

Influence of factor VIII level and its inhibitor titer on the therapeutic response to corticosteroids alone in the management of acquired hemophilia

A retrospective single-center study

Mathieu Vautier^{a,*}, Hubert de Boysson^a, Christian Creveuil^b, Yohan Repesse^c, Annie Borel-Derlon^c, Xavier Troussard^c, Gandhi L. Damaj^d, Boris Bienvenu^a, Philippe Gautier^c, Achille Aouba^a

Abstract

The treatment of acquired hemophilia (AH) involves discussing whether corticosteroids should be administered alone or combined with immunosuppressant drugs, which increase the risk of infection especially in elderly patients and/or those with autoimmunity or neoplastic diseases, who represent the target population of the disease. Prognostic factors highlighting adequate responses to corticosteroids alone must be identified for satisfactory clinical response and lower infectious risk.

We aimed to evaluating the efficacy of corticosteroids alone in the management of AH depending on factor VIII (FVIII, \geq or $<$ 1 IU/dL) levels and/or inhibitor (INH, \leq or $>$ 20 Bethesda units per milliliter [BU/mL]) titer.

We conducted a retrospective single-center study including 24 patients treated for AH with corticosteroids alone.

Time to achieve partial remission (PR: absence of hemorrhage and FVIII levels $>$ 50 IU/dL) was significantly shorter in the FVIII \geq 1 IU/dL group than in the FVIII $<$ 1 IU/dL group (20 [10–55] vs 39 [20–207] days, $P=0.044$) and in the INH \leq 20 BU/mL and FVIII \geq 1 IU/dL group than in the FVIII $<$ 1 IU/dL and/or INH $>$ 20 BU/mL group (15 [11–35] vs 41 [20–207] days, $P=0.003$). In both subgroups, time to achieve complete remission (CR: negative INH and corticosteroids below 10mg/d) was also significantly shorter than that observed in the opposite subgroups. INH titer, considered alone, did not affect the length of time to onset of PR or CR. CR and PR rates did not differ significantly depending on these variables.

Our study suggests that in AH, patients with FVIII levels \geq 1 IU/dL considered alone or combined with INH titer \leq 20 BU/mL could be treated by corticosteroids alone, given that this subgroup of patients displayed faster therapeutic responses to this strategy.

Abbreviations: AH = acquired hemophilia, BU = Bethesda unit, CR = complete remission, FVIII = factor VIII, INH = inhibitor, MGUS = monoclonal gammopathy of unknown significance, PR = partial remission.

Keywords: acquired hemophilia, corticosteroids, FVIII antibody titer, FVIII level, prognosis factors

1. Introduction

Acquired hemophilia (AH) is a rare autoimmune disease (incidence of 1–1.5 cases/millions/y), linked to the production of an antibody directed against procoagulant factor VIII (FVIII).^[1] It results in severe bleeding phenotypes in patients with no personal or family history of hemorrhagic diseases. The majority of cases are reported in patients aged over 70 years. The

clinical features include widespread, superficial hematomas, occurring spontaneously or following a trauma as well as life-threatening visceral bleeding. The risk of bleedings persists as long as the inhibitor (INH) can be detected. An underlying cause is detected in approximately 50% of cases including neoplasia, autoimmune diseases, monoclonal gammopathy of unknown significance (MGUS) and iatrogenic disorders.^[2,3] Treatment for AH is directed at bleeding control with bypassing agents, INH eradication to prevent subsequent bleeding episodes, and treatment of any underlying causative disease. International recommendations published in 2009 suggest that all patients suffering from AH should be treated with corticosteroids either alone or in combination with an immunosuppressant drug, generally cyclophosphamide.^[4] The initial choice of treatment is difficult because of the lack of controlled, randomized prospective studies to demonstrate the superiority of corticosteroids combinations with immunosuppressant versus corticosteroids alone. The most robust analysis of first-line immunosuppression comes from the European Acquired Haemophilia (EACH2) registry of 331 patients. Patients treated with prednisone alone were compared to those treated with prednisone and oral cyclophosphamide. The study reported an odd ratio of 3.25 (95% confidence interval 1.51–6.96) of achieving a stable remission using combined therapy compared to prednisone, despite the prednisone-alone arm receiving a higher dose of steroids.^[5] Furthermore, patients involved in AH are often elderly, presenting with several debilitating comorbidities, or

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^a Department of Internal Medicine, ^b Department of Biostatistics and Clinical Research, ^c Haematology Laboratory and Haemophilia Reference Centre,

^d Department of Clinical Haematology, Centre Hospitalier Universitaire de Caen, Caen, France.

