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Short-term emicizumab in patients with acquired hemophilia A

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Running heads: Short-term emicizumab in AHA

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Conflicts of interest

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Authors' Contributions

Quentin Van Thillo and Cedric Hermans conceived the project. Margot Erard and Quentin Van Thillo drafted the manuscript. Cedric Hermans, Thomas Vanassche, Peter Verhamme, Catherine Lambert, Marc Jacquemin and Bas Calcoen all read and commented on the manuscript. Margot Erard summarized and visualized available patient data. Cedric Hermans, Thomas Vanassche, Peter Verhamme, Catherine Lambert and Quentin Van Thillo supervised patient care.

MAIN TEXT

We retrospectively evaluated the use of emicizumab in 34 patients with acquired hemophilia A treated at two Belgian referral centers. The study assessed treatment duration, clinical outcomes, and factors associated with emicizumab use in routine clinical practice.

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by inhibitory autoantibodies against factor VIII (FVIII). [1] Patients usually present with a new-onset mild to severe bleeding phenotype and an isolated prolongation of the activated partial thromboplastin time (aPTT). The diagnosis of AHA can be confirmed by a reduced FVIII activity and the identification of an inhibitor in the Bethesda assay. The management of AHA comprises a dual approach.[2] First, early-phase treatment focuses primarily on controlling and preventing bleeding events through rapidly acting bypassing agents, such as recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (aPCC), and recombinant porcine FVIII (rpFVIII).[3] Second, re-establishing functional endogenous FVIII levels is achieved by eradicating the inhibitor through immunosuppression.[4] Emicizumab is a bispecific monoclonal antibody that mimics the co-factor role of FVIII by bridging activated factor IX (FIXa) and factor X (FX).[5,6] While its upfront use has been shown to be effective in the acute management of AHA, data on its long-term use remain sparse.[7] Therefore, we aim to evaluate the duration and clinical outcomes of emicizumab therapy in patients with AHA in Belgium.

To this aim, we performed a retrospective, multicenter (University hospitals Leuven [UZL] and Cliniques universitaires Saint-Luc [UCL]) study and included all patients who were diagnosed with AHA from January 2020 to June 2025. Since the availability of emicizumab (Hemlibra®, Roche) in our centers, it was initiated upon diagnosis and administered according to dosing regimens used in congenital hemophilia A (starting 3 mg/kg weekly for 4 weeks, followed by 3 mg/kg every two weeks). Following publication of the AGEHA and GTH-AHA-EMI trial designs, an accelerated dosing regimen (starting with 6 mg/kg on day 1 and 3 mg/kg on day 2) was adopted.[8,9] In the acute phase of bleeding, rFVIIa (eptacog alfa, Novoseven®, 90 µg/kg) was administered to achieve hemostasis. Immunosuppressive therapy consisted of systemic corticosteroids, rituximab and other drugs such as cyclophosphamide and mycophenolate mofetil. Treatment with emicizumab was stopped after remission, which was defined as clearance of the inhibitor (< 1 BU/mL) and restoration of

endogenous FVIII activity (> 50%). FVIII activity was measured by a one-stage clotting assay and two chromogenic assays (bovine and human reagents) as described in our previous work.[10] The assay with human reagents assesses both the emicizumab FVIII-like activity and native patient FVIII-activity, while the assay with bovine reagents only measures the patients' endogenous FVIII-activity.[10] FVIII inhibitor levels were measured according to the Bethesda method with the Nijmegen modifications. Continuous variables are reported as medians and interquartile ranges (IQR); categorical variables are reported as frequencies and proportions. The primary endpoint was time from emicizumab initiation to either discontinuation (due to remission) or death, whichever occurred first. Group differences in treatment persistence, stratified by immunosuppressive regimen, inhibitor level at diagnosis, and emicizumab dosing regimen, were assessed using the Mantel-Cox log-rank test. Multivariable quantile regression (median model) was performed after log-transformation of duration and inhibitor levels due to right-skewed distributions. Statistical significance was defined as p-value < 0.05. Analyses were performed using IBM SPSS Statistics version 30 and GraphPad Prism version 10. The Ethics Committee at both participating centers approved the study (S71237).

