

Successful multi-modal immune tolerance induction for factor IX deficiency with inhibitors and allergic reactions

1 | INTRODUCTION

A 12-year-old male was diagnosed with factor IX deficiency at birth. Both the patient and older brother had factor IX levels of <1% and a > 50 bp gene deletion (c.Exon1-Exon8del). At age 2 years, an inhibitor titre of 2.6 Bethesda units (BU) was detected, and ITI with recombinant factor IX 100 units/kg was initiated. The patient developed an allergic reaction to therapy including wheezing and vomiting, and therefore recombinant factor VIIa was prescribed for the management of acute bleeds. His course was complicated by recurrent joint and soft tissue bleeds and port infections. He also was found to have growth factor deficiency. By age 11 years, the increased frequency of joint bleeds and decreased efficacy of recombinant factor VIIa, as measured by clinical response and thromboelastogram (TEG), led the team to administer anti-inhibitor coagulant complex for management of acute bleeds despite concerns about exposure to factor IX. The patient tolerated the therapy and responded well both clinically and with improved TEG results with an improvement in reaction time from 10.3 minutes to 3.0 minutes. However, his inhibitor titre went from undetectable to 11.8 BU.

A month later when the inhibitor titre decreased to less than 10 BU, ITI with rituximab and plasma-derived factor IX (Mononine®) was initiated. Rituximab 375 mg/m² once weekly for 4 total doses was combined with an escalating dose of Mononine®, starting at 30 units/kg with a target dose of 100 units/kg. Administration of the first dose of Mononine® resulted in an allergic reaction that included vomiting, flushing, difficulty breathing and dizziness, which resolved with administration of diphenhydramine and methylprednisolone. Paediatric allergy and immunology were consulted and reported the patient's total tryptase was not elevated at 2.4 ng/mL from baseline of 2.1 ng/mL. Although tryptase value was not consistent with anaphylaxis to mononine, an IgE mediated reaction was not able to be ruled out and a mononine desensitization protocol was recommended. Per family request, the patient was discharged in stable condition and was instructed to continue recombinant factor VIIa 90 mcg/kg every 2 to 4 hours as needed for moderate to severe bleeds.

One week later, the patient was admitted to the paediatric intensive care unit to initiate a mononine desensitization protocol. The second dose of rituximab was also administered at this time. The patient tolerated the rituximab well and the following morning

the mononine desensitization protocol #1 was initiated without premedication (Table 1). The desensitization protocol was 9 days in duration with a cumulative day 1 dose of 27 units/kg and was adapted from published factor IX desensitization protocols.¹⁻³ The patient tolerated each day of the desensitization protocol with no signs or symptoms of allergic reaction. The third dose of rituximab was given on day 7, and the patient was discharged home on day 9 without any signs or symptoms of allergic reaction. Discharge education was provided to patient's mother to administer Mononine® 27 units/kg IV push over 5 minutes once daily. A prescription for intramuscular epinephrine was also provided, and home nursing was arranged to assist his parent during the first several doses in the event of a reaction.

Eleven days after being discharged, the patient presented to the paediatric emergency department with concern for anaphylaxis to Mononine®. Rituximab therapy was completed 6 days earlier. Patient's mother reported no missed doses of Mononine® and self-documented the administration of each dose between a one-hour timeframe each night. Thirty minutes after his home Mononine® dose, the patient developed hives, emesis, burning and itching of ears and numbness of fingers and toes. His mother administered oral diphenhydramine and intramuscular epinephrine with resolution of symptoms. In the emergency room, the patient was at baseline except for an erythematous right knee. The patient was admitted to the paediatric intensive care unit to initiate a second Mononine® desensitization protocol. The Mononine® desensitization protocol #2 was 1 day in duration with a cumulative day 1 dose of 40 units/kg. The protocol was 9 steps starting at a dose of Mononine® 0.003 units/kg (1 unit/mL) to the target dose of Mononine® 27 units/kg (100 units/mL) infused over 30 minutes. No premedication was administered. The patient tolerated the desensitization protocol #2 well until the final step of the protocol. Approximately 15 minutes into the final administration of Mononine® 27 units/kg, the patient developed diffuse hives and focal tongue angioedema, which resolved after the administration of diphenhydramine. The estimated Mononine® cumulative daily dose received was 28 units/kg. It was recommended to give the target dose of Mononine® 27 units/kg IV push over 10 minutes the following day under direct observation, with premedication of cetirizine 10 mg. The next day, the patient developed hives on his upper extremities, chest and face shortly after the completion

TABLE 1 Mononine[®] desensitization protocol

Day	Mononine [®] concentration (Units/mL)	Mononine [®] dose (Units/Kg)	Time of infusion	Interval between doses (min)
1	0.1	0.003	5 min	10
		0.008		
		0.01		
		0.02		
	1	0.04		
		0.08		
		0.1		
		0.2		20
	10	0.4	5 min	20
		0.6		
		0.8		
		1		
		1.5		
	10	3	30 min	5
		5		
		6		
		8	60 min	
2	20	27	10 h	
3	20	27	8 h	
4	33	27	6 h	
5	50	27	4 h	
6	100	27	2 h	
7	100	27	1 h	
8	100	27	30 min	
9	100	27	5 min	

of the Mononine[®] dose. The hives resolved on their own without intervention.

