International Journal of Immunopathology & Pharmacology

Case Report

Development and desensitization therapy of high-response factor VIII inhibitors with severe allergic reaction in a moderate hemophilia A patient

International Journal of Immunopathology and Pharmacology
Volume 35: 1–5

DOI: 10.1177/2058738420980259
journals.sagepub.com/home/iji
SAGE

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Abstract

Neutralizing antibodies (inhibitors) against factor VIII/IX (FVIII/FIX) poses a serious and challenging complication in the hemophilia treatment. Allergic reaction is more common in hemophilia B and always companion with FIX inhibitors, but it is rare in hemophilia A (HA). So far only few cases demonstrated FVIII-specific allergic response in hemophilia A. Coexistence of allergic reactions with inhibitors was contraindicated for immune tolerance induction (ITI) regimen which is the only proven therapy to eliminate inhibitor. We report a rare case of a 11-year-old boy with moderate HA who developed high titer inhibitor and severe allergic reaction to both plasma derived and recombinant FVIII concentrates. Inhibitor was eliminated with the use of prednisone. Further desensitization protocol by administering rFVIII of increasing does from 0.01 IU/kg to 40 IU/kg with a pre-determined time schedule allowed patient tolerance to the normal dose and infusion time to FVIII.

Keywords

allergic reactions, anti-FVIII inhibitor, desensitization therapy, Hemophilia A

Date received: 28 July 2020; accepted: 19 November 2020

Introduction

Hemophilia A (HA) is a congenital bleeding disorder characterized by coagulation factor VIII (FVIII) deficiency.[1,2] Prophylactic replacement therapy with FVIII remained as mainstay of the management of HA.[3] Further, 30% of severe and 5% of mild and moderate HA patients will develop inhibitors (FVIII neutralizing antibodies) which inhibit the activity of infused FVIII.[4–6] Allergic manifestations are rare complications in HA patients,[7] and only evidenced by a few cases which suggested to be mediated by IgE.[8,9] Here, we report a rare case in a moderate HA patient developed high-titer inhibitor and severe allergic reaction to both plasma derived FVIII (pdFVIII) and recombinant FVIII (rFVIII) concentrates, but controlled by desensitization therapy.

Case report

The patient was a 11-year-old boy, diagnosed with moderate HA (FVIII coagulant activity of 2.6%)

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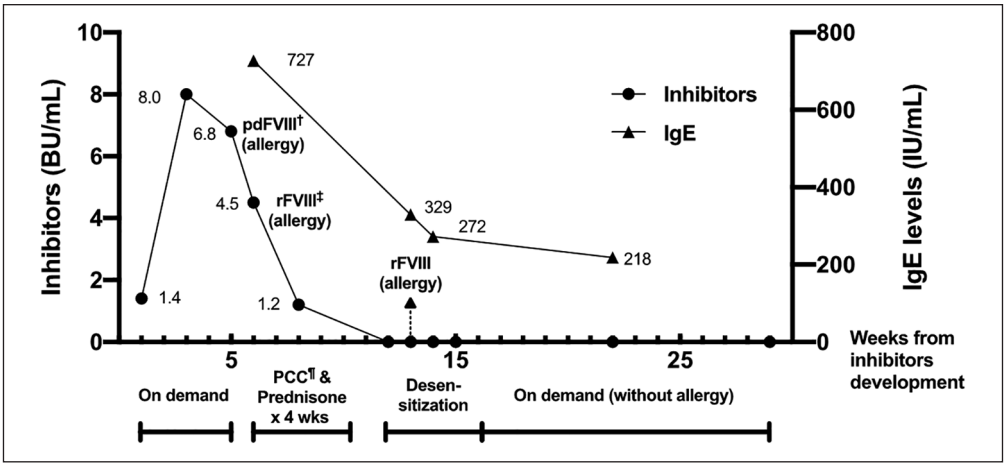

Figure 1. Inhibitor titer and Immunoglobulin E (IgE) level during FVIII infusion and desensitization therapy.
pdFVIII, plasma derived factor VIII; rFVIII, combinant factor VIII; PCC, prothrombin complex concentrate.

and impaired FVIII protein secretion due to F8 missense mutations (c.5590A>G) at the age of 2 years after intracranial hemorrhage for which he received continuous fresh frozen plasma infusion and completely recovered. Later, at the age of 9-year-old, he suffered a gastrointestinal bleeding for which he received FVIII (Xyntha) at a dose of 36 IU/kg/day for 5 days and 18 IU/kg/day for 2 days without using tranexamic acid. After that, prophylaxis with FVIII (Xyntha) was initiated at a dose of 18 IU/kg/three times weekly (TiW) and no bleeding episodes appeared during the first 1.5 months. However, three bleeding episodes (one time in muscle and two times in knee) occurred after 25 exposure days. At this point inhibitor was considered developing and confirmed with 8 Bethesda Unit (BU) mL^{-1} at the 48 exposure days. Further, inhibitor titer measured after 1 month exhibited 6.8 BU mL^{-1} and the patient was not tested for FVIII level at this time.

