Fig. 1). The most common bleeding symptoms were multiple ecchymoses, followed by soft tissue hematoma and mucosal bleeding (Table 1). Concomitant femoral nerve neuropathy (because of compression from retroperitoneal hematomas) developed in four patients (6%), and bleeding occurred in 31 patients (48%), with identifiable associated disorders or conditions (Table 2). Abnormal bleeding in 11 patients was blamed on medications, including antibiotics, unknown herbal drugs, and antianginal and antipsychotic drugs. The incidence of mucosal bleeding was higher in eight patients with active cancer (88% vs. 37% of patients without active cancer; $p = 0.017$), but the incidence of hematoma formation (13% vs. 72%, respectively; $p = 0.002$) and ecchymosis (50% vs. 86%, respectively; $p = 0.033$) was lower.

Laboratory results

Forty-two patients (65%) had severe FVIII deficiency (FVIII:C $<$ 1%), and the remaining 23 patients (35%) had residual FVIII:C (median = 3.8%; range = 1.1—17%) detectable. At AHA diagnosis, the median titer of FVIIIi was 19.4 BU (range = 0.74—2414), and 31%, 11%, 29%, and 29% of patients had low, intermediate, high, and very high FVIII inhibitor titers, respectively. All patients had prolonged APTT (median = 73.7 seconds; range = 39.2—149.2 seconds), which could note be corrected by the addition of normal plasma (data not shown). All other test results were generally within the reference range, except for the Hb level (median = 9.6 g/dL; range = 2—16 g/dL), indicating anemia, and the LDH level (median = 527 IU/L; range = 203—1764 IU/L; reference range = 360—465 IU/L).

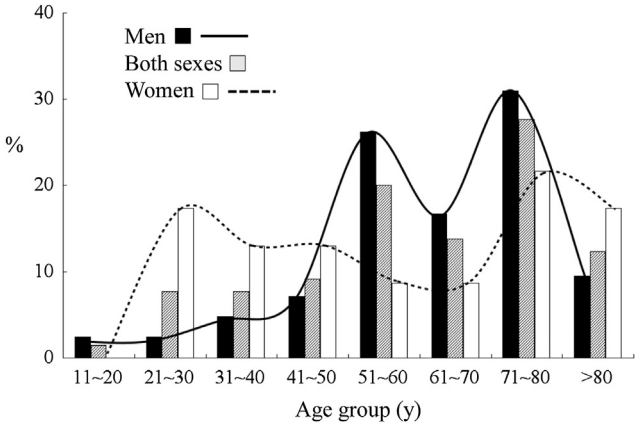

Figure 1 The age distribution of 65 patients with acquired hemophilia A.

Arrest of acute bleeding

At the time of preparation of this manuscript, 393 episodes of acute bleeding [median, 3 episodes per patient (range = 1—138)] had occurred in 54 patients (83%) at presentation or follow-up. Among these episodes, 54 (14%) were severe hemorrhages that occurred in 33 of these 54 patients (61%).

There was no significant difference in FVIIIi titers between patients with acute bleeding and patients with no acute bleeding (mean $\pm$ SD, 125.9 $\pm$ 352.5 BU vs. 8.4 $\pm$ 13.4 BU, respectively; $p = 0.276$) and between patients with severe hemorrhage and patients with mild or moderate

Table 1 Clinical presentations of the 65 patients with acquired hemophilia A.

Clinical presentation	Patient, *n* (%)
Ecchymosis	53 (82)
Hematoma	42 (65)
Soft tissue	37 (57)
Retroperitoneal	5 (8)
Mucosal bleeding	28 (43)
Gastrointestinal tract	19 (29)
Urinary tract	8 (12)
Intracranial	1 (2)
Prolonged postoperative bleeding	14 (22)
Hemarthrosis	2 (3)

Table 2 Associated conditions of the 65 patients with acquired hemophilia A.

Associated condition	Patient, *n* (%)
Not identified	34 (52)
Identified	31 (48)
Medications[a]	11 (17)
Malignancy[b]	8 (12)
Autoimmune disorder[c]	4 (6)
Skin disorder[d]	3 (5)
Post-partum complication	3 (5)
Interstitial lung disease	2 (3)

[a] Antibiotics belong to penicillins (4 patients); herbal drugs (5); cardiovascular medicine (1); antipsychotics (1).
[b] Lymphoma (3 patients); bladder cancer (2); oral cancer (1); hepatoma (1); lung cancer (1).
[c] Systemic lupus erythematosus (3 patients), motor neuron disease (1).
[d] Psoriasis (1 patient); photosensitive dermatitis (1); lichen planus (1).

hemorrhage (mean ± SD, 138.5 ± 424.4 BU vs. 106.1 ± 200.9 BU, respectively; $p = 0.746$).

