A Tailored primary prophylaxis program with escalation for severe haemophilia A in Iran

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Introduction

Haemophilia A is a sex-linked genetically determined hemorrhagic disorder resulting from FVIII deficiency. The clinical hallmark of hemophilia is bleeding into muscles and joints especially the ankles, knees and elbows(1).Repeated hemarthroses can lead to chronic arthropathy and this is one of the most severe complications of haemophilia. The best way to treat acute joint bleeding is through the administration of concentrated clotting factor, whether plasma-derived or recombinant . Despite the overall relative rarity of patients with severe haemophilia (FVIII ≤1%),the disease has an important socioeconomic effect (2).

The goal of the prophylactic treatment of haemophilia is to convert severe forms of the disorder into milder forms. (3) . All current reports show the superior efficacy of primary prophylaxis in mitigating the risk of long-term joint damage, in comparison with on-demand therapy (by about 84% in a NHF study)(4).

Today, prophylactic treatment is available to only a minority of haemophilia patients in the world, although it is recommended by the World Health Organization (WHO)and the World Federation of Haemophilia as an optimal form of treatment for severe haemophilia(4).However, the timing of initiation; the optimal protocol design and frequency of factor concentrate infusion, remain controversial (5).

Methods

Nineteen boys with severe haemophilia A (FVIII <1%), aged <5 years (median 26 months) with no inhibitor or target-joint history were randomised to receive prophylactic pdFVIII 30-50 IU/kg once a week with escalation to 2-3 times a week (25 IU/kg) as required(6). Seven ODT patients were investigated retrospectively. Numbers of bleeds; haemarthrosis frequency and physical and radiological scores were evaluated at the Iranian Comprehensive Haemophilia Care Centre for 54 months.

Our patients received treatment only via peripheral veins. Three patients developed a low-titre inhibitor, but 2 returned to prophylaxis after ITI.

Our physiotherapist examined 6 joints (ankles, elbows and knees) for every patients and recorded a score based on the Manco-Johnson Physical Instrument (7). These examinations were repeated every 6 months.

MRI and joint X-rays were performed before treatment and although we were not able to do final MRIs for lack of sufficient funding, we were nevertheless able to carry out joint X-Rays at the end of the study. Scoring of radiologic and MRI examinations were performed by a single radiologist, who based himself upon the Pettersson scoring system(8) and a modified MRI score(9),respectively.

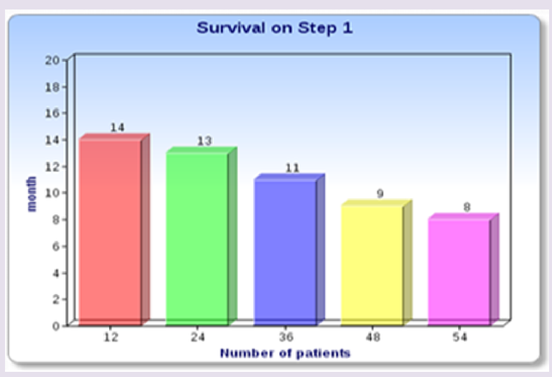
Genotyping were performed for all patients in the prophylactic group by our Genotypic Laboratory at the IHCC.

Results

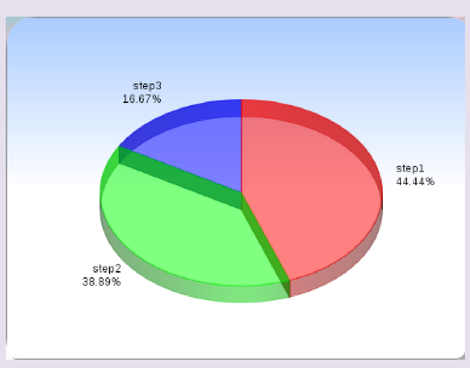
Among the subjects with severe HA chosen for inclusion in our prophylaxis study, only 26% (5/19) had a positive family history, while a surprising 74% had no family history of haemophilia, and were new cases(14/19).

Inhibitor-formation occurred in 3 patients after 5,6 and 11 injections for prophylaxis, but two of them responded well to Immune Tolerance Induction (ITI) and were able to return to prophylaxis treatment, after 26 and 103 weeks.Target joints developed in 5 PP cases (28%), and in 3 ODT patients (43%).

Children on prophylaxis had fewer haemarthrosis compared to ODT children (4.1 vs. 6.2 per person/year), respectively . At 54 months, follow-up showed a median total joint score on physical examination of 1.5 for the PP group and 3.4 for ODTs. The radiological scores were 0.05 for PPs and 0.5 for ODTs. However even before initiation of prophylaxis MRI already showed detectable osteochondral changes in 12/19 (65%) of boys.



End of study



	Target Joints	*CVC*	*Median time to escalate to step2*	*Hemarthrosis*
Canadian	9 (36%)	10	3.42	1.2
Our Clinic	5 (27.7%)	0	2.3	3.2

Table1:**Comparison Iranian with Canadian study**

Treatment	Mean Bleeding (Times/person/y)	Percent Hemarthrosis	Hemarthrosis (/person/year)	FVIII consumption (U/kg/Year)
Prophylaxis	10.4	40	4.1	2517 prphyaxis+ bleeding
On-demand	9.5	65	6.1	2095

Table2:Comparison Prophylaxis and on-demand treatment

index joint	target joint	median physio score		median Radiology score	
		Before	*After 54mo*	*Before*	*After 54 mo*
R.Elow	2	1	4	0	0
L.Elbow	1	0	4	0	0
R.Knee	0	4	2	0	0
L.Knee	1	3	2	2	1
R.Ankle	1	0	11	0	0
L.Ankle	0	1	4	0	0

Table3:Incidences of target joints ,physiotherapy and radiology score in any index joint.

index joint	MRI (before prophylaxis)
R.Elbow	5
L.Elbow	2
R.Knee	3
L.Knee	5
R.Ankle	7
L.Ankle	3

Table4:MRI score only before prophylaxis treatment

Conclusions

With tailored, low -dose prophylaxis, joint bleeding can be decreased; deterioration of radiological scores can be achieved, and near- normal physical scores in boys with severe haemophilia A, can be maintained. Finally, this protocol is more affordable and can therefore be more readily implemented in developing countries, because it calls for the use of less FVIII than most other prophylactic regimens.

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