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BRIEF REPORT

Emicizumab initiation and bleeding outcomes in people with hemophilia A with and without inhibitors: A single-center report

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Abstract

Background: Emicizumab, a bispecific antibody factor VIII mimetic, is approved for prophylaxis in hemophilia, and has different risks and side effects compared to factor VIII products.

Objective: To better understand the early impact of emicizumab on our patients at the University of Colorado Hemophilia and Thrombosis Center (UCHTC), we evaluated adverse reactions, factor prophylaxis overlap, and bleeding rates after starting emicizumab through a quality improvement project.

Patients/Methods: A retrospective chart review and structured phone interview were conducted from June to September 2019 for all patients who had started emicizumab at the UCHTC. Data about emicizumab dosing, reactions, bleeding events, and bleeding treatment were collected in 68 children and adults (aged 0.55-79.8 years, on emicizumab a median 213 days; range, 51-1229 days) with hemophilia A (35.3% with past or current inhibitor).

Results: Adverse reactions were primarily skin reactions, with no anaphylactic reactions or thrombosis. Bleeding events, defined as pain or swelling treated with factor or supportive measures, demonstrated wide variability, with 25 of 68 experiencing zero bleeds and 5 of 68 experiencing >8 bleeds per year. The most prevalent bleed type was traumatic musculoskeletal bleeding. Bleeding events occurred more often in the first 10 weeks after starting emicizumab, but no time period was without bleeding events. The majority of patients were prescribed every-week or every-2-week dosing, but some had alternative dosing frequency.

Conclusions: Real-world emicizumab use in our center was characterized by variations in prescribing practices and bleeding outcomes and lack of severe adverse reactions.

KEYWORDS
bleeding, emicizumab, factor VIII, hemophilia, hemophilia A

Essentials

- Patients on emicizumab should be closely monitored for bleeding or other adverse outcomes.
- No thrombotic events occurred in patients from our clinic while using emicizumab.
- Wide variability was seen in bleeding rates and types.
- Continued surveillance is needed.

1 | INTRODUCTION

Hemophilia A is a disorder characterized by recurrent bleeding episodes treated with factor VIII (FVIII) replacement. In severe hemophilia A, prophylaxis via regular FVIII intravenous infusion is the standard of care to minimize bleeding.[1] Emicizumab (HEMLIBRA, Genentech/Roche, San Francisco, CA, USA) is a bispecific antibody that binds activated factor IX and factor X, simulating the action of FVIII. Because emizicumab is given subcutaneously and less frequently than FVIII prophylaxis, with clinical trials showing low bleeding rates,[2-6] it has been increasingly adopted by persons with hemophilia A of all severities with and without inhibitors since its approval by the US Food and Drug Administration and European Medicines Agency in 2018. However, given the relative novelty of this new class of medication, real-world uncertainties and questions remain, including the importance of concomitant FVIII prophylaxis during the loading period, medication side effects, dose frequency flexibility, and the management of bleeding events.

To better understand the early impact of emicizumab on persons with hemophilia A at the University of Colorado Hemophilia and Thrombosis Center (UCHTC), we developed local guidelines and carefully tracked patients starting emicizumab. Here, we report our single-institution real-world experience with the initiation of emicizumab in pediatric and adult patients, with a focus on (1) practice variation in medication initiation, (2) adverse reactions, and (3) bleeding episodes while on emicizumab.

2 | MATERIALS AND METHODS

2.1 | Institutional guidelines

Because the UCHTC has many providers (three adult, six pediatric, and two advanced practice) and patients (≈450 persons with hemophilia A), clear communication and consistency are important. We created guidelines for emicizumab administration. These recommended that the first dose of emicizumab be administered and observed at a medical facility. Dosing recommendations were consistent with the package insert (PI)[7] but allowed for altered frequency of maintenance emicizumab dosing (with total monthly dose 6 mg/kg) to decrease drug waste and cost. Decisions about overlapping factor prophylaxis during emicizumab loading were made using shared decision making with patients, based on individual patient intravenous access limitations and perceived bleeding risk.