Table 3 shows the rates of response to different treatments used to stop the bleeding. The rates of response to APCC and rFVIIa were 85% and 90%, respectively, and these agents had no marked adverse effects. Only one patient died; the cause of death was acute ischemic stroke and myocardial infarction 2 days after PCC infusion.

Response to FVIIIi elimination therapy

Fifty-six patients (86%) received FVIIIi elimination therapies, including conventional IS ($n = 46$), ITT ($n = 3$), and Rb ($n = 7$) regimens. The other 9 patients did not receive these therapies because of poor clinical conditions ($n = 6$), trivial hemorrhagic symptoms ($n = 2$), and refusal of treatment ($n = 1$). The results, after a median treatment duration of 11 weeks (range = 2–164 weeks) and a follow-up of 115 months, are summarized in Table 4. In brief, 12 of 30 patients (40%) who received prednisolone alone as their initial therapy, had CR, and the median TCR was 12 weeks. Among the 18 patients who did not have CR to this treatment, CTA was subsequently added for 11 patients. Overall, the results of conventional IS therapy including prednisolone alone initially, prednisolone subsequently combined with CTA, and PCTA for a median treatment period of 15 weeks (range = 2–164), indicated a CR rate of 63% and median TCR of 16 weeks. Of the seven patients who received the Rb regimen as their initial therapy for a median treatment period of 4 weeks (range = 3–38), three patients (43%) had a CR with a median TCR of 10 weeks. Four patients died of sepsis before achieving a response. The data for all FVIIIi elimination therapies indicate that CR was achieved in 60% of cases with a median TCR of 16 weeks.

Table 3 The percentage of acute bleeding episodes responsive to treatment in patients with acquired hemophilia A.

Therapy	No. of episodes [a]	Response (%)
Bypassing agent	355	
Porcine FVIII	6	83
PCC	137	80
APCC	74	85
rFVIIa	138	90
Human FVIII	38	
Without plasmapheresis	5	38
With plasmapheresis	31	46
Immunoabsorption	2	0
Overall	393	81

APCC = activated prothrombin complex concentrates; FVIII = factor VIII; PCC = prothrombin complex concentrates; rFVIIa = recombinant activated FVII.
[a] Total documented episodes of acute bleeding requiring hemorrhage control.

Outcome

At the median follow-up of 115 months, 34 of the 65 patients (52%) were dead. Causes of death included FVIIIi-related bleeding [including intracranial ($n = 5$), gastrointestinal ($n = 3$), and retroperitoneal bleeding ($n = 1$), and hemothorax ($n = 1$)], sepsis ($n = 14$), malignancy ($n = 5$), cardiac failure ($n = 1$), chronic lung disease ($n = 1$), and others ($n = 3$). The median time from diagnosis to death of the 10 patients who died of bleeding was 2 months (95% CI = 0.0–8.2). The cumulative 1-, 2-, and 5-year BSM percentages in the 65 patients were 15%, 18%, and 22%, respectively. Among the 56 patients treated for FVIIIi, the cumulative 1-, 2-, and 5-year BSM was significantly higher in the patients without a CR than in patients with a CR (19%, 33%, and 49% vs. 4%, 4%, and 4%, respectively; $p = 0.0042$) (Fig. 2).

In this sample, 13 of the 56 treated patients (23%) died of sepsis, but only 11 of these 13 patients suffered from fatal sepsis during the treatment period (median = 2.7 months; 95% CI = 2.0–3.4). Therefore, 20% of the mortality caused by sepsis may have been treatment-related (11 of 56 patients). These 11 patients had received FVIIIi elimination therapy for a median of 7 weeks (range = 2–16). There was a significantly higher rate of treatment-related sepsis mortality in those treated with the Rb regimen ($n = 4$) than in those treated with IS and IT therapies ($n = 7$) (57% vs. 14%, respectively; $p = .022$). Among the four patients treated with the Rb regimen who died of fatal sepsis, two received rituximab alone, and two (one patient had B-cell lymphoma and another had idiopathic interstitial lung disease) received concomitant prednisolone and cyclophosphamide. Treatment-related neutropenia appeared in the latter two patients. Compared to the other three patients who survived from the Rb regimen treatment, these fatal patients were older and had a lower Alb level (median = 69 vs. 75 years, $p = 0.682$; 3.9 vs. 2.4 g/dL, $p = 0.085$, respectively). The use of the Rb regimen, as a covariate, along with other clinical parameters, was compared between the AHA patients who died of fatal sepsis ($n = 11$) and those who did not ($n = 45$). Table 5 presents a summary of the results. These two factors (the

Table 4 Response rate and time to respond to FVIIIi elimination therapy.