* Correspondence: Mathieu Vautier, Department of Internal Medicine, Caen University Hospital, University of Caen-Normandie, Avenue de la Côte de Nacre, 14000 Caen, France (e-mail: matvautier@gmail.com).

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exhibiting autoimmune or neoplastic diseases, with thereby an increased risk of infection because of the intense immunosuppressive impact. If concomitant use of by-passant agents and immunosuppressant drugs improve the overall prognosis of AH, the cause of death due to infections tends to be equal to or even greater than hemorrhagic causes.^[6] Cases of persistent complete remission (CR) of AH have been described with the use of corticosteroids alone, which remains the historical treatment with a supposedly lower risk of infection than that observed when combined with immunosuppressant drugs.^[3,5]

To date, there are no validated criteria to help decide whether or not to combine immunosuppressive therapy with corticosteroids in the treatment of AH. It was recently suggested that in patients treated with corticosteroids alone, the subgroup with FVIII ≥ 1 IU/dL and an INH titer ≤ 20 Bethesda units per milliliter (BU/mL) was the most likely to obtain partial remission (PR) at 21 days, which is defined by increase in FVIII levels exceeding 50 IU/dL and disappearance of the clinical signs of hemorrhage.^[7]

Within the scope of a personalized therapeutic strategy, prognostic factors highlighting an adequate response to corticosteroids alone must be identified in order to ensure satisfactory clinical efficacy coupled with a lower risk of infection. Therefore, the aim of this study is to evaluate the efficacy of corticosteroids alone in the management of AH as a function of initial FVIII levels (< 1 IU/dL or ≥ 1 IU/dL) and/or INH titers (INH, ≤ 20 BU/mL or > 20 BU/mL) in the single-center patient cohort followed at CAEN University Hospital.

2. Patients and methods

2.1. Study design

We conducted a retrospective, single-center study involving a cohort of patients with AH followed at CAEN University Hospital.

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. In accordance with the Public Health French Law (art L 1121-1-1, art L 1121-1-2), formal approval from an ethics committee is not required for this type of study. The manuscript was prepared in accordance with STROBE guidelines.

2.2. Inclusion and exclusion criteria, study population

AH was diagnosed on the basis of FVIII levels < 50 IU/dL and the presence of an INH of FVIII titer > 0.6 BU/mL, the laboratory detection limit. The FVIII level was assessed using 1-stage clotting assays. INH titer was determined using a modified Nijmegen Bethesda assay. Inclusion criteria involved treatment with corticosteroids alone as first-line therapy and the availability of data relating to FVIII levels and INH titers on diagnosis and during follow-up. Patients who had received immunosuppressive therapy combined with corticosteroids on diagnosis, either for AH or for an underlying disorder, were excluded. Conversely, patients who received immunosuppressive treatment as second-line therapy, either because of the lack of improvement under corticosteroids or poor tolerance to the latter, were enrolled and corticosteroids alone was deemed to have failed. Prednisone was introduced uniformly at the daily dose level of 1 mg/kg via oral or intravenous route until FVIII levels reverted to normal and/or the INH disappeared; then, corticosteroid therapy was gradually reduced with verification of INH titers at each increment and discontinuation at variable times, at the prescriber's discretion.

Between January 1988 and January 2016, 34 patients were followed up at the CHU de Caen for AH. Ten patients were excluded from the study: 2 had previously received cyclophosphamide, 1 had not taken corticosteroids, and the remaining 7 had incomplete data.