2.2 | Data collection

Data were tabulated on all patients, with or without inhibitors, who were treated with emicizumab for at least 4 weeks as of September 1, 2019, and entered into a Research Electronic Data Capture database. An active inhibitor at the time of starting emicizumab was determined if the bleeding treatment plan used a bypassing agent rather than FVIII. Data were collected from the electronic medical record system via chart review, focusing on treatment before emicizumab initiation (on demand, prophylaxis, or immune tolerance induction [ITI]), emicizumab start date, dosing regimen, location of administration, documentation of reactions, clinical bleeding events, and change in physical activity. To ensure no bleeding events or reactions were missed, structured phone interviews were conducted with patients/parents/guardians at the end of the observation period. Bleeding episodes were defined as pain and/or swelling treated with supportive measures (rest, ice, compression, etc) or medications. This effort was designated as quality improvement by the Colorado Multiple Institutional Review Board (#20-1394).

2.3 | Statistical analysis

Annualized bleeding rate (ABR) was calculated for patients followed for >6 months by dividing the number of bleeding events by the annualized time of follow-up. Because there have been fewer clinical trials with emicizumab in children, and because differences in movement patterns, skeletal development, and previous joint damage between children and adults could lead to bleeding differences, bleeding rates in children (<18 years old) relative to adults (≥18) were compared using the Mann-Whitney *U* test, and the percentage of children versus adults with bleeding events was compared using the chi-squared test. The follow-up times for children versus adults were compared using the *t* test. Number of bleeds during the first month on emicizumab (loading period) for patients with or without

overlapping FVIII prophylaxis and with active inhibitors were compared using the Kruskal-Wallis test.

3 | RESULTS AND DISCUSSION

3.1 | Demographics and pre-emicizumab clinical status

Our data set included 68 individuals who received emicizumab for >1 month, for a total of 55.2 person-years. A current or past history of an inhibitor was present in 24 of 68 (35.3%), and 8 of 68 (11.8%) had active inhibitors at the time of starting emicizumab. The observed age of the cohort ranged from 0.55 to 79.8 years, with a median age of 12.8 years. Most patients (79%) had severe hemophilia A, although 12 of 68 (18%) had moderate and 2 of 68 (3%) had mild hemophilia A (FVIII activity levels 5.1% and 7.8%). Before emicizumab, 49 of 68 (72%) used standard or extended half-life factor prophylaxis, with the remainder on on-demand treatment. Our FVIII prophylaxis practice is to start standard half-life FVIII 20 to 25 U/kg 3 to 4 times per week within the first year of life, and increase to higher doses or extended half-life FVIII products if breakthrough bleeding occurs. Patients switched to emicizumab after a shared decision-making discussion of risks and benefits with the provider. In general, patients with difficult venous access or poorly controlled bleeding were more likely to switch to emicizumab. The median duration of emicizumab use was 213 days (observed range, 51-1229). Hemophilia Joint Health Scores (HJHS)[8] before emicizumab initiation were available for 53 patients. The per-joint HJHS averages were 0.72 (range, 0-13) for 3- to 9-year-olds, 2.45 (range, 0.9-6.3) for 10- to 18-year-olds, and 5.65 (range, 0.8-10.1) for >18-year-olds, similar to an age-based HJHS analysis of persons with severe hemophilia A from the UCHTC before emicizumab's approval.[9]

TABLE 1 Descriptive statistics on emicizumab treatment and patient parameters

Treatment or patient parameter	Patients, n (%)
Received emicizumab >1 month (completed loading)	68 (100)
Age <18 y	41 (60.3)
History of inhibitor	24 (35.3)
History of inhibitor >5 BU	17 (25)
Plan for rFVIIa as first-line bleed treatment on emicizumab ("active inhibitor")	8 (11.8)
Inhibitor titer >5 BU when starting emicizumab[a]	3 (4.8)
Duration on emicizumab (as of September 1, 2019)	
<3 mo	5 (7.4)
3-6 mo	20 (29.4)
6-12 mo	28 (41.2)
>12 mo	15 (22.1)
Factor VIII overlap with emicizumab	
None	35 (51.5)
1 wk	4 (5.9)
2 wks	25 (36.8)
4 wks	3 (4.4)
10 wks	1 (1.5)
Maintenance dosing	
1.5 mg/kg/dose wk	29 (42.6)
3 mg/kg/dose, every 2 wks	29 (42.6)
6 mg/kg/dose, every 4 wks	7 (10.3)
6 mg/kg/mo, alternative dosing schedule	3 (4.4)

Abbreviations: BU, Bethesda units; rFVIIa, recombinant activated factor VII.

