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Cyclophosphamide vs rituximab for eradicating inhibitors in acquired hemophilia A: A randomized trial in 108 patients

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ABSTRACT

Background: Acquired hemophilia A (AHA) is a rare autoimmune disorder due to autoantibodies against Factor VIII, with a high mortality risk. Treatments aim to control bleeding and eradicate antibodies by immunosuppression. International recommendations rely on registers and international expert panels.

Methods: CREHA, an open-label randomized trial, compared the efficacy and safety of cyclophosphamide and rituximab in association with steroids in patients with newly diagnosed AHA. Participants were treated with 1 mg/kg prednisone daily and randomly assigned to receive either 1.5–2 mg/kg/day cyclophosphamide orally for 6 weeks, or 375 mg/m² rituximab once weekly for 4 weeks. The primary endpoint was complete remission over 18 months. Secondary endpoints included time to achieve complete remission, relapse occurrence, mortality, infections and bleeding, and severe adverse events.

Results: Recruitment was interrupted because of new treatment recommendations after 108 patients included (58 cyclophosphamide, 50 rituximab). After 18 months, 39 cyclophosphamide patients (67.2 %) and 31 rituximab patients (62.0 %) were in complete remission (OR 1.26; 95 % CI, 0.57 to 2.78). In the poor prognosis group (FVIII < 1 IU/dL, inhibitor titer > 20 BU mL⁻¹), significantly more remissions were observed with cyclophosphamide (22 patients, 78.6 %) than with rituximab (12 patients, 48.0 %; $p = 0.02$). Relapse rates, deaths, severe

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infections, and bleeding were similar in the 2 groups. In patients with severe infection, cumulative doses of steroids were significantly higher than in patients without infection ($p = 0.03$).

Conclusion: Cyclophosphamide and rituximab showed similar efficacy and safety. As first line, cyclophosphamide seems preferable, especially in poor prognosis patients, as administered orally and less expensive.

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ClinicalTrials.gov number: NCT01808911.

1. Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder secondary to the development of inhibitory autoantibodies against the circulating factor VIII (FVIII:C) in patients without a family or personal history of bleeding [1]. However, it is possible that patients with other bleeding disorders or antithrombotic drugs develop acquired hemophilia. AHA incidence is approximately 1.5 cases/million/year. Large registers and meta-analyses have described demographics, clinical data, underlying disorders, bleeding characteristics, treatment and outcome of AHA patients [2–9]. AHA occurs mainly in elderly patients with comorbidities and is associated with high mortality from underlying comorbidities, bleeding, or treatment complications.

The risk of bleeding persists as long as FVIII is low [10]. Once the diagnosis is achieved, immediate eradication of antibodies is recommended since the level of inhibitor is associated with poor outcomes. These recommendations are based on retrospective data, registries and international expert panels [11–14]. Although in some cases inhibitors can spontaneously disappear, immunosuppressive therapy is recommended for all adults with AHA. While steroids alone may be considered in patients with low inhibitor titer [8,14], it is generally recommended to associate steroids with a cytotoxic agent to shorten the time to remission. In association to steroids, cyclophosphamide is the most widely used, but rituximab has been proposed also as second line [13,15–18]. In France, rituximab is largely used, despite lack of evidence [17–20]. Additionally, data on tardive relapse are scarce and immunosuppression in the elderly is associated with frequent early but also delayed adverse events including infections as a leading cause of death especially in patients treated with rituximab.

This French multicenter randomized study was set up to evaluate steroids associated to cyclophosphamide or rituximab in achieving long-term complete remission, and to compare the rates of severe adverse events and relapses of AHA.

2. Methods

2.1. Study design

The Cyclophosphamide versus Rituximab Et Hémophilie Acquis (CREHA) study was an academic multicenter, randomized, open-label, controlled trial conducted at 29 French Internal Medicine or Hematology centers dealing with AHA management. The study was designed by the coordinating center investigators (Rouen University Hospital), in collaboration with the French National Society of Internal Medicine, the French Hemostasis and Thrombosis Study Group and the French Society of Hematology. The study was awarded a national grant that allowed the funding of trial treatments; it was referenced in [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT01808911. The study protocol was approved by the Ethics committee CPP Nord-Ouest 1 and the National Data Protection Committee in accordance with national legislation. All patients gave their written informed consent. The database was held by the coordinating center; data were analyzed by the CREHA steering committee, which consisted of the two principal investigators (HL, YB) and the coordinating center. An independent Data Monitoring Committee Board (DMCB), composed of one methodologist and 3 physicians not involved in this study, oversaw the safety monitoring of the trial and the primary endpoint achievement. The study was conducted according to the principles of the

Declaration of Helsinki.

