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BRIEF REPORT

# Anti-emicizumab antibodies and their relevance in clinical practice

Carla Valsecchi[1] | Lucia Schiavone[1] | Sara Arcudi[1] | Adriana Torri[1] | Cristina Novembrino[1] | Flora Peyvandi[1,2]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

[2]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

**Correspondence**
Flora Peyvandi, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9 - 20122, Milan, Italy.
Email: flora.peyvandi@unimi.it

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## Abstract

**Background:** Emicizumab is licensed for treatment of people with hemophilia A (HA) of all ages, with and without factor (F)VIII inhibitors. It is well tolerated, and most of the treatment-related adverse events are of mild intensity and transient. As for other therapeutic proteins, the potential of emicizumab to induce anti-drug antibodies (ADAs) should be considered when a decrease in treatment efficacy is observed. Data from 7 phase 3/3b pivotal studies showed that 5.1% of treated patients developed ADAs, <1% being activity neutralizing. Among them, 1 case required discontinuation of emicizumab due to loss of treatment efficacy. To date, among several thousands of patients treated with emicizumab, 5 cases of ADAs requiring treatment discontinuation have been reported.

**Objectives:** Monitoring anti-emicizumab antibodies in 67 subjects with congenital HA who switched to emicizumab prophylaxis from FVIII products or bypassing agents.

**Methods:** The anti-emicizumab antibodies were tested, depending on patient availability, at baseline and longitudinally at 5, 10, 20, and 50 weeks after the first dose, as well as when clinically required.

**Results:** ADAs were detected in 4 of 67 cases (5.9%) on at least 2 occasions and were not necessarily associated to significant decreased emicizumab concentration, activated partial thromboplastin time prolongation or bleeding episodes. Only 1 of 4 ADA-positive patients required emicizumab discontinuation due to treatment failure.

**Conclusion:** The present findings confirm that the development of anti-emicizumab antibodies is a rare event, particularly those with neutralizing activity. Routine monitoring should be reserved only for patients with clinical manifestations of bleeding when therapy failure is suspected.

## Essentials

- Data on clinical impact of anti-emicizumab antibodies in real-life context are limited.
- In total, 67 subjects with HA switched to emicizumab were monitored for ADAs.
- Development of neutralizing anti-emicizumab antibodies is a rare event.
- Antibodies monitoring is required when bleeding occurs and treatment failure is suspected.

KEYWORDS
anti-drug antibody, bispecific antibody, emicizumab, hemophilia A

## 1 | INTRODUCTION

The humanized, bispecific monoclonal antibody emicizumab, mimicking the cofactor function of activated factor (F)VIII, has been the first non-clotting factor approved for subcutaneous administration in people with hemophilia A (HA). After the initial 4 to 5 doses, the drug reaches a stable concentration of about 50 μg/mL, which ensures effective hemostasis avoiding the fluctuations typically associated with FVIII replacement products. Emicizumab is not affected by FVIII inhibitors, so that it is also efficacious for the treatment of patients with this complication [1–3]. Efficacy and safety of emicizumab prophylaxis have been widely demonstrated during the pivotal clinical studies, obtaining a significant reduction in the annualized bleeding rate in several hundreds of HA cases [4]. Besides its use for the prophylactic treatment of people with congenital HA, the off-label use of emicizumab has recently been approved for the treatment of acquired HA in several regions, including Japan, Europe, and the United States [5–14].

As for other therapeutic monoclonal antibodies [15–18], emicizumab has the potential to produce anti-drug antibodies (ADAs), which might influence pharmacokinetics (PK) and pharmacodynamics (PD). Anti-emicizumab antibodies were first described in 34 of 668 (5.1%) people with congenital HA enrolled in 7 pivotal studies [19]. Because of their heterogeneous characteristics, these antibodies variably affected the PK/PD profiles. In a single patient antibody development led to loss of treatment efficacy that required emicizumab discontinuation. This first described, fully neutralizing anti-emicizumab antibody was purified by our group and characterized as a polyclonal antibody binding to both the Fab and Fc fragments of the emicizumab molecule [20]. In the post-marketing period, 5 additional reports described anti-emicizumab antibodies, leading to loss of treatment efficacy in people with congenital HA [21–25]. Of them, 4 had neutralizing activity, and 1 did fasten the plasma clearance of the drug. However, data on the incidence and clinical impact of anti-emicizumab antibodies in the real-life context remain limited. With this gap of knowledge, we chose to investigate longitudinally the frequency and clinical relevance of anti-emicizumab antibodies in a series of 67 congenital HA cases switched to emicizumab since its approval up to April 30, 2024.