We identified 34 patients diagnosed with AHA (16 at UZL and 18 at UCL), of whom 7 had been included in a previously published cohort.[10] Median age was 74 (IQR 67-78) and most patients were male (22 men, 12 women) (**Table 1)**. In 16 patients (47%) an underlying condition was identified that contributed to the development of AHA, including cancer (29%), autoimmune diseases (15%), and postpartum period (6%). One patient had both cancer and an autoimmune disease. Patients presented with spontaneous skin hematoma (n=28), intramuscular bleeding (n=13), hematuria (n=5) and gastrointestinal bleeding (n=9). All but one patient were treated with emicizumab; this patient presented with low inhibitor levels, FVIII activity of 36%, and no severe bleeding phenotype at diagnosis, and was therefore excluded from further analysis. At diagnosis, 17 patients (50%) experienced major bleeding (conforming to the definition of the International Society on Thrombosis and Haemostasis) for which additional rFVIIa and transfusion of blood products was required in 9 (27%) and 14 patients (42%), respectively. Median aPTT at diagnosis was 84 seconds (IQR 62.5-102.8), median FVIII levels were 1% (IQR 0.2-4.5) and median inhibitor concentration was 53 Bethesda units per mL (BU/mL) (IQR 21.5-110.2). Baseline FVIII and inhibitor levels

were not measured for one patient who was excluded from further correlation analyses. In 22 patients (67%) emicizumab was administered according to congenital hemophilia A dosing, whereas 11 patients (33%) were treated with the accelerated dosing regimen (AGEHA/GTH-AHA-EMI regimen). Emicizumab was immediately started (median 0 days, IQR 0-1) after diagnosis of AHA. Thirty patients (91%) received immunosuppressive treatment: monotherapy with steroids (n=2) or rituximab (n=8), or a combination therapy (n=20). Patients were classified according to the immunosuppressive regimen chosen at treatment initiation; treatment categories did not reflect escalation from mono- to dual- or triple-agent therapy during follow-up. Across the entire cohort, immunosuppressive therapy was started 6 days (median, IQR 0-66) after diagnosis. Patients treated according to the AGEHA/GTH-AHA-EMI regimen experienced a longer delay to initiation of immunosuppressive therapy than those treated according to the congenital hemophilia A dosing regimen (5 weeks vs. 0 weeks, p=0.037) (**Figure S1**). Three patients treated according to the AGEHA/GTH-AHA-EMI regimen did not receive immunosuppressive therapy. Twenty-three patients (77%) achieved remission following successful eradication, allowing emicizumab to be discontinued after a median of 149 days (IQR 85-167) (**Figure 1**). In 6 patients (18%), emicizumab was continued until the patient's death with a median duration of emicizumab treatment of 244 days (minimum 8, maximum 636). At the time of data analysis, four patients (12%) remained on emicizumab, with a median treatment duration of 542 days (minimum 137, maximum 976). While emicizumab treatment duration did not differ between immunosuppressive regimens (p=0.33) or emicizumab dosing regimens (p=0.44), higher inhibitor levels at diagnosis were associated with longer treatment duration (76 days [inhibitor levels < 20 BU/mL] vs. 168 days [inhibitor levels ≥ 20 BU/mL], p < 0.001) and remained independently predictive in multivariable analysis (β=0.30, 95% CI 0.10–0.50; p=0.005) (**Figure 2**). To account for competing risks, outcomes (remission, death before remission, and no remission) were compared across immunosuppressive regimens, inhibitor level groups, and emicizumab dosing strategies, with no significant differences observed (p=0.05, p=0.07, and p=0.38, respectively) (**Figure S2)**. No arterial or venous thrombotic events and no major bleeding episodes occurred after initiation of emicizumab. Median follow-up time was 2.1 years (IQR 1.1-3.6, maximum 5.2). Seven patients died due to either infection (n=2), underlying disease (n=3) or other unrelated events (n=2). There was no bleed-related mortality.