2.2. Patients, and procedures

We recruited adult patients (≥ 18 years) with newly diagnosed acquired hemophilia (AHA), defined by FVIII < 30 IU/dL and presence of a neutralizing FVIII inhibitor > 0.6 Bethesda units (BU)/mL. All patients gave their written informed consent. Patients with relapsing disease or women with postpartum AHA were not eligible for enrolment. Other exclusion criteria were: pregnant or breastfeeding woman, acquired hemophilia associated with postpartum, or occurring in the postpartum period < 180 days after delivery, history of drug addiction, alcoholic intoxication, mental illness, pre-menopausal woman without effective contraception for the entire duration of the study, patient not affiliated with the French National Health Insurance System, congenital hemophilia with inhibitors, confirmed history of AHA exceeding one month, serum hepatic transaminase levels > 2.5 times the upper normal limit, severe acute infection requiring antibiotic therapy for < 7 days, active tuberculosis, HIV positive serology, known history of recurrent opportunistic germ infections such as herpes virus infection, severe renal failure (Cockcroft creatinine clearance < 30 ml/min), white blood cell count < 4 G/L or neutrophilic polynuclear cell less than 1.0 G/L, platelet count < 50 G/L, severe heart failure (NYHA class III–IV), acute or chronic liver disease severe enough to preclude the ability to participate in the trial, patient suffering from a chronic affection, metabolic or not, or for whom clinical or paraclinical data are compatible with a condition which could be a contraindication to one or the other of the molecules tested in the project, life expectancy < 6 months, neoplastic disorders requiring specific chemotherapy, contraindication to the use of one of the immunosuppressive drugs, known hypersensitivity to the active substance or to any of the excipients or to murine proteins, treatment with rituximab in the year preceding inclusion, patients having received corticosteroid treatment at a dosage > 20 mg for more than a month, another immunosuppressive or cytotoxic treatment (azathioprine for example) or biotherapy (such as anti-TNF), corticosteroid therapy at a dosage of > 0.7 mg/kg for > 10 days preceding inclusion.

2.3. Randomization and procedures

Random allocation sequence, stratified by center, was computer-generated and centralized by the coordinating center, allowing for treatment allocation concealment. Patients were randomly assigned in a 1:1 ratio to receive cyclophosphamide plus prednisone or rituximab plus prednisone. All patients received prednisone (1 mg/kg/day) for at least 6 weeks or until remission, with gradual tapering for 6 weeks. Cyclophosphamide, 1.5–2 mg/kg/day, adjusted for renal function, was administered orally for 6 weeks, possibly extended to 12 weeks in case of antibody persistence. Rituximab (MabThera, Roche laboratory) 375 mg/m² of body surface, was administered intravenously once weekly for 4 weeks; before infusion, patients were premedicated with intravenous methylprednisolone (100 mg), acetaminophen (1000 mg) and dexchlorpheniramine (5 mg). After the 6- or 12-week immunosuppressive period, patient management, including any treatment administered for antibody persistence or potential relapse, was at the treating physician's discretion.

Study visits occurred at baseline, at weeks 1, 2, 3, 4, 6 and 9 and at months 3, 6, 12 and 18. At each visit, data on bleeding manifestations,

adverse events and infections were recorded. Bleeding episodes treated with hemostatic agents such as recombinant factor VIIa or factor activated prothrombin complex concentrate were considered severe.

Until complete remission was achieved, collected follow-up data included treatment information: start and stop dates, immunosuppressive drugs, possible hemostatic drugs, and transfusion. Severe adverse events (bleeding, infections requiring intravenous antibiotics, or leading to hospitalization or death, malignancy, and death) were recorded. Local laboratory baseline FVIII activity and inhibitor levels were assessed using the one stage clotting time and classic Bethesda method respectively. Individual patient data entered in standardized case report forms were controlled by a research technician and the local study coordinator.

2.4. Study objectives — outcomes

The primary efficacy endpoint was complete remission at month 18, defined by an inhibitor titer <0.6 BU/mL, associated with a normal FVIII level > 50 IU/dL, without bleeding symptoms.

Secondary efficacy endpoints included complete remission at month 18 in the subgroup of patients with initial inhibitor titer >20 BU/mL and FVIII < 1 %, complete remission at 3, 6 and 12 months, time to achieve complete remission, and number of relapses at 6, 12 and 18 months. Relapse was defined by reoccurrence of an inhibitor titer >0.6 BU/mL, associated with a FVIII level < 50 IU/dL, with or without bleeding symptoms.

Safety endpoints included mortality, bleeding, and iatrogenic events, especially infections, and number and severity of adverse events. Severe bleeding, infusion-related chronic or opportunistic infections, severe infections and death were considered serious adverse events and graded from 1 to 4, according to the World Health Organization toxicity criteria, with grades 3 and 4 being severe adverse events. Severe infections were defined as those resulting in hospitalization or intravenous antibiotic treatment or death. A composite endpoint combined severe infections and/or death linked to treatment and infections, excluding competing risks, i.e., death due to bleeding, comorbidities or of unknown reason.

2.5. Sample size determination

Sample size was based on findings from the EACH2 registry [6] that reported complete remission among 80 % and 61 % of patients respectively treated with combined corticosteroids and cyclophosphamide and rituximab-based regimens. To obtain 80 % power for a 20 % difference between the two groups (60 vs. 80 %) for Pearson's chi-square test with 0.05 two-sided Type I error, the target sample size was 164 patients, 82 patients per group. A four-year recruitment period was anticipated from mid-2012 but, despite the large number of participating centers, recruitment was slower than expected. In its 2018 meeting, the DMCB noted a high frequency of severe infections overall. In view of changes in international guidelines recommending the use of steroids alone in patients with FVIII > 1 IU/dL and inhibitor titer <20 BU/mL, the DMCB recommended ending recruitment to avoid potential overtreatment and the consequential increased risk of severe infections in those patients. The steering committee implemented this recommendation, and the last patient was included in May 2019, with 108 patients included overall. This sample size yielded 80 % statistical power to detect a 24.6 % difference between the two treatment groups (57.7 vs. 82.3 %).

