Early elimination of Factor VIII inhibitor by ITI with high dose immunoglobulin in hemophilia A children

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Summary

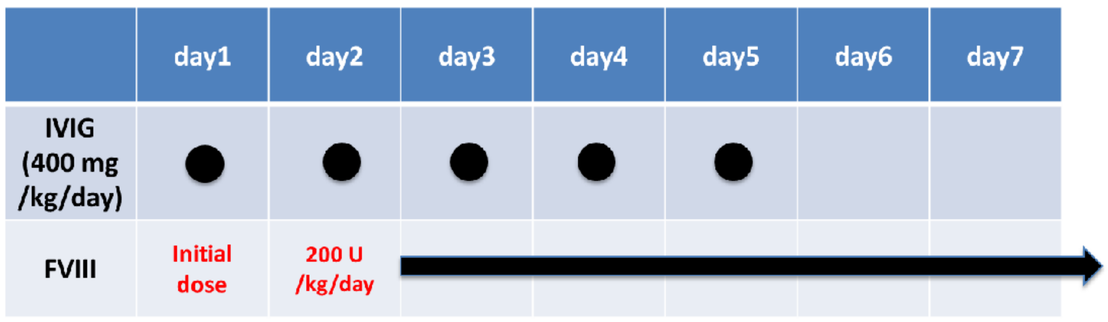
(Introduction) The production of factor VIII (FVIII) inhibitory antibodies, inhibitors, is a serious problem for patients with hemophilias. Approximately 30 % of hemophilia A patients generate antibodies (inhibitor) against therapeutically administered FVIII, typically during the first 20 exposure days (ED), as a result of interactions between multiplegenetic and environmental factors. Immune tolerance induction (ITI) is the only strategy proven to eradicate persistent inhibitors in severe hemophilia A patients and success rate of ITI commonly ranges between 60% and 80%. However, a minority of hemophilia patient will have life-long inhibitors. To eliminate the inhibitors, we designed intravenous immunoglobulin (IVIG) therapy in combination with high dose recombinant FVIII (rFVIII) for ITI in hemophilia A children with inhibitors.

(Methods) Four children with hemophilia A who were previously untreated aged five to 15 months developed inhibitors within 25 exposures to rFVIII. The peak titers of inhibitor in patients were ranged from 3 to 14 BU/ml. All patients received ITI combined with high dose IVIG administration. The initial dosage of rFVIII was determined based on the titer of inhibitor to neutralize. Consecutively, patients received 5 days of IVIG infusion and daily high dose of rFVIII.

(Results) In all patients, the administration of rFVIII with immunoglobulin eliminated the inhibitor without any anamnestic response. The inhibitor had been confirmed to be negative within a month from ITI start in all patients. The recovery of FVIII activity 30 min after infusion of rFVIII was normalized within two months after initiation of ITI. However, the recovery of rFVIII 24 hours after infusion was not completely sufficient. Additional course of IVIG treatment led to increase the recovery of FVIII 24 hours after infusion in all patients.

(Conclusion) ITI with IVIG could be effective for the early elimination of inhibitor against FVIII without anamnestic response. Accumulation of cases and further analysis are necessary to assess the efficacy of modified ITI therapy.

Figure 1 : Immune tolerance induction (ITI) regimen



Initial dose = the sum of the inhibitor neutralizing dose plus the incremental dose