2.3. Variables studied

Data concerning patient's age at diagnosis and gender, initial FVIII levels, INH titers and changes in those over time, symptoms of hemorrhage, idiopathic or secondary nature of AH, whether or not a hemostatic treatment should be administered, the treatment of any underlying condition and the time taken to reduce the daily dosage to less than 10 mg prednisone were collected. Adapted from the study from Collins et al (EACH2 study), we defined severe bleedings as a hemoglobin level below 8 g/dL or a decrease of more than 2 g/dL, or life- or limb-threatening, central nervous system, deep muscle or retroperitoneal bleeding.

As previously described, the patient population was divided into several subgroups depending on FVIII level (≥ 1 IU/dL vs < 1 IU/dL), INH titer (> 20 BU/mL vs ≤ 20 BU/mL), and, finally, according to a composite criterion (FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL vs FVIII < 1 IU/dL and/or INH > 20 BU/mL).

2.4. Endpoints

The primary endpoint was the time to achieve PR, defined by the length of time taken to obtain a FVIII level > 50 IU/dL without hemostatic treatment for at least 24 hours and no active bleeding from the start of the corticosteroid therapy. This definition corresponds to that mentioned in the study by Tiede et al.^[7]

Secondary endpoints were PR rates; CR rates, defined by INH elimination and a reduction in the corticosteroids dose strictly below 10 mg/d; the length of time taken to obtain CR, number of relapses (defined by recurrence of the anti-FVIII antibody after CR); and mortality data.

2.5. Statistical analysis

Qualitative data are expressed in figures (percentage) and quantitative data as a median value (range). Qualitative data were analyzed according to the χ^2 test or Fisher exact test. Quantitative data were evaluated via the Mann-Whitney test. CR, PR, and recurrence as a function of VIII level and INH titer and according to the composite criterion were compared using Fisher exact test. The length of time taken to eliminate the INH and achieve PR was compared using the Mann-Whitney test. Survival curves were plotted using the Kaplan-Meier method. The significance threshold was 5%. The statistical analyses were carried out with GraphPad Prism (5.0c); GraphPad Software Inc., San Diego, CA.

3. Results

3.1. General characteristics of the overall and the study populations

3.1.1. Patients excluded from the study. Amongst the 10 patients excluded for whom data were available, the gender ratio was 1 and the median age on diagnosis was 74 (47–97) years. Amongst these 10 patients, the cause of AH was known for 8: 37% of AH cases were idiopathic, 2/8 (25%) were of neoplastic origin, 2/8 (25%) of supposed iatrogenic origin, and 1/8 (13%) was related to an autoimmune disease. Median FVIII levels and INH titers were 4 (< 1 –14) IU/dL and 7.95 (0.75–80) BU/mL, respectively.

Table 1**Partial remission with corticosteroids alone and demographic data according to FVIII levels and inhibitor titers.**

	FVIII		P	INH		P
	FVIII < 1% (n=11)	FVIII ≥ 1% (n=13)		INH ≤ 20 BU (n=12)	INH > 20 BU (n=12)	
PR	7 (63)	11 (84)	0.36	11 (91)	7 (58)	0.15
Time to achieve PR	39 (20–207)	20 (10–55)	0.04	20 (11–207)	39 (20–86)	0.12
Age	80 (56–88)	80 (41–90)	0.64	80.5 (63–90)	78.5 (41–88)	0.95
Sex (male/female)	7/4	10/3	0.65	8/4	9/3	>0.99
Idiopathic AH	6 (55)	8 (62)	>0.99	6 (50)	8 (67)	0.68
Neoplasia	3 (27)	3 (23)	>0.99	4 (33)	2 (17)	0.64
MGUS	1 (9)	2 (15)	>0.99	2 (17)	1 (8)	>0.99
Iatrogenic	1 (9)	0 (0)	0.45	0 (0)	1 (8)	>0.99
Bypassing agent	10 (90)	10 (77)	0.59	11 (91)	9 (75)	0.59

Data expressed in numbers (percentages), median value (range). AH = acquired hemophilia, BU = Bethesda unit, FVIII = factor VIII, INH = inhibitor, MGUS = monoclonal gammopathy of unknown significance, PR = partial remission.

