

Allergy and inhibitors in hemophilia - a rare complication with potential novel solutions



Sarina Levy-Mendelovich^{a,b,*}, Tami Livnat^{a,b}, Assaf Arie Barg^{a,b}, Mona Kidon^{a,c},
Tami Brutman-Barazani^b, Gili Kenet^{a,b}

^a Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^b The Israeli National Hemophilia Center and Thrombosis Unit, The Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Israel

^c Pediatric Allergy Clinic, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel

ARTICLE INFO

Editor: Mohandas Narla

Keywords:

Hemophilia A

Hemophilia B

Allergy

Anaphylaxis

Thrombin generation

ABSTRACT

Introduction: Hemophilia is a rare bleeding disorder caused by a deficiency of the plasma coagulation factors VIII and IX (hemophilia A [HA] and hemophilia B [HB], respectively). Replacement therapy with clotting factor concentrates is the mainstay of treatment. Unlike in patients with HB, anaphylaxis in patients with HA is extremely rare.

Methods: A retrospective study of prospectively collected data on patients with hemophilia who experienced anaphylaxis was conducted in our center. Demographic and clinical data were collected, and laboratory workups that included thrombin generation were conducted.

Results: Our first patient underwent successful immune tolerance induction (ITI) following the administration of rituximab. The second patient was transitioned to emicizumab. The third patient receives recombinant activated VIIa (rFVIIa) on demand. Thrombin generation was performed following current medical management protocols for supporting hemostasis.

Discussion: Our case series illustrates the difficulty in managing patients with anaphylaxis to replacement therapy. In the era of novel therapies, such as emicizumab, the management of HA patients who experience anaphylaxis to replacement therapy is becoming easier and may obviate the need for ITI. Current treatment strategies for HB patients with such anaphylaxis, however, are limited to rFVIIa, and it continues to pose a challenge.

1. Introduction

Hemophilia is a rare bleeding disorder caused by a deficiency of plasma coagulation factors VIII and IX (hemophilia A [HA] and hemophilia B [HB], respectively). Replacement therapy with clotting factor concentrates is the mainstay of treatment [1], but inhibitor formation (30% in HA and 1–6% in HB) may render it ineffective [2,3]. Interestingly, anaphylactic reactions to factor (F) IX concentrates among patients with HB have been reported in association with inhibitor occurrence [4], and mostly among patients with complete gene deletions. Since anaphylactic reactions typically occur early, i.e., following the first 5-to-20 exposure days (ED), caution is often required, with administration taking place in a clinical setting equipped to manage such emergencies [5].

Unlike patients with HB [6–8], anaphylaxis to replacement therapy in patients with HA is extremely rare. In the few cases that have been published, it was associated with the use of cryoprecipitates [9], with low and intermediate purity plasma-derived (P-d) Factor VIII (FVIII) concentrates [10,11,15], and with some recombinant products [12,13].

The underlying mechanism of such adverse reactions remains to be delineated. It may be attributed to human anti-mouse antibody or to the presence of antibodies to human albumin. For example, clotting concentrates were purified using mouse anti-FVIII antibody, and some recombinant products were stabilized with additional albumin [14]. Some reports suggested that it may be mediated by immunoglobulin E (Ig E) or complement [16], while others suggested IgG2 or IgG4 as the causative agents [12,17].

Notably, the ideal treatment for the eradication of inhibitors is

* Corresponding author at: National Hemophilia Center & Coagulation Unit, Amalia Biron Research Institute of Thrombosis & Hemostasis, Sheba Medical Center, Tel Hashomer 52621, Israel.

E-mail address: Levysarina@gmail.com (S. Levy-Mendelovich).

<https://doi.org/10.1016/j.bcmd.2019.102370>

Received 24 August 2019; Accepted 22 September 2019

Available online 20 October 2019

1079-9796/© 2019 Elsevier Inc. All rights reserved.

immune tolerance induction (ITI) with high-dose replacement therapy [2,18]. Additional bypass agents (e.g., recombinant activated FVII [rFVIIa]) or activated prothrombin concentrates (APCC) are often applied to treat breakthrough bleeds. Unfortunately, neither the use of high-dose FVIII or FIX concentrates nor the application of APCC (in HB anaphylaxis) are feasible in the setting of anaphylaxis.