2.6. Statistical analysis

2.6.1. Efficacy endpoints

The proportion of patients achieving complete remission at month 18 was compared between the two treatment groups using Pearson's chi-squared test, on the Intent-To-Treat (ITT) population. Patients who withdrew from the study were considered as not having reached complete remission. The same method was used to analyze the subgroup of

patients with high inhibitor titer. Time to achieve remission was analyzed using Gray's test, to take into account competing risks of death.

2.6.2. Safety endpoints

Dichotomous endpoints were analyzed by Pearson's chi-square test or Fisher's exact test; odds ratios (ORs) and corresponding 95 % confidence interval (95 % CI) were estimated from unadjusted logistic regression. The number of events per patient was compared between groups using exact Poisson regression. The composite endpoint first infection and/or death linked to treatment was analyzed using Gray's test, allowing for competing risk of death due to other causes (i.e., bleeding, comorbidities or unknown reason).

A joint frailty model for recurrent events was used to compare the rate of recurrent infectious complications and/or death related to treatment between groups considering non-treatment related deaths as competing risks.

All statistical tests used two-sided 0.05 level as significance threshold. Quantitative variables were described by mean (standard deviation) or median (interquartile interval). All analyses were performed with SAS® software (version 9.4, SAS Institute, Cary, NC).

2.7. Data sharing statement

Deidentified individual participant data that underlie the reported results, and the study protocol will be made available 3 months after publication for a period of 5 years after the publication date by contacting Herve.Levesque@chu-rouen.fr or the Clinical Research and Innovation Directorate (DRCI) of CHU de Rouen (E-mail: Delegation.Research@chu-rouen.fr).

2.8. Role of funding source

The study was awarded a national grant from the French Ministry of Health that allowed the funding of trial treatments, clinical research assistant, insurance contract, drafts and editorial assistance during preparation of the manuscript.

3. Results

3.1. Patients' characteristics

From June 2012 to May 2019, 110 patients were enrolled. Two patients declined participation, and 108 patients were randomized to receive study treatment: cyclophosphamide prednisone for 58 patients and rituximab plus prednisone for 50 patients (Fig. 1). All patients except three completed their treatment according to the protocol: two patients received only 2 infusions of rituximab and 1 patient did not receive cyclophosphamide. Patients' characteristics at baseline are shown in Table 1. Demographics, disease characteristics, underlying disorders, FVIII activity, inhibitor titer and hemoglobin level were similarly distributed between groups. Fifty-three patients had FVIII <1 IU/dL and inhibitor titer >20 BU/mL which is considered a poor prognosis. In 22 patients, AHA was associated to an autoimmune disease: four rheumatoid arthritis, four autoimmune thyroiditis, one systemic lupus erythematosus, one systemic sclerosis, one Sjögren syndrome, one type III cryoglobulinemia, one celiac disease, one temporal arteritis and eight polymyalgia rheumatica. In 13 patients AHA was associated with active cancer: prostate (n = 4), bladder (n = 2), thyroid (n = 1), lung (n = 1), cutaneous (n = 1), unknown (n = 3).

3.2. Follow-up and outcomes

The proportions of complete remission (CR) achieved by timepoint are displayed in Table 2. After 18 months, they were similar between groups. Half of the patients reached complete remission within 6 weeks, and 2/3 within 3 months. CR at 3 month was reported in 41 (70.7 %) of