3.1.2. Patients included in the study. Twenty-four patients were finally enrolled in this study: based on FVIII levels, 13 in the FVIII ≥ 1 IU/dL group and 11 in the FVIII < 1 IU/dL group; based on INH titers, 12 in the INH > 20 BU/mL group and 12 others in the INH ≤ 20 BU/mL group; according to the composite criterion combining both biological parameters, 15 in the FVIII < 1 IU/dL and/or INH > 20 BU group and 9 in the FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL group. The median age on diagnosis in the study population was 78.5 years, ranging from 41 to 90 for the 24 patients included. The M/F gender ratio was 2.43.

AH was idiopathic in 58% of cases (14/24), secondary to neoplasia in 25% of cases (6/24); 1 patient presented with AH supposedly of iatrogenic origin (pyostacine) and 3 others presented with AH secondary to MGUS (1 immunoglobulin G kappa, 1 IgM kappa, and 1 IgM lambda). No patient received immunosuppressant or cytotoxic drugs for an underlying disease during the 6 months preceding the diagnosis of AH and during corticosteroid therapy.

The median FVIII value was 1 (<1–14) IU/dL and the median INH titer was 25 (1.8–114) BU/mL, in the overall study population.

3.1.3. Clinical signs of hemorrhage on diagnosis. The main clinical features were ecchymosis (75%); muscular hematoma (29%); gastrointestinal (21%); urologic (21%); and ear, nose, and laryngeal bleeding (21%). Fourteen patients (58%) presented life-threatening bleeding at diagnosis with 6 cases of hemorrhagic shock (secondary to 1 hemopericarditis, 1 postoperative bleeding, 1 renal hematoma, 2 deep muscle bleeding, and 1 epistaxis), 1 subdural hematoma, and 7 patients with hemoglobin below 8 g/dL. All patients with severe bleeding, except 1 who had gastrointestinal bleeding with hemoglobin below 8 g/d, were transfused. Ten (42%) patients presented with minor bleeding on diagnosis, essentially ecchymosis, muscular bleeding, and hematuria, without criterion of gravity. Three of them were transfused. FVIII level and INH titer did not differ significantly between the 2 groups of patients according to severe bleeding event.

3.2. Influence of FVIII level (<1 vs ≥1 IU/dL) or INH titer (≤20 vs >20 BU/mL) on partial remission

Data concerning PR rate, length of time to achieve PR, and demographic data according to FVIII levels and INH titers are shown in Table 1.

The length of time to achieve PR was significantly shorter in the FVIII ≥ 1 IU/dL group (20 [10–55] vs 39 [20–207] days,

$P=0.044$). Conversely, no significant difference was observed in terms of PR rates according to FVIII level or INH titer.

By combining both factors, the group of patients presenting with INH ≤ 20 BU/mL and FVIII ≥ 1 IU/dL achieved PR over a significantly shorter period of time than the group with FVIII < 1 IU/dL and/or INH > 20 BU/mL (15 [11–35] vs 41 [20–207] days, $P=0.003$, respectively), as shown in Table 2. A higher, but not statistically significant, rate of PR was recorded in the INH ≤ 20 BU/mL and FVIII ≥ 1 IU/dL group than in the FVIII < 1 IU/dL and/or INH > 20 BU/mL group (8/9 patients [89%] vs 10/15 patients [67%], $P=0.350$, respectively).

Throughout the cohort, 18 (75%) patients achieved PR within 27 (10–207) days. Patients who did not achieve PR did not present with demographic, clinical, or therapeutic characteristics that differed significantly from those recorded in patients who achieved PR.

PR-free survival curves as a function of FVIII, INH, and the composite criterion show that PR times were always significantly shorter in the groups of patients with FVIII level ≥ 1 IU/dL, INH titer ≤ 20 BU/mL, or combined levels of FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL, compared to values recorded in the respective opposite patient groups with FVIII < 1 IU/dL, INH > 20 BU/mL or FVIII < 1 IU/dL and/or INH > 20 BU/mL (Fig. 1).

