Brief Communication

Different treatment strategies for Haemophilia A with Low Inhibitor

Narges Mirbehbahani[1], Azam Jahazi[2]

ABSTRACT

Objective: To compare the cost-effectiveness of treatment options in three patients with haemophilia A and low titer inhibitors.

Methodology: We used a longitudinal before-and-after design that was conducted in two phases assessed retrospectively: Phase I was 6 months preceding the introduction of recombinant activated factor VII (rFVIIa), during which patients received on–demand usual care with plasma derived factor VIII regimes, phase two was 6 month treatment on rFVIIa. We determined the clinical response and the cost of treatment with NovoSeven in three patients with low titer inhibitors to factors VIII compared with other treatment regime previously used in these patients (Plasma derived factor VIII).

Results: Total number of bleeding episodes, re-treatments and need of hospitalization were 21, 11 and 12 in phase 1 vs. 19, 0 and 0 in phase two respectively. Total cost of rFVIIa and plasma derived factor VIII treatment was USD 98600 vs. USD 77000.

Conclusion: rFVIIa is clinically effective. It resulted in 100% reduction in the number of re-treatments, hospitalization and 21.9% reduction in the total cost compared to treatment with plasma derived factor VIII regime.

KEY WORDS: Haemophilia A, Inhibitors, rFVIIa, Plasma derived factor VIII.

Pak J Med Sci January - March 2011 Vol. 27 No. 1 229-232

How to cite this article:

Mirbehbahani N, Jahazi A. Different treatment strategies for Haemophilia A with Low Inhibitor. Pak J Med Sci 2011;27(1):229-232

INTRODUCTION

Inhibitors in haemophilia A against FVIII is problematic, challenging, and difficult to manage. While the frequency of bleeding is not increased in haemophilia patient with inhibitors, once bleeding occurs, its control is more difficult and often unpredictable.[1] rFVIIa is a bypassing agent evaluated in compassionate use and investigational studies. rFVIIa appears to be effective in 69-90% of treatment courses encompassing different types of hemorrhages and surgical procedures.[2] The administration of exogenous rFVIIa in high concentrations has been found to initiate and maintain haemostasis in haemophilia patients with inhibitors to FVIII/FIX. This effect seems to be due to an increased generation of thrombin on the platelet surface after this has been activated by the thrombin molecules formed through the initial FX activation by the tissue factor (TF)–FVIIa complex formed on the TF-bearing cells.[3] rFVIIa provides site-specific thrombin generation through pharmacological manipulation of the coagulation mechanism at the site of vessel injury. Endothelial damage is associated with collagen and TF exposure. Under normal physiological conditions, trace amounts of circulating FVIIa, in the order of 3.58 ng/mL, bind to form the TF: FVIIa complex. This

1. Narges Mirbehbahani,
Hematologist,
Faculty Member of Golestan University of Medical Sciences,
Gorgan, Golestan, Iran.
2. Azam Jahazi,
Master Science of Midwifery, Midwifery Department,
Faculty Member of Islamic Azad University Gorgan Branch,
Gorgan, Golestan, Iran.

Correspondence:

Azam Jahazi,
Midwifery Department,
Islamic Azad University Gorgan Branch, Golestan, Iran.
E-mail: ajahazi@gorganiau.ir

* Received for Publication: April 22, 2010
* 1st Revision Received: April 26, 2010
* 2nd Revision Received: September 6, 2010
* Final Revision Accepted: September 8, 2010

Table- I: Number of bleeding episodes in 3 patients.

Type of bleeding episode	*Phase 1*	*Phase 2*	*Difference*	*% Difference*
Moderate muscle bleeding	1	0	-1	-100
Moderate mouth bleeding	1	0	-1	-100
Sever muscle bleeding	2	0	-2	-100
Mild haemarthrosis	16	10	-6	-37.5
Moderate haemarthrosis	1	9	8	800
Total	21	19	-2	-9.5

complex has now been recognized as the pivotal activator of the coagulation cascade and results in localized thrombin generation. Through thrombin-mediated platelet activation and feedback up-regulation of the clotting mechanism, haemostatis occurs. At pharmacological concentrations in the order of 50 nM, rFVIIa has been shown to generate significantly more thrombin in a model simulating normal plasma, compared to haemophilic plasma.[4]

In the French multicenter study, patients assessed the efficacy of NovoSeven in serious bleeding episodes 8h after an initial dose of rFVIIa (90-120 μg/kg/dose). One hundred thirty two episodes of acute hemarthrosis were treated and analyzed. Haemostasis was judged excellent or effective in 90% of episodes, partially effective in 9%, and ineffective in 0.6% of the bleeding episodes. The mean number of doses was 2.9 per bleeding episode.[5]

In this paper we analyzed the responses and costs of giving rFVIIa vs. plasma-derived factor VIII to patients with low-titer inhibitors.