## 2 | MATERIAL AND METHODS

### 2.1 | Study design and sample collection

People with congenital hemophilia A switched to emicizumab at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center in Milan and with at least 6 months of follow-up were included in the study. Patients enrolled in ongoing clinical trials were excluded. Each case, according to the protocol based on the HAVEN pivotal studies, received a 4 weekly loading doses consisting of 3 mg/kg of the drug, followed by maintenance doses of either 1.5 mg/kg weekly or 3 mg/kg biweekly. Blood samples were collected before the first administration of emicizumab (baseline) and, depending on patient availability, at 5, 10, 20, and 50 weeks after the first dose, as well as when clinically required owing to the occurrence bleeding. For this purpose, patients were instructed to contact the 24-hour emergency service of our center in case of bleeding or other adverse events. The study protocol was approved by the Ethics Committee of Milan Area 2 (approval number 0026709-U; June 16, 2021), and written informed consent was obtained from all patients.

### 2.2 | Emicizumab concentration and activated partial thromboplastin time (aPTT) measurement

Emicizumab plasma concentration, expressed in micrograms per milliliter, were determined by using a modified one-stage FVIII clotting assay using the emicizumab standard calibrator (r2 Diagnostics) on ACL Top with the Synthasil APTT and FVIII deficient plasma (Werfen) [26]. The aPTT was performed with the Synthasil reagent and expressed as ratio of patient to normal plasma.

### 2.3 | Anti-emicizumab antibody assays

Anti-emicizumab antibodies were detected in the total immunoglobulin G (IgG) fraction purified from plasma samples by using a previously described Western blot method [20]. For each sample and control, the same amount of total IgG, corresponding to 2 μg, was loaded on the polyacrylamide gel, transferred to the Western blot membrane, and ADAs were detected by using in-house biotinylated emicizumab. Purified IgG from a normal subject and from our historical patient first described with ADAs [20] were used as negative and positive controls, respectively.

The anti-emicizumab antibodies were also evaluated in plasma samples using an in-house ELISA [27]. This assay is based on the ability of the bivalent IgG molecules to simultaneously bind both the immobilized and the biotin-labeled drug. High-density drug concentration was used as both capturing (10 μg/mL) and detection molecule (20 μg/mL); plasma samples were prediluted and incubated in 300 mM acetic acid to dissociate potentially

circulating immune complexes. The acidified sample and the biotinylated emicizumab were loaded simultaneously into the wells, and the plate was then incubated overnight at 4 °C. The detailed assay development and procedure, including IgG recovery (Supplementary Figure 1) and assay specificity (Supplementary Figure 2), are described in the Supplementary Methods.

### 2.4 | Statistical analysis

Continuous and categorical variables were analyzed using descriptive statistics: age and exposure time were reported as median (range), laboratory data as median (IQR), and the incidence of ADAs as counts and percentages.

For each patient, aPTT ratios and emicizumab concentrations were calculated as the mean of all available steady-state values collected during prophylaxis, regardless of the ADA status. Given the large difference in size between ADA-positive and ADA-negative patients, a comparative statistical analysis of emicizumab concentrations and aPTT ratio was not performed, as it might not provide reliable results.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Participants

As of April 30, 2024, 82 subjects with HA had been switched to emicizumab from standard/extended half-life FVIII products or bypassing agents. Of these, 15 cases were excluded from this study: 7 because of enrolment in ongoing clinical trials (HAVEN 7 and BEYOND ABR) and 8 were with <6 months of follow-up. Therefore, a total of 67 patients were included in this study (Supplementary Figure 4).