In conclusion, this multicenter study demonstrates that emicizumab can be used as a time-limited bridge therapy in AHA, with most patients discontinuing treatment after approximately five months following successful inhibitor eradication. This is consistent with the 18-week median reported by Poston et al. in a US multicenter cohort, and aligns with the treatment durations observed in the prospective GTH-AHA-EMI trial, collectively supporting that prolonged, and particularly indefinite, emicizumab therapy is not required in patients who achieve remission.[9,11] Baseline inhibitor titer was independently associated with treatment duration in multivariable analysis, consistent with its established role as a prognostic marker for immunosuppressive intensity and remission likelihood.[12] Following publication of the AGEHA and GTH-AHA-EMI study protocols, our centers adopted a more individualized approach to immunosuppressive therapy, leading to delayed treatment initiation in approximately one third of the entire cohort.[8,9] Despite this postponement, we observed no significant differences in overall emicizumab treatment duration, remission rates, or other clinical outcomes between the two treatment paradigm eras. These findings are in line with the strategy described by Schimansky et al., who reported a 61% reduction in mortality with delayed immunosuppression.[13] In contrast to the predefined 12-week postponement strategy evaluated in that study, immunosuppressive therapy in our cohort was tailored to the patient's clinical condition and overall fitness. Although the limited sample size precludes firm conclusions, the overall rates of remission and survival observed in our cohort were comparable to those reported by Schimansky et al., further highlighting the potential role of individualized immunosuppressive strategies in the management of AHA.

This study provides real-world data on emicizumab use in AHA. Although limited by its retrospective design, small sample size, and the competing risk of death before inhibitor eradication in a predominantly elderly population, our findings support the efficacy and time-limited nature of emicizumab therapy in AHA. Prospective studies are warranted to further define the optimal duration of prophylaxis and evaluate individualized immunosuppressive strategies.

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TABLES and FIGURES

Table 1. Patient characteristics

Patient characteristics	Patients with AHA n=34
Baseline characteristics	
Age at diagnosis, years – median (IQR)	74 (67-78)
Male sex – n (%)	22 (64.7%)
AHA linked to underlying conditions	16 (47.1%)
Autoimmune disease – n (%)	5 (14.7%)
Cancer – n (%)	10 (29.4%)
Postpartum period – n (%)	2 (5.9%)
Idiopathic AHA – n (%)	18 (52.9%)
Bleeding phenotype	
Spontaneous skin hematoma – n (%)	28 (82.4%)
Intramuscular bleeding – n (%)	13 (38.2%)
Hematuria – n (%)	5 (14.7%)
Gastrointestinal bleeding – n (%)	9 (26.5%)
Major bleeding* – n (%)	17 (50%)
Laboratory findings	
aPTT at diagnosis, seconds – median (IQR)	83.8 (62.5-102.8)
FVIII at diagnosis, % – median (IQR)¶	1 (0.2-4.5)
FVIII inhibitor levels at diagnosis, BU/mL – median (IQR)¶	53 (21.5-110.2)
Hemostatic therapy¶	
Emicizumab	33 (100%)
Congenital hemophilia A dosing regimen	22 (67%)
AGEHA/GTH-AHA-EMI dosing regimen	11 (33%)
Recombinant activated factor VII	9 (27.3%)
Immunosuppressive therapy¶	
Monotherapy	10 (30.3%)
Corticosteroids	2 (6.1%)
Rituximab	8 (24.2%)
Dual combination therapy	18 (54.5%)
Corticosteroids + rituximab	13 (39.4%)
Rituximab + mycophenolate mofetil	3 (9.1%)
Corticosteroids + mycophenolate mofetil	1 (3.0%)
Corticosteroids + cyclophosphamide	1 (3.0%)
Triple or more combination therapy	2 (6.1%)
Corticosteroids + rituximab + mycophenolate mofetil	1 (3.0%)
Corticosteroids + rituximab + mycophenolate mofetil + azathioprine	1 (3.0%)
No immunosuppressive therapy	3 (9.1%)
Therapeutic delay¶	
Time from diagnosis till start emicizumab, days – median (IQR)	0 (0-1)
Time from diagnosis till start immunosuppression, days – median (IQR)	6 (0-66)
Follow-up¶	