[a]Five patients had missing data, i.e., did not have inhibitor assays drawn immediately before starting emicizumab.

3.2 | Emicizumab Loading and Maintenance

Of the 68 patients in the data set, 65 (95.6%) started emicizumab with loading doses. FVIII prophylaxis overlap during emicizumab loading is shown in Table 1. One toddler with a strong family history of inhibitor received daily FVIII for 50 doses of factor to minimize inhibitor risk before transitioning to on-demand FVIII. No patients developed new FVIII inhibitors on emicizumab. No patients on ITI before emicizumab continued ITI after starting emicizumab.

All initial doses were administered under medical supervision to monitor for allergic reactions and provide patient education. Subsequent doses were given either at home or at medical facilities depending on educational needs of the patient/family. Thirty-seven percent (24/65) of patients had only one dose in a medical facility, with 26% (17/65) receiving all four loading doses in a medical facility.

Of 48 patients who clarified adverse reactions to emicizumab via follow-up phone interview, 7 of 48 (14.5%) reported a reaction at the start of emicizumab, primarily localized reactions including redness, swelling, welts, stinging, burning, bruising, or itching at injection site; 9 of 47 (19.1%) reported a reaction to emicizumab over their treatment course. Injection site reactions are reported for 22% of patients in the PI and 15% to 25% of patients in the literature.[2,3] No patients experienced anaphylaxis, symptomatic thrombosis, or death. Maintenance emicizumab doses are shown in Table 1. All patients were prescribed a total of 6 mg/kg/mo. Eight (12%) patients reported missing doses of emicizumab.

3.3 | Bleeding episodes

A total of 135 bleeding episodes were reported in 43 of 68 (63.2%) of patients while using emicizumab. Bleeding events from chart review were confirmed by phone in 48 of 68 patients. Bleeding occurred more frequently in the first 10 weeks (Figure 1). We did not observe any difference between bleeding episodes during the loading period when comparing persons with hemophilia A using FVIII prophylaxis overlap, no prophylaxis overlap, or with active inhibitors ($P = 0.7$).

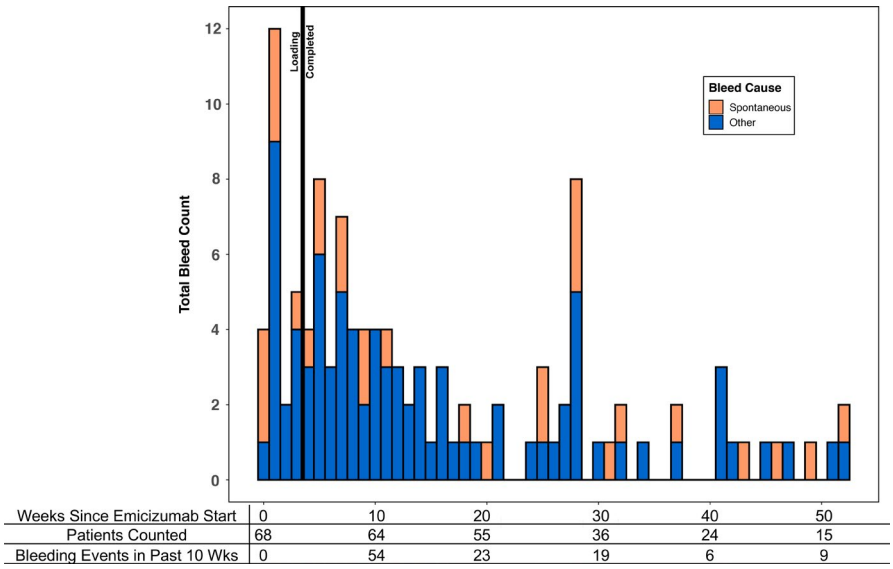

FIGURE 1 Bleeding pattern after starting emicizumab. The total number of bleeds are charted after starting emicizumab. Spontaneous bleeds are shown in orange and traumatic or other bleeds are shown in blue in the stacked histogram