3.3. Long-term outcomes and latest data

The median follow-up period for the entire cohort was 419.5 days (16–3752). During follow-up, 15 patients reached CR with corticosteroids alone. CR data, the length of time to reach it, relapses as a function of FVIII level, INH titers and the composite criterion (FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL vs FVIII < 1 IU/dL and/or INH > 20 BU/mL) are presented in detail in Table 3. The length of time taken to reach CR was significantly shorter in the FVIII ≥ 1 IU/dL group compared to the FVIII < 1 IU/dL group (86 [39–138] vs 132 [102–512] days, $P=0.032$). This difference remained significant using the composite criterion where the FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL group also reached CR within a shorter period of time compared to the opposite group (83 [52–123] vs 129.5 [64–512] days, $P=0.028$). CR-free survival, as a function of FVIII, INH, and composite criterion are shown in Fig. 2. As for the PR criterion, CR-free survival was significantly shorter in the groups of patients with FVIII ≥ 1 IU/dL, or even levels of FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL (composite criterion) versus that recorded in the opposite group of patients with FVIII < 1 IU/dL, and combined levels of FVIII < 1 IU/dL and/or INH > 20 BU/mL, respectively. As regard

Table 2

Partial remission with corticosteroids alone and demographic data considering both the factor VIII and inhibitor levels (composite criterion).

	FVIII ≥ 1 IU/dL and INH ≤ 20 BU (n=9)	FVIII < 1 IU/dL and/or INH > 20 BU (n=15)	P
PR	8 (89)	10 (67)	0.35
Time to achieve PR	15 (11–35)	41 (20–207)	0.003
Age	81 (63–90)	80 (41–90)	0.83
Sex (male/female)	6/3	11/4	>0.99
Idiopathic AH	5 (55)	9 (60)	>0.99
Neoplasia	3 (34)	3 (20)	0.63
MGUS	1 (11)	2 (13)	>0.99
Iatrogenic	0	1 (7)	>0.99
Bypassing agent	8 (89)	12 (80)	>0.99

Data expressed in numbers (percentages), median value (range). AH = acquired hemophilia, BU = Bethesda unit, FVIII = factor VIII, INH = inhibitor, MGUS = monoclonal gammopathy of unknown significance, PR = partial remission.

to INH titers taken in isolation, the difference in CR-free survival was not statistically significant between the INH > 20 BU/mL versus INH ≤ 20 BU/mL groups.

Among patients who reached CR, 3 patients relapsed during follow-up, without statistical difference according to FVIII level and/or INH titers.

Out of the 24 patients enrolled, 9 died during follow-up. The causes of death are summarized in Fig. 3. Five patients died prematurely during treatment with corticosteroids alone, before

reaching CR. Of these, 3 died before reaching PR: the first patient died from sepsis due to a Gram-negative bacillus on day 16 of the start of corticosteroids, the second from uncontrolled gastrointestinal hemorrhaging, and the third from multiple organ failure with pulmonary sepsis in postoperative intensive care following surgical correction of hemorrhage. The other 2 patients died from unknown causes after having achieved PR but not CR, 23 and 187 days after starting corticosteroids, respectively. One patient achieved CR with corticosteroids alone and died 304 days later from cardiogenic shock secondary to massive myocardial infection.

Three patients (all 3 with FVIII < 1 IU/dL and INH > 20 BU/mL) required the addition of an immunosuppressant given the inefficacy of or intolerance to corticosteroids alone; all died—the first patient died from terminal heart failure 162 days after starting corticosteroids combined with rituximab, the second patient died from small cell bronchial carcinoma 516 days after the diagnosis of AH treated with corticosteroids combined with cyclophosphamide as second-line therapy, and the third patient died from inhalation pneumopathy 10 years after being cured of the AH with corticosteroids and cyclophosphamide, which had been discontinued.