We report our experience with three hemophilia patients, two with HA and one with HB, who experienced anaphylactic reactions to replacement therapy. Treatment strategies, including the application of novel therapies and means of monitoring, will be discussed.

2. Patients and methods

2.1. Patients

The Israeli National Hemophilia Center is a tertiary referral institute providing comprehensive care to about 700 patients with hemophilia. A retrospective study of prospectively collected data was conducted in our center, and it included all the patients with hemophilia who experienced anaphylaxis to replacement therapy. The study was approved by the institutional ethical committee in compliance with the Declaration of Helsinki.

2.2. Laboratory workup

The patients' plasma samples were obtained in citrated tubes for the assessment of coagulation parameters and thrombin generation (TG) during routine clinic visits. Coagulation assays on including: activated partial thromboplastin time, FVIII, and FIX, and inhibitor tests (measured as Bethesda units [BU]) were performed using an ACL-TOP autoanalyzer (Instrumental Laboratories, Bedford, MA, USA), and HemosIL reagents. Testing for an inhibitor anti-FVIII/FIX according to Triplett & Harms was carried out in all patients [19].

2.2.1. Thrombin generation

TG was measured in platelet poor plasma (PPP) using the calibrated automated thrombinography method as described elsewhere [20,21] IgE antibodies against Chinese hamster ovary (CHO) host cell proteins (HCP) were also investigated among the patients who presented with allergic response after treatment with extended half-life pegylated products, since the protein expression is made using a CHO cell line [22].

2.2.2. Allergic investigation

All patients were referred to our pediatric allergy clinic for skin testing, which is an indirect measure of allergen-specific IgE bound to mast cells. The skin prick test involved the use of a device that pricked the skin through a droplet of the relevant factor at full concentration, followed by an intradermal test with 0.01 ml of the relevant factor at 1:100 and 1:10 dilutions. The local skin reaction was measured after 15–20 min [23]. A positive test was considered as the formation of a wheal equal to or larger than the histamine control or, alternatively, a wheal larger than 3 mm above the negative control [24].

3. Results

3.1. Patient 1

This 13-year-old boy had received on-demand therapy consisting of full-length rFVIII (Table 1). At the age of two years following 20 ED, he experienced abdominal pain, severe hypotension, respiratory distress, and a urticarial rash 10 min after the injection. He was managed with adrenaline, fluids, and hydrocortisone. Shortly thereafter, FVIII inhibitor at a level of 40 BU was diagnosed, and it peaked to 120 BU after 3 weeks. A skin prick test and an intradermal test at a concentration of 1:100 were negative, while a 1:10 concentration of rFVIII produced an

Table 1
Demographic and clinical characteristics.

Patient no., sex	Current age (years)	Type of hemophilia	Gene mutation	Family history of hemophilia	Clinical presentation of hemophilia	Inhibitor (BU)
1, male	13	A	Inversion of intron 22	No	Bleeding at circumcision at 8 days of life	40–120
2, male	5.5	A	c.3439C > T p.Gln1147X	Yes	Tested after delivery due to family history	30–90
3, male	5	B	c.54C > p.Cys18X	No	Bleeding at circumcision at 8 days of life	60

BU, Bethesda units.

immediate wheal and flare reaction of 8 mm, consistent with an IgE-mediated response to this drug. A port-a-cath was inserted, and ITI was started with various P-d concentrates given one at a time. Each concentrate was stopped after an allergic reaction was encountered, and treatment was switched to an alternative concentrate. These concentrates included Optivate (BPL, England), Koate-DVI (Grifols, Spain), and Hemophil-M (Baxter, US) at a dose of 100 IU/Kg thrice weekly. The patient continued to sustain multiple hemarthroses and had recurrent admissions to the hospital following traumatic bleeding episodes which were difficult to treat. Hemostasis was eventually controlled by combined concomitant therapy consisting of APCC (FEIBA 50 IU/kg/dose [Baxalta Innovations, GmbH, Wien, Austria]) and rFVIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark, 270 µg/kg). Fortunately, following Rituximab (375 mg/m²) therapy, as previously described [25], the continuous search by skin testing for a therapy option revealed that he did not harbour IgE against haemate P (CSL Behring, Italy). That finding enabled the administration of haemate P. Two years following therapy no inhibitor was measures. The patient's condition is currently well-controlled with haemate P prophylaxis at a dose of 50 units/kg thrice weekly. Further support of the achievement of hemostasis was demonstrated by means of TG analysis that showed a dramatic increase in TG in the patient's plasma following haemate P administration (Fig. 1A). It should be noted that this child exhibited multiple food allergies, which may explain the pathogenesis underlying his anaphylaxis to multiple replacement agents.

