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The Impact of Factor VIII Inhibitors on Factor Consumption in Haemophilia A: A Case-Control Study in South of Iran

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Abstract: Inhibitors in patients with haemophilia are rare complication causing pain, disability and impairment. There is a general perception that it has a determinant impact on costs of care in these patients. The costs of factor consumption in 6 Iranian hemophiliacs with high responding inhibitors as the case group and 6 hemophiliacs without inhibitors as the control during 12 months were studied in a clinical centre in south of Iran. The data concerning clinical and demographic characteristics of patients were retrieved from their medical records. Results indicated that all patients suffered from severe haemophilia. The mean weight of inhibitors and non-inhibitors groups was 67.33 (±18.67) and 66 (±15.23) respectively. Overall 1.79 (±0.75) and 1.95 (±1.66) bleeding per patient monthly were recorded for inhibitors and non-inhibitors groups, respectively. The median annual costs of care were three time higher for inhibitors than non-inhibitors patients (US$ 67987.875 vs. US$ 21415.145). in conclusion: Based on the finding from the current study, presence of inhibitor affects the cost of factor replacement therapy in treating of haemophilia A in short-term.

Key words: Haemophilia A · Factor VIII Inhibitors · Costs · Iran

INTRODUCTION

Haemophilia A is a sex-linked hereditary bleeding disorder caused by a complete or partial deficiency of clotting factor VIII (FVIII) [1] and is more common than hemophilia B, representing 80-85% of the total of haemophilic patients [2]. There are three type of haemophilia A which are determined based on the level of FVIII in the blood: Mild (5-25% of normal levels), Moderate (2-5% of normal levels) or Severe (<1% of normal levels) [3].

Since 1964 that Pool *et al*.[4] reported a simple method to purify FVIII using human plasma, the missing clotting factor is intravenously administered to either stop or prevent bleeding. The replacement therapy has improved the life quality of haemophilic patients. However, some patients with haemophilia A develop specific inhibitors to factor VIII, which result in partial or complete lack of efficacy of clotting factor concentrates [5]. The incidence of this complication is greatly unstable, with values ranging from 1.5 to 39 per 1000 patient years [6-7]. Inhibitors have been estimated to occur in 4-20% of

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all patients with severe hemophilia A [8-9]. The development of FVIII inhibitors continues to be one of the most difficult challenges in the management of haemophilia A [10-11].

Major therapeutic approaches are used for this complication include: a) Recombinant factor VIIa (NovoSeven®1), which don't have risk of transmission of human viruses such as hepatitis and HIV, because no material of human origin is used during its manufacture or formulation [12]; b) intravenous activated prothrombin complex concentrate (aPCC; also known as factor eight inhibitor bypassing activity [FEIBA®])[13]; c) FVIII derived from porcine plasma [14] and d) immune tolerance induction (IIT) therapy, which tries to suppress inhibitor levels by the administration of frequent doses of factor VIII or IX over a prolonged time [15-18].

The treatment costs of patients with haemophilia A is high and incurs a considerable economic burden on healthcare systems [3]. Generally, the cost of treatment in patients with inhibitors appears to be higher than that in patients without inhibitors [19,20], although, this has not been confirmed by all case-control studies [3].

According to World Federation of Hemophilia, Iran has 3980 patients with haemophilia A that 170 0f them clinically identified with inhibitors [21]. Furthermore, a national study on burden of disease showed that haemophilia was responsible for 2213 Disability Adjusted Life Years ($DALY_s$) in 2003 [22]. The government of Iran annually spends about $ 60 million subsidies for drugs of haemophilia patients [23]. The current study was designed to gain understanding of impact of inhibitors on costs of care in hemophilia A in an Iranian setting. In this study we conducted a retrospective case controlled study for haemophilia A patients with and without inhibitors, over 1 year period in the south of Iran.

MATERIALS AND METHODS

We identified 6 severe haemophilia A patients with high titer (>5 Bethesda units) who were treated in Fars Hemophilia Society in the south of Iran. Six non-inhibitor patients were chosen from the same centre as a control group and were matched for age and severity of the disease (<1%). Inhibitor patients were defined as those who had a high titer inhibitor to FVIII during the study period. All patients were treated based on on-demand strategy.

In a retrospective chart review, the factors consumed over 1 year period ending September 1, 2008 were collected from the hospital records. Applying the price of different factors, the total cost of factor consumption was calculated for each study group.

Moreover, demographic characteristics including age and gender, were collected from the medical records of the patients.

The paired-samples t-tests were used to identify significant differences in demographic and clinical variables between the inhibitor cases and matched controls.

RESULTS

The main demographic and clinical characteristics of inhibitors and non-inhibitors patients have been shown in table 1. Mean age in inhibitors and non-inhibitors groups was 25.5 (±7.8) and 25.6 (±8.5), respectively. Mean weight for inhibitors and non-inhibitors was 67.33 (±18.67) and 66 (±15.23), respectively. There were no significant differences between two groups in terms of age and weight. There were no differences in severity of haemophilia as all patients suffered from severe hemophilia A and there were no patients with hepatitis and HIV infectious. All 6 patients in case group had high levels of inhibitors (>5BU).

Inhibitors patients had, on average, 21.5 (±9.07) bleeding events per year compared 23.5 (±19.95) in controls non-inhibitors patients. This difference was not statistically significant.

Most inhibitors patients were treated with rFVIIa and FEIBE during the study period. Only one inhibitor patient (I-6) treated with single product (FVIII). All non-inhibitors patients received FVIII over the study period.