Duration of follow-up, years – median (IQR)	2.1 (1.1-3.6)
Thrombotic event – n (%)	0 (0%)
Major bleeding – n (%)	0 (0%)
Deaths – n (%)	7 (21.2%)
Cause of death	
Infection – n (%)	2 (6.1%)
Bleeding – n (%)	0 (0%)
Underlying disease – n (%)	3 (9.1%)
Other unrelated events – n (%)	2 (6.1%)

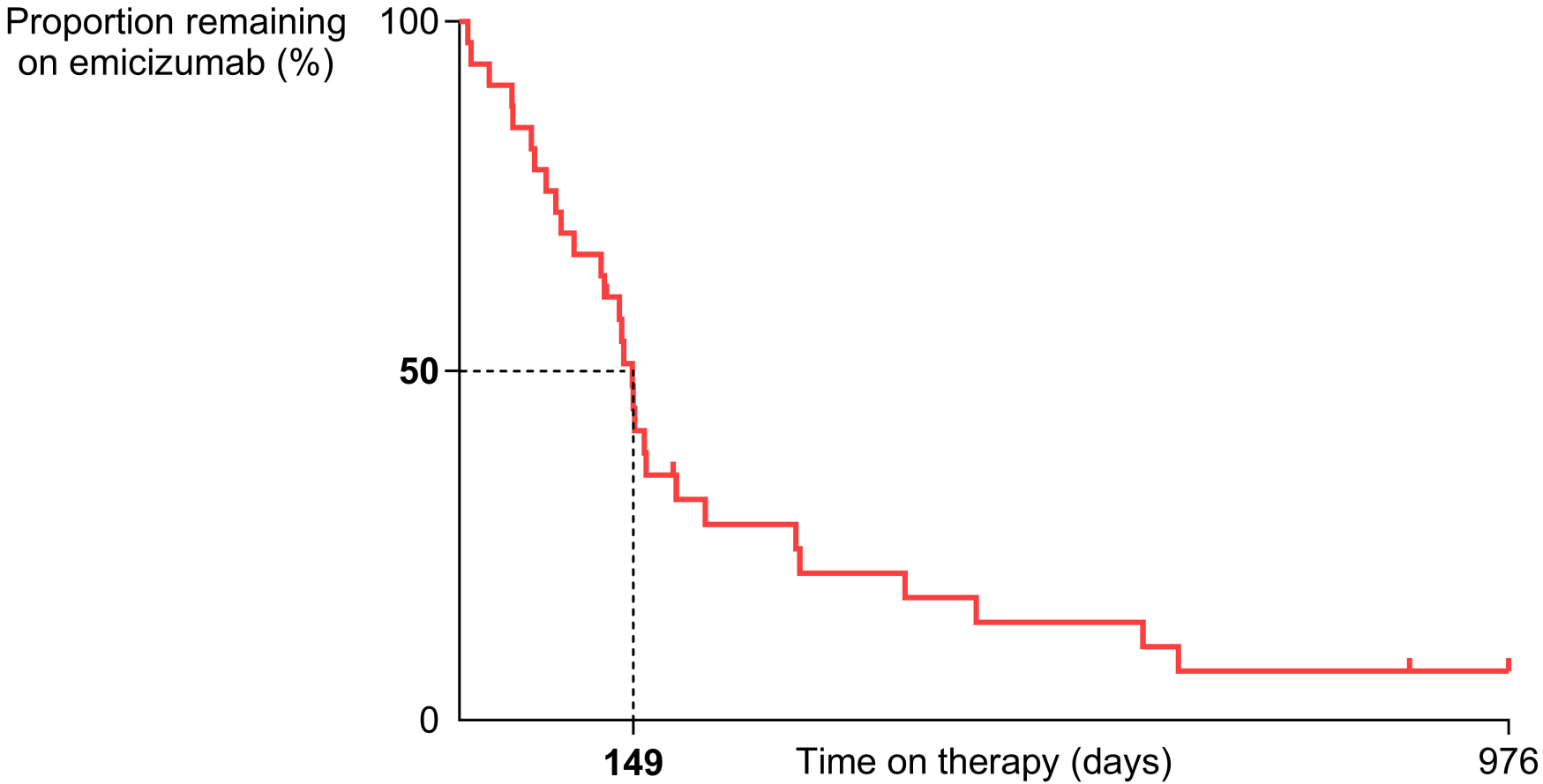
Data are presented as median (interquartile range) or number (percentage). AHA: acquired hemophilia A; aPTT: activated partial thromboplastin time; FVIII: factor VIII; ISTH: International Society on Thrombosis and Haemostasis. *Major bleeding defined according to ISTH criteria. ¶Data available in 33 patients.

