Infant and toddlers with Severe Hemophilia A with Inhibitor on Prophylaxis with Emicizumab

Jessica Garcia[1-2] and Ayesha Zia[1-2]

[1] UT Southwestern, Dallas, Texas, USA

[2]Children's Medical Center, Dallas, Texas, USA

Correspondence: Jessica Garcia, MD

University of Texas Southwestern Medical Center

Pediatric Hematology/Oncology

5323 Harry Hines Blvd, Dallas, Texas

Email: Jessica.Garcia@utsouthwestern.edu

Phone: 214-456-8556

Fax: 214-648- 2764

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Abbreviations	
BU	bethesda unit
CVC	central venous catheter
ED	exposure day
F	factor
Fc	fragment crystallizable
ICH	intracranial hemorrhage
ITI	immune tolerance therapy
mo.	months
PHA	persons with hemophilia A
r	recombinant
SHA	severe hemophilia A
TMA	thrombotic microangiopathy
yr.	years

Abstract:

Emicizumab is a recombinant, humanized, and bispecific monoclonal antibody that bridges activated factor (F) IX and FX in place of FVIII to restore hemostasis in persons with hemophilia A (PHA). Data on the efficacy and safety of emicizumab in young children is limited. Immunologic naivety, physiologically decreased production of vitamin K dependent proteins, specifically FIX, and enhanced clearance of emicizumab in infants may support decreased emicizumab effectiveness. We report on the facilitation of care rendered by using emicizumab in young PHA with inhibitors and extend data on the efficacy and safety in PHA < 3 years.

Introduction:

The therapeutic landscape for persons with hemophilia A (PHA) has undergone significant changes with the introduction of non-factor(F) VIII (FVIII) products, such as emicizumab. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges the enzyme activated FIX and substrate, FX to restore the function of missing FVIII to promote hemostasis .[1] Emicizumab is administered subcutaneously, which is appealing for young patients or those with difficult venous access, therefore, abolishing the need for central venous catheter (CVC) insertion and by extension, reduction in the possible risk of infection and line-associated thrombosis. Randomized controlled trials have shown the efficacy and safety of emicizumab in PHA with and without inhibitors; however, data are limited for PHA <3 years of age in these studies.[2] Despite the limited clinical trial data in very young patients, the Medical and Scientific Advisory Council recommends that infants be considered for prophylaxis with emicizumab any time after birth, given the increased risk for spontaneous intracranial hemorrhage (ICH) before FVIII prophylaxis.[3] Efficacy and safety concerns in infants are biologically plausible , given the differences in the hemostatic system and pharmacokinetics in the very young. Herein, we

present three cases, an infant and two toddlers with severe hemophilia A (SHA) with inhibitors, on emicizumab and their clinical outcomes.

Results:

Case 1: A 6-month-old male presented with spontaneous ICH requiring emergent decompressive craniectomy and was diagnosed with SHA. On recombinant FVIII (rFVIII) replacement therapy, the patient developed a FVIII inhibitor (0.6 BU) on exposure day (ED) 20, which continued to climb (0.9 BU) on ED 26. Given a complicated social situation, immune tolerance induction (ITI) was not undertaken, and via shared decision-making, we initiated prophylaxis with emicizumab. He continues on emicizumab without the need for a CVC at the time of writing this report (almost one year) and has not experienced breakthrough bleeding or any adverse events. He is managed by other providers for his ICH sequela (blindness, cerebral palsy, and feeding difficulties). We plan to reintroduce FVIII when older and peripheral infusions are feasible.

Case 2: A 6-month-old male presented with spontaneous ICH requiring emergent decompressive craniectomy and was diagnosed with SHA. He was initiated on rFVIII replacement therapy and developed a FVIII inhibitor (0.9 BU) on ED 24. He underwent CVC placement and was started on ITI with rFVIII (200 units/kg/day). His peak FVIII inhibitor titer was 448.0 BU after 14 months of ITI. He developed a knee joint bleed and was initiated on emicizumab for prophylaxis at 19 months of age. The most recent chromogenic FVIII inhibitor level is 358.4 BU. He has continued ITI with rFVIII (100 units/kg MWF) and prophylaxis with emicizumab for 9 months. Emicizumab prophylaxis has allowed less frequent port accesses, and he continues without a breakthrough bleed or side effects from emicizumab.

Case 3: A 3-day-old male presented with post-circumcision bleeding and was diagnosed with SHA. At 17-months-of-age he received recombinant FVIII Fc-fusion protein (rFVIII-Fc) for strabismus surgery. He was not initiated on prophylaxis, given the lack of bleeding symptoms. A month later, he developed a spontaneous elbow joint bleed and received 4 doses of rFVIII-Fc with minimal improvement. A high-titer FVIII inhibitor level was detected at 64.6 BU. He received recombinant factor VIIa for acute bleeding and prophylaxis of bleeding until the high-titer FVIII inhibitor fell to <10 BU. Via a shared decision-making process, emicizumab alone was initiated for bleeding prophylaxis compared to our preferred option of ITI with rFVIII-Fc with emicizumab without requiring a CVC . The patient remains on emicizumab for prophylaxis at the time of writing this report (~15 months) and has not experienced breakthrough bleeding nor any side effects from emicizumab.

Discussion:

This report extends real-world data on three cases of young pediatric patients with SHA with inhibitors where emicizumab facilitated clinical care incorporating caregiver preferences or social situations without comprising care (Table 1). Further, emicizumab was safe and provided effective hemostatic control following life-threatening and major bleeding during ITI in young pediatric patients.

The HAVEN trials have established emicizumab as the standard of care in PHA with and without inhibitors. Of the 4 HAVEN trials, the HAVEN 2 trial was specifically designed for children <12 years of age with allowance for participants <2 years of age after the protocol-defined interim data review criteria were met. Eight children <2 years were ultimately included in the trial. The HAVEN 2 trial showed lower bleeding rates on emicizumab than bypassing agents; however, efficacy data and reduction in treatment burden and quality of life data were not

separately reported for the < 2-year cohort. However, real-world data on emicizumab in very young PHA and inhibitors is in line with our paper, which shows that emicizumab is efficacious and safe in very young PHA and inhibitors. In a study from Israel, 11 patients with SHA with inhibitors initiated on emicizumab between the ages 9 to 80 months and a 2-month-old patient with ICH, all followed prospectively had a reduction in bleeds, without adverse events.[4] Corroborated by another study on patients < 3 years of age with inhibitors [5] In contrast to these data, a 2-month-old patient from Israel initiated on emicizumab experienced a severe post-circumcision bleed when receiving emicizumab alone and required a blood transfusion.[4] An immature hemostatic system given the age and/or the need for FVIII replacement before the procedure may have contributed. FIX, and FX are lower in newborns and very young infants'.[6] and required for emicizumab to bind and promote hemostasis.

In conclusion, we summarize real-world data demonstrating that prophylaxis with emicizumab was efficacious and safe in very young patients with SHA and inhibitors when administered alone or in conjunction with ITI. Emicizumab may provide a weekly, subcutaneous, prophylactic, therapeutic option for very young children with hemophilia A with inhibitors, specifically when CVC placement is not possible, or ideal for bleeding prophylaxis while receiving ITI for the eradication of an inhibitor. Further studies are needed, especially for patients < 6 months when the hemostatic system is particularly immature, and/or pharmacokinetics differ from older children and adults.

Conflicts of interest statement: The authors have no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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Legends:

Table 1 Graph summarizing current real-world data on safety and efficacy of emicizumab in children <3 years of age with severe hemophilia A and inhibitor.