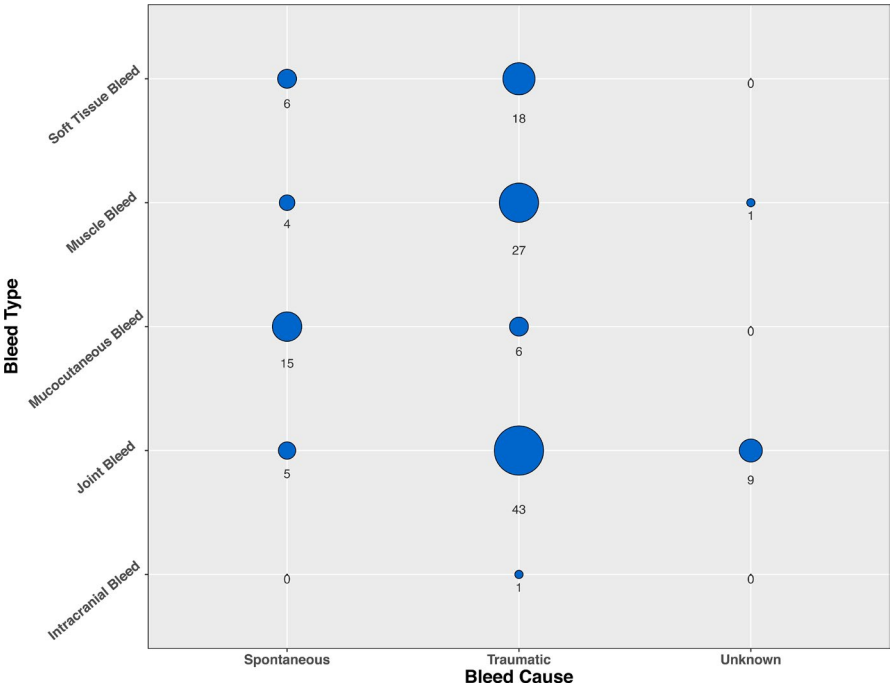

FIGURE 2 Location and nature of bleeding events in emicizumab-treated persons with hemophilia A. All 135 bleeding events were categorized by their bleeding type and patient-identified underlying cause. Numbers represent number of bleeds in each category

The sample size was underpowered (β = 6%) to detect a difference, but the achieved effect size ($\eta^2 = 0.05$) was small, suggesting a low likelihood of clinically significant differences among these groups.

The median ABR of patients treated with emicizumab >6 months (n = 48) was 1.21 (mean, 2.3; observed range, 0-17.8; interquartile range, 0-2.53). This suggests wide variability in emicizumab bleeding rates, with half of patients having ≤1.21 bleeding events per year. Eight (12%) patients had an ABR >5, including six who were followed for <1 year, and five (7%) patients had an ABR >8, including four who were followed for <1 year. Bleeding rates did not differ significantly between the patients on an active inhibitor (median, 0.80; mean, 1.4; range, 0-6.1) and the patients not on an inhibitor (median, 1.9; mean, 2.5; range, 0-17.8; $P = 0.60$), but did differ between children (median, 1.9; mean, 3.0; range, 0-17.8) and adults (median, 0; mean, 0.6; range, 0-10.7; $P = 0.007$). More children than adults had at least one bleeding episode after emicizumab loading (26/41 [63%] children vs 10/27 [37%] adults; $P = 0.05$), although children were followed somewhat longer than adults (mean, 324.8 days for children, 252.9 days for adults; $P = 0.22$).

The majority of bleeding events were characterized by patients as trauma-related (95/135; 70.4%), with 30 of 135 (22.2%) categorized as spontaneous (Figure 2). This supports the hypothesis that emicizumab transforms severe-moderate hemophilia to a milder phenotype, in which the majority of bleeding is attributable to traumatic injuries.[10,11]

Forty-seven patients reported their physical activity changes with emicizumab, with 26 (55%) reporting more physical activity than before starting emicizumab, 21 (45%) reporting similar physical

activity, and no patients reporting a decrease in physical activity after starting emicizumab. Twelve patients (seven children and five adults) reported trying new types of physical activities after starting emicizumab, ranging from walking more to lifting weights to playing dodge ball. Two children who started new activities reported a total of five bleeds related to soccer, dodge ball, kickball, and weightlifting. Specific bleeding data related to sports started before emicizumab were not available.