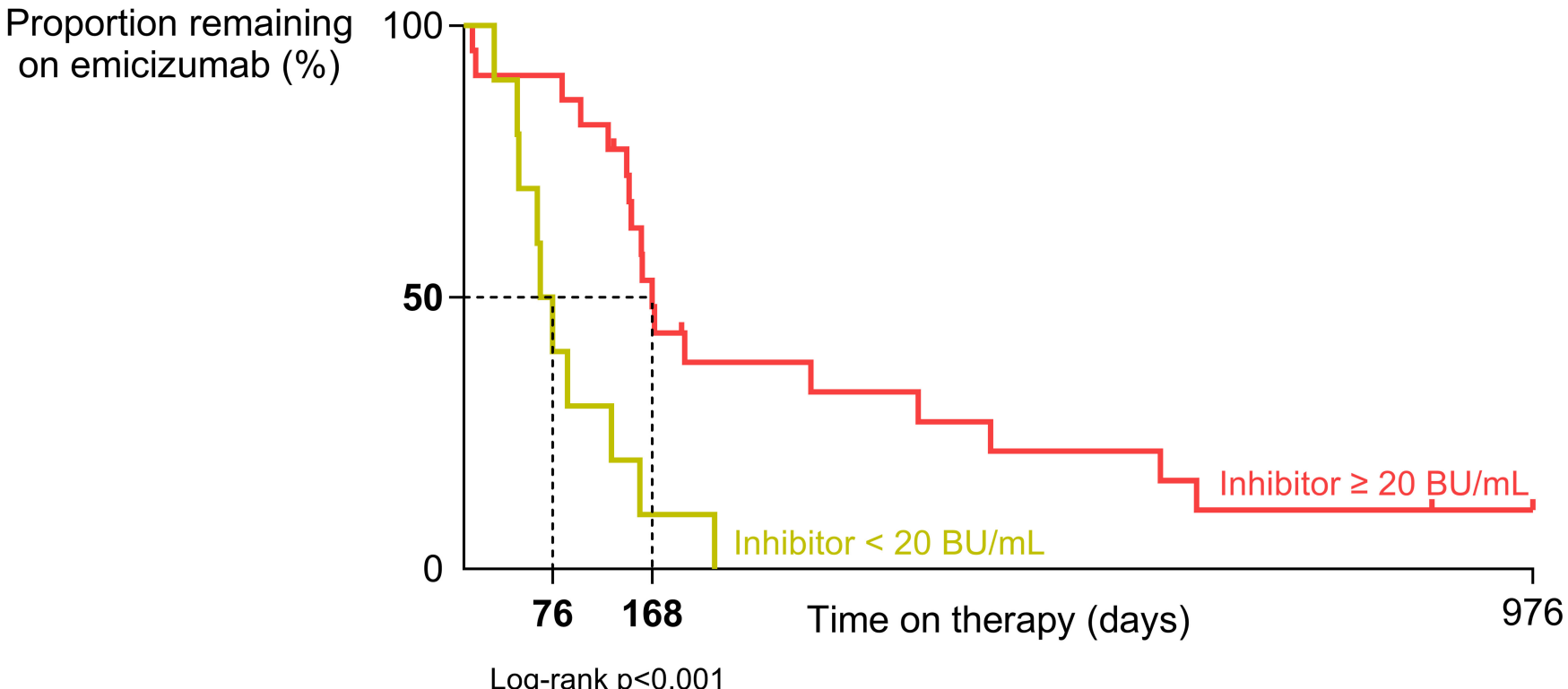
Figure 1. Duration of emicizumab treatment in patients with acquired hemophilia A (n = 33)

Kaplan-Meier curve depicts the proportion of patients remaining on emicizumab over time. The dashed lines indicate the median treatment duration of 149 days. Patients still receiving treatment at last follow-up were censored.