At baseline, 15 patients had a detectable FVIII inhibitor, including 2 previously diagnosed with mild HA who developed a severe bleeding phenotype and FVIII levels of <5%. The patient cohort included 52 adults, 4 adolescents, 8 children, and 3 infants (<1 year old). The demographic and clinical characteristics of the patient population are summarized in Table 1.

**TABLE 1** Study population: demographics and clinical characteristics.

| Study population | |
|---|---|
| Type of hemophilia A (No. of patients) | |
| Severe | 65 |
| Mild | 2 |
| Factor VIII inhibitor (No. of patients) | |
| Positive | 15 |
| Negative | 52 |
| Age (y), median (minimum-maximum) | 40 (1-80) |
| Emicizumab exposure (wk), median (minimum-maximum) | 73 (27-374) |
| Maintenance dosing regimen (No. of patients) | |
| 1.5 mg/kg weekly | 48 |
| 3 mg/kg biweekly | 19 |

### 3.2 | aPTT ratio, emicizumab level, and anti-emicizumab antibody

The distribution of the mean aPTT ratio had a median value of 0.72 (IQR, 0.69-0.77), ranging from 0.64 to 0.92. The distribution of the mean emicizumab concentration had a median value of 49.8 (IQR, 40.8-59.8), ranging from 19.3 to 87.7 μg/mL (Supplementary Figure 5). Anti-emicizumab antibodies were detected on at least 2 occasions in 4 of 67 cases (5.9%) (Supplementary Figure 3). In these ADA-positive patients, the individual mean aPTT ratio values were 0.92, 0.77, 0.81, and 0.81, and the individual mean emicizumab concentrations were 27.7, 41.2, 33.8, and 22.6 μg/mL.

On the whole, the present results are in line with previous reports [19] and confirm the low incidence of ADAs. Moreover, clinically significant antibodies that affect PK, causing a decrease in PK and leading to treatment discontinuation, are rare.

### 3.3 | Patients with ADAs: PK/PD profiles

The characteristics of the 4 ADA-positive patients and their PK/PD profiles are shown in Table 2 and Figure. Patient 1, after participating in the HAVEN 1 clinical trial without experiencing bleeding episodes, continued emicizumab prophylaxis. At a certain time, he suffered from a severe medical condition due to the presence of a pseudotumor that required 2 separate surgeries for its removal. After the second surgery, the patient developed an infection with *Klebsiella pneumoniae*, which progressed to sepsis. During hospitalization, emicizumab levels decreased from 39.7 to 18.9 μg/mL, and the aPTT ratio increased from 0.82 to 1.04. Concurrently, the patient experienced a bleeding episode, followed by the detection on 2 occasions of antibodies against emicizumab, which spontaneously disappeared with the partial recovery of his clinical complication.

Patient 2 developed ADA after his fourth dose of emicizumab, concomitantly with a slight reduction in drug levels and the occurrence of a spontaneous bleeding episode. Up to week 25, despite emicizumab levels never falling <31.7 μg/mL and ADAs becoming undetectable after week 7, he experienced 3 additional spontaneous bleeding episodes and 1 posttraumatic episode. At week 25, due to perceived treatment failure, emicizumab prophylaxis was discontinued.

In patients 3 and 4, ADAs were detected at weeks 15 and 9, respectively. These patients did not experience bleeding episodes even though ADAs persisted much longer than those in patients 1

**TABLE 2** Characteristics of ADA-positive patients.

| | Patient 1[a] | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age (y) | 62 | 34 | 12 | 77 |
| FVIII inhibitor at baseline | Yes | No | Yes | Yes |
| Dosing regimen (mg/kg weekly) | 1.5 | 1.5 | 3 | 1.5 |
| First ADA detection (weeks from the first dose) | 309 | 4 | 15 | 9 |
| No. of spontaneous bleeding | 1 | 4 | No | No |
| Site of bleeding | Elbow | Elbow, knee, ankle | No | No |
| Minimum emicizumab level reached (μg/mL) | 17.9 | 31.7 | 25.0 | 17.0 |
| Maximum aPTT ratio reached | 1.04 | 0.81 | 0.88 | 0.92 |

ADA, anti-drug antibody; aPTT, activated partial thromboplastin time.
[a]Patient 1 started emicizumab prophylaxis during the HAVEN 1 clinical trial.