3.2. Patient 2

This 5.5-year-old boy presented at the age of 1.5 years with diffuse urticarial rash several minutes following the administration of recombinant polyethylene glycol (PEG) FVIII on ED 22 (Table 1). The allergic reaction resolved following administration of methylprednisolone and antihistamine. IgE directed against various FVIII products was detected following this episode. There was no IgE against PEG or CHO HCP, thus confirming that the allergy was against the FVIII alone [26]. Allergy skin prick testing was negative, however, intradermal tests at relevant concentrations yielded positive results of wheal and flare with multiple rFVIII products, as well as with pdFVIII, all of which are reactions consistent with an IgE-mediated reaction to FVIII. Since ITI was contraindicated, prophylaxis therapy with rFVIIa 270 µg/kg thrice weekly was provided. Following negative skin prick testing results to emicizumab, he was transitioned to the novel subcutaneous therapy (3 mg/kg loading dose for 4 weeks followed by 1.5 mg/kg once weekly) and there have not been any allergic reactions since. TG was performed

following a steady state of emicizumab and it confirmed its hemostatic efficacy (Fig. 1B).

3.3. Patient 3

This 5-year-old boy was started on demand therapy with a long-acting pegylated recombinant factor IX (rFIX) concentrate and developed a rash after the second ED (Table 1). Re-exposure using another FIX concentrate was attempted in a hospital setting and it caused rash and angioedema for which the boy was treated with epinephrine, steroids, and fluids. Following this episode, allergy skin prick testing was performed with negative results. However, intradermal tests at relevant concentrations yielded positive results of wheal and flare with multiple FIX products, consistent with an IgE-mediated reaction to FIX. He is currently being treated with rFVIIa 270 µg/kg/dose on demand.

4. Discussion

This study highlights the challenging nature of the management of patients with hemophilia who sustain anaphylaxis to factor replacement therapy. Allergic reactions to factor concentrates preceding inhibitor formation are a rare complication, especially in HA, and they pose management challenges for clinicians and patients. Our first HA patient underwent successful ITI following the administration of rituximab. Our second HA patient was transitioned to emicizumab. Our HB patient is being treated with rFVIIa on demand. The current therapy management was supported by thrombin-generation studies (Fig. 1).

There is a special need for novel alternative therapies in children with anaphylaxis to factor replacement therapy. Emicizumab [27] is a bispecific recombinant antibody able to bind FIXa and FX, mimicking the cofactor function of FVIII. It is administered subcutaneously and currently registered for HA patients with and without inhibitors. The structure of Emicizumab is different from that of FVIII [28]. Its activity is not affected by antibodies directed against FVIII and may, therefore, successfully and safely control bleeding in patients with anaphylaxis to FVIII.

There are no registered alternative treatments for HB at this time, however, some studies that may change the therapy paradigm are underway. Concizumab (Novo Nordisk) [29], which targets tissue factor pathway inhibitor, has already shown a favorable safety profile, but pediatric studies are not yet available. Another potential future drug may be Fitusiran, a synthetic small interference RNA therapeutic molecule, designed to suppress liver production of antithrombin mRNA [30,31]. Its subcutaneous monthly administration resulted in improved