Table 2 shows the costs of factor consumption for inhibitors and non-inhibitors patients during study period. Mean annual costs for inhibitors patients was US$55793.26 compared with US$34122.21 in non-inhibitors patients. This shows the cost of replacement therapy is 1.6 times higher in inhibitors than non-inhibitors. As the skewness nature of cost data, the median of annual cost between two groups were compared and showed that difference between two groups was more considerable (US$ 67987.875 vs. 21415.145). As it can be seen from table 2, four patients in inhibitors group had more costs than their matched controls.

Table 1: Demographic and clinical characteristics of inhibitors (I) and non-inhibitors (C) patients with severe haemophilia A.

Patient number	Age	Weight	Severity	Annual Bleeding Events	Products used
I-1	32	70	S	18	rFVIIa FEIBA
I-2	25	65	S	30	rFVIIa FEIBA
I-3	30	80	S	20	rFVIIa FEIBA
I-4	24	90	S	25	rFVIIa FEIBA
I-5	11	35	S	30	rFVIIa FEIBA
I-6	31	64	S	6	FVIII
C-1	33	80	S	30	FVIII
C-2	25	62	S	17	FVIII
C-3	30	78	S	4	FVIII
C-4	24	70	S	60	FVIII
C-5	10	38	S	20	FVIII
C-6	32	68	S	10	FVIII

Table 2: Annual costs of factor consumption among inhibitors and non-inhibitors in patients with severe haemophilia A.

Matched pair number	Inhibitors (US$)	Non-inhibitors (US$)	Differences (US$)
1	80121.21	61442.42	18678.79
2	73191.91	23769.69	49422.22
3	69133.33	3363.63	65769.7
4	66842.42	85212.12	-18369.7
5	37173.73	19060.6	18113.13
6	8296.96	11884.84	-3587.88
Mean	55793.26 (±22557.89)	34122.21(±32034.95)	21671.04
Median	67987.875	21415.145	46572.73

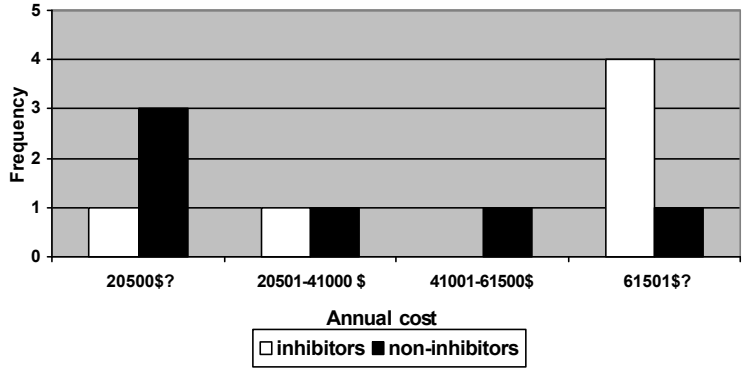

Fig. 1: Frequency distribution of patients according to annual cost.

There was a significant variation in frequency distribution of patients based on the annual costs (Figure 1.). While one-half of non-inhibitors patients had less than or equal to US$20500 annual costs, only one inhibitors patient placed in this cost category. On the other hand, four inhibitors patients had equal or more than US$61501 annual costs, while only one non-inhibitor patient generated this cost. Moreover, this figure shows the skewness of the costs data.

DISCUSSION

The current study aimed to test this general perception that treatment costs are higher for patients with inhibitors than for those without inhibitors. The study showed that treatment of patients with haemophilia with or without inhibitors incurs an important economic burden on health system of Iran. The mean annual cost in our sample patients (inhibitors and non-inhibitors) was US$ 44976 (±30655).

The mean annual costs in inhibitors and non-inhibitors groups were US$ 55793.26 and 34122.21, respectively. This difference in annual mean costs is economically significant and shows a considerable difference between the two groups.

The results of current study are comparable with those have been seen in other economic analysis of haemophilia A. Ginger *et al*. [24] reported that inhibitors

is a determinant factor in cost of care in patients with haemophilia. In another longitudinal retrospective study, Goudemand [19] found that the annual mean cost of treatment in patients with high responding inhibitors was about 1.3 and 3 times higher than non-inhibitor patients, before and after the introduction of rFVIIa, respectively.

In a previous study in Iran, Karimi *et al*. [25] reported that cost of patient care was significantly correlated to presence of inhibitor in patients.

Some studies showed that cost differences between inhibitors and non-inhibitors may create because of presence the patients with outlier figures in samples. For example Chang *et al*. [26] compared the costs of clotting factor concentrate therapy for haemophilia A in nine patients with inhibitors and nine non-inhibitors control patients matched by age and severity of disease during a 3.5-year period in Canada. Mean of cost in inhibitors was 2.25 fold greater than non-inhibitors control, however in two-thirds of the pairs (six of nine), the costs of haemostatic therapy for the inhibitor patients were less than the control. This subject was not case in our study, as 66% patients in inhibitor group had higher cost than non-inhibitor controls. Moreover, cost differences between two groups would have increased if we excluded outlier non-inhibitor patient (patient in pair 4).

In interpreting the results of the current study, as one of the first studies which compared the cost of care in inhibitors and non-inhibitor patients with haemophilia A in Iran, several limitations require consideration. The study was a retrospective analysis and relied on the hospital's records data which usually are not complete resources in Iran. Furthermore, the number of patients was too small and this issue may affect our results. One-year time horizon of our study is another potential limitation that may be effective in our findings. Moreover, we used the Health Ministry perspective as third party payer while most published guidelines for economic analysis have recommended the adoption of a societal perspective. Moreover, as a cost-analysis, this study is time sensitive and is greatly specific to the study setting.

We suggested that there is a need for large sample prospective studies considering societal perspective in long-term to detect the real impact of inhibitors on costs of care in patients with haemophilia A, especially when one consider the considerable financial burden of haemophilia on health system resources.

Note: The exchange rate used in this study was 1Rial = US$ 0.0001.

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