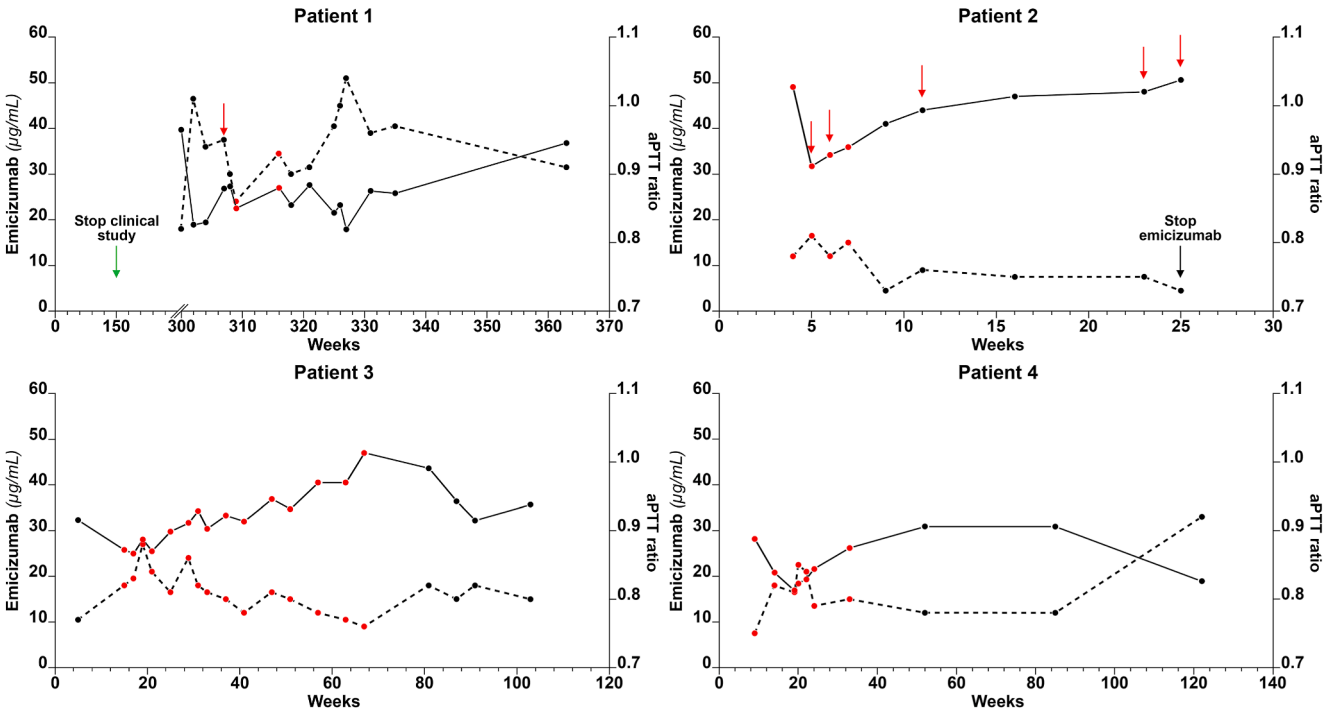


**FIGURE** Variations of emicizumab concentration (solid line) and aPTT ratio (broken line) in patients who developed the anti-emicizumab antibody: red dot, the times of the antibodies' positivity; red arrow, the times of bleeding events. aPTT, activated partial thromboplastin time.

and 2. The minimum emicizumab level reached was 25 and 17 μg/mL in patients 3 and 4, respectively.

Patient 2 had the worst clinical outcome requiring treatment discontinuation. Compared with the 5 previously reported cases in whom emicizumab prophylaxis failure was associated with very low or undetectable emicizumab levels due to completely neutralizing or clearing ADAs [21–25], patient 2 presented treatment failure and ADA positivity without a decrease in emicizumab levels.