4. Discussion

This study shows that the detection of a residual level of FVIII ≥ 1 IU/dL considered in isolation and, in addition, its combination with lower titers of INH (≤ 20 BU/mL) according to a composite criterion (FVIII ≥ 1 IU/dL and INH ≤ 20 BU/mL) are factors indicating an improved response to corticosteroids alone in the management of AH. The length of time taken to achieve a PR or a CR in these settings was significantly shorter compared to the periods observed with undetectable levels of FVIII (FVIII < 1 IU/dL) considered alone or combined with elevated titers of INH (INH > 20 BU/mL). This difference is also observed as a significantly shorter remission-free survival period in patients with FVIII ≥ 1 IU/dL and according to the composite criterion. The rates of PR or CR did not differ significantly, regardless of the criteria considered. Conversely, INH titers, studied in isolation, did not appear to be a crucial factor for an improved response to corticosteroids alone, whether considered in terms of PR or CR. Using the identical and close criteria for PR and CR definitions (lower tapered dose of corticosteroids chosen in our study), which were considered in the large prospective study conducted by Tiede et al,¹⁷ respectively, this study confirms that the use of a composite criterion combining FVIII ≥ 1 IU/dL and INH

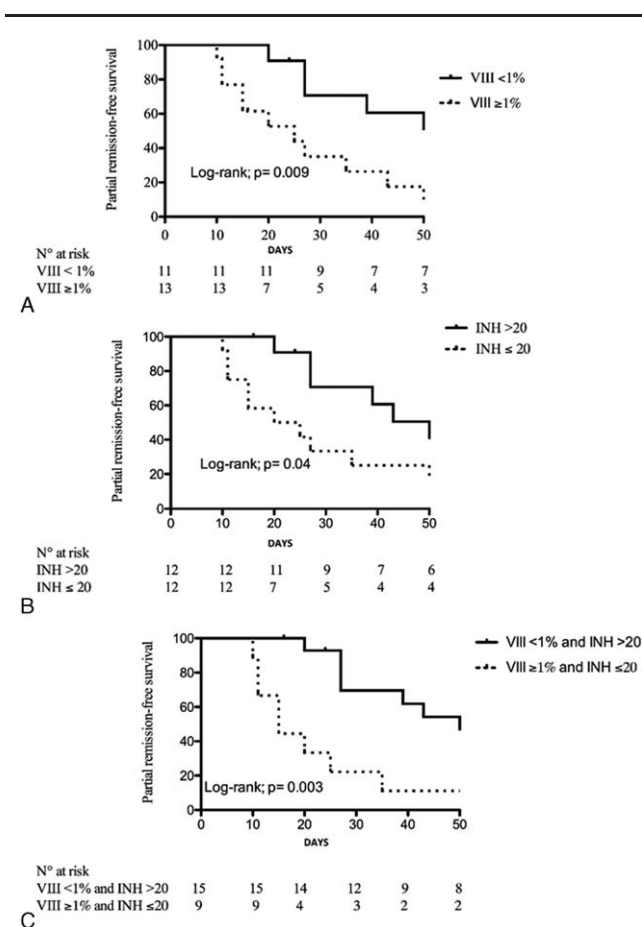


Figure 1. Partial remission-free survival as a function of factor VIII level (A), inhibitor titer (B), and the composite criterion (C). BU = Bethesda unit, FVIII = factor VIII, INH = inhibitor.

Table 3
Complete remission under corticosteroids alone and relapse as a function of FVIII, inhibitor, and composite criterion levels.

	FVIII < 1 IU/dL (n=11)	FVIII ≥ 1 IU/dL (n=13)	P	INH ≤ 20BU (n=12)	INH > 20BU (n=12)	P	FVIII ≥ 1 IU/dL and INH ≤ 20BU (n=9)	FVIII < 1 IU/dL and/or INH > 20BU (n=15)	P
CR	5 (45)	10 (77)	0.20	10 (83)	5 (41)	0.08	7 (78)	8 (53)	0.38
Time to achieve CR	132 (102–512)	86 (39–138)	0.03	122 (52–512)	123 (64–138)	0.73	83 (52–123)	129.5 (64–512)	0.02
Relapse	1 (20)	2 (20)	>0.99	2 (20)	1 (20)	>0.99	1 (14)	2 (25)	>0.99

Data expressed in figures (percentages), median value (range). AH = acquired hemophilia, BU = Bethesda unit, CR = complete remission, FVIII = factor VIII, INH = inhibitor.

