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Outcome of CARE: a 6-year national registry of acquired haemophilia A in China

Boyang Sun,[1] Feng Xue,[1] Ying Feng,[2] Jing Sun,[3] Ziqiang Yu,[4] Ming Hou,[5] Jingyu Zhang,[6] Xiaojing Zeng,[7] Yongqiang Zhao,[8] Shimei Lian,[9] Meijuan Huang,[10] Ting Niu,[11] Zhongguang Cui,[12] Jingsheng Wu[13] and Renchi Yang[1]

[1]State Key Laboratory of Experimental Haematology, National Clinical Research Centre for Haematological Disorders, Institute of Haematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin Laboratory of Blood Disease Gene Therapy, CAMS Key Laboratory of Gene Therapy for Blood Diseases, Tianjin, [2]Department of Haematology, Second Affiliated Hospital of Guangzhou Medical University, [3]Nanfang Hospital, Nanfang Medical University, Guangzhou, [4]Department of Haematology, The First Affiliated Hospital of Soochow University, Suzhou, [5]Department of Haematology, Qilu Hospital, Shandong University, Jinan, Shandong, [6]Department of Haematology, Key Laboratory of Haematology of Hebei Province, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, [7]Department of Blood Transfusion, The Affiliated Hospital of Guizhou University, Guiyang, [8]Department of Haematology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, [9]Department of Haematology, Dalian Municipal Central Hospital, Affiliated Hospital of Dalian Medical University, Dalian, China, [10]Fujian Institute of Haematology, Fujian Medical University Union Hospital, Fuzhou, [11]Department of Haematology, West China Hospital, Sichuan University, Chengdu, Sichuan, [12]The Affiliated Hospital of Qingdao University, Qingdao and [13]Department of Haematology, Anhui Provincial Hospital, Anhui Medical University, Hefei, China

Summary

Acquired haemophilia A (AHA) is a rare haemorrhagic disorder caused by autoantibodies directed against the functional epitopes of coagulation factor VIII (FVIII). Its management relies on prompt diagnosis, control of bleeding and eradication of the inhibitor by immunosuppression. China Acquired Hemophilia Registry (CARE), a nationwide multicentre registry, was intended to survey the status of AHA and standardize its diagnosis and therapy in China. One hundred and eighty-seven registered patients had an average age of 52 years. Diagnosis was delayed in 46·5% patients. There was a significant delay from diagnosis to immunosuppressive therapy in 68·3% patients. Bleeding control was significantly higher in patients treated with prothrombin complex concentrate (PCC) *versus* FVIII replacement therapy (84·6% vs. 34·4%; $P < 0·001$). Inhibitor eradication with a combination of steroids and cyclophosphamide showed a higher partial remission (PR) rate (92·2% vs. 70·3%) and stable complete remission (CR) rate (82·8% vs. 48·6%) than with steroids alone. Logistic regression model showed age and malignancy were significantly related to survival at final follow-up. The mean age for the survivors [51 years (IQR, 35–65 years)] was significantly lower than that of the non-survivors [79 years (IQR, 67–86 years)] ($P < 0·001$). Overall survival was higher in non-malignancy group than malignancy group (94·9% vs. 70%) (OR = 1·313; 95% CI, 0·913–1·889, $P = 0·015$).

Keywords: acquired haemophilia A, registry, diagnosis, haemostatic treatment, immunosuppression, outcome.

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Correspondence: Feng Xue and Renchi Yang, State Key Laboratory of Experimental Haematology, National Clinical Research Centre for Haematological disorders, Institute of Haematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin Laboratory of Blood Disease Gene Therapy, CAMS Key Laboratory of Gene Therapy for Blood Diseases, Tianjin, China.
E-mails: justmexf@163.com and rcyang@ihcams.ac.cn

Acquired haemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies directed against the functional epitopes of coagulation factor VIII (FVIII) (Collins, 2011). AHA is characterized by excessive bleeding that is either spontaneous or induced by an injury or invasive procedure in patients without previous family or personal history of bleeding (Collins *et al*, 2010). The evaluation and diagnosis of AHA are usually precipitated by bleeding symptoms and sometimes by an isolated prolonged activated partial thromboplastin time (APTT). Low awareness of AHA among healthcare professionals and a lack of local coagulation laboratory facilities often delay diagnosis, which may impact treatment initiation and have serious consequences. The reported incidence of AHA is about 1·5 per million and often occurs in the elderly (Collins *et al*, 2007). Due to its rarity, current perspectives on AHA come from several large cohort retrospective studies (Collins *et al*, 2007; Baudo *et al*, 2012; Collins *et al*, 2012; Knoebl *et al*, 2012; Yang *et al*, 2015). The European Acquired Haemophilia Registry (EACH2), with 501 cases, represents the largest collection of consecutive cases of AHA to date (Knoebl *et al*, 2012). In China, previous studies on AHA are mostly from single-centres with small sample size, limiting the information available on diagnosis and optimal therapy regimen. The China Acquired Haemophilia Registry (CARE) was established to generate a national database that collects information from AHA patients from China, in order to study the status of AHA in China, improve our understanding of the disease and standardize treatment.

Methods

Patients and criteria

CARE, designed as a nationwide multicentre registry, was formally launched on 21 October 2012. Clinical data were collected and registered in the database once the diagnosis of AHA was confirmed. From October 2012 to June 2017, a total of 187 patients with AHA were enrolled consecutively from 25 centres in 15 provinces of China. Inclusion criteria include plasma FVIII coagulant activity (FVIII:C) <50 μ/dl, detectable inhibitor to FVIII and signed informed consent. There is no age restriction. All patients were followed immediately from definite diagnosis. Data recorded on each patient include demographics, underlying disorders, clinical course of diagnosis and management, clinical characteristics and treatment of haemorrhage, inhibitor eradication regimen, adverse events both disease- or treatment-related.

Severe bleeding was defined as the presence of one or more of the following: life-threatening, limb or organ function-threatening, central nervous system affected, deep muscle bleeding, more than one bleeding location, haemoglobin level below 80 g/l or drop by more than 20 g/l, more than 2 units of red blood cells transfused in 24 h. A second bleeding events was defined as new bleeding at a different site from first bleeding episode or recurring at same site(s) after recovery.

The regimen for inhibitor eradication was decided by local investigators at each centre and divided into four groups for efficacy and outcome analysis: steroids alone, steroids with cyclophosphamide, rituximab-based regimens and other regimens. The primary end point was complete remission (CR), defined as follows: inhibitor titre <0·6 Bethesda units (BU)/ml, FVIII:C >50 iu/dl and cessation of immunosuppressive therapy. Stable CR was defined as continuous CR with no relapse. Another end point was partial remission (PR), defined as FVIII:C >50 iu/dl, but with ongoing immunosuppression (IS) with or without inhibitor.