To date, when emicizumab discontinuation is needed, patients must resume treatment with other available drugs, thereby losing the benefits provided by this bispecific antibody. For them, it would be of interest to assess whether or not they may benefit from second-generation FVIII-mimetic bispecific antibodies such as mim8 (Novo Nordisk) and NXT007, a novel improved version of emicizumab (Chugai). In this context, we recently reported that the anti-emicizumab antibodies that were developed in people with HA treated with emicizumab did not cross-react *in vitro* with the mim8 molecule [28]. Furthermore, Shima et al. [29] showed that antibodies that developed against NXT007 in people with HA enrolled in a phase 1/2 Study (NXTAGE) do not cross-react with emicizumab [29]. These preliminary data support the views that patients experiencing emicizumab treatment failure due to ADA may soon have the option to switch to other FVIII-mimetic

**TABLE 3** Characteristics of patients without anti-emicizumab antibodies who experienced bleeding.

| Patient | Time to follow-up (wk) | Times to first bleeding (wk) | No. of spontaneous bleeding (site) | Minimum emicizumab level reached (μg/mL) |
|---|---|---|---|---|
| BL-1[a] | 370 | 320 | 1 (knee); 1 (shoulder) | 42.3 |
| BL-2[a] | 311 | 311 | 1 (elbow) | 54.1 |
| BL-3 | 89 | 58 | 1 (ankle) | 64.0 |
| BL-4 | 99 | 8 | 1 (ankle) | 53.5 |
| BL-5 | 193 | 86 | 1 (knee); 7 (treated hip pain) | 35.4 |
| BL-6 | 157 | 131 | 1 (elbow) | 35.8 |
| BL-7 | 49 | 19 | 1 (knee) | 32.3 |
| BL-8 | 106 | 59 | 1 (ankle) | 72.0 |
| BL-9 | 46 | 15 | 1 (shoulder); 1 (elbow); 2 (treated synovitis) | 35.0 |
| BL-10 | 100 | 67 | 1 (ankle) | 55.4 |

[a]Patients BL-1 and BL-2 participated in pivotal clinical trials, during which bleeding episodes were also reported.

bispecific antibodies and thus maintain the benefits associated with this therapeutic approach.

### 3.4 | Patients without ADAs experiencing bleeding episodes

Episodes of spontaneous bleeding have been observed also in 10 patients who tested negative for ADAs and maintained normal emicizumab levels (Table 3). The bleeding episodes were mainly in the joints; furthermore, patient BL-5 experienced several episodes of hip pain, while patient BL-9 had 2 episodes of synovitis.

Patients BL-1 and BL-2, who had previously experienced the first bleeding episode within the first 15 weeks during the pivotal HAVEN trial, also bled after >300 weeks of exposure. For the remaining 8 cases (BL-3 to BL-10), the median time to the first bleed was 58.5 weeks (range, 8-131 weeks). The minimum emicizumab level observed in the group of 10 bleeding patients experiencing bleeding episodes was 32.3 μg/mL.

A summary table comparing clinical and demographic characteristics of ADA-negative and ADA-positive patients experiencing bleeding episodes is provided in Supplementary Table 1.

## 4 | CONCLUSION

On the basis of the present longitudinal cohort study with rigorous interval-based evaluation of cases switched to emicizumab, we confirm that the incidence of anti-emicizumab antibodies is low (5.9%) particularly with regard to those of clinical relevance, and that routine monitoring of ADAs may not be warranted in the absence of clinical suspicion. Therefore, monitoring for anti-emicizumab antibodies is advocated in patients presenting with bleeding manifestations and/or when treatment failure is suspected.

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## AUTHOR CONTRIBUTIONS

C.V. and F.P. designed the study. S.A. and A.T. collected patients' data. C.V., L.S., and C.N. performed the experiments. C.V. and L.S. analyzed the results. C.V. wrote the manuscript. F.P. critically revised the manuscript. All authors revised and approved the final manuscript.

## RELATIONSHIP DISCLOSURE

F.P. has received honoraria for participating as a speaker in education meetings and symposia organized by Takeda and Sanofi and is a consultant/member of the advisory boards for CSL Behring, Biomarin, Roche, Sanofi, Sobi, and Pfizer. The remaining authors declare no competing financial interests.

## ORCID

*Flora Peyvandi* https://orcid.org/0000-0001-7423-9864


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## SUPPLEMENTARY MATERIAL

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