Long-term course of anti-factor VIII antibody in patients with hemophilia A at a single center

Ki Young Yoo, Sang Chun Joo, Yong Mook Choi
Korea Hemophilia Foundation, Seoul, Korea

Correspondence to
Ki Young Yoo, M.D., Ph.D.
Korea Hemophilia Foundation 70 Saimdang-ro, Seocho-gu, Seoul 06641 Korea
E-mail: gowho@hanmail.net

INTRODUCTION AND OBJECTIVES

Inhibitors comprising IgG antibodies bind to active sites of factor VIII molecules and neutralize clotting function of factor concentrates. Once inhibitor develops, it makes hemostasis more difficult and increases disability [1], reduces quality of life [2] and shortens the life expectancy [3].

The incidence of inhibitors is known to be about 30% of severe hemophilia A [4], 0.9-7% of mild to moderate hemophilia A [5]. The prevalence of inhibitors reported as high as 8.9-16.4% [6] in severe hemophilia A

For transient inhibitors, large dose infusion of factor concentrates or bypassing agents can be used. Persistent inhibitors can be only eliminated by ITI. Due to the large amount of factor concentrates spent in ITI, commencing ITI becomes a sophisticated matter in terms of eligibility, timing and the protocol.

Immune tolerance induction (ITI) can reduce inhibitors against factor VIII concentrates by 70–80%. In this study, we elucidated the characteristics of inhibitors and attempted to determine the proper indications and timing for ITI.

METHODS

The medical record and infusion diary of hemophilia A patients registered in the Korea Hemophilia Foundation from 1991 to 2014 were investigated retrospectively. Phenotypes, age at diagnosis of hemophilia A, exposure days, interval of inhibitor testing, age at detection of inhibitor, peak inhibitor titer and duration of inhibitor presence, treatment strategy and type of *F8* gene mutation were collected .

Low titer group included patients having historical peak titer of inhibitors recorded between 0.6 BU/mL and less than 2 BU/mL, moderate titer group between 2 BU/mL and less than 5 BU/mL, high titer group between 5 BU/mL and less than 10 BU/mL and very high titer group 10 BU/mL or more. Persistent inhibitors were inhibitors tested positive consistently since factor VIII concentrates had been challenged. The inhibitor was defined as transient if it disappeared within a short period of time while the patient remained on standard treatment .

RESULT

Table 1. Characteristics of patients with inhibitors against factor VIII.

	Age at hemophilia diagnosis (yr)	Age at INH detection (yr)	Exposure days	Peak INH titer (BU/mL)	Interval of INH test (mo)
All inhibitor patients (N=350)					
N[a)]	348	224	142	349	348
Mean (CI[b)])	7.4 (6.1–9.0)	14.7 (13.0–16.7)	67.9 (50.6–86.3)	68.7 (30.1–133.0)	11.8 (10.9–12.7)
Median (CI)	2.0 (1.3–3.0)	12.0 (8.5–14.0)	31.5 (25.0–45.0)	1.3 (1.2–1.5)	10.0 (9.0–11.0)
Persistent inhibitor patients (N=100)					
N	96	70	26	82	97
Mean (CI)	11.6 (8.1–15.8)	11.7 (8.2–15.3)	31.3 (19.9–44.8)	278.6 (119.6–509.0)	8.7 (6.9–10.7)
Median (CI)	3.0 (1.1–6.5)	4.0 (2.0–9.0)	16.0 (12.0–34.0)	61.6 (32.4–80.0)	6.0 (4.5–7.1)
Transient inhibitor patients (N=250)					
N	250	154	116	250	250
Mean (CI)	5.8 (4.7–6.9)	16.1 (14.0–18.0)	76.1 (58.5–100.9)	5.0 (3.3–6.9)	13.0 (12.0–13.8)
Median (CI)	1.8 (1.0–2.0)	14.0 (12.0–15.0)	37.5 (29.0–50.0)	1.0 (1.0–1.1)	12.0 (10.4–12.0)
P	0.109	0.000	0.032	0.000	0.000

[a)]Number of patients that could be investigated for each variable. [b)]95% CI.
Abbreviations: INH, inhibitor; BU, Bethesda unit; CI, confidence interval.

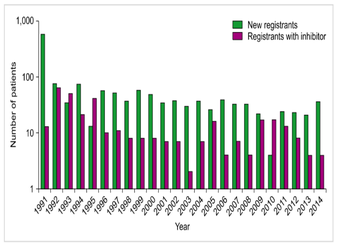

Fig. 1. Annual number of new registrants and patients with inhibitors registered in the Korea Hemophilia Foundation. The high proportion of patients with inhibitors are observed in the early 5 years, 2005 , 2009, 2010 and 2011.

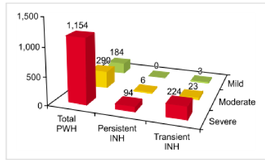

Fig. 2. Inhibitor status according to hemophilia A phenotypes. The severer phenotypes patients have, the more frequent inhibitors the patients developed ($P < 0.001$). However the proportion of persistent inhibitors to transient inhibitors was not significantly higher in severe patients in comparisen with the mild and moderate patients ($P = 0.221$).
Abbreviations: PWH, patient with hemophilia; INH, inhibitor.

Table 2. Long-term follow up of patients with transient inhibitors against factor VIII.

