

Natural course of inhibitors in Korean Hemophilia A patients

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Objectives

Inhibitor development against exogenous factor VIII is a major challenge in the treatment of hemophilia. Immune tolerance induction therapy (ITI) has been known as the ultimate treatment for inhibitors. Even though success rate of ITI reaches 70~80%, it takes a lot of costs. Moreover, some inhibitors may disappear spontaneously. So it is important to elucidate natural course of inhibitors in order to determine the subjects and timing of ITI.

Methods

We reviewed medical records of 1,579 hemophilia A patients registered to Korea Hemophilia Foundation from 1991 to May 2013. Cut-off value of inhibitors was 0.6 BU/mL or more on Bethesda assay. Patient who had developed inhibitors at least once was regarded as an inhibitor positive patient. When the titers remained less than 0.6 BU/mL for at least 2 years, the patient was classified as an inhibitor negative patient. Analysis of related patients, we surveyed peak inhibitor titer, exposure days, duration of inhibitor positivity and treatment modality during inhibitor positive period.

Results

Two-hundred forty nine (15%) in 1,579 patients were identified as inhibitor positive patients. Sixty five (4%) patients' inhibitor had never disappeared and 16 patients among them underwent ITI. Remaining 49 patients are still having inhibitors. One-hundred eighty four (11% in hemophilia A, 73% in inhibitors) patients' inhibitors were transient. As for transient inhibitors, median titer was 1.2 BU/mL and lasted for 10 months. Low titer (<2 BU/mL) inhibitors lasted for 9.5 months, moderate titer (2-5 BU/mL) was 8 months, high titer (>5 BU/mL) was 16 months ($p=0.001$). Thirty (34%) in 87 high titer, 11 (84%) in 13 moderate titer and 144 (97%) in 149 low titer inhibitors were spontaneously disappeared without ITI. Most patients, even high titer patients were kept to the same medication and dosing requirement, especially in early 90s.

Transient inhibitors		Inhibitor titer (BU/mL)	Exposure days	Test interval (month)	Duration of inhibitor positivity (month)
Overall (n=184)	median (IQR*)	1.2 (0.96-1.73)	26 (11-54.5)	9.6 (6-14)	10 (5-19)
Low titer (n=143)	median (IQR)	1.08 (0.88-1.3)	26 (11-56)	9.3 (6-14)	9.5 (5-17.3)
Moderate titer (n=11)	median (IQR)	3.0 (2.3-4.0)	25 (9.3-41.5)	9.6 (5-16)	8 (1-19)
High titer (n=30)	median (IQR)	11.5 (6.35-19.5)	25.5 (13.3-56.3)	9.8 (4.9-13)	16 (7-26.5)

*Interquartile range

Conclusion

As ITI costs very much, it is worthwhile to wait and observe the natural course of inhibitors for at least 10 months. But for the high titer inhibitor, it is unlikely to disappear without ITI.