Therapy	Patients, *n*	CR	TCR (wk)
		n (%)	Median (95% CI)
Pred. alone initially	30[a]	12 (40)	12 (0.0–29.4)
Pred. subsequently combined CTA	11[a]	5 (46)	44 (5.3–82.7)
Pred. simultaneously combined CTA	14[b]	11 (79)	9 (2.6–15.4)
CTA alone	2[c]	1 (50)	19
Immunosuppression	46[a+b+c]	29 (63)	16 (3.1–29.0)
Immunotolerance	3	1 (33)	6
Rituximab-based	7	3 (43)	10 (8.4–11.6)
Overall	56	33 (60)	16 (9.3–22.7)

CI = confidence interval; CR = complete response; CTA = cytotoxic agent; Pred = prednisolone; Pt = patient; TCR = time to complete response.

[a] The 11 patients were part of the 18 patient group who did not obtain CR after the induction treatment of prednisolone alone.

[b] The number of patients who received prednisolone and CTA simultaneously.

[c] The number of patients who received CTA alone.

use of the Rb regimen and PLA $< 1.5 \times 10^{11}$/L) were significantly related to fatal sepsis by univariate analysis. In addition, other factors had a high odds ratio associated with fatal sepsis, but were not significant on univariate analysis. These factors included age $>$ 65 years, LDH $>$ 465 IU/L, and WBC $< 4.0 \times 10^{9}$/L, and all proceeded into multivariate analysis. The use of the Rb regimen, and PLA $< 1.5 \times 10^{11}$/L, were both verified as independent predictors by multivariate analysis.

Two patients whose AHA was refractory to conventional IS therapy, recovered spontaneously 13 and 23 months after discontinuation of all treatment. Another three patients, who received no FVIIIi treatment, also recovered spontaneously a median of 2 months (range = 1–5) after diagnosis of AHA. Conversely, four of the 33 patients (12%) who had a documented CR, relapsed at a median of 5 months (range = 2–14) after discontinuation of all treatment. Thereafter, one of these patients died of bleeding despite treatment, and three others responded to the resumption of conventional IS therapy.

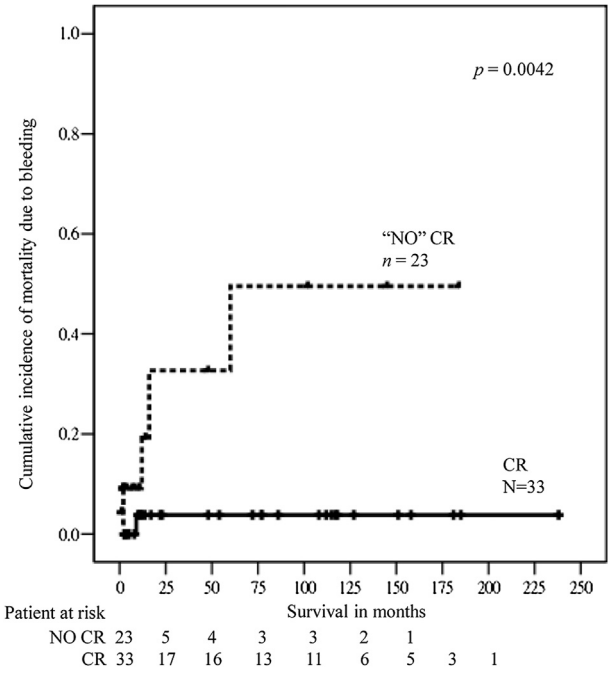

Figure 2 Comparison of the cumulative incidence of mortality due to bleeding of patients who had CR to FVIIIi elimination therapies and those who did not ("NO" CR).