Data cleaning was performed by clinicians at each centre before the data was uploaded to the ResMan website (www.medresman.org). The data-corrected clinical research forms were sent to the Institute of Haematology and Blood Diseases Hospital, at the Chinese Academy of Medical Science (CAMS) and Peking Union Medical College (CAMS-PUMC). We reviewed all data and, where necessary, contacted the clinicians from each centre to update the follow-up information. The study was approved by the Human Research Ethics

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Committee of the Institute of Haematology and Blood Diseases Hospital, CAMS-PUMC and all involved centres.

Laboratory diagnosis

Full blood counts, serum biochemistry, immunological studies, peripheral blood lymphocyte subsets (flow cytometric analysis), lupus anticoagulants, coagulation tests, including screening test, FVIII:C (one-stage APTT based assay), APTT mixing test and inhibitor assay (Bethesda assay), were performed at local centres. Mixing test was used as a screening measure to detect the presence of FVIII inhibitor. Specifically, normal and patients' plasma were mixed in a 1:1 ratio and incubated at 37°C for 2 h. If the prolonged APTT could not be corrected, the test was considered to be positive. Inhibitor against FVIII was detected by both qualitative (APTT mixing test) and quantitative (Bethesda assay) methods.

Statistical analysis

Descriptive data were reported using frequency or median and interquartile range (IQR) for categorical and continuous variables respectively. Mann-Whitney *U* test was used for comparison between continuous variables and the Chi-square test for categorical variables. Correlation between continuous variables was assessed using Spearman rank correlation. Efficacy of bleeding control was compared between the bypassing agent group and FVIII replacement agent group using Chi-square test. The primary endpoint of immunosuppressive treatment was the achievement of CR. The CR rate of each group was compared using Chi-square test. Propensity score (PS) methodology was used to eliminate influences of compounding factors. Age, gender, FVIII:C, inhibitor titres, weight and aetiology of AHA were included in the PS match model: patients were matched in pairs according to PS using 1:1 matching algorithm. Analysis of immunosuppressive outcome and time to CR (considered as an event) were performed using the Kaplan–Meier method and log-rank test, and patients were censored if their status were not available at last follow-up. Time-to-event endpoints were analysed using a Cox proportional hazards regression model. Odds ratio (OR) and hazard ratio (HR) were used to report binary endpoints and time-to-event endpoints, respectively.

$P < 0{\cdot}05$ was considered to indicate a significant difference. All analyses were performed using SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics

Between October 2012 and June 2017, a total of 187 patients were enrolled in the CARE from 25 centres in 15 provinces (registered at the Chinese Clinical Trial Registry: chictr.org.cn ChiCTR-RRC-17013381). All participating centres are listed in Appendix S1. Baseline characteristics of the cohort are listed in Table I. The median age at diagnosis was 52 years (IQR, 36–67). Age and gender distribution demonstrated a low number of children and teenagers, with about 35·8% of the total cohort aged over 60 years (Fig 1). A male preponderance was observed in this cohort, particularly in the older age group. On the other hand, a female preponderance (40/48, 83·3%) was evident in the childbearing age group (20–37 years). There was no seasonal variation in the occurrence of AHA.

Underlying disorders

The underlying disorders that could be associated with AHA are detailed in Table II. Of the 184 patients, 100 (54·3%) were regarded as idiopathic AHA with no underlying disorders identified.

In our cohort, malignancy was reported in 11 patients (5·98%), with 73% of malignancy-related cases being solid tumours: see Table II for details of categories, therapeutic regimens and response to treatment. Twenty-three patients (12·5%) had autoimmune disease, including rheumatoid arthritis, autoimmune haemolytic anaemia, immune thrombocytopenia, sicca syndrome, undifferentiated connective tissue diseases and other inflammatory diseases. Nineteen (82·6%) of 23 patients with autoimmune disorders had prior immunosuppressive therapy but the disease status was not reported. Three patients (13·0%) did not receive any treatment but no reasons were provided. Treatment information was absent in 1 patient (4·3%).

Table I. Baseline characteristics of the CARE cohort.

Characteristic	Patients, *n* (%)
Age, years (*n* = 187)	
1–15	3 (1·6)
16–40	55 (29·4)
41–65	77 (41·2)
66–89	52 (27·8)
Gender (*n* = 187)	
Female	102 (54·5)
Male	85 (45·5)
FVIII:C at diagnosis, iu/dl (*n* = 172)	
Severe, ≤1	73 (42·4)
Moderate, >1, <5	54 (31·4)
Mild, >5, <50	45 (26·2)
Inhibitor titre: at diagnosis, BU/ml (*n* = 155)	
0–10	71 (45·8)
11–100	66 (42·6)
101–1000	17 (11·0)
>1000	1 (0·6)
Hb, g/l (*n* = 169)	
≤60, ≤6	16 (9·5)
>60, <90	56 (33·1)
≥90, <120	61 (36·1)
≥120	36 (21·3)

BU, bethesda units; CARE, China Acquired Haemophilia Registry; FVIII:C, factor VIII coagulant activity; Hb, haemoglobin.

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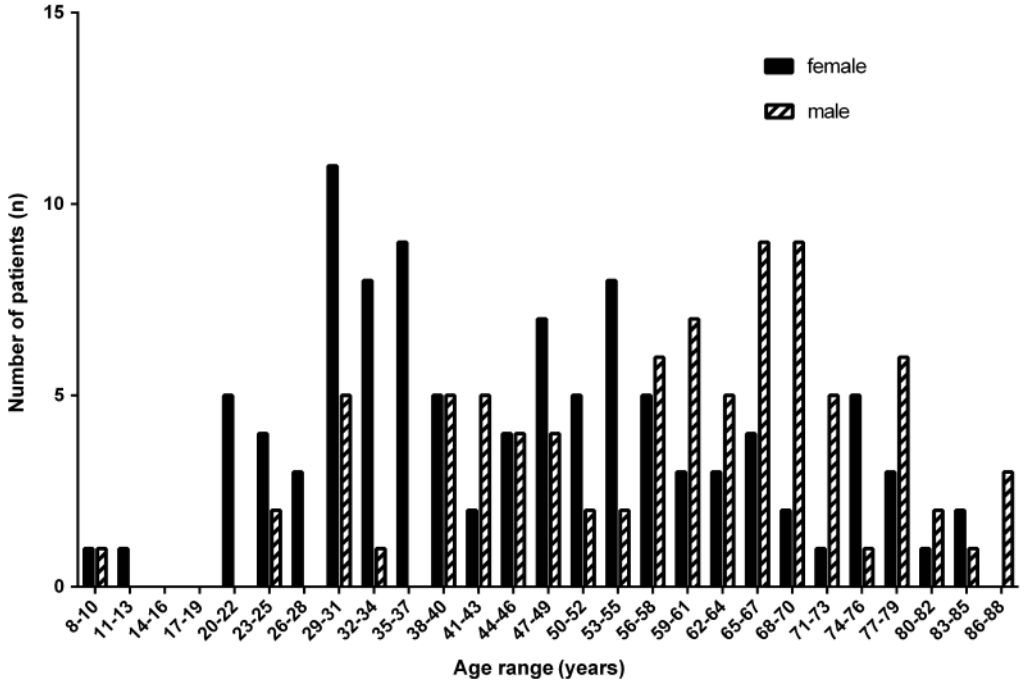