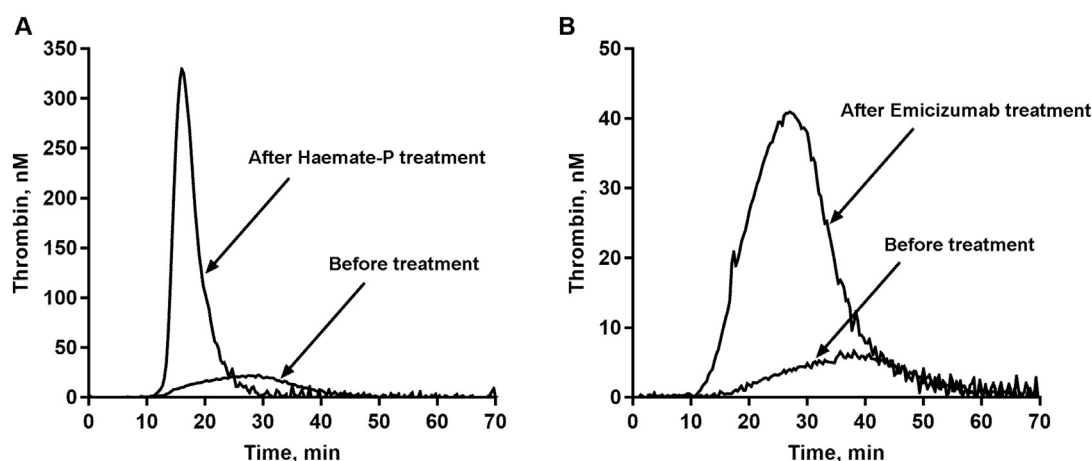


Fig. 1. Thrombin generation curves of hemophilia A patients before and after treatment.

Platelet-poor plasma (PPP) samples were taken before and after therapy with haemate P (patient #1) and emicizumab (patient #2). Thrombin generation was initiated by recalcification with the addition of 1 pM tissue factor in the presence of 4 µM phospholipids. All of the patients' plasma samples were tested simultaneously. Note the gradual increase in thrombin generation following treatment.

thrombin generation and hemostasis in clinical trials on adult patients with HB.

5. Conclusions

Our case series demonstrates the difficulties in managing patients with hemophilia, inhibitors, and anaphylaxis to replacement therapy. In the era of novel therapies, such as Emicizumab, the management of patients with HA has become easier and may eventually terminate the need for ITI. However, treatment strategies for HB patients with anaphylaxis are currently limited to rFVIIa and, therefore, continue to pose a challenge to their management.

Acknowledgements

The authors stated that they have no interests which might be perceived as posing a conflict or bias.

Sarina Levy-Mendelovich: Designed the study, cared for the patients and wrote the paper.

Tami Livnat: Performed the research and wrote the paper.

Assaf Arie Barg: Cared for the patients and wrote the paper.

Mona Kidon: Cared for the patients and wrote the paper.

Tami Brutman-Barazani: wrote the paper.

Gili Kenet: Designed the study, cared for the patients and wrote the paper.

We thank Orly Katz for editing and reviewing the paper.