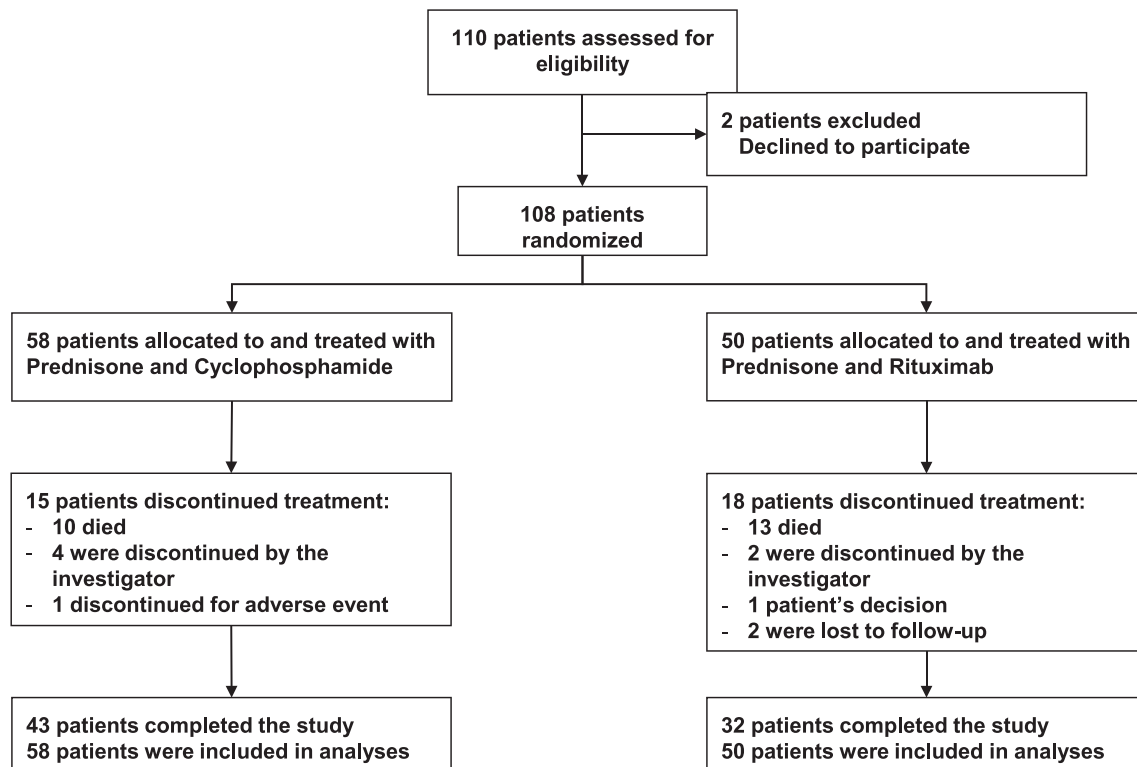


Fig. 1. Flow diagram of study progress — enrolment, intervention allocation, follow-up, and data analysis.

58 patients in the cyclophosphamide group and 34 (68 %) of the 50 patients in the rituximab group. In the subgroup of patients with poor prognosis at baseline, a higher rate of remission was observed in patients treated with cyclophosphamide (22 out of 28 patients (78.6 %) vs 12 out of 25 (48 %) in the rituximab group, $p = 0.02$). The median time to CR was similar in two groups (46 days for cyclophosphamide vs. 48 days for rituximab, $p = 0.39$) (Fig. 2A). Relapses occurred at a similar rate in the two treatment groups. Two relapses were observed in the cyclophosphamide group in the first 6 months after CR, then two others in each group at 12 months and one in each group at 18 months of follow-up. Median time to relapse after CR, was 215 days (179–645) in the cyclophosphamide group and 412 days (347–550) in the rituximab group. No information on the treatment of relapse is available, left at the treating physician's discretion.

At 6 months, at least one severe bleeding was observed in 17 of 58 patients (29.3 %) in the cyclophosphamide group and 12 of 50 patients (24.1 %) in the rituximab group. All patients received activated prothrombin complex concentrate or recombinant activated factor VII, left at the treating physician's discretion.

All patients received prednisone for at least 6 weeks or until complete remission, with gradual tapering for 6 weeks. At Day 45, 60 and 90, respectively 57, 53 and 44 patients were still on steroids. In the cyclophosphamide group, patients still with cyclophosphamide were 26 of 58 at days 45 and 60, and only 2 at day 90. Mean cumulative doses of steroids (mg) were similar between the two groups (4516 ± 1800 vs 4578 ± 1670 at D90, 5858 ± 2768 vs 6168 ± 2848 at D180 and 6202 ± 3036 vs 6697 ± 3483 at D360).

Bleeding mortality (3.7 %) and infection-associated mortality (9.3 %) were similar in the two groups (Table 3). Nearly all patients experienced adverse events. The number of patients with adverse events and severe adverse events was not different between groups.

The number of severe infections was slightly higher in patients treated with rituximab without reaching significance, although the rate of patients with two or more infections in the rituximab group was twice that of cyclophosphamide. Among the infections considered as severe,

two-thirds of them were of pulmonary origin and a quarter of them of urinary origin. No correlation was observed between cumulative dose of cyclophosphamide and severe infection (no new complication infection, on cyclophosphamide between day 45 and day 90). In 8 cases death was considered secondary to sepsis, 2 in the cyclophosphamide group (once associated with severe leucopenia) and 6 in the rituximab one. Death was considered secondary to severe lung infection in 5 cases, blood stream infection in 2 cases and secondary to sepsis after colic perforation in 1 case.

When considering cumulative dose of steroids, no difference was observed between the two groups ($p = 0.48$). However, patients with severe infectious events received higher doses of steroids compared to patients without infection (mean 8461 ± 2840 mg vs 5854 ± 2840 mg, $p = 0.03$). The composite endpoint death linked to treatment and/or severe infection was also similar between groups whether considering only the first event occurrence (Fig. 2B) or all recurrent events, with a hazard ratio (rituximab relative to cyclophosphamide) of 1.89 (95 % CI 0.88–4.03) for the latter analysis. No difference for bleeding events or others drug's related adverse events (diabetes, psychiatric disorders, cytopenia associated with serious events) was observed between the two groups. Cytopenia was observed in 12 patients (20.6 %) in the cyclophosphamide group and 7 (14 %) in the rituximab group. Two patients in each group had diabetes decompensation requiring the use of insulin.