Fig 1. Distribution of age at diagnosis according to gender.

Pregnancy, mostly primigravida cases, was associated with AHA in 23 patients (22·5% of female patients). Data on 5 patients showed that AHA manifested postpartum, at days 28, 61, 62, 70 and 123, earlier than those in the cohort reported by Tengborn *et al* (2012).

Diagnosis

In most cases (93·6%), the reason for initiation of consultation was a spontaneous bleeding event leading to a further bleeding workup and final definite diagnosis. Ten patients (4·8%) had unexpected bleeding during the perioperative period. Three patients (1·6%) presented with isolated prolonged APTT without bleeding symptoms.

Unfortunately, the primary hospital established the diagnosis in only 53·5% of all patients. There was no difference in the rate of diagnosis between departments. The delay in diagnosis had a significant impact on the interval from bleeding to haemostatic therapy and immunosuppressive therapy (Kruskal Wallis test, $P < 0·001$). Figure 2 shows time from bleeding to definite diagnosis, time from first visit to diagnosis and time from diagnosis to immunosuppressive therapy, representing both diagnosis and treatment delays.

A prolonged APTT (median 88·8 s, IQR, 76·1–104·3 s) was found in all patients. The median (IQR) FVIII:C in the whole cohort was 1·7 (1–5·025) μ/dl, and most patients (74·1%) had FVIII:C <5 μ/dl. The inhibitor titre ranged between 0·1 and 2150·4 BU/ml (median 13, IQR 5·3–54 BU/ml) but there was inter-laboratory variability. Inverse correlation was found between FVIII and inhibitor titre (Spearman, $r = -0·535$, $P < 0·001$). APTT mixing test was performed in 61 patients, and was positive in 54 patients (88·5%). The level of immunoglobulin was in the normal range in most patients, with median values of 2·24 g/l (IQR, 1·57–2·79) for IgA, 1·1 g/l (IQR, 0·78–1·7 6) for IgG and 11·78 g/l (IQR, 9·70–13·6) for IgM. There was no significant abnormality in peripheral blood lymphocyte subsets.

Bleeding

Initial bleeding episodes. A total of 184 patients (98·40%) experienced at least 1 bleeding episode and only 3 patients (1·60%) were reported to have no bleeding. Of the 184 patients with at least one bleed, 101 (54·9%) were female and 83 (45·1%) were male. The categories of initial bleeding and causes are shown in Fig 3. Consistent with previous AHA studies (Tay *et al*, 2009; Baudo *et al*, 2012; Huang *et al*, 2015; Yang *et al*, 2015), in our cohort, mucocutaneous bleeding was common (78·3%) while haemarthrosis was not (5·4%).

According to the predefined criteria, bleeding was defined as severe in 112 (60·9%), mild in 70 (38%) cases and absent

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Table II. Underlying disorders of the CARE cohort.

Underlying disorders (n = 184)	Patients, n (%)	
	Of total	Of subgroup
None	100 (54·4)	
Autoimmune disease	23 (12·5)	
Rheumatoid arthritis		2 (8·7)
Autoimmune haemolytic anaemia		6 (26·1)
Immune thrombocytopenia		1 (4·3)
Sicca syndrome		1 (4·3)
Undifferentiated connective tissue disorders		3 (13·0)
Other inflammatory diseases		10 (43·5)
Malignancy	11 (6·0)	
Colon		2 (18·18)
Oesophagus		1 (9·09)
Blood system		3 (27·27)
Lung		1 (9·09)
Gastric		2 (18·18)
Other solid tumour		2 (18·18)
Treatment of malignancy (n = 11)		
Chemotherapy		3 (27·27)
Radiotherapy		1 (9·09)
Surgery		4 (36·36)
Stem cell transplantation		1 (9·09)
No treatment		2 (18·18)
Response to cancer treatment (n = 8)		
Remission		4 (50)
Partial remission		3 (37·5)
Progression		1 (12·5)
Dermatological	10 (5·43)	
Pemphigoid		5 (50)
Psoriasis		3 (30)
Urticaria		2 (20)
Infectious disease	46 (25·00)	
Respiratory infection		39 (84·78)
Limbs		2 (4·35)
Gum		1 (2·17)
Urinary tract		3 (5·52)
Skin		1 (2·17)
Antibiotics		42 (91·30)
Pregnancy or perinatal period	23 (12·5)	

in 2 (1·1%) cases. Severe and mild cases differed in age (57 vs. 46 years, $P < 0·001$), Hb level (87 vs. 108·5 g/l, $P = 0·01$) and bleeding sites (muscle, 55·0% vs. 29·2%, $P < 0·001$), while sex, FVIII:C, inhibitor titre, APTT, underlying conditions, causes of bleeding and diagnosis delay were similar. Patients with anaemia were older than those with normal haemoglobin level (55 vs. 46, $P = 0·001$).

Eighty-two patients received haemostatic treatment for the initial bleeding and 23 (28%) of them experienced further bleeding. In 102 patients who did not receive haemostatic therapy, 98 (96·1%) suffered continuous bleeding while bleeding ceased spontaneously in other 4 (3·9%) patients. Those who received haemostatic therapy at the first bleeding episodes had a lower likelihood of further bleeding [OR = 0·016, 95% confidence interval (CI) 0·005–0·048, $P < 0·001$].