Figure 2. Time to discontinuation of emicizumab stratified by baseline inhibitor level

Kaplan-Meier curves depict the proportion of patients remaining on emicizumab over time, stratified by inhibitor titer at diagnosis (< 20 BU/mL vs. ≥ 20 BU/mL). Median treatment duration was 76 days in patients with inhibitor levels < 20 BU/mL and 168 days in those with inhibitor levels ≥ 20 BU/mL. Differences were assessed using the log-rank test ($p < 0.001$). A more detailed description of event types by regimen is given in the Supplementary Material.


Proportion remaining on emicizumab (%)
100
50
0
149
Time on therapy (days)
976


Proportion remaining on emicizumab (%)
100
50
0
76
168
976
Time on therapy (days)
Inhibitor ≥ 20 BU/mL
Inhibitor < 20 BU/mL
Log-rank p<0.001

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SUPPLEMENTARY FIGURES and TABLES

Figure S1. Time from diagnosis to initiation of immunosuppressive therapy according to emicizumab dosing regimen

Median time from diagnosis to initiation of immunosuppressive therapy was 5 weeks in the AGEHA/GTH-AHA-EMI group and 0 weeks in the congenital hemophilia A (CHA) group (p=0.0365; Mann–Whitney U test). The three patients in the AGEHA/GTH-AHA-EMI group who never initiated immunosuppressive therapy were excluded from this analysis, as no time to immunosuppressive therapy could be determined.

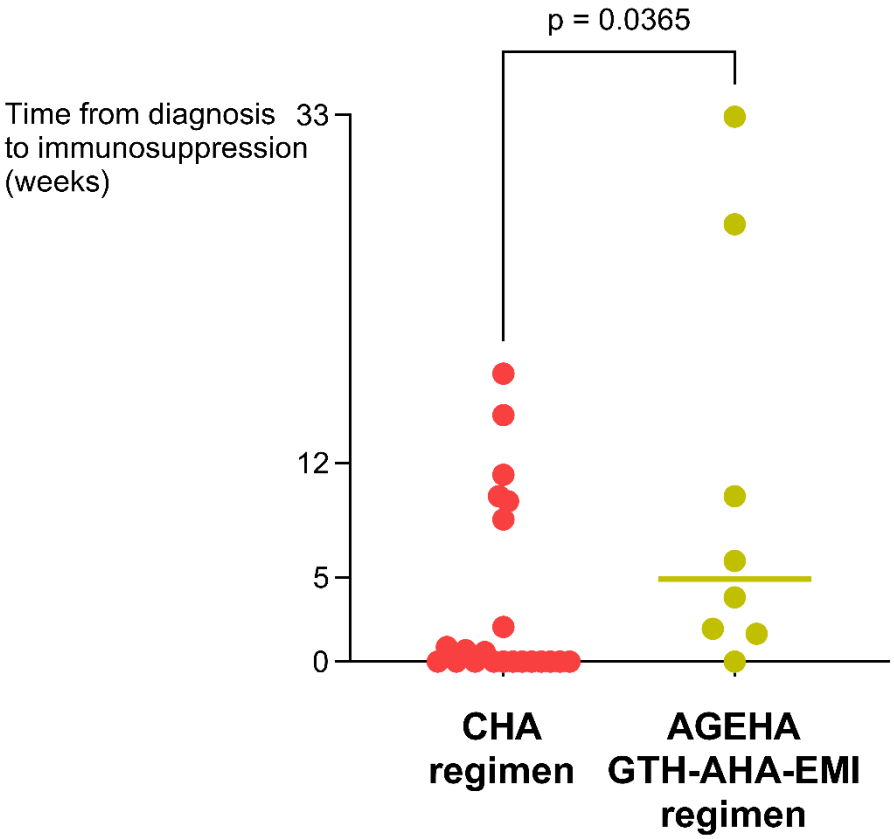

Figure S2. Clinical outcomes according to treatment and disease characteristics

To account for the competing risk of death before remission, outcomes were additionally summarized according to immunosuppressive regimen, baseline inhibitor level and emicizumab dosing regimen. HA: hemophilia A; AGEHA study[8]; GTH-AHA-EMI study[9].