The following morning, 48 hours after Mononine[®] desensitization protocol #2, a third Mononine[®] desensitization protocol was initiated. The Mononine[®] desensitization protocol #3 was 1 day in duration with a cumulative day 1 dose of 52 units/kg. The protocol was 16 steps starting at a dose of Mononine[®] 0.0003 units/kg (0.1 unit/mL) to the target dose of Mononine[®] 27 units/kg (100 units/mL). Premedication cetirizine was administered prior to the first step of the desensitization protocol and each Mononine[®] dose was administered by IV push over 10 minutes. The patient tolerated Mononine[®] desensitization protocol #3 without any signs or symptoms of an allergic reaction. He was discharged home three hours after the completion of the last Mononine[®] dose with instructions to give Mononine[®] 27 units/kg IV push over 10 minutes once daily with cetirizine daily. The patient tolerated the third Mononine[®] desensitization protocol without signs or symptoms of an allergic reaction and continued on Mononine[®] 27 units/kg daily with cetirizine premedication. Six weeks into ITI, an inhibitor was no longer detected (Figure 1). One year after initiating ITI and

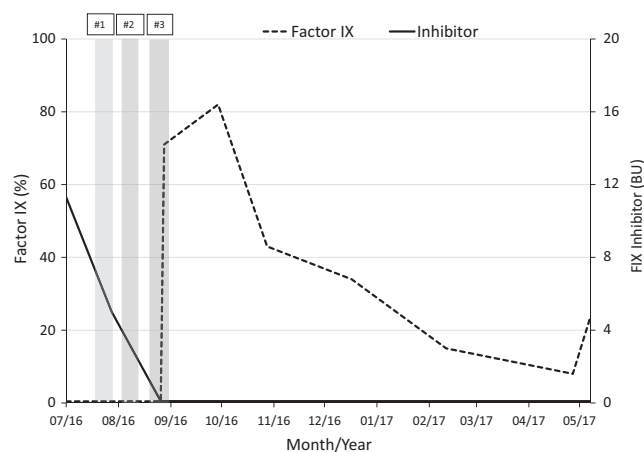


FIGURE 1 Factor IX levels and inhibitor titres before and after three rounds of ITI and desensitization with plasma-derived factor IX and concurrent rituximab therapy. The three rounds of ITI are delineated by #1, #2 and #3. Rituximab was infused 1 d before the start of ITI#1 and continued once weekly for four consecutive weeks. Factor IX levels were measured by one-stage factor assays. Inhibitor titres were measured by Bethesda assay

Mononine® desensitization protocols, the patient has had no further allergic reactions, signs of nephrotic syndrome and continues to have an undetectable inhibitor level. He has returned to treating acute bleeds with Mononine® and has had only two trauma-related acute bleeds to date both occurring approximately 11 and 12 months after the first Mononine® desensitization protocol was initiated. The first was a knee bleed after playing kickball, and the second was an elbow bleed after playing with a friend.

2 | DISCUSSION

Inhibitor development is significantly less prevalent in factor IX deficiency than factor VIII deficiency. In the latter, inhibitors develop in 10%-30% of patients as compared to 1%-3% in patients with factor IX deficiency.⁴ There are also several major differences in inhibitor formation in the two patient populations.^{5,6} Inhibitors in patients with factor IX deficiency appear to occur only in severely affected patients and can lead to significant morbidity due to severe allergic reactions (up to 63% of patients), as well as the development of nephrotic syndrome.⁵⁻⁷ The study of inhibitors in factor IX deficiency has been limited due to the low prevalence of this disorder. In addition, ITI, which has been successfully used in patients with factor VIII deficiency, has an inhibitor eradication rate of only 13%-33% in patients with factor IX deficiency.⁵ There is no consensus or recommendation for optimal ITI, and almost all information has been gleaned from isolated case reports.^{1-3,5} This case is of unique significance to the current body of literature as it addresses the most complex issues of ITI including allergic reactions, product choice and multimodal therapy.

Major gene deletions contribute to inhibitor development in patients with factor VIII and IX deficiency. Patients with factor IX deficiency have a higher incidence of missense mutations than null mutations, and this in part may explain why the development of inhibitors is lower and only occurs in severely affected patients.^{1,8} Our patient had a significant gene deletion. In addition, after successful ITI, the patient also underwent chromosomal microarray analysis, which showed a 2293 kb deletion of Xq27.1 to Xq27.2 arr[CRCh37] Xq27.1q27.2(138270178-140563347)×0. This region includes 9 genes, including the factor IX gene (*F9*), as well as *SOX3* gene, which is associated with growth hormone deficiency. Thus presumably the large deletion of factor IX gene as well as the neighbouring *SOX3* gene may both play a role in inhibitor development as well as anaphylaxis.⁵⁻⁷ However, other factors such as early and intensive exposure to factor concentrate and immunological, infectious or inflammatory events must also be at play, as the patient's older brother, who has the same gene deletion and growth hormone deficiency, has never developed an inhibitor.

Studies are also lacking on the possible mechanisms of immunomodulation on tolerance induction and the development of anaphylaxis in patients with factor IX deficiency. Inhibitor development and anaphylaxis are often temporally linked and anaphylaxis may be a predictor of future inhibitor development. Factor IX has a structural analogy to other vitamin K dependent factors, which may confer

some tolerance.¹ In addition, the considerably smaller molecular weight of factor IX makes for its distribution in both intra- and extravascular space.⁹ In contrast, factor VIII is confined to the intravascular space. The extravascular distribution of factor IX may induce mast cell activation and lead to IgE mediated hypersensitivity.¹⁰

In any case, ITI in patients with severe factor IX deficiency appears to require a multimodal approach, which includes immune modulation with rituximab, desensitization to factor IX and use of plasma-derived product. As the prevalence of factor IX deficiency and the rate of inhibitor development are significantly lower in factor IX than factor VIII deficiency, evidence-based approaches to immune tolerance are primarily based upon case studies. Given the risks of anaphylaxis and proteinuria associated with this population, it is imperative to share these experiences until a prospective international collection of data on factor IX inhibitors develops evidence-based treatment options.

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DISCLOSURES

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

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