Further bleeding episodes. Sixty-three (34·2%) of the 184 patients with bleeding events at presentation had only one bleeding episode [55 (87·3%) had no further bleeding following successful haemostatic therapy and the bleeding ceased spontaneously without relapse in 8 (12·7%)]. In the remaining 121 patients, 72 (59·5%) patients had two bleeding events, 39 (32·2%) patients had three bleeding events and 10 (8·3%) patients had more than three bleeding events, with a maximum of five. Similarly, most further bleeding episodes (86·4%) were spontaneous, with the most common sites being subcutaneous (74·2%) and muscle (38·7%). The mean interval between the first bleed and further bleeding was 5 days (IQR, 3–12 days).

Haemostatic therapy

Haemostatic therapy was initiated in 44·6% (82) of patients with bleeding events, 50·9% of which were severe and 33·3% were mild. Details of the regimens used are shown in Table III. In general, bypassing agents were used in patients with higher inhibitor titres irrespective of FVIII:C.

In 82 patients receiving haemostatic therapy, first-line therapy alone was employed in 43 patients (52·4%), ancillary treatment alone was employed in 8 patients (9·8%) and combined therapy was employed in 31 patients (37·8%). The ancillary therapies, used in 39 patients, included red blood cell transfusion (n = 35), antifibrinolytic agents (n = 11), topical therapy (n = 2), plasmapheresis (n = 1) and other (n = 2).

Activated prothrombin complex concentrate (aPCC; FEIBA®) is not available in China, and so prothrombin complex concentrate (PCC) was used as an alternative. Among 74 patients treated for initial bleeding episodes, 61 patients (82·4%) received FVIII replacement (8 also received 1-desamino-8-D-arginine-vasopressin) and 13 patients (17·6%) received PCC. There was no significant difference in baseline characteristics, including age, gender, FVIII:C, inhibitor titre, haemoglobin level, platelet count and bleeding severity, between the two treatment groups. Bleeding was controlled in 21/61 (34·4%) patients receiving FVIII replacement and in 11/13 (84·6%) patients receiving PCC. Bleeding was more likely to be controlled with PCC than replacement agents (OR = 10·476, 95%CI 2·122–51·709, $P < 0·001$).

In 2 patients not responding to PCC as initial therapy, bleeding was resolved after receiving recombinant activated factor VII (rFVIIa). Of the 40 patients who failed initial FVIII replacement therapy, 4 patients received bypassing agents (rFVIIa), and 23 patients received PCC as salvage therapy. Bleeding resolved in all 4 patients receiving rFVIIa and in 18/23 (78·3%) patients receiving PCC. Of the 5 patients with no response to salvage PCC therapy, bleeding was controlled in 3 patients with rFVIIa. Data regarding the time to cessation of bleeding was available for 9 patients

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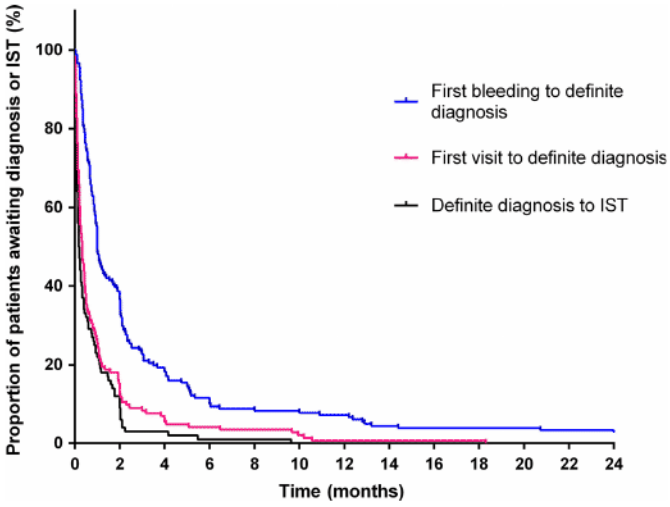

Fig 2. Diagnosis and IS treatment delay in Chinese acquired haemophilia A patients. The median time was 30 days [interquartile range (IQR), 15–76] from bleeding to definite diagnosis, 7 days (IQR, 1–24) from first visit to diagnosis and 6 days (IQR, 3–23) from diagnosis to immunosuppressive therapy (IST).

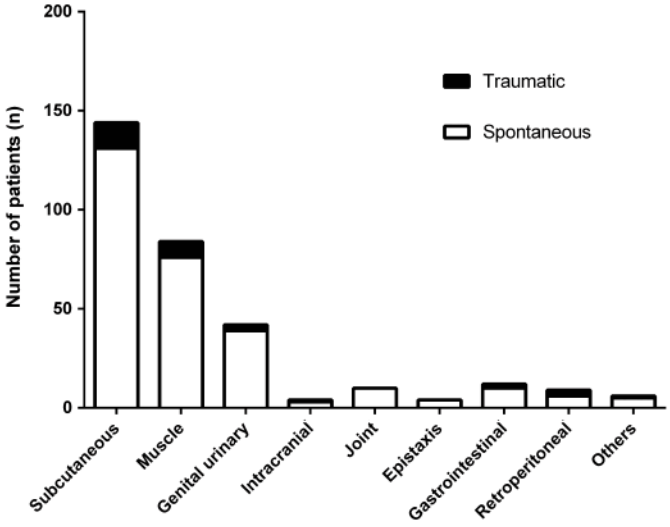

Fig 3. Sites of bleeding in patients with acquired haemophilia A. Most patients had more than one type of bleeding.

treated with rFVIIa, 29 patients with PCC and 21 patients with FVIII replacement. The median time to cessation of bleeding was 5 h (IQR, 2·5–6·75) for patients treated with rFVIIa, 72 h (IQR, 42–317) for patients receiving PCC and 250 h (IQR, 202–306) for patients receiving FVIII replacement agents (Fig 4).

Immunosuppressive therapy

First-line immunosuppressive regimens. In total, 167/187 patients received immunosuppressive therapy for inhibitor eradiation. Regimens employed included steroids alone, steroids with cyclophosphamide, rituximab-based regimens and others (detailed in Table IV). Rituximab-based regimen was defined as rituximab used as first-line immunosuppressive therapy with other concomitant agents. The most common rituximab-based regimen used was rituximab combined with steroids. Dosage and frequency of rituximab varied widely, but the most common one was 100 mg weekly for 4 weeks.

It is worth pointing out that there was a significant delay from definite diagnosis to immunosuppressive therapy in many patients, at a median of 6 days (3–23 days) (Fig 3),

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Table III. Information on first-line haemostatic agents used for patients with acquired haemophilia A at first bleeding episode.