Following this, the patient received ITI therapy to eradicate inhibitors with domestic plasma derived FVIII (pdFVIII) containing full length pdFVIII, von Willebrand factor (VWF) (1:1 ratio), albumin and other proteins at a dose of FVIII 50 IU/kg/QOD. Immediately after the first infusion, he developed allergic reaction (rash and pruritus) with Immunoglobulin E (IgE) level of 727 IU/mL. Further, pdFVIII was replaced by rFVIII (Advate and Kogenate) however, rFVIII led to more severe allergic reactions as respiratory compromise requiring ventilatory support and symptomatic treatment (dexchlorpheniramine and methylprednisolone). The allergic reaction (manifested as skin rash) occurred immediately after rFVIII infusion and infusion was stopped. In consideration of his allergic reaction and poor knee status, prednisone 1 mg/kg/day for 4 weeks was prescribed initially and then tapered gradually with domestic plasma derived prothrombin complex concentrates (pdPCC) (30 IU/kg/QoD) prophylaxis. Eleven weeks after, he had a negative inhibitor without any clinical manifestations of allergic reactions (rash, laryngeal edema, etc.). However, it occurred again after rFVIII (Xyntha) infusion where he developed allergic reaction that manifested as increased heart rate and laryngeal edema. The IgE level was detected on the next day of allergic reaction as 329 IU/mL (Figure 1).

Further, the patient received desensitization treatment to FVIII which was initiated with prednisone infusion at a dose of 40 mg (1 mg/kg) 30 min^{-1}, an hour before each rFVIII (ADVATE) infusion (Table 1). On the first day of desensitization treatment, rFVIII (ADVATE) was given from 0.01 IU/kg increased to 10 IU/kg i.v. gradually with total amount of 31.15 IU/kg in 8 h. From the second day to the 18th day, FVIII was given as 40 IU/kg daily with a gradually decreasing infusion time from 10 h to 20 min which was a normal dose and speed of FVIII infusion. The total course of desensitization treatment is 22 days. Allergic reactions appeared at the 5th and 11th days manifested with the increasing heart rate and rash which could relief after prolonging the infusion time. Further, upon more than 1 year of follow-up, the patient did not suffer any joint bleeds and other serious bleeding episodes and his inhibitor titer remained

Table 1. FVIII desensitization protocol.

	Dose (U/kg)	Cumulative dose (U/kg)	Actual dose (U)	Infusion time (min)	Interval from previous dose (min)
Day 1	0.01	0.01	0.48	5	0
	0.02	0.03	0.96	5	10
	0.04	0.07	1.92	5	10
	0.08	0.15	3.84	5	10
	0.1	0.25	4.8	5	10
	0.2	0.45	9.6	5	20
	0.4	0.85	19.2	5	20
	0.8	1.65	38.4	5	20
	1.5	3.15	72	5	20
	3	6.15	144	30	–
	6	12.15	288	30	–
	9	21.15	432	60	–
	10	31.15	480	60	–
Day 2	40	1920	1920	600	–
Day 3	40	1920	1920	480	–
Day 4	40	1920	1920	360	–
Day 5	40	40	1920	600	–
Day 6	40	40	1920	600	–
Day 7	40	40	1920	480	–
Day 8	40	40	1920	360	–
Day 9	40	40	1920	240	–
Day 10	40	40	1920	120	–
Day 11	40	40	1920	180	–
Day 12	40	40	1920	120	–
Day 13	40	40	1920	60	–
Day 14	40	40	1920	30	–
Day 15	40	40	1920	30	–
Day 16	40	40	1920	60	–
Day 17	40	40	1920	30	–
Day 18	40	40	1920	20	–
Day 19	40	40	1920	20	–
Day 20	40	40	1920	20	–
Day 21	40	40	1920	20	–
Day 22	40	40	1920	20	–

negative. However, the patient did not test FVIII recovery. The FVIII level had not been measured during the time the patient with inhibitor. Therefore, we do not know whether there is an antibody against endogenous FVIII. He only confirmed with negative inhibitor and the similar FVIII:C (3.3%) to baseline level (2.6%).