When classifying bleeds by type, the highest proportion of bleeds (57/135; 42.2%) were joint bleeds, with 32 of 135 (23.7%) muscle, 24 of 135 (17.8%) soft tissue, 21 of 135 (15.6%) mucocutaneous, and 1 (0.7%) traumatic intracranial bleed (Figure 2). Treatment of bleeds consisted of supportive measures without factor for 30 of 135 bleeds (22%), treatment with FVIII for 74 of 135 (55%), and treatment with recombinant activated factor VII (rFVIIa) for 29 of 135 (21%); for 2 bleeds, treatment was not reported. For bleeding episodes treated with FVIII, 45 of 74 (62%) were treated with a single dose, 11 of 74 (15%) were treated with two doses, and 17 of 74 (23%) required more than two doses of factor. For bleeds treated with rFVIIa, 21 of 29 (70%) were treated with a single dose, 1 of 29 (3%) required two doses, and 8 of 29 (28%) required more than two doses.

A recent report on the use of emicizumab in a pediatric population with inhibitors with a follow-up of 22 to 58 weeks demonstrated no reported joint bleeding but the requirement of rFVIIa for other hemostatic challenges (surgery and trauma).[12] We found a higher rate of patients with joint bleeding (36.8%). This could be due to our cohort including adults with hemophilia A who may have had more baseline joint disease and synovial fragility than the pediatric patients described by Barg et al[12]; however, in our study, more children than adults had at least one bleed. Another recently published experience with emicizumab in 42 patients with and without inhibitors demonstrated an overall bleeding rate of 33.3%, divided equally among patients on inhibitors and patients not on inhibitors.[13] We found similar percentages of total bleeds: 42.2% versus 44% for joint bleeds and 57.8% versus 56% for nonjoint bleeds.[13] One limitation of our work is the methodology of data collection regarding bleeding. As this project was focused on the early impact of emicizumab at our local center, we did not collect data similar to the HAVEN 1-4 clinical trials. However, we ensured that our data collection was consistent, and we feel it is similar to other reports.[13] Another significant limitation of our work is our relatively short follow-up, and thus it may be subject to more variability.

Variations in prescribing practices were noted. First, overlap of factor prophylaxis during the loading period was variable, with factor regimens ranging from no overlap to 10 weeks. The emicizumab PI states, "The prophylactic use of factor VIII (FVIII) products may be continued during the first week of HEMLIBRA prophylaxis."[7] Our variation in concomitant factor prophylaxis decisions is likely due to variations in physicians' perception of individual bleeding risk weighed against the individual's intravenous infusion challenges. The duration of overlapping prophylaxis was not significantly associated with bleeding rates, however. Second, although the majority of patients were treated according to PI dosing, in three cases alternative dosing regimens were chosen to minimize medication waste while maintaining an overall monthly dose of 6 mg/kg. Although it is difficult to draw any statistical conclusions, the three patients on alternative dosing did not seem to bleed more than patients on PI dosing.

In conclusion, we report our real-world experience using emicizumab in a large US hemophilia treatment center with pediatric and adult patients. We report a range of emicizumab and factor prophylaxis overlap dosing regimens. Our bleeding data suggest that patients on emicizumab continue to have bleeding events and that the majority of these are trauma-related. Additional studies are needed—for example, the American Thrombosis and Hemostasis Network ATHN-7 study (https://clinicaltrials.gov/ct2/show/NCT03619863)—to better understand the long-term effects of emicizumab.

RELATIONSHIP DISCLOSURE

MM-J reports personal fees from Biomarin, CSL Behring, Genentech, Freeline, Sparks Therapeutics, and Takeda, outside the submitted work. TWB reports personal fees from Tremeau Pharmaceuticals, uniQure, BioMarin, CSL Behring, Pfizer, Genentech/Roche, Kedrion, Spark, Novo Nordisk, and Takeda, outside the submitted work. MW reports personal fees and nonfinancial support from Bayer Healthcare, Bioverativ, CSL Behring, Novo Nordisk, Roche/Genentech, HEMA Biologics, and Takeda; and personal fees from Biomarin, outside the submitted work. CJN reports personal fees from Takeda and CSL Behring, outside the submitted work. The remaining authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

BBW contributed to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. AC contributed to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. MM-J contributed analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. BRB contributed analysis and/or interpretation of data; critical writing or revising the intellectual content, and final approval of the version to be published. TWB contributed analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. GM contributed analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. EG contributed analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. DT contributed analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. MW contributed to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual

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