Predictors of survival

Univariate analysis showed that severe bleeding, no CR to therapy, PLA $< 1.5 \times 10^{11}$/L, Alb $<$ 3.5 g/dL, and APTT $>$ 75 seconds, were associated with a shorter EFS. Subsequently, multivariate Cox regression analysis identified no CR to therapy as the only independent predictor of shorter EFS [Hazard ratio (HR), 12.6 (95% CI = 1.5–108.4); $p = 0.021$]. Univariate analysis showed an association of age $>$ 65 years, severe bleeding, hematoma formation, mucosal bleeding, associated conditions, active cancer, no CR to therapy, PLA $< 1.5 \times 10^{11}$/L, Alb $<$ 3.5 g/dL, and LDH $>$ 465 IU/L with a shorter OS. However, only age $>$ 65 years [HR = 4.3 (95% CI = 1.5–12.0), $p = 0.005$], PLA $< 1.5 \times 10^{11}$/L [HR = 5.1 (95% CI = 1.2–21.8), $p = 0.027$], and no CR to therapy [HR = 3.6 (95% CI = 1.1–12.4), $p = 0.041$] remained as independent predictors of shorter OS after multivariate analysis.

Discussion

To the best of our knowledge, this study of 65 AHA patients is the largest case series of AHA in a Chinese population, and has the best long-term follow-up at almost 10 years. These patients have clinical characteristics similar to those reported for other patient series,[3,10,15–17] suggesting a common underlying pathophysiology of AHA across ethnic populations. However, no patient had rheumatoid arthritis, which is commonly reported among patients with AHA.[15] The overall treatment response and time to response (i.e., arrest of acute bleeding and elimination of FVIIIi) in these patients were also similar to those in the other reports.[1,4,15–17]

Table 5 Comparison of clinical characteristics between acquired hemophilia A patients who had immunosuppressive therapy related fatal sepsis and those who did not.

Item	With fatal sepsis (n = 11)	Without fatal sepsis (n = 45)	Univariate analysis	Multivariate analysis
	n (%)		Odds ratio (95% CI)	
Age > 65 y	7 (63.6)	21 (46.7)	2.0 (0.5–7.8)	1.0 (0.2–6.0)
Sex, male	6 (54.5)	28 (62.2)	1.4 (0.4–5.2)	—
Underlying condition	5 (45.5)	18 (40.0)	1.3 (0.3–4.7)	—
FVIII:C < 1%	7 (63.6)	30 (66.7)	1.1 (0.3–4.5)	—
FVIIIi titer (BU)				
Low < 5	2 (18.2)	14 (31.1)	ref	—
5< = intermediate = <10	1 (9.1)	4 (8.9)	1.8 (0.1–24.7)	—
10 < high = <50	6 (54.5)	12 (26.7)	3.5 (0.6–20.7)	
50 < very high	2 (18.2)	15 (33.3)	0.9 (0.1–7.6)	—
Hb < 8 g/dL	5 (45.4)	15 (33.3)	1.6 (0.4–6.2)	—
WBC < 4.0×10^9/L	2 (18.2)	1 (2.2)	9.8 (0.8–119.8)	2.1 (0.0–968.7)
PLA < 1.5×10^{11}/L	3 (27.3)	1 (2.2)	16.5 (1.5–179.2)*	38.5 (1.3–1107.6)*
Alb < 3.5 g/dL	6 (54.5)	19 (42.2)	1.4 (0.4–5.9)	—
LDH > 465 IU/L	9 (81.8)	22 (48.9)	4.7 (0.9–24.6)	8.2 (0.8–83.7)
APTT > 75 s	5 (45.5)	21 (46.7)	0.9 (0.2–3.4)	—
Rituximab-based regimen	4 (36.4)	3 (6.7)	8.0 (1.5–43.7)*	8.0 (1.1–68.2)*

*Statistically significant.
Alb = albumin; APTT = activated partial thromboplastin time; BU = Bethesda units; FVIIIi = autoantibodies against the factor VIII coagulant protein ; Hb = hemoglobin; LDH = lactate dehydrogenase; PLA = platelet count; WBC = white blood cell count; ref = reference.