Haemostatic agent	Patients treated, *n* (%)	Median baseline FVIII:C (IQR), iu/dl	Median baseline inhibitor titre (IQR), BU/ml	Median interval time, hour (IQR)	Total number of doses per patient, *n*	Median value of total dose (IQR)
rFVIIa	11 (13·4)	1·1 (0·9–16·53)	10·6 (3·075–45·2)	4 (2–6)	1 (1–3)	3·5 mg (3–7·25)
PCC	36 (43·9)	1 (1–2·75)	13·2 (6–30)	12 (12–24)	5 (2–10)	4000 units (2175–10 800)
FVIII	61 (75)	1·6 (1–5·5)	7·4 (2·9–24·5)	12 (8–24)	6 (2–12)	2800 units (1150–8400)
DDAVP	8 (8·5)	1 (1–1·5)	8·2 (5·6–13·6)	12 (12–24)	8 (7–14)	150 μg (116·25–225)

BU, bethesda units; DDAVP, 1-desamino-8-D-arginine-vasopressin; FVIII:C, factor VIII coagulant activity; IQR, interquartile range; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

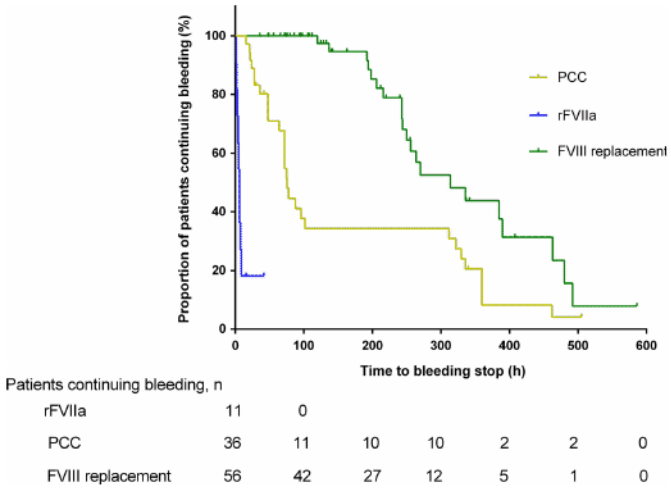

Fig 4. Interval from haemostatic treatment to cessation of bleeding with different agents. The median time to cessation of bleeding was 5 h [interquartile range (IQR), 2·5–6·75] for patients treated with rFVIIa, 72 h (IQR, 42–317) for patients with PCC and 250 h (IQR, 202–306) for patients with FVIII replacement agents. FVIII, coagulation factor VIII; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

longer than those of previous studies (Collins *et al*, 2007; Knoebl *et al*, 2012; Pathirana *et al*, 2014). Of 167 patients who underwent immunosuppressive therapy, only 53 (31·7%) started treatment without delay after the first bleeding episode. Recurrent bleeding was significantly more prevalent when immunosuppression initiation was delayed (108/114 patients, 94·7%) in comparison to those started on immunosuppression without delay (13/53 patients, 24·5%) ($P < 0·001$).

Outcome of immunosuppressive therapy

PR rate and Initial CR rate. The outcome of 155 of 167 patients who received immunosuppressive therapy was recorded, and 137 (88·4%) patients achieved PR. The median days to PR ranged from 36 to 70 days among regimens. As a first-line therapy, the PR rate of patients treated with steroids alone was 70·3% (26/37), significantly lower than that of patients treated with steroids and cyclophosphamide (92·2%, 59/64) ($P = 0·002$). A total of 127 (81·9%) patients achieved CR. The CR rate of patients treated with steroids alone was 62·2% (23/37), significantly lower than that of patients treated with steroids and cyclophosphamide (87·5%, 56/64) ($P = 0·003$). In particular, four patients receiving steroids alone failed to achieve CR but remitted after the addition of cyclophosphamide. Forty of 44 patients (90·9%) receiving rituximab-based regimens as first line immunosuppressive therapy achieved a CR –including the 4 patients who received rituximab alone. Five patients who previously received oral steroids for autoimmune diseases were resistant to steroid therapy for AHA, but remitted when rituximab was added. In patients treated with other regimens, CR was achieved in 8/10 (80%). Due to the variation of treatment regimens, it was not possible to analyse the data of the each smaller group to make useful comparisons (Table V).

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Table IV. Agents for first-line immunosuppressive therapy.

Regimens and agents	*n*	Administration route	Median dose, mg/kg (IQR)
Steroids alone	38		
Prednisone	18	Oral	1 (0·875–1)
Methylprednisolone	13	Intravenous	1·18 (0·8–2)
Dexamethasone	6	Intravenous	0·25 (0·2125–0·8125)
Hydrocortisone sodium succinate	1	Intravenous	5
Steroids + cyclophosphamide	64		
Prednisone	32	Oral	0·915 (0·5–1)
Methylprednisolone	29	Oral or intravenous	1 (0·7–1·375)
Dexamethasone	3	Intravenous	0·15
Cyclophosphamide	64	Oral or intravenous	1·9 (1–5)
Rituximab-based	52		
Rituximab alone	4	Intravenous	
Rituximab + steroid	30		
Methylprednisolone	28	Intravenous	0·65 (0·6–0·9)
Prednisone	2	Oral	0·55, 0·8†
Rituximab + steroid + cytotoxic	18		
Methylprednisolone	7	Oral or intravenous	0·7, 0·8, 0·4, 1†
Prednisone	7	Oral	0·8, 0·55, 1†
Dexamethasone	2	Intravenous	0·2, 0·25†
Unknown steroid	2	ND	ND
Cyclophosphamide	14	Oral or intravenous	1·95 (1·5–2·95)
Azathioprine	1	Oral	1
Others	13		
Steroid + ciclosporin	6		
Prednisone	3	Oral	0·5, 1†
Dexamethasone	2	Intravenous	0·2, 0·2†
Hydrocortisone	1	Intravenous	5
Ciclosporin	6	Oral	4 (3–5)
Steroids + cyclophosphamide + others	7		
Prednisone	3	Oral	ND
Methylprednisolone	4	Oral	ND
Cyclophosphamide	7	Oral	0·4, 1·5, 5†
Ciclosporin	3	Oral	2†
Plasmapheresis	4	–	–

IQR, interquartile range; ND, no data; –, not applicable.
*Doses listed due to limited data

The median (IQR) time to FVIII:C rising to >50 iu/dl and inhibitor decreasing to <0·6 BU/ml are shown in Table V.

