Case series report – low-dose immune tolerance (ITI) in Iran

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Introduction

The most serious complication associated with the treatment of hemophilia A is development of anti-factor VIII antibodies. Inhibitors occur in up to 30% of patients with severe hemophilia A (FVIII <1% of normal) [1–2], 0.9–7% of patients with mild to moderate hemophilia A [3]. The presence of an inhibitor does not increase mortality, but it complicates treatment and increases disease-related morbidity because bleeding episodes do not respond to standard therapy (4).Inhibitors usually occur after 50 exposure days(5). Genetic factors that have been related to an increased risk of inhibitor development are a positive family history of inhibitors [6-7], a high risk FVIII gene defect [8-9] and ethnicity [10],as well as polymorphisms in the immune-regulating genes coding for interleukin 10 (IL-10), tumor necrosis factor alpha (TNF-a). Environmental factors for such as:type of factor concentrate, age at first exposure to FVIII, and intensive treatment are also very important.

METHODS

We selected 5 patients under 3 years of age, who were registered at the Iranian Comprehensive Hemophilia Care Centre in Tehran (ICHCC). They all suffer from severe hemophilia A (FVIII≤1%), and have developed a FVIII inhibitor. In all cases, treatment has exclusively been with plasma- derived FVIII (pdFVIII). and 3 patients were on primary prophylaxis. At the start, we described for their parents, the different forms of treatment currently available for dealing with inhibitors, together with the benefits and possible complications which might occur.
They all signed a consent form and were given diaries for documenting : the number of bleeding episodes, as well as the number of injections administered for ITI. Their median age was 21 months, and inhibitors had developed after 11 (between 5 and 20) exposure days. At the start of ITI, the average inhibitor titre was 7.4 BU. Immune tolerance was initiated with pd FVIII at 50 to 100 IU/kg twice weekly. Treatment of bleeding was solely with rFVIIa. Clinical recovery was declared when inhibitors decreased below 0.6 BU, and no anamnestic response to FVIII occurred.
For ITI, we used the same pdFVIII habitually employed for treatment before the development of an inhibitor. All coagulant factor administrations were given via peripheral veins.
Patients were routinely followed up by a pediatrician monthly, or more frequently if clinically indicated. Factor VIII inhibitor titers were measured monthly for 3 months and every 2-3 months thereafter, to recovery.
FVIII genetic analysis for the determination of the family mutation was carried out in all cases by our genotypic laboratory.

RESULTS

The results of genotypic analysis demonstrated: 2 patients showed an intron 22 inversion; a further 2 had a frame-shift in exon 14, and one patient had a frame-shift mutation in exon 1.
The highest inhibitor titers were seen in the 2 patients with an intron 22 inversion, reaching peaks of 54 and 15 BU respectively.
Earlier inhibitor eradication occurred in the 2 patients with exon 14 frame-shift mutations.
One patient with an inhibitor titer of >5 BU had to be excluded after 16 weeks because of uncooperative parents. This patient currently has a FVIII inhibitor titre of 7 BU, and requires frequent treatment with bypassing agents for bleeding.

The remaining patients recovered after 9; 26; 64 and 103 weeks respectively. They have since remained inhibitor-free for 2 years.

case	age	Exposure days	initial titer	peak titer	Dose	time to recovery	Exon	Nucleotide change	Amino Acid Change	Mutation Type
1	19	24	2	6	50u/kg	26 weeks	14	c.2945 ins. A	p.Asn982LysfsX9	Frame shift
2	36	40	4	7	100u/kg	9 weeks	14	c.4379 ins. A	p.Asn1460LysfsX2	Frame shift
3	12	5	17	54	100u/kg	103 weeks	**Intron 22 inversion**			
4	18	20	6	15	75u/kg	64weeks	**Intron 22 inversion**			

Table 1:The patients' clinical and genetic information

CONCLUSIONS

Low-dose ITI even twice weekly, without the need for central vein catheterization, can be effective in eradicating FVIII inhibitors, despite the presence of unfavorable mutations. Although our cases are few in number, we consider this protocol to be particularly appropriate and cost-beneficial, for use in developing countries.

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DOI: 10.3252/pso.eu.WFH2012.2012