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Prednisone and low-dose activated prothrombin complex concentrates for FVIII inhibitor in nonhaemophilic patients

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Summary. Eight nonhaemophilic patients with factor VIII (FVIII) inhibitors were reported. There was no difference in sex distribution. Median age at diagnosis was 62 years (ranging from 14 to 73 years). No associated disorders were revealed and all the patients were presented with severe muscular or arthral bleeding. Inhibitor titre was measured by the Bethesda method, which were 6.4, 126.0, 155.0, 4.8, 56.0, 13.5, 35.0 and 150.0 BU mL^{-1}, respectively, at diagnosis. FVIII:C levels were less than 1 U dL^{-1} in seven patients and less than 2 U dL^{-1} in one patient. The median vWF:Ag level was 210% (ranging from 80% to 340%). All the patients had good response to activated prothrombin complex concentrates for acute bleeding episodes and prednisone for inhibitor elimination. Inhibitors completely eliminated in seven patients within a follow-up duration over 1 year, and one patient died of intracranial haemorrhage when her inhibitor titre decreased to 4.5 BU mL^{-1} and FVIII:C increased to 21 U dL^{-1}.

Keywords: acquired FVIII inhibitor, aPCC, nonhaemophilia, prednisone.

The spontaneous appearance of FVIII inhibitor in nonhaemophiliacs is very rare and often severe, life-threatening and refractory to FVIII concentrates infusion. Green *et al*. [1] reported that 87% patients had severe bleeding and 22% patients died. Treatment options for bleeding episodes include high-dose human FVIII concentrate, porcine FVIII concentrate, factor VIII inhibitor bypass activity and extracorporeal protein A – sepharose absorption [2–4]. The cost is very high and may be in excess of one million dollars [5]. Treatment options for suppressing FVIII inhibitors include prednisone, cyclophosphamide, etc. [4–10].

The purpose of this study was to clarify the role of prednisone and low-dose activated prothrombin complex concentrate (aPCC) in the treatment of our eight nonhaemophilic patients with acquired FVIII inhibitors.

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Materials and methods

Patients. The eight patients were nonhaemophilia patients with FVIII inhibitors diagnosed and treated in our hospital in the past 10 years. All the patients were referred because of unexplained bleeding events in the months before diagnosis, including mucous bleeding, ecchymoses, subcutaneous or muscular haematoma, haematuria, haemarthrosis, etc.

Laboratory assays. Bleeding time (BT), platelet count (PC), platelet aggregation by ADP (PAgT), prothrombin time (one-stage method) (PT) and partial thromboplastin time with kaolin (KPTT) were performed according to established procedures [11]; von Willebrand factor antigen (vWF:Ag) was measured by Laural electropheresis [11]; FVIII coagulant activity (FVIII:C) was measured by a one-stage method [11]; inhibitor screening test (IST) was performed by the KPTT method, mixing normal and patient plasma in a 1:1 ratio and incubating at 37 °C for 1 h; inhibitor titre (IT) assay was performed by the Bethesda method [12].

Treatment protocol. aPCC (PROTHORAAS, Shanghai RAAS Blood products Co. LTD, China) 40–50 u k^{-1} day^{-1} for 2–3 days was administered

for acute bleeding episodes. The product is virus-inactivated by the S/D method; 1 unit of this product is determined with the factory standard made by the pooled fresh frozen plasma from more than 100 normal donors, and is defined as the amount of FIX clotting activity in 1 mL of this standard material. All patients were treated with prednisone 0.5–0.75 mg kg^{-1} day^{-1} until 2–3 months after the inhibitor titre has disappeared. All patients were in preventive nursing care until the inhibitors disappeared.

Results

Patient characteristics. Table 1 summarizes the main clinical and laboratory data. None of the patients had a history of excessive bleeding, nor a family history of bleeding disorders. None of the patients had associated diseases (e.g. SLE, lymphoma, etc.) as determined by careful examination and none received any drugs within the month before the onset of bleeding events. The longest course of bleeding episode before diagnosis was 8 months. Five of the patients had high-titre inhibitor (> 30 BU), one had moderate high-titre inhibitor (10 to ≈ 30 BU) and two had low-titre inhibitor (< 10B.U).

Replacement therapy. Eight bleeding episodes (Table 1) in six patients were treated with aPCC after hospitalization, and 7/8 bleeding episodes were effective, i.e. the local pain disappeared, the haematoma absorbed gradually and the haematuria stopped. Only the intracranial haemorrhage (case 7) was ineffective and the patient died in 2 h after the event. Two patients (cases 1 and 4) did not receive aPCC because of no new bleeding episode after diagnosis.

Immunosuppressive therapy. When patients received prednisone, the time for the disappearance of bleeding symptoms varied (except for case 7), with a median of 2 weeks (range 1–6 weeks). The ITs decreased by 50% after 2–4 weeks and were undetectable at a median of 5 weeks (range 3–11 weeks). The FVIII:C increased to 5 U dL^{-1} after 3–7 weeks and to normal level (50–200 U dL^{-1}) at a median of 5 weeks (range 4–12 weeks) (Table 2).

Case 7 was an elderly woman; her FVIII:C and IT after prednisone therapy were 4 U dL^{-1} and 20 BU (2 weeks), 6 U dL^{-1} and 15 BU (4 weeks), 9 U dL^{-1} and 13 BU (5 weeks), 15 U dL^{-1} and 8 BU (6 weeks), 21 U dL^{-1} and 4.5 BU (7 weeks), respectively. She died of intracranial haemorrhage 2 days after the last FVIII:C and IT assay. The time course of IT and FVIII:C level for case 8 following prednisone and aPCC therapy are shown in Fig. 1.

Discussion

Inhibitor to FVIII in nonhaemophiliacs occurs predominantly in adults, and may be seen in patients with rheumatoid arthritis, systemic lupus erythematosus and other immunological conditions; during pregnancy or in the postpartum period; or in association with allergy to penicillin and phenytoin. About half of these patients have no underlying diseases [1, 4, 5]. The eight patients in our series had no underlying diseases, which may reflect some referral bias.

Replacement therapy for the bleeding episodes of FVIII inhibitor include high-dose human FVIII concentrates, recombinant FVIII (rFVIII), porcine FVIII concentrates, aPCC, extracorporeal immunoadsorption and recombinant FVIIa (rFVIIa) [2–5, 13].

Table 1. Clinical and laboratory characteristics.

No.	Age/ sex	Bleeding symptoms	Course (months)	PC	BT	PAgT	PT	KPTT	vWF:Ag (%)	FVIII:C (U dL^{-1})	IT (BU)
1	23/F		3/4	N	N	N	N	P	80	< 1	6.4
2	73/F	haematuria haemarthrosis	4	N	N	N	N	P	260	< 1	126.0
3	63/M	iliac haematoma	4.5	N	N	N	N	P	340	< 1	155.0
4	60/F		4	N	N	N	N	P	220	< 1	4.8
5	27/M	iliac haematoma	4	N	N	N	N	P	225	< 1	56.0
6	14/F	subcutaneous haematoma	5	N	N	N	N	P	140	< 1	135.0
7	65/F	hip haematoma intracranial haemorrhage	6	N	N	N	N	P	145	< 2	35.0
8	67/M	hip haematoma	8	N	N	N	N	P	230	< 1	150.0

BU, Bethesda unit; IT, inhibitor titre.

Table 2. Outcome of treatment and follow-up.

No.	No bleeding (week after treatment)	IT decrease > 50% (weeks)	IT elimination (weeks)	FVIII:C > 5 U dL^{-1} (weeks)	FVIII:C normal (weeks)	FVIII:C off hospital (U dL^{-1})	Follow-up (years)
1	2	2	3	3	4	58	1, NR*
2	2	3	5	3	5	80	2, NR†
3	6	2	11	7	11	62	2, NR
4	4		4	3	5	57	2, NR‡
5	3	4	8		8	71	1.5, NR
6	2		8	4	12	76	2, NR
7		4		4			Died§
8	1	2	5	4	5	116	1, NR

*NR-no relapse. †Case 2 relapsed 1.5 months after the discontinuation of prednisone and achieved a second elimination of inhibitor after restarting prednisone. Prednisone was discontinued 3 months later, and the patient remained free of inhibitor with a follow-up 2 years. ‡Case 4 died of lung cancer 2 years after stopping prednisone therapy without inhibitor present. §Case 7 died of intracranial haemorrhage in 8th week of prednisone therapy when her IT was 4.5 BU mL^{-1} and F VIII: C was 21 U dL^{-1}.

Because our patients could not afford the expense of high-dose FVIII concentrates, whereas porcine FVIII concentrates, rFVIII, rFVIIa and extracorporeal immunoadsorption were not available, only low-dose aPCC (40–50 u kg^{-1} day^{-1}) was delivered to stop bleeding in addition to preventive measures, and the effect was satisfactory. Only one patient (case 7) died of intracranial haemorrhage when her FVIII:C increased to 21 U dL^{-1}; this event was unexpected. Whether there had been cerebral vascular abnormality is unknown. The dosage of aPCC we used is relatively low compared with those described by others [4, 5]. It may be partly due to the relative delayed referral to our hospital after bleeding occurred and most of the bleeding being non life-threatening, or may be related to the aPCC we used. It may be invalid to compare the aPCC we used with other aPCC agents (e.g. FEIBA, Autoplex etc.) because the latter are not available in our country. The potential side-effects of aPCC include viral transmission, especially hepatitis, and the occurrence of thrombotic events [13]. Fortunately, no such side-effects were seen in our patients.

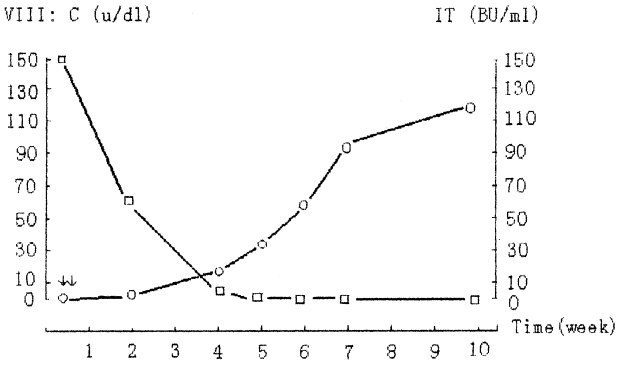

Fig. 1. The time course of FVIII inhibitor titre and FVIII:C level of Case 8 with prednisone (40 mg day^{-1}) therapy. (□) FVIII inhibitor titre (BU); (○) FVIII:C level (U dL^{-1}); (↓) aPCC.

The long-term aim of treatment with acquired FVIII inhibitor is to eliminate the inhibitor. The options include prednisone, cyclophosphamide, or prednisone and cyclophosphamide in combination with vincristine, etc. [4–6, 8, 10]. The low dose (0.5–0.75 mg kg^{-1} day^{-1}) and long course (> 3 months) of prednisone that our patients received is effective in inhibitor elimination and may have fewer side-effects. The median time for inhibitor elimination in our patients was 5 weeks (range 3–11 weeks). Prednisone was continued for 2–3 months after inhibitor disappeared. Six patients did not relapse with a follow-up over 1 year, and case 2 relapsed after discontinuation of prednisone and remitted after restarting prednisone; this patient had not relapsed with 2 years follow-up. Long-term prednisone therapy may be associated with a lower occurrence of relapse in our patients.

Our data suggest that prednisone and low-dose aPCC may be effective in some patients with acquired inhibitors.

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References

1 Green D, Lechner K. A survey of 215 non-haemophilic patients with inhibitors to factor VIII. *Thromb Haemost* 1981; **45**: 200–3.
2 Gatti L, Manucci PM. Use of porcine factor VIII in the management of seventeen patients with factor VIII antibodies. *Thromb Haemost* 1984; **51**: 379–84.

3 Nilsson IM, Jonsson S, Sundqvist *et al.* A procedure for removing high titer antibodies by extracorporeal protein A-sepharose absorption in hemophilia. *Blood* 1981; **58**: 38–44.
4 Hoyer LW. Acquired anticoagulants. In: Beutler E, *et al.*, eds. *Williams Hematology*, 5th edn. New York: McGraw-Hill, 1995, 1486–9.
5 Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. *Thromb Haemost* 1993; **70**: 753–7.
6 Dibona E, Schiavoni M, Castaman G, Ciavarella N, Rodeghiero F. Acquired haemophilia: experience of two Italian centres with 17 new cases. *Haemophilia* 1997; **3**: 183–8.
7 Sohngen D, Specker C, Bach D, *et al.* Acquired factor VIII inhibitors in nonhemophilic patients. *Ann Hematol* 1997; **74**: 89–93.
8 Crenier L, Ducobu J, Grottes JD, Cerny J, Delaunoit C, Capel P. Low response to high-dose intravenous immunoglobulin in the treatment of acquired factor VIII inhibitor. *Br J Haematol* 1996; **95**: 750–3.
9 Lian EC-Y, Larcada AF, Chiu AY-Z. Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. *Ann Intern Med* 1989; **110**: 774–8.
10 Hauser I, Schneider B, Lechner K. Post-partum factor VIII inhibitors: a review of the literature with special reference to the value of steroid and immunosuppressive treatment. *Thromb Haemost* 1995; **73**: 1–5.
11 Austen DEG, Rhymes IL. *A Laboratory Manual of Blood Coagulation*. Blackwell Scientific Publications, Oxford, 1975, 27–54.
12 Kasper CK, Aledort LM, Counts RB, *et al.* A more uniform measurement of tactor VIII inhibitors. *Thromb Diath Haemorrh* 1975; **34**: 869–72.
13 Macik BG. Treatment of factor VIII inhibitors: products and strategies. *Semin Thromb Hemost* 1993; **19**: 13–23.