Relapse and stable CR. After achieving CR, most patients underwent regular follow-up. A total of 123 relapses were recorded in all patients who achieved CR, resulting a stable CR in 115 of 155 (74·2%) patients. Relapse occurred in 21·7% patients (5/23 whose outcome was recorded) who had achieved CR with steroids alone, resulting in a stable CR rate at 48·6% (18/37) after first-line treatment with steroids alone. Four relapses occurred in the steroid and cyclophosphamide regimen group, resulting in stable CR in 53/64 (82·8%) patients. Two patients (5%) relapsed with rituximab-based regimen, resulting in a stable CR rate of 86·4% (38/44). Two relapses in the group treated with other regimens resulted in a stable CR rate of 60% (6/10) (Table V). The median days to CR ranged from 47 to 74 days among regimens, with the shortest observed for rituximab-based therapy (median 47 days).

We only compared the rate of PR and CR between the steroids group and steroid plus cyclophosphamide group, because the concomitant agents used in the rituximab-based group were too varied to be compared directly. However, differences in patients' characteristics and steroids doses are likely to have an impact on the outcomes. To reduce errors, a PS match was performed in terms of age, sex, weight, FVIII:C and inhibitor titre at present, idiopathic or not and steroids dosage. The baseline covariables of two groups were balanced after PS matching (Table VI). According to the PS matching analysis, a higher proportion of patients treated with steroids and cyclophosphamide (30/34, 88·2%) achieved PR compared with those treated with steroids alone (23/34, 67·6%) (OR = 2·75; 95% CI, 0·971–7·788, $P = 0·041$). Patients treated with steroids and cyclophosphamide were

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Table V. Response to first-line immunosuppressive therapy.

Regimen	Patients treated, *n*	Patients with recorded outcome, *n*	Initial CR, *n* (%)	Days from start of immunosuppression, median (IQR) FVIII:C >50 iu/dl	Inhibitor <0·6 BU/ml	CR	Relapse, *n* (%)	Stable CR, *n* (%)
Steroids alone	38	37	23 (62·2)	56 (28–104)	63 (49–114)	69 (48–117)	5 (21·7)	18 (48·6)
Steroids + cyclophosphamide	64	64	56 (87·5)	42 (26–102)	39 (21–94)	62 (35–98)	3 (5·4)	53 (82·8)
Rituximab-based	52	44	40 (90·9)	42 (27–76)	43 (20–82)	47 (27–91)	2 (5)	38 (86·4)
Others	13	10	8 (80)	217, 84, 78†	272, 84, 41, 78†	74 (47–97)	2 (25)	6 (60)
Total	167	155	127 (81·9)	42 (28–89)	46 (21–95)	60 (33–98)	12 (9·4)	115 (74·2)

BU, bethesda units; CR, complete remission; FVIII:C, factor VIII coagulant activity; IQR, interquartile range.
*Actual days listed due to limited data.

Table VI. Baseline covariates of patients in two groups after propensity score matching.

Variable	Steroids + oral cyclophosphamide	Steroids alone	*P*-value†
N	34	34	
Age, years	54 (20)	56 (18)	0·708
Sex, *n* (%)			
Female	15 (44·1)	18 (52·9)	0·467
Male	19 (55·9)	16 (44·4)	
FVIII:C at diagnosis, iu/dl	3·7 (4·3)	3·3 (3·6)	0·563
Inhibitor titre at diagnosis, BU/ml	32·3 (41·5)	26·5 (24·6)	0·907
Weight, kg	58·6 (10·7)	58·8 (5)	0·892
Steroid dose, mg/kg	1·3 (1·4)‡	1·2 (1)‡	0·719
Aetiology, *n* (%)			
Idiopathic	18 (52·9)	16 (47·1)	0·628
Secondary	16 (47·1)	18 (52·9)	

Values given are mean (standard deviation), unless otherwise indicated. BU, bethesda units; FVIII:C, factor VIII coagulant activity; N, number.
**P*-values refer to chi-squared test or Mann–Whitney *U*-test, respectively.
†Doses have been converted to equivalent doses of prednisone.

more likely to achieve a stable CR than those treated with steroids alone (OR = 3·63; 95% CI, 1·238–10·644, $P = 0·016$). Furthermore, time from starting immunosuppressive therapy to PR was longer for patients treated with steroids alone compared with those treated with steroids and cyclophosphamide (HR = 2·062; 95% CI, 1·292–3·289, $P = 0·002$; Fig 5). Similarly, time to CR was longer for the steroids alone group than the steroids and cyclophosphamide group (HR = 2·746; 95% CI, 1·48–5·095, $P < 0·001$; Fig 6).

A variety of other regimens were employed, of which the most common was rituximab combined with steroids. Other regimens included the combination of rituximab and one or more drugs, such as cyclophosphamide, ciclosporin, immunoglobulin, azathioprine and plasmapheresis.

The dosage and frequency of rituximab administration varied widely, with the most common one being 100 mg per week for 4 weeks. The proportion of patients achieving a second CR and suffering subsequent relapse could not be analysed because data were unavailable for many patients. After CR, steroids dosage was tapered prior to stopping, except in those cases who needed to continue steroids for an underlying disorder.

Adverse events and adverse reactions

Thrombotic events were reported in 3 patients, all receiving PCC. These included a lower limb venous thromboembolism (Patient 153), myocardial infarction (Patient 260) and disseminated intravascular coagulation (DIC) (Patient 250). The interval from PCC infusions to thrombotic events was 4 days for Patient 153, 19 days for Patient 260 and 1 day for Patient 250. Patient 153, a 39-year-old female at diagnosis, with no underlying disorders, presented with pain and swelling in legs after 4 PCC infusions at 400 μ (8 μ/kg) per dose. Patient 250 is a 71-year-old male, with underlying conditions of coronary artery disease and autoimmune haemolytic anaemia. DIC occurred after 38 PCC infusions at 600 iu/12 h (total 22 800 iu). Patient 260, an 86-year-old male with hypertension and coronary artery disease (CAD), had a myocardial infarction after only one dose (400 iu) of PCC infusion. In our cohort included 8 other patients diagnosed with coronary artery disease. Five of them (age 51–83 years) were treated with PCC and none developed myocardial infarction. Adverse events associated with immunosuppressive therapy were reported in 8 patients, the types and the times from start of immunosuppression to occurrence of each adverse event are as follows: 1 osteonecrosis of the femoral head (2 months after oral steroid), 4 sepsis (15, 18, 53 and 69 days after oral steroid), 1 leucopenia (22 days after oral cyclophosphamide), 1 thoracolumbar fracture (3 months after oral steroid) and 1 Cushing syndrome (20 days after oral steroid). The dose of immunosuppressive agents used in these patients was similar to those of others in the cohort.