Study definitions of successful tolerance

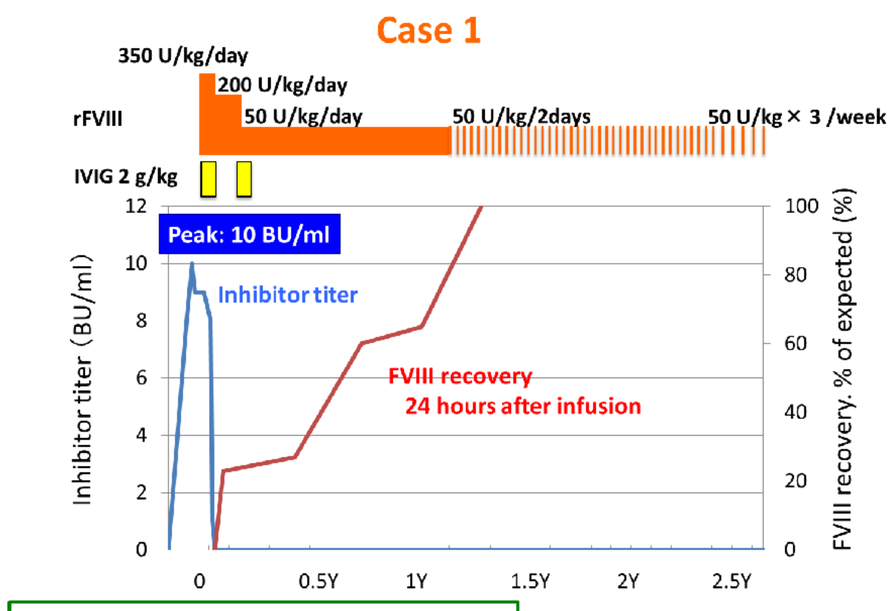
FVIII recovery ≧ 66% of expected
FVIII recovery 24 hours after infusion ≧ 60-100% of expected

Table 1 : Characteristics of patients

Patient no.	FVIII level (%)	Family history of inhibitor	Age at detection of inhibitor	EDs bofore detection of inhibotor	Peak inhibitor titer (BU/ml)	Inhibitor titer at ITI initiation (BU/ml)	Time between inhibitor detection and ITI start (months)
1	<1	No	15 months	9	10	8	1.5
2	<1	No	5 months	16	14	14	1.5
3	<1	Yes	10 months	13	3	3	1.5
4	<1	Yes	11 months	7	9	9	1.5

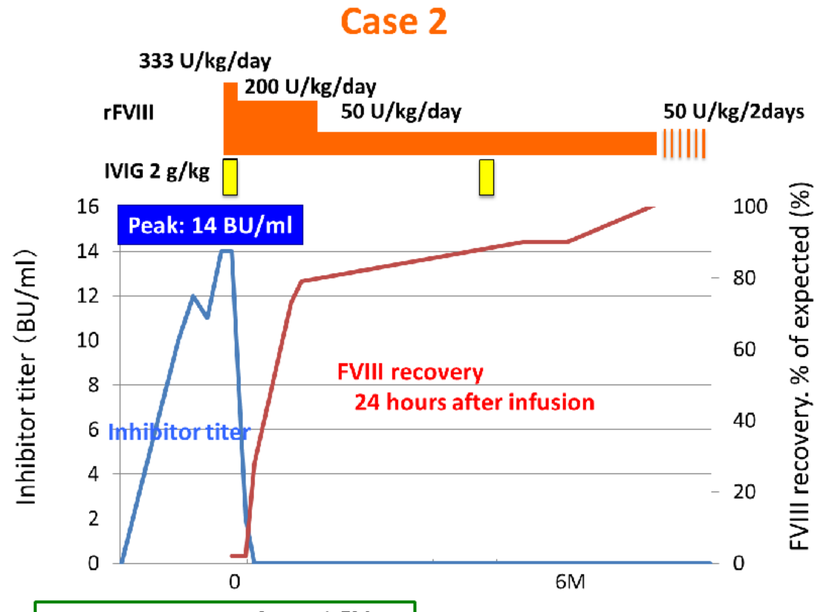
Figure 2 : Clinical course

Case 1



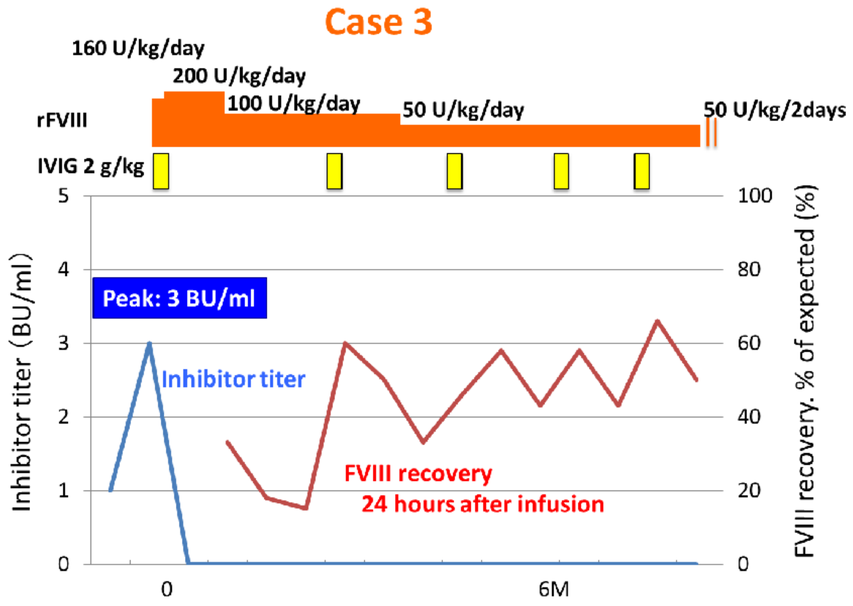
FVIII recovery	2w	9M	1Y2M
	53%	75%	116 %