References

- [1] T. Livnat, A.A. Barg, S. Levy-Mendelovich, G. Kenet, Rare bleeding disorders-old diseases in the era of novel options for therapy, *Blood Cells Mol. Dis.* 67 (2017) 63–68.
- [2] N.S. Curry, S.A. Misbah, P.L. Giangrande, D.M. Keeling, Achievement of immune tolerance in a patient with haemophilia B and inhibitory antibodies, complicated by an anaphylactoid reaction, *Haemophilia* 13 (2007) 328–330.
- [3] J.G. Kadar, et al., IGE mediated anaphylactic reaction to purified and recombinant factor VIII in a patient with severe Haemophilia A, *Haemophilia* 13 (2007) 104–105.
- [4] Warrier, et al., Development of anaphylactic shock in haemophilia B patients with inhibitors, *Blood Coagul. Fibrinolysis* (1998) S125–S128.
- [5] E.C. Thorlac, et al., Anaphylactic response to factor IX replacement therapy in haemophilia B patients; complete gene deletions confer the highest risk, *Haemophilia* 5 (1999) 101–105.
- [6] Chuansumrit, et al., The use of rituximab as an adjuvant for immune tolerance therapy in a hemophilia B boy with inhibitor and anaphylaxis to factor IX concentrate, *Blood Coagul. Fibrinolysis* 19 (2008) 208–211.
- [7] S. Alexander, S. Hopewell, S. Hunter, A. Chouksey, Rituximab and desensitization for a patient with severe factor IX deficiency, inhibitors, and history of anaphylaxis, *J Ped Hematol/Oncol* 30 (2008) 93–95.
- [8] M. Mauro, et al., Recurrent episodes of anaphylaxis in a patient with haemophilia B: a case report, *Blood Transfus.* 14 (2016) 582–584.
- [9] R. Clapp, et al., Reaction to rapidly infused AHF cryoprecipitate, *N. Engl. J. Med.* 281 (1969) 329.
- [10] J.G. Erskine, et al., Anaphylactic reaction to low molecular weight porcine factor VIII concentrates, *Br Med J Clin Res Ed* 282 (1981) 2011–2012.
- [11] J.R. Bove, Anaphylactic reaction to purified antihemophilic factor concentrate, *Transfusion* 26 (1988) 603.
- [12] Tsuchiya, et al., Anaphylaxis response to factor VIII preparation in a haemophilic child with an inhibitor of high titre during the tolerance induction, *Eur. J. Pediatr.* 157 (1998) 85.
- [13] R.I. Shopnick, et al., Anaphylaxis after treatment with recombinant factor VIII in a patient with severe hemophilia A, *Transfusion* 36 (1996) 358–361.
- [14] M. Jadhav, I. Warrier, Anaphylaxis in patients with hemophilia, *Semin. Thromb. Hemost.* 26 (2000) 205–208 (Review).
- [15] R.E. Helmer, et al., Anaphylactic reactions following infusion of factor VIII in a patient with classical hemophilia, *Am. J. Med.* 69 (1980) 953–957.
- [16] A.F. Dioun, B.M. Ewenstein, R.S. Geha, L.C. Schneider, IgE-mediated allergy and desensitization to factor IX in hemophilia B, *J. Allergy Clin. Immunol.* 102 (1998) 113–117.
- [17] F. Shakib, et al., IgG4: a possible mediator of anaphylaxis in a haemophilic patient, *Clin Allergy* 9 (1979) 597–603.
- [18] Massimo Franchini, et al., Anaphylaxis in patients with congenital bleeding disorders and inhibitors, *Blood Coagul. Fibrinolysis* 20 (2009) 225–229.
- [19] D.A. Triplett, C.S. Harms, Physiologic and pathologic inhibitors, *Procedures for Coagulation Laboratory*, 1981, pp. 69–75.
- [20] H.C. Hemker, P. Giesen, R. Al Dieri, et al., Calibrated automated thrombin generation measurement in clotting plasma, *Pathophysiol. Haemost. Thromb.* 33 (2003) 4–15.
- [21] A.A. Barg, et al., Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors- a single center cohort, *Pediatric blood and cancer* 66 (2019) (Excepted for publication), <https://doi.org/10.1002/pbc.27886>.
- [22] L. Söderström, A. Kober, S. Ahlstedt, et al., A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases, *Allergy* 58 (2003) 921–928.
- [23] K. Brockow, Skin test concentrations for systemically administered drugs—an ENDA/EAACI drug allergy interest group position paper, *Allergy* 68 (2013) 702–712.
- [24] M.I. Kidon, Y. See, C.Y. Bun, et al., Bimodal skin reactivity to histamine in atopic children in Singapore: influence of specific sensitizations, *Pediatr. Allergy Immunol.* 15 (2004) 545–550.
- [25] C. Leissinger, C.D. Josephson, S. Granger, et al., Rituximab for treatment of inhibitors in haemophilia A. A phase II study, *Thromb. Haemost.* 112 (2014) 445–458.
- [26] L. Söderström, A. Kober, S. Ahlstedt, et al., A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases, *Allergy* 58 (2003) 921–928.
- [27] J. Oldenburg, J.N. Mahlangu, B. Kim, et al., Emicizumab prophylaxis in hemophilia A with inhibitors, *N. Engl. J. Med.* 377 (2017) 809–818.
- [28] P.J. Lenting, C.V. Denis, O.D. Christophe, Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood* 130 (2017) 2463–2468.
- [29] P. Chowdhary, S. Lethagen, U. Friedrich, et al., Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial, *J ThrombHaemost* 13 (2015) 743–754.
- [30] A. Sehgal, S. Barros, L. Ivanciu, et al., An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia, *Nat. Med.* 21 (2015) 492–497.
- [31] K.J. Pasi, S. Rangarajan, P. Georgiev, et al., Targeting of antithrombin in hemophilia A or B with RNAi therapy, *N. Engl. J. Med.* 377 (2017) 819–828.