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Follow-up and outcomes

Patients were followed up for a median time of 205 days (IQR, 93–430 days), and the status of 165 patients at final follow-up were recorded. Among these, 154 (93·3%) were alive and 11 (6·7%) (of whom 9 were in remission) had died. Causes of death included heart failure induced by pulmonary infection ($n = 1$), bleeding ($n = 6$), underlying malignancy ($n = 2$) and sepsis in patient with neutropenia related to immunosuppressive therapy ($n = 2$). Mean time from initial symptoms to death was 54 days (IQR, 7–98 days). Logistic regression model shows age was the only risk factor significantly related with survival at final follow-up, with median age at 51 years (IQR, 35–65 years) for the survival group compared with 79 years (IQR, 67–86 years) for the non-survivor group ($P < 0·001$). Overall survival rate was higher in non-malignancy group than the malignancy group (94·9% vs. 70%) (OR = 1·313; 95% CI, 0·913–1·889, $P = 0·015$). A trend to lower rate of survival was observed in patients with FVIII:C <1 μ/dl and inhibitor >20 BU/ml compared to others (88·2% vs. 96·3%) ($P = 0·061$).

Discussion

The China Acquired Haemophilia Registry (CARE) was designed as a nationwide multicentre prospective observational research and was intended to survey the status of AHA, raise the awareness of the disease among Chinese physicians and aid in standardising the diagnosis and therapy in China. The nationwide collection of data, consecutive case series, prospective design and long-term follow-up make it the largest and most comprehensive collection of patients with AHA in China.

It's well known that the incidence of AHA increases with age, with many previous studies reporting a median age of over 70 years and a biphasic age distribution:, one peak in aged patients and another peak occurring in childbearing-age patients (Tay *et al*, 2009; Knoebl *et al*, 2012; Tiede *et al*, 2015a). However, in the CARE cohort, the median age is 52 years, and the two peak ages are also younger than that reported in some previous studies (Bossi *et al*, 1998; Yee *et al*, 2000; Tay *et al*, 2009; Baudo *et al*, 2012; Knoebl *et al*, 2012; Borg *et al*, 2013; Huang *et al*, 2015; Kessler *et al*, 2016). Comparison of CARE data with the largest cohort previously reported in a single-centre in China shows similar age characteristics, although the proportion of women is higher in the previous cohort study. We speculate that both diagnostic bias and referral bias could have an impact on the age characteristics of our cohort. We speculate that young patients are more likely to be referred for further consultation compared to older patients. CARE showed a preponderance of women presenting with AHA, and is consistent with a large scale UK study (Collins *et al*, 2007) but in contrast to a male preponderance observed in the EACH2 cohorts (Knoebl *et al*, 2012). The higher proportion of females in reproductive age in our study also reduced the average age.

Regarding underlying conditions, compared other studies, our cohort shows a similar proportion of idiopathic AHA, a higher proportion of pregnancy-related AHA and a lower proportion of tumours (Green & Lechner, 1981; Bossi *et al*, 1998; Delgado *et al*, 2003; Collins *et al*, 2007; Knoebl *et al*, 2012; Borg *et al*, 2013; Huang *et al*, 2015; Kessler *et al*, 2016; Napolitano *et al*, 2018; Zanon *et al*, 2019). The difference probably represents referral bias in our cohort. Younger patients, especially pregnant women, are more likely to seek consultation, more so than older patients with tumours.

In most patients, the diagnosis was precipitated by spontaneous bleeding. Unfortunately, nearly half (46·5%) of the patients were not diagnosed in time, this was probably related to a low awareness of AHA and a lack of local coagulation laboratory facilities. CARE includes only a small number of asymptomatic patients identified with prolonged APTT. These patients are more likely to be missed, especially in those hospitals lacking haematologist and a coagulation laboratory. There was no significant relationship between diagnosis delay and severity of bleeding, but diagnostic delay produced a significant delay in the initiation of treatment.

In our study, APTT mixing tests were conducted in some patients and showed a relatively high positive rate for inhibitors. Therefore, it is a useful screening test for screening for circulation anticoagulants. A previous study reported IgA subclass antibody as a poor prognostic marker in AHA (Tiede *et al*, 2016). However, details regarding antibody type was not included in our study. Based on our data, CR bears no relationship to total serum IgA levels, other Ig fractions or lymphocyte subsets.

Our study showed that elderly AHA patients are prone to suffer severe bleeds and anaemia, indicating that we should be more alert to potential fatal bleeding in elderly patients and be more aggressive in haemostatic treatment after weighing the advantages and disadvantages. Our results showed that 55·4% of patients overall did not receive haemostatic treatment, and 49·1% of severe casesdid not receive haemostatic agents. In our study, FVIII:C and inhibitor titre were not related to the severity of bleeding.

Two currently available major haemostatic interventions are bypassing agents and FVIII replacement agents. The two frequently-used bypassing agents for bleeding patients with FVIII inhibitors, rFVIIa and aPCC (FEIBA®) have equivalent efficacy (Astermark *et al*, 2007; Young *et al*, 2008). Our results shows that the haemostatic efficacy of PCC is comparable to that of previous studies of aPCC use for AHA (Baudo *et al*, 2012; Borg *et al*, 2015). The most common PCC product used in China is KangShuNing (Hualan Biological Engineering, Inc., Xinxiang, China), which contains the proenzymes of the prothrombin complex factors, prothrombin, FVII, FIX and FX, supplemented with heparin sodium, glycine, arginine and L-lysine salt. Another commonly used PCC product is PuShuLaiShi (Shanghai RAAS Blood Products Co., Ltd., Shanghai, China), with similar ingredients to KangShuNing. Most factors are in the

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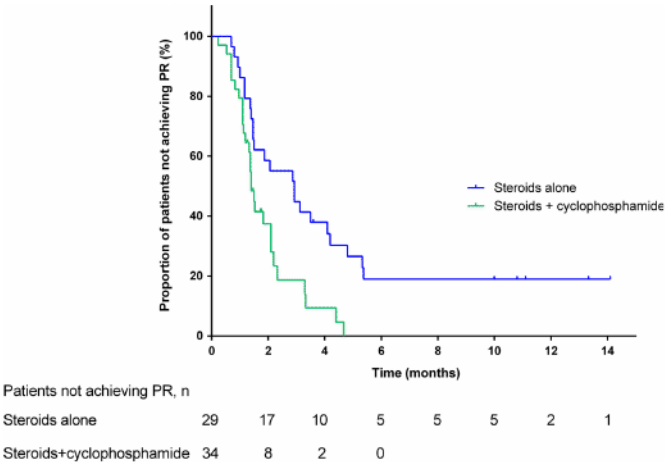

Fig 5. Time to partial remission of propensity score-matched groups. Time from starting immunosuppressive therapy to partial remission (PR) was longer for patients treated with steroids alone compared with those treated with steroids and cyclophosphamide (hazard ratio = 2·062; 95% confidence interval, 1·292–3·289, P = 0·002). Hazard ratios and P values are from univariate Cox regression analysis.