Case 2



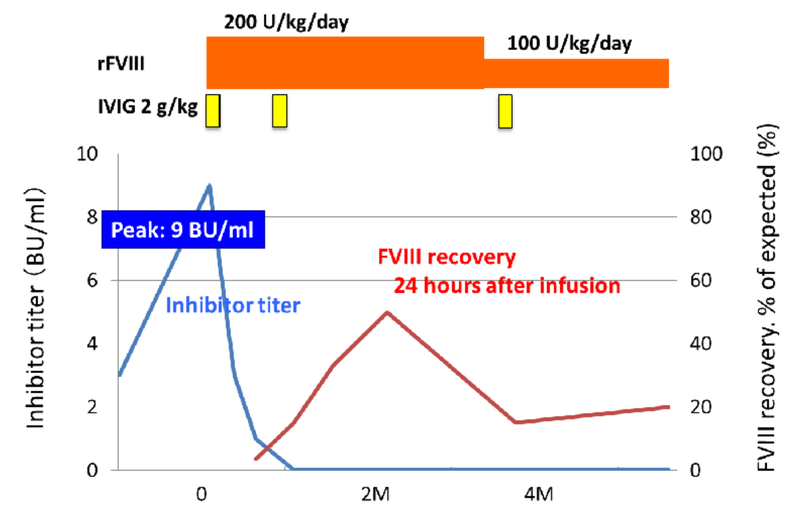
FVIII recovery	3w	1.5M
	12.5%	214%

Case 3



FVIII recovery	1 M
	105%

Case 4



FVIII recovery	1.5 M
	100%

Discussion

In this study, we treated with the modified ITI regimen including high dose of rFVIII and high dose of IVIG for 4 hemophilia A patients developing inhibitors. All cases rapidly achieved a negative titer for inhibitor after the initiation of ITI without anamnestic response. The recoveries of FVIII were also increased up to normal level within two months in 3 out of 4 cases. The international immune tolerance study showed the median months from ITI start to negative titer are 9.2 months (Low dose ITI) and 4.6 months (High dose ITI), respectively (Hay CR et al. *Blood* 2012). The duration to achieve negative inhibitor in this regimen was shorter than that of previous reports. This successful finding may be dependent on the initial inhibitor titer (3-14 BU/ml) and/or on the absence of anamnestic response at the beginning of ITI.

Our study also showed that the additional IVIG increased the recovery of FVIII clearance as shown in Case 3. The mechanisms of effective IVIG treatment remains to be clarified. IVIG administration may restores idiotypic-anti-idiotypic network (Freiburghaus C et al, *Haemophilia* 1999, Sultan Y et al, *The Lancet* 1984), expand regulatory T cells and the modulate B cell and T cell immunities. Taken togerther, IVIG confer some positive effects for inhibitor suppression.

In conclusion, ITI with IVIG may be effective to rapidly eradicate inhibitors without anamnestic response. To understand the pathology, accumulation of cases and further analysis are necessary to assess the efficacy of modified ITI therapy.

Table 2 : Outcomes of patients

Patient no.	Anamnestic response	Start of ITI to negative titer (days)	Negative titer to first normal recovery (months)	Start of ITI to tolerance (months)	Bleeding episodes after ITI	Follow-up time from start of ITI (years)
1	No	7	< 9	14	none	3.5
2	No	15	1.5	9	none	1.5
3	No	3	1	-	none	1
4	No	28	1	-	none	0.5

Disclosure information:
We have no financial relationships to disclose.

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