Quality Improvement Project

Medication-Use Evaluation of Recombinant Human Factor VIIa

Abrar Al-Subhi, Mansoor Ahmed Khan, Mohammed A. Aseeri

Pharmaceutical Care Department, King Abdul-Aziz Medical City-Western Region, King Abdullah International Medical Research Center/King Saud bin Abdulaziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabia

Address correspondence to Abrar Al-Subhi (Alsubhiab@ngha.med.sa)

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ABSTRACT

Introduction: Medication-use evaluation (MUE) is a performance improvement method used to achieve optimal patient outcomes. The recombinant human factor VIIa (rFVIIa) (NovoSeven) is an expensive agent approved by the U.S. Food and Drug Administration (FDA) for specific indications. However, in clinical practice, rFVIIa is often used for conditions unrelated to the one approved, with limited evidence. The use of rFVIIa has been associated with expenditures of more than Saudi riyal (SR)30 million ($8 million) annually at King Abdul-Aziz Medical City-Western Region (KAMC-WR). Therefore, we planned a MUE of rFVIIa. The primary purpose was to determine the off-label use of rFVIIa, and the secondary purpose was to evaluate the cost impact of off-label use of rFVIIa at KAMC-WR. **Methods:** This was an observational retrospective cohort study conducted to assess the off-label usage pattern and the direct cost of rFVIIa for one year. **Results:** A total of 27 patients who received rFVIIa were included. Two out of the 27 patients had hemophilia A with inhibitors (7%), and 23 of the 27 patients received rFVIIa with off-label indications (85%). The total cost associated with the use of rFVIIa was SR18.61 million ($4.96 million). The cost of the rFVIIa used for the appropriate purpose was SR17.83 million ($4.75 million), which represented 95.8% of the expenditures. **Conclusions:** Recombinant FVIIa is one of the most expensive medications in our hospital. It has been used mostly in patients having hemophilia A with inhibitors.

Keywords: hemophilia with inhibitors, recombinant factor VIIa, formulary management of bypassing agents, Saudi Arabia

INTRODUCTION

Medication-use evaluation (MUE) is a performance improvement method used to improve medication-use processes to achieve optimal patient outcomes.[1] Recombinant human factor VIIa (rFVIIa; NovoSeven) is an expensive hemostatic agent that was approved by the U.S. Food and Drug Administration (FDA) in 1999. It is indicated to treat bleeding episodes in patients with hemophilia A or B with inhibitors to factor VIII or factor IX, respectively.[2] The FDA-approved indications for rFVIIa include treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital factor VII deficiency, Glanzmann thrombasthenia with refractoriness to platelet transfusions, and treatment of bleeding episodes and perioperative management in adults with acquired hemophilia. However, rFVIIa is often used in clinical practice for conditions unrelated to hemophilia, with limited evidence, including massive hemorrhage such as warfarin-related intracerebral hemorrhage (ICH) and treatment of refractory bleeding after cardiac surgery in non-hemophiliac patients that has proven unresponsive to all other methods of intervention.

A systematic review[3] was conducted to assess the benefits and risks of off-label use of rFVIIa in patients without hemophilia, which included 12 randomized controlled trials on off-label therapeutic use ($n = 2538$). It showed a nonsignificant decrease in mortality and a non-significant increase in thromboembolic events. In a study by Mayer et al,[4] which was conducted to address the efficacy and safety of rFVIIa for acute ICH, 841 patients were randomly assigned to receive placebo ($n = 268$ patients), 20 μg rFVIIa per kg body weight ($n = 276