≤20BU/mL can highlight a subgroup of patients with a good response profile to corticosteroids alone.

The demographic data of our cohort population are consistent with those observed in previous AH studies.^[2,3] The rate of PR under corticosteroids alone and the time to achieve it in our study are comparable to those published in the study by Tiede et al,^[7] irrespective of the treatments administered (corticosteroids alone or combined with various immunosuppressant drugs), 75% in 27 (10–207) days or 83% in 31 (7–362) days, respectively.

The CR rate in our overall population is comparable to the CR rate published in the EACH2 study for patients under corticosteroids alone (62.5% and 58%, respectively).^[5] However, in this latter study, 80% of patients achieved CR with a combination of corticosteroids and immunosuppressant. Such a

high rate of CR was observed in our cohort in the subgroup of patients with FVIII ≥ 1 IU/dL or INH ≤ 20 BU/mL or the composite criterion. In a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organization, CR rates under corticosteroids and cyclophosphamide reached 78% in a median time of 39 (34–57) days.^[8] In a meta-analysis focused on therapy and prognostic factors published in 2003 by Delgado et al,^[9] the CR rate observed with corticosteroids and cyclophosphamide was 83%. Conversely, in our subgroups of patients with FVIII < 1 IU/dL, INH > 20 BU and the composite criterion, we observed a lower CR rate (45%, 41%, and 53%, respectively) than those reported in the published studies (80% for patients with corticosteroids and cyclophosphamide and 58% for patients treated with corticosteroids alone in EACH2 study), which may argue for the use of combination of corticosteroids and immunosuppressant in those groups of patients.^[5] This could be explained by the fact that patients were treated and analyzed, regardless of their FVIII levels and INH titers.^[5] The rate of relapse in our study appeared to be lower than those reported in EACH2 with corticosteroids alone and in Tiede et al studies (12.5% vs 18% and 24%, respectively).^[5,7]

International expert societies recommend starting treatment to eliminate the INH as soon as the diagnosis of AH is confirmed.^[4,10] Therapeutic strategy should be based on corticosteroids alone, or initially combined with cyclophosphamide or another immunosuppressive agent. However, AH is a highly heterogeneous disorder in terms of etiology and gradual prognosis. Although the combination of corticosteroids with immunosuppressive therapy recently displayed better remission rates than those observed with corticosteroids alone (EACH2), overall survival should also be assessed, given the risk of frequent life-threatening infections.^[5] In fact, whereas AH-related deaths due to hemorrhage is continuously decreasing since the availability of effective bypassing agents, those associated with infections are increasing.^[6,11] Given that the risk of hemorrhage persists as long as the INH persists, the latter should thereby be eliminated as quickly as possible. Therefore, it seems to be essential to pinpoint the factors predicting a response to corticosteroids alone in order to identify patients not requiring a potentially harmful increase in immunosuppressive treatments that expose to more severe and frequent infectious processes.

The differences in terms of CR and PR rates as a function of FVIII, INH, or the composite criterion observed in our study were not significant but this may be linked to a lack of power in relation to its low cohort. Our study is also subject to several types of bias because of its retrospective nature. However, few clinical and biological data were missing in this study, among the patients included. As regard to corticosteroids, the total individual doses of prednisone actually administered could not be specified. However, the single-center nature of the study limits this bias since the practitioners treating AH at the Caen