METHODOLOGY

Three patients, with severe haemophilia A participated in this study. They were attending in the Gorgan treatment center of Iran. Their ages in baseline were 7, 23 and 43 years old. Their weights were 23, 55 and 70kg respectively. Duration of inhibitors presence was not applicable. Maximum inhibitor levels were 3.8, 2.9, 1.3 Bethesda units (BU) respectively.

We used a longitudinal before-and-after design that was conducted in two phases. Phase one was six months preceding the rFVIIa treatment (NovoSeven) during which all patients were treated with an on-demand plasma derived factor VIII regime. Phase two was six months of on-demand treatment with rFVIIa. The treatment regime consisted of intravenous push injection of rFVIIa in a dose of 90 μg/Kg and was repeated after two hours if bleeding continued.

This study was conducted in the perspective of the Iranian Ministry of Health. Due to the un-availability of other medical resources unit costs, study focused on treatment costs and excluded outpatient and inpatient costs associated with the bleeding episodes.

Effectiveness of treatments was assessed through the need for hospitalisation and need for re-treatment (a treatment was considered as effective if bleeding episode could be controlled in the outpatient setting within 24 hours). All bleeding episodes occurring during one of the two phases of the study were treated first in outpatient setting and, if bleeding episode remained uncontrolled, patients were transferred to hospital. Clinical response to treatment and therefore need for hospitalisation was assessed by a physician. A written informed consent was obtained from the patients. In one patient that was less than 18 years old, that was obtained from his parents.

RESULTS

Total number of bleeding episodes, re-treatments and of hospitalization were 21, 11 and 12 in phase one vs. 19, 0 and 0 in phase two respectively (Tables I, II and III). In phase two, there was a 9.5% reduction in bleeding episodes; 100% reduction in re-treatments and 100% reduction in hospitalization. Study results confirm that rFVIIa is clinically effec-

Table- II: Number of hospitalization according to type of bleeding episode in 3 patients.

Type of bleeding episode	*Phase 1*	*Phase 2*	*Difference*	*% Difference*
Bleeding	4	0	-4	-100
Haemarthrosis	8	0	-8	-100
Total	12	0	-12	-100

Table- III: Number of re-treatments within 24h according to type of bleeding episode in 3 patients.

Type of bleeding episode	*Phase 1*	*Phase 2*	*Difference*	*% Difference*
Bleeding	4	0	-4	-100
Haemarthrosis	7	0	-7	-100
Total	11	0	-11	-100

tive. Indeed, each bleeding managed with rFVIIa was managed in outpatient setting (i.e. did not require transfer to emergency room visit) within 24 hours. Table-IV demonstrates total factor consumption and associated cost for three patients in each study phase. Study results showed that total cost of treatment with rFVIIa for three patients was USD21600 (21.9%) lower than total cost of treatment with plasma derived FVIII.

DISCUSSION

There are many published studies which report the success of different treatments for hemophilia A patients with low titer inhibitors, but very few, if any attempt to compare the result between plasma derived factor VIII and rFVIIa. In published papers, effectiveness of rFVIIa and high dose plasma-derived F VIII data were 89.3% and 71.4% respectively.[6] Cost analysis data are now extremely valuable for the development of treatment guidelines where there is debate over the most appropriate treatment in terms of cost-benefit ratio. Cost-effectiveness of using rFVIIa vs. activated prothrombin complex concentrate (aPCC) in patients with high titer inhibitors is well documented worldwide.[3-8] This is perhaps the first study assessing the cost and effectiveness of giving rFVIIa to patients with low titer inhibitors. It is also one of the only studies (with the exception of Dundar S et al[5]) comparing the cost and effectiveness of rFVIIa vs. high dose factor VIII.

Looking at the effectiveness and the costs, results from our study actually support the use of rFVIIa vs. plasma derived factor VIII in patients with low titer inhibitors. Moreover, because this study did not account for outpatient and inpatient costs, but only for drug costs, it is expected that the cost-savings associated with the use of rFVIIa in this patients' population would be even bigger since none of the patients taking rFVIIa were sent to hospital and none of them required re-treatment within 24 hours.

Finally, if the health-related quality of life (HRQoL) of patients was not assessed through the use of externally validated questionnaires, it is expected that the HRQoL of patients receiving rFVIIa would actually be improved due to the shorter resolution of bleeding episodes and absence of hospitalisation. Similar study results were actually described in a cost-utility study performed in Australia.[9]

Study limitations include the absence of accounting for outpatient and inpatient costs associated with the bleeding episode, but also time to treatment which might actually have significant impact on the total cost of treating bleeding episodes. Further data collection will account for these parameters.

ACKNOWLEDGMENT

Authors gratefully acknowledge Patricia Tan Wai Ling and Yan Cai, Juliette Anne Plun and Dr. Elif Coskuncay Yener from NovoNordisk for their help in writing and assistance.

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Table- IV: Total factor consumption and associated cost.

	Phase 1 (Plasma factor VIII)	*Phase 2 (rFVIIa)*	*Difference*	*% Difference*
Total factor consumption	340,000 IU	84 mg	-	-
Total cost (USD)	98,600	77,000	-21,600	-21.9

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