Discussion

Patients with hemophilia A are rarely to develop anti-FVIII allergic reaction coexisted with anti-FVIII inhibitors, which was reported to be induced either by FVIII itself or by other proteins in FVIII products only in a few case reports.[10–13] In this case, the patient was not allergic to rFVIII until inhibitor development. ITI therapy with pdFVIII lead to allergic reactions with elevated IgE levels and did not subside even after switching back to rFVIII suggesting that the allergic reaction could be caused by FVIII or also by other proteins like albumin or by both. We cannot ensure which substance the patient against with because he did not try pdFVIII before inhibitor development to prove no allergic reaction to it. The patient was a moderate HA child and FVIII:C was 2.6%, and the patient was without other immune diseases when the inhibitor is produced. So we speculate the FVIII antibodies was caused by the exogenous FVIII.

Further, the patient turned to prophylaxis using domestic pdPCC and with prednisolone to cool down immune system. No allergic reactions or inhibitors development was observed even though the pdPCC had a trace amount of FVIII, other proteins similar to pdFVIII. We considered that the trace amount of allergen would induce allergic reaction, but the prednisone would lower the anamnestic response thereby his inhibitor titer remained negative. We anticipate that trace amounts of FVIII in the pdPCC and endogenous FVIII could have been part of the immune tolerance induction. Afterward, the patient infused rFVIII again, however, the infusion still led to respiratory compromise. Thus, the allergic response was inferred causing by FVIII. Although the IgE level (329 IU/mL) detected was much lower than the last detection, the allergic response could still exist for the following two reasons. Firstly, IgE level was monitored on the next day of rFVIII infusion instead of at the time of allergic reaction occurrence, in which it should be much higher. Secondly, IgE level was not investigated while receiving prednisone. Therefore, the trough level of IgE was unknowable which was possible to lower than that we detected this time. However, we still cannot exclude the reason for allergic reaction by other components of pd products because the patient never tried pdFVIII or pdPCC before allergic reaction with inhibitor development or after successful desensitization.

Inhibitors can hardly be tolerized without FVIII.[14] However, the present case eliminated inhibitor by prednisone alone which has a general immunosuppressive effect instead of inducing antigen-FVIII tolerance. Although inhibitor turned to negative, FVIII was not tolerated by the patient. Earlier, Kadar et al, reported IgE mediated grade 3 anaphylactic reaction in 51-year-old HA patient that triggered by rFVIII.[13] Similarly, with the observation of the high serum IgE level in patient during treatment, we consider his inhibitor for FVIII antigen is probably triggered by an anti-FVIII IgE, but very regrettable, we have not been able to detect the type of antibody to confirm. Desensitization protocol is the other inhibitor eradication strategy found effective in a few patients with allergic reactions.[10] In current case, patient achieved tolerance to FVIII through the desensitization protocol where it downregulates the expression of mast cells and basophils thereby inhibiting the release of inflammatory mediators (β-hexosaminidase, prostaglandins and leukotrienes), however the exact mechanism underlying this still remained elusive.[15] Further, the current report cannot be generalized as this was a single case report therefore the potential role of desensitization regimen in eliminating the inhibitor and allergic reaction to FVIII still need to be confirmed.

All previously reported cases with inhibitor and allergic reaction were severe hemophilia A/B, which were desensitized successfully. But this case refers to a moderate HA patient the inhibitors and allergic reactions developed could be either due to endogenous or exogenous FVII. However, after desensitization therapy, the allergic reaction toward FVIII disappeared, the inhibitor turned negative, and the FVIII:C recovered to normal.

Conclusion

In summary, we report a rare case of coexistence of high-titer inhibitor and severe allergic reaction to both pdFVIII and rFVIII concentrates in moderate HA patient which was contraindicated for ITI treatment but controlled with the adoption of desensitization therapy.

Acknowledgements

The authors acknowledge Dr Zekun Li (MD) from Beijing Children's Hospital for drawing the figure and providing revision of the manuscript for intellectual content. Dr Vengal Rao Pachava (PhD) and Dr Anuradha Nalli (PhD) from Indegene Pvt. Ltd., Bangalore, India, for providing medical writing support in the development of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from Beijing Municipal Science and Technology Commission (code Z181100001718182).

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the parent for their anonymized information to be published in this article.

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