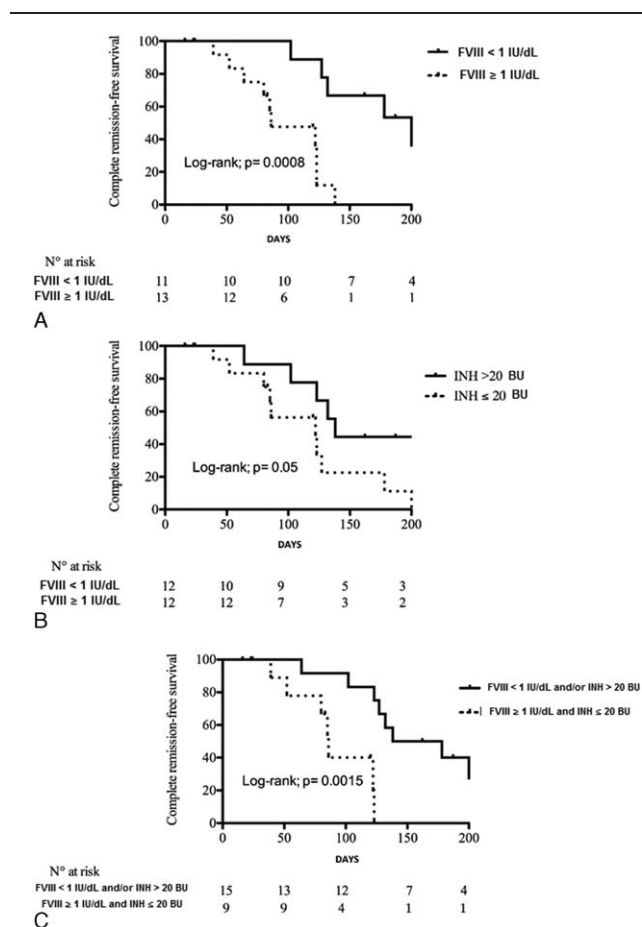


Figure 2. Complete remission-free survival as a function of factor VIII level (A), inhibitor titer (B), and the composite criterion (C). BU = Bethesda unit, FVIII = Factor VIII, INH = inhibitor.

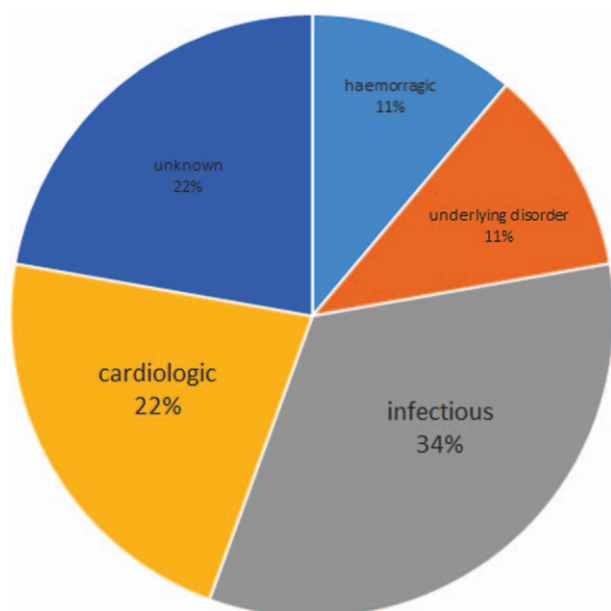


Figure 3. Distribution of the causes of death.

University Hospital share uniform practices in terms of globally comparable decreasing regimens. Furthermore, the exclusion of patients who previously took an immunosuppressant combined with corticosteroids could have triggered a selection bias for patients with a less clinically severe condition. However, analysis of the data recorded for excluded patients showed a higher median FVIII than that observed in the study group. On the other hand, the inclusion of all FVIII levels and INH titers, the absence of any strict correlation between the laboratory parameters and the severity of the clinical signs, which varies considerably throughout the disease, are all arguments that refute the impact of this potential bias in this study.

In confirming part of the prospective data recorded by Tiede et al,^[7] our study highlights and strengthens the paradigm

supporting that the choice of the initial treatment in AH may be guided to some extent by FVIII levels. Indeed, patients showing $FVIII \geq 1$ IU/dL, and especially combined with INH titers ≤ 20 BU/mL, may be treated by corticosteroids alone, since this subgroup showed the shortest delay to achieve remission. Conversely, patients with $FVIII < 1$ IU/dL and/or $INH > 20$ BU may be given a combination of corticosteroids and immunosuppressant. These findings should be confirmed in a larger controlled prospective study.

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