In our study, sepsis resulting from FVIIIi elimination therapy was the main cause of death other than bleeding, and accounted for 20% of the mortality. A meta-analysis showed that the mortality rate caused by infectious complications of treatment is 15%.[4] Data from the acquired hemophilia registry in the United Kingdom indicate that 33% of AHA patients developed sepsis, and 11% of AHA patients died of sepsis.[18] A substantial proportion of AHA patients, especially elderly AHA patients, receiving cyclophosphamide, died because of neutropenia-related infections, and immunosuppressant-related side effects appeared in as many as 53% of AHA patients treated in a single center.[4] In this study, 14% of patients treated with conventional IS and IT therapies died of sepsis, but this rate was significantly higher in patients receiving the Rb regimen (57%) as their initial therapy. Although the deaths caused by sepsis during the administration of the Rb regimen could be attributed to patient conditions (extreme age and low Alb) and comorbidities (1 patient had lymphoma, and another had idiopathic interstitial lung disease), rituximab depletes the B lymphocytes. Therefore, patients treated with rituximab alone or rituximab and CTA concomitantly, could experience serious or even fatal systemic infection.[19] Similarly, two of the six (33.3%) AHA patients treated with rituximab and concurrent prednisolone and/or cyclophosphamide in one study died of sepsis.[20] Because of the limited number of patients in this study, the finding of higher treatment-related fatal sepsis associated with the Rb induction regimen, compared to other treatments, must be verified by a prospective study with more patients enrolled. A recent report from the European Acquired Hemophilia Registry (EACH2) did not suggest that rituximab, as the first-line treatment, improves outcomes or reduces side effects in patients with AHA.[21] Nonetheless, other studies using prednisolone and/or cyclophosphamide concurrently with rituximab, have shown no related infectious complications.[6,7] One possible explanation is that T lymphocyte counts and serum immunoglobulin (sIg) levels remain stable after the administration of rituximab.[6] Therefore, it might be necessary to monitor T lymphocyte counts and sIg levels before and during the period of rituximab administration in patients with AHA.

This is also the first study to show that a low platelet count (< 1.5×10^{11}/L) at AHA diagnosis is significantly and independently associated with TRS. This mechanism is unclear, but a low platelet count is associated with adverse outcomes in critically ill patients, because it may aggravate the bleeding risk.[22] Moreover, a decrease in platelet count may indicate ongoing coagulation activity on disrupted integrity of the vessel wall, which contributes to microvascular failure and organ dysfunction.[22] A platelet count decline also precedes other signs of sepsis.[23] Alternatively, a low platelet count might reflect the severity of underlying diseases for AHA, regardless of whether it is identifiable. Thus, patients with AHA and a low platelet count at diagnosis may require some prophylactic strategies to prevent sepsis, such as prophylactic antibiotics and frequent monitoring for any sign of ongoing infection during the FVIIIi eliminating treatment.

The BSM in our patients was 15%, which is comparable to rates in other reports (estimated rate = 8–22%).[2,4,15] Although age, response to IS therapy, associated conditions, and inhibitor titers are prognostic for EFS and OS,[15,17] this study shows that no CR (i.e., the absence of complete response to therapy) was the only independent predictor of both shorter EFS and OS. This finding is consistent with the results of a meta-analysis.[4] Therefore, although the inhibitor can spontaneously disappear in approximately 14–35% of patients within 12–18 months without FVIIIi elimination,[15,24]

it is still important to achieve a CR in AHA patients, because of the risk of fatal bleeding, unless FVIIIi is completely eliminated.[1,4,25]

The optimal first-line regimen to eradicate FVIIIi remains controversial in AHA patients.[1] A regimen might be considered superior if CR is achieved in more patients more rapidly. This study suggests that treatment with PCTA may be better in these respects. Likewise, interim data from the EACH2 suggest that treatment with a combination of steroids and a CTA (predominantly cyclophosphamide) achieves CR in more patients (77%) than treatment with steroids alone (58%) or an Rb regimen (61%). However, the median TCR in those who responded was similar in the steroid alone and steroid and cytotoxic groups (approximately 5 weeks) but slower in those treated with an Rb regimen (approximately 9 weeks).[21] In EACH2, the 12 patients treated with rituximab alone had only a 42% response rate,[21] which was relatively similar to the efficacy of the Rb regimen (43%).

This study has several limitations. One is its retrospective nature. The patient number was small, and the collection period crossed over two decades, whereas the supportive care method, including antimicrobial agents, changed over time. Treatments of either acute bleeding episodes, or FVIIIi elimination therapies, were heterogeneous. Therefore, these findings should be confirmed by prospective controlled studies in the future.

In summary, the clinical characteristics of the AHA patients in this study were similar to those of AHA patients elsewhere. These data also confirm that CR to treatment is a crucial predictor of fair EFS and OS. The choice of treatment modality should consider TRS. Two independent factors (the use of an Rb regimen and PLA $< 1.5 \times 10^{11}$/L at diagnosis) were significantly associated with TRS.

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