4. Discussion

This is the prospective, randomized, controlled study comparing the efficacy and safety of cyclophosphamide and rituximab in association with steroids in the treatment of acquired hemophilia A. Our population in terms of comorbidities is similar to that of registries with specified data on cardiovascular comorbidities [21,22]. We found a comparable efficacy of cyclophosphamide and rituximab for inhibitor eradication after 18 months of follow-up, with a complete remission rate of 67.2 % with cyclophosphamide and 62.0 % with rituximab, suggesting that none of the two drugs is superior. However, in the subgroup of patients

Table 1
Demographic and baseline characteristics of patients with acquired hemophilia.

	Prednisone + Cyclophosphamide (N = 58)	Prednisone + Rituximab (N = 50)	All (N = 108)
Male sex — n (%)	32 (55.2)	29 (58.0)	61 (56.5)
Median age [q1; q3] — yr	76.8 [68.8; 84.1]	78.7 [69.8; 83.4]	78.0 [69; 84]
Age ≥ 74 yr — n (%)	34 (58.6)	33 (66.0)	67 (62.0)
Underlying disorder			
Idiopathic — n (%)	36 (62.1)	24 (48.0)	60 (55.6)
Autoimmunity — n (%)	11 (19.0)	11 (22.0)	22 (20.4)
Malignancy — n (%)	7 (12.1)	6 (12.0)	13 (12.0)
FVIII activity (IU/dL) ⁽¹⁾	n = 42	n = 41	n = 83
Median [q1; q3]	3 [1.6; 6]	3 [1; 7.0]	3 [1; 7]
Activity <1 % — n (%)	18 (32.1)	10 (20.0)	28 (26.4)
Inhibitor titer (BU/mL)	n = 56	n = 48	n = 104
Median [q1; q3]	8 [4; 28.2]	14.5 [5.9; 47]	10.2 [4.6; 37.0]
Titer ≥20 BU/mL — n (%)	19 (33.9)	22 (45.8)	41 (39.4)
Poor prognosis — n (%)			
FVIII < 1 % and			
Inhibitor > 20 BU/mL	28 (48.3)	25 (50.0)	53 (49.1)
Inhibitor titer (BU/mL)	n = 26	n = 23	n = 49
Median [q1; q3]	32.3 [17.0; 80.0]	54.0 [26.0; 102.3]	38.0 [24.0; 90.0]
FVIII activity (IU/dL) ⁽¹⁾	n = 12	n = 16	n = 28
Median [q1; q3]	1.0 [0.6; 2.0]	2.0 [1.0; 4.6]	1.5 [1.0; 3.0]
Severe bleeding before randomization — n (%)	n = 57	n = 48	n = 105
Median [q1; q3]	48 (84.2)	36 (75.0)	84 (80.0)
Albuminemia (g/dL)	n = 46	n = 44	n = 90
Median [q1; q3]	3.5 [3.05; 3.8]	3.4 [3.15; 3.9]	3.42 [3.1; 3.8]
Hemoglobin level (g/dL)			
Median [q1; q3]	10.4 [9.8; 11.3]	10 [8.7; 11.6]	10.3 [9.4; 11.5]
Concomitant disorders			
High blood pressure — n (%)	32 (55.2)	32 (64.0)	64 (59.3)
Type 2 diabetes — n (%)	14 (24.1)	13 (26.0)	27 (25.0)
Renal failure — n (%)	12 (20.7)	10 (20.0)	22 (24.4)
Coronary heart disease — n (%)	8 (13.8)	13 (26.0)	21 (19.4)
Heart failure — n (%)	3 (5.2)	7 (14.0)	10 (9.3)

¹ 2 missing values and 23 values lower than detection limit.

with poor prognosis, a higher rate of complete remission was observed with cyclophosphamide. As expected, a high level of severe adverse events or mortality was observed without significant differences between the two treatment regimens.

The present overall remission rate is comparable to that of the prospective protocol GTH [8], where 61 % of patients experienced complete remission, or to the rates observed in the EACH registry [6]. In both series, complete remission occurred early (medians of 46 and 48 days respectively).

To date, international guidelines are mainly based on uncontrolled studies, retrospective registries, or case series. American [12] and recent international guidelines on AHA [13] now suggest combining corticosteroids with rituximab or cyclophosphamide as first-line therapy in patients with FVIII <1 IU/dL or inhibitor titer >20 BU/mL, and giving steroids alone to patients with a better prognostic profile. In our study, as in the EACH2 registry, 50 % of patients had good prognosis with FVIII > 1 IU/dL and inhibitor titer <20 BU/mL, suggesting that steroids alone could achieve partial remission (FVIII > 50 IU/dL and no active bleeding after stopping any hemostatic drug for >24 h) [6]. However, we aimed at obtaining complete, not partial remission. Interestingly, dual therapy offers favorable results regardless of the baseline prognostic profile,

Table 2
Outcomes at 18 months, primary end point (complete remission CR) and secondary end points. Intention-to-treat population.