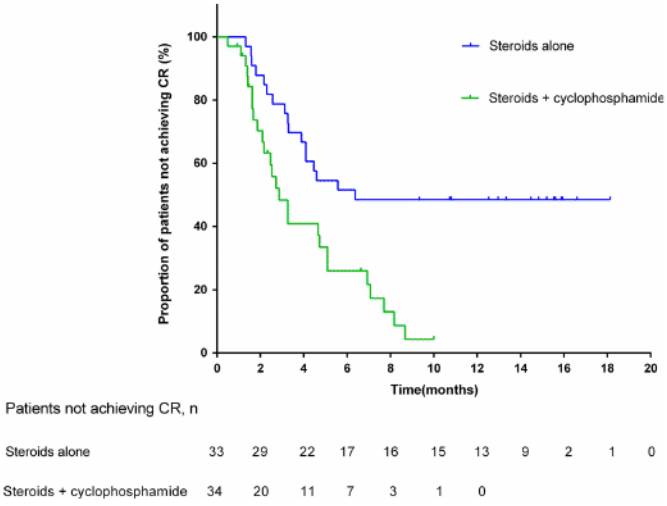

Fig 6. Time to complete remission of propensity score-matched groups. Time to complete remission (CR) was longer for the group treated with steroids alone than the group treated with steroids and cyclophosphamide (hazard ratio = 2·746; 95% confidence interval, 1·48–5·095, P < 0·001). Hazard ratios and P values are from univariate Cox regression analysis.

nonactivated form but an unknown amount factors, maybe including FVIIa, are unavoidably activated during production, which contributes to the haemostatic effect.

A sufficient dose of human FVIII replacement agents can overcome the inhibitor in congenital haemophilia patients with low titre inhibitors, whereas AHA patients are generally resistant to FVIII replacement agents. The dosage administered is mostly based on the experience in congenital haemophilia patients with alloantibody inhibitors and guidelines derived from cohort studies. The results of CARE confirm

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previous study results that bypassing agents are more efficacious than FVIII replacement agents (Tiede *et al*, 2015b). In the CARE study, rFVIIa was mostly used as second- or third-line salvage treatment in patients with poor response to PCC, principally because of its much higher cost in China. Bleeding episodes were controlled with rFVIIa at relatively low doses (Table III).

The most common regimens used for inhibitor eradication are either steroids alone or the combination of steroids with cyclophosphamide, and the use of rituximab is increasing. Nevertheless, the optimal regimen remains uncertain, particularly when considering side-effects and costs. Prospective and randomized research is the ideal means to compare the efficacy between immunosuppressive regimens. Until the trial data is available, our study, using PS matching, represents the most rigorous analysis and robust evidence to investigate the outcome of immunosuppressive therapy. This shows higher PR and CR rate for steroids with cyclophosphamide than steroids alone.

Initial analysis showed that regimens consisting of steroids and cyclophosphamide resulted in higher PR and stable CR rates than steroids alone. PS-matched analysis confirmed that a combination of steroids and cyclophosphamide resulted in more patients achieving PR and stable CR and took less time to the endpoints. Time to CR in each group was almost twice as long in our study, which may due to the relatively lower doses of immunosuppressive agents used. In contrast with previous studies, rituximab-based regimens resulted in CR in a shorter time than either steroids alone or steroids combined with cyclophosphamide. Our study shows that patients with autoimmune diseases, such as rheumatic arthritis, are resistant to steroids alone although they are likely to achieve CR with rituximab-based regimens.

Relapse of AHA is an important feature and patients should be continuously followed up (Borg *et al*, 2013). In our study, 9·4% of patients suffered relapse after discontinuation of immunosuppressive therapy. The proportion of relapsed patients might be even higher if the time of follow-up of stable CR group was prolonged.

Thrombotic adverse events associated with bypassing agents should not be ignored. During the period of treatment and follow-up, thrombotic events were observed in 3 patients who received PCC. Apparently, advanced age and high dose of PCC should be both risk factors of thrombosis. However, in our cohort, some patients with CAD who were older or who received more PCC did not experience thrombotic events. The choice of using PCC in these patients should be considered on case-by-case basis.

It is advocated that immunosuppressive treatment should be initiated soon after diagnosis to reduce the risk of fatal bleeding. However, the benefit should be weighed against potential complications of immunosuppression, such as sepsis, osteonecrosis of the femoral head and neutropenia. Advanced age is probably a risk factor for side effects, but available data are insufficient to identify definite predictive factors, so that further enrolment and study is required. As reported previously (Aouba *et al*, 2012), the most frequent cause of death was bleeding, followed by infectious events and thrombosis events. The total mortality was 6·7%, and age was the only factor associated with survival.

Some limitations exist in this study. According to the known incidence of AHA, the number of cases enrolled only accounts for approximately 3·5% of the estimated number of patients with AHA in the areas served by the participating centres. The main reasons are as follows: First, limited physician knowledge regarding AHA and lack of laboratory facilities may leave the disorder unrecognized in a substantial number of patients. Second, 27 centres represent a limited number for a nationwide registry. Third, subtle symptoms, early death and economical consideration meant that some patients did not present to the participating centres. The centres were, however, mostly specialist centres, so that referral bias exists, possibly leading to the inclusion of more severely affected younger patients. CARE is an observational study, and a lack of intervention randomization further results in selection bias.

In conclusion, our study reports the largest cohort of AHA in China and comprehensively describes the characteristics of AHA patients and evaluates the outcome of haemostatic and immunosuppressive treatment. Chinese AHA patients are younger than those previous reported in other geographic backgrounds. The issue of delayed diagnosis and treatment is serious. The data show the optimal choice to control bleeding is bypassing agents, although attention should be paid to the risk of arterial and venous thrombotic events. A combination of steroids and cyclophosphamide is more likely to result in stable CR in patients with AHA. Aging and malignancy were associated with poor overall survival. Further enrolment of patients and analysis are required to find more prognostic markers.

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competing financial interests and approve the final version to be published.

Conflict of Interest

The authors have no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Participating centers involved.

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