Group	Exposure days	Interval of INH test (mo)	Peak INH titer (BU/mL)	Duration of INH presence (mo)
All (N=250)				
N[a)]	116	250	250	244
Median (CI[b)])	37.5 (29.0–49.0)	12.0 (10.3–12.0)	1.0 (1.0–1.1)	11.0 (10.0–12.0)
Low[c)] (N=205)				
N	104	205	205	200
Median (CI)	41.5 (29.0–51.0)	12.0 (10.5–12.0)	1.0 (0.9–1.0)	10.0 (8.5–12.0)
Moderate[d)] (N=13)				
N	7	13	13	13
Median (CI)	26.0 (8.0–37.0)	10.0 (6.0–16.0)	3.2 (2.3–4.4)	8.0 (3.0–11.0)
High[e)] (N=11)				
N	3	11	11	11
Median (CI)	20.0 (8.0–56.0)	12.0 (7.0–13.3)	6.0 (5.6–8.8)	13.0 (7.0–34.0)
Very high[f)] (N=21)				
N	2	21	21	20
Median (CI)	65.5 (25.0–106.0)	10.2 (5.3–13.0)	17.4 (13.6–23.2)	19.0 (16.0–36.0)
High and very high (N=32)				
N	5	32	32	31
Median (CI)	25.0 (8.0–106.0)	11.1 (7.5–13.0)	13.4 (10.0–17.3)	18.0 (13.0–31.0)

[a)]Number of patients that could be investigated for each variable. [b)]95% CI. [c)]Peak titer <2 BU/mL. [d)]Peak titer 2 to <5 BU/mL. [e)]Peak titer 5 to <10 BU/mL. [f)]Peak titer ≥10 BU/mL.
Abbreviations: INH, inhibitor; BU, Bethesda unit; CI, confidence interval.

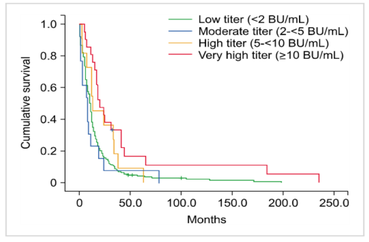

Fig. 3. Kaplan–Meier survival curve of transient inhibitors according to peak titer. The duration of inhibitor presence was longer in very high titer, transient inhibitor group than in other 3 groups ($P = 0.001$).

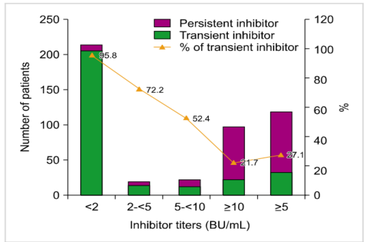

Fig. 4. Number of patients with persistent and transient inhibitors and the percentage of transient inhibitors, according to the peak inhibitor level.

Table 3. Characteristics of patients treated with recurrent factor VIII inhibitors (N=71).

	EDs for each episode	Interval of INH test (mo)	Peak INH titer (BU/mL)	Duration of each episode (mo)	Time lapse of episodes (yr)	Recurrent number of episode
N[a)]	150	155	155	154	155	155
Median (95% CI)	28.5 (20.5–35.5)	8.4 (7.5–9.8)	0.9 (0.9–1.0)	8.0 (6.0–9.0)	3.0 (2.5–3.0)	2.0 (2.0–4.0[b)])

[a)]Number of episodes that could be investigated for each variable. [b)]Range.
Abbreviations: EDs, exposure days; INH, inhibitor; BU, Bethesda unit; CI, confidence interval.

Table 4. Anti-FVIII inhibitor development by *F8* gene mutation.

Mutation type	Cases[a)] (N=83)	Controls[b)] (N=269)	Odds ratio (95% CI)	*P*
Missense	12	89	0.34 (0.17–0.66)	0.001
Nonsense	8	34	0.73 (0.32–1.64)	0.564
Large deletion	11	3	13.38 (3.34–49.20)	0.000[c)]
Frame shift	16	42	1.28 (0.68–2.41)	0.500
Intron22 inversion	35	89	1.45 (0.88–2.39)	0.153
Splicing	1	12	0.26 (0.03–2.02)	0.205

[a)]Cases: Combined persistent inhibitor and transient inhibitor patients. [b)]Controls: Inhibitor(-) patients. [c)]Fisher's exact test.
Abbreviation: CI, confidence interval.

CONCLUSION

Given the spontaneous disappearance of inhibitors and high cost of ITI, it is worthwhile to postpone ITI for 11 months unless the peak inhibitor titer is greater than 10 BU/mL.

REFERENCES

1. Brackmann HH, Schwaab R, Effenberger W, Hess L, Hanfland P, Oldenburg J. Antibodies to factor VIII in hemophilia A patients. Vox Sang 2000;78(Suppl 2):187-90.
2. Colowick AB, Bohn RL, Avorn J, Ewenstein BM. Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper. Blood 2000;96:1698-702.
3. Yoo KY, Kim SK, Kwon SS, et al. Life expectancy of Korean haemophiliacs, 1991-2012. Haemophilia 2014;20:e356-8.
4. Brackmann HH, Wallny T. Immune tolerance:high-dose regimen. In: Rodriguez-Merchan E, Lee C, eds. Inhibitors in Patients with Haemophilia. Oxford: Blackwell Science; 2002:45-8.
5. Darby SC, Keeling DM, Spooner RJ, et al. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977-99. J Thromb Haemost 2004;2:1047-54.
6. Alfonso Iorio. Epidemiology of inhibitors in hemophilia. In:Christine A Lee, Erik E Berntorp, W Keith Hoots, eds. Textbook of Hemophilia. 3rd ed. Chichester; John Wiley & Sons;2014:53-58.1