	Prednisone + Cyclophosphamide	Prednisone + Rituximab	P	Odds ratio [95 % CI] [†]
Complete remission				
All patients — n (%)	N = 58	N = 50		
Week 6	31 (53.5)	32 (64.0)	0.570*	1.26
Month 3	41 (70.7)	34 (68.0)		[0.57;
Month 6	41 (70.7)	35 (70.0)		2.78]
Month 12	38 (65.5)	31 (62.0)		
Month 18	39 (67.2)	31 (62.0)		
Patients with poor prognosis i.e., titer > 20 BU/mL and FVIII < 1 IU/dL — n (%)	N = 28	N = 25		
Month 3	21 (75.0)	13 (52.0)	0.0204*	3.97
Month 6	21 (75.0)	14 (56.0)		[1.20;
Month 12	20 (71.4)	12 (48.0)		13.14]
Month 18	22 (78.6)	12 (48.0)		
Time to 1st complete remission — days				
Median (Q1; Q3)	46 (43; 59)	48 (45; 52)		
Relapse — n (%)				
Month 3	0 (–)	0 (–)		
Month 6	2 (4.4)	0 (–)		
Month 12	2 (4.4)	2 (4.9)		
Month 18	1 (2.2)	1 (2.4)		

* Pearson's Chi-square test.

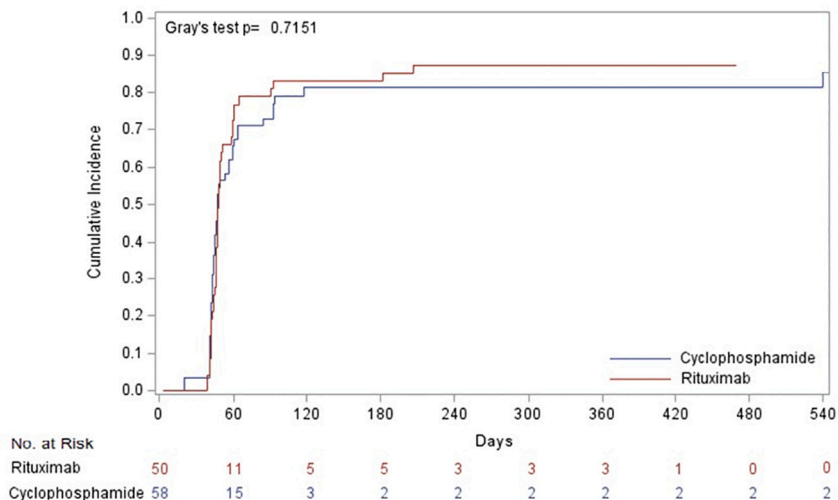
† From logistic regression

suggesting that the combination of immunosuppressive agents can overrule the negative impact of biomarkers. In the subgroup of patients with a poor prognostic profile, the difference in favor of cyclophosphamide should be taken with caution in view of the small sample size and the wide 95 % CI on OR. Our results are comparable to those of the recent randomized open non inferiority trial which showed similar efficacy and safety of a single dose of RTX [24 (77.4 %) patients in the rituximab group and 22 (68.8 %) in the cyclophosphamide group achieved CR within 8 weeks. However, patients were younger (42 [31, 59] for the single-dose rituximab group and 55 [34, 67] for the cyclophosphamide group), and an autoimmune disease was the most common underlying disease in both groups [23].

As expected, many adverse events occurred during this study, at a same rate than in recent cohorts [3,7–9,20,21], which showed that intensive immunosuppression (IST)-related mortality, in particular due to infection, exceeds the current risk of fatal bleeding in AHA. The use of IST requires caution especially in frail patients. Although the 1-year survival rate was 68 % in the GTH study [8], the most common cause of death among the 34 patients who died was infection (n = 16) while death from hemorrhage occurred in only three patients. In addition, 14 deaths were considered directly related to IST. Similar data was reported in the Dutch cohort study [20], where infections occurred in 36 % of patients, with a significantly higher infection rate with combination therapies than with steroids alone (37.5 % with cyclophosphamide, 40 % with rituximab and 10.6 % with steroids alone). Finally, in the EACH2 registry [3], infection occurred in 16 % of patients with steroids alone, 27 % in patients with steroids and cyclophosphamide and 12 % with rituximab. Recently, the Spanish registry [21] reported that the overall mortality was high (23.8 %), with 15 patients (i.e., almost 10 % of the cohort) dying from infection-related disorders.

Mortality rates were similar in the two groups, as were occurrences of bleeding events, metabolic (induction or deterioration of diabetes mellitus) or psychiatric disorders. Our study did not show that rituximab

A – Complete remission



B – First infection or death due to infection or treatment

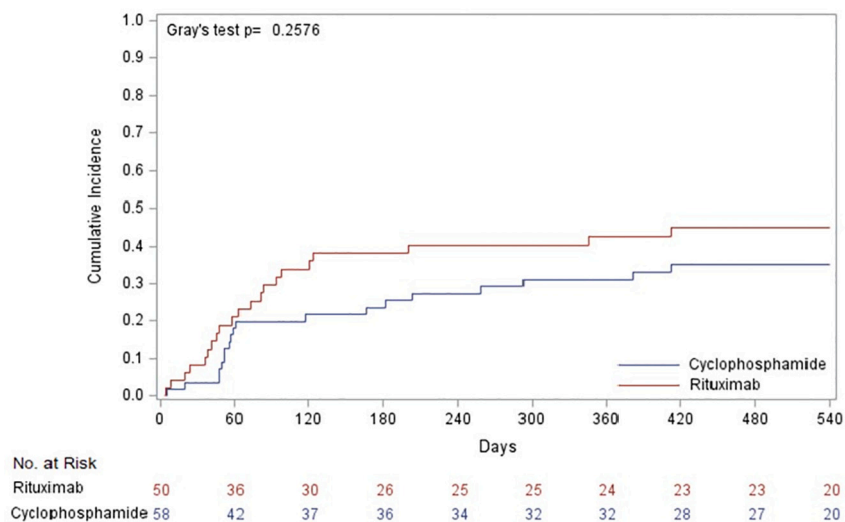


Fig. 2. Time-to-event curves for A: complete remission taking deaths as competing risks, and B: first infection or death due to treatment or infection, taking deaths of other causes as competing risks.

induced a higher risk of infections, unlike Guillet et al. [19] who analyzed hospital records of 180 AHA patients. They showed that rituximab had been prescribed more often than recommended by guidelines and was associated to infections in half of the cases; rituximab-treated patients experienced more infections in the 6 months after the first infusion (20/44 [45.5%]) than those who never received rituximab (34/120 [28.3%]; OR 2.11 [95% CI: 1.03–4.31]; $P = 0.04$). However, in our study, there was only a non-significant trend for more frequent severe infections with rituximab, although the proportion of patients with two or more infections in the rituximab group was twice that of cyclophosphamide.

The analysis of pooled data from 356 patients that received rituximab monotherapy for various conditions [24] showed an overall infection incidence of 30% (19% bacterial infection, 10% viral infection, 1% fungal infection and 6% infections of unknown etiology including 1% of severe infectious events during treatment and 2% during follow-up). In autoimmune diseases, rituximab has been reported as a possible risk factor for infection, but in the prospective randomized double-blind study comparing steroids plus rituximab or plus cyclophosphamide in ANCA-associated vasculitis, no difference in serious

adverse events including infections was observed [25]. Our results are consistent with this prospective study. However, when considering the effects of steroids in patients with infections we observed significantly higher cumulative doses of steroids, suggesting a major effect of steroids over rituximab or cyclophosphamide. Conversely, in the study of ANCA-associated renal vasculitis [26], more infections were noted among older patients in the rituximab group (36%) compared to the cyclophosphamide group (27%). The risk of infection requiring hospitalization is commonly associated with higher age, Kurtzke's expanded disability status scale, and comorbidities before treatment initiation [27].

Emicizumab, a bispecific humanized recombinant antibody with FVIII mimetic activity, is sometimes used off-label in AHA and should be considered as an agent to reduce recurrent bleeding episodes, facilitate outpatient management and even decrease inhibitor titer [28,29]. In the recent single-arm, open-label, phase 2 clinical trial (GTH-AHA-EMI), the authors suggest that emicizumab prophylaxis prevents bleeding in patients with AHA and that immunosuppressive therapy can be deferred while patients are receiving this treatment [30].

The main limitation of our study is its reduced power due to stopping recruitment at about two thirds of the planned sample size, to comply

Table 3
Safety outcomes.

	Prednisone + Cyclophosphamide N = 58	Prednisone + Rituximab N = 50	P	Odds ratio (95 % CI) [†]
Deaths — n (%)	10 (17.2)	13 (26.0)	0.267*	0.59 (0.23–1.50)
– Infections	2 (3.4)	2 (4.0)		
– Bleeding	4 (6.9)	1 (2.0)		
– Concomitant disorders	2 (3.4)	2 (4.0)		
– Unknown cause				
Patients with at least				
1 adverse event — n (%)	55 (94.8)	48 (96.0)	1*	0.76 [0.12; 4.77]
1 severe grade 3–4 adverse event — n (%)	44 (75.9)	35 (70.0)	0.493*	1.35 [0.57; 3.16]
Patients with severe infections — n (%)	19 (32.8)	20 (40.0)	0.435*	0.73 [0.33; 1.61]
None — n (%)	39 (67.2)	30 (60.0)	0.090**	
1 infection — n (%)	17 (29.3)	12 (24.0)		
≥2 infections — n (%)	2 (3.5)	8 (16.0)		
Number of infections by patient			0.101***	
Median (min; max)	0 (0; 3)	0 (0; 3)		
Mean (SD)	0.38 (0.62)	0.62 (0.90)		
Patients with severe infections or death due to treatment (composite) — n (%)	19 (32.8)	21 (42.0)	0.321*	0.67 [0.31; 1.48]
Patients with severe bleeding — n (%)	11 (19.0)	6 (12.0)	0.322*	1.72 [0.59; 5.04]
None — n (%)	47 (81.0)	44 (88.0)	0.638**	
1 bleeding — n (%)	8 (13.8)	5 (10.0)		
≥2 bleedings — n (%)	3 (5.2)	1 (2.0)		
Number of bleedings by patient			0.162***	
Median (range)	0 (0; 4)	0 (0; 3)		
Patients with treatment complications — n (%)	13 (22.4)	10 (20.0)	0.760*	1.16 [0.46; 2.92]
None — n (%)	45 (77.6)	40 (80.0)	0.353**	
1 complication — n (%)	8 (13.8)	9 (18.0)		
≥2 complications — n (%)	5 (8.6)	1 (2.0)		
Number of complications by patient			0.475***	
Median (range)	0 (0; 2)	0 (0; 2)		
Patients with other events — n (%)	31 (43.3)	21 (42.0)	0.235*	1.59 [0.74; 3.40]
None — n (%)	27 (46.6)	29 (58.0)	0.304**	

Table 3 (continued)

	Prednisone + Cyclophosphamide N = 58	Prednisone + Rituximab N = 50	P	Odds ratio (95 % CI) [†]
1 event — n (%)	16 (27.6)	14 (28.0)		
≥2 events — n (%)	15 (25.8)	7 (14.0)		
Number of events by patient			0.309***	
Median (range)	1 (0; 3)	0 (0; 4)		

* Pearson's chi-square test.

** Fisher's exact test.

*** Exact Poisson regression.

† Logistic regression

with the IDMC recommendation, concerned with severe infection rates. Running a futility analysis, we found that in view of results observed on the 108 randomized patients, the probability of obtaining a significant difference with respect to the primary endpoint would have been only 13.6 % had recruitment continued up to the target sample size of 164 patients, with the 20 % difference between the two groups (60 vs. 80 %) used to calculate sample size. Another potential limitation is that 11 patients (six in the cyclophosphamide + prednisone group and five in the rituximab + prednisone group) could not be assessed for the primary endpoint (Fig. 1). These 11 patients were considered as not having reached complete remission in the main analysis. Two separate sensitivity analyses were run with respect to the primary endpoint, one based on complete cases only, i.e., excluding these 11 patients, and one based on the maximal bias assumption in which the six patients in the cyclophosphamide + prednisone group were considered as failures and the five patients in the rituximab + prednisone group were considered as successes. Results did not change appreciably as the *p*-value ranged from 0.57 with the main analysis (Table 2) to 0.50 and 0.59 with the two sensitivity analyses respectively.

The results of this large randomized study should lead to review the present guidelines [12,13] for AHA treatment. When using an association of steroids and immunosuppressive treatments, cyclophosphamide might be preferred to rituximab, in view of its oral administration, lower cost and quicker reversibility of immunosuppressive action. Rituximab should be considered as second line, and probably with reduced dosage in vulnerable patients as suggested by recent case series with low doses of rituximab [31]. Only case reports with rituximab at a lower dose (100 mg week for four weeks) were published. In a non-randomized series of 24 patients where 11 patients were treated with corticosteroids alone, three with corticosteroids and cyclophosphamide and 10 with corticosteroids and rituximab including six at a dose of 100 mg/week for four weeks, no difference in terms of remission, duration of remission or relapse was observed with the two dosages of rituximab [31]. Association of immunosuppressive agents (cyclophosphamide, dexamethasone, rituximab) could be an acceptable option for AHA patients especially those considered with poor prognosis [32]. But with cyDRi treatment, the median time to reach first CR was 77 days (range, 19–939 days; interquartile range, 31–115 days) vs 46 or 48 days (interquartile range 43–59 days or 45–52 days) in our prospective randomized study [32]. Careful individual consideration of pros and cons of immunosuppressive therapy type, intensity and timing is warranted in frail patients with AHA.

5. Conclusion

Our study showed that cyclophosphamide and rituximab have similar efficacy and safety in AHA; although the inhibitor titers seem higher with rituximab, there was no significant difference between

groups. As first line, oral cyclophosphamide at the dose of 1.5 to 2 mg/kg/day seems preferable, especially in patients with FVIII <1 IU/dL and inhibitor titer >20 BU/mL. Significant association between severe infection and cumulative doses of steroids suggest developing novel therapeutic strategies to limit total steroids.

CRedit authorship contribution statement

H. Lévesque: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **J.F. Viillard:** Investigation, Resources. **E. Houivet:** Conceptualization, Formal analysis, Methodology. **B. Bonnotte:** Data curation, Resources. **S. Voisin:** Data curation, Funding acquisition. **V. Le Cam-Duchez:** Data curation, Funding acquisition, Investigation. **F. Maillot:** Data curation, Investigation. **M. Lambert:** Data curation, Investigation. **E. Liozon:** Data curation, Investigation. **B. Hervier:** Data curation, Investigation. **O. Fain:** Data curation, Investigation. **B. Guillet:** Data curation, Investigation. **J. Schmidt:** Data curation, Investigation. **L.E. Luca:** Conceptualization, Investigation. **M. Ebbo:** Data curation, Investigation. **N. Ferreira-Maldent:** Data curation, Investigation. **A. Babuty:** Data curation, Investigation. **L. Sailler:** Data curation, Investigation. **P. Duffau:** Data curation, Investigation. **V. Barbay:** Data curation, Investigation, Resources. **S. Audia:** Data curation, Investigation. **J. Benichou:** Data curation, Formal analysis, Funding acquisition, Methodology, Validation, Writing – original draft, Writing – review & editing. **J. Graveleau:** Data curation, Investigation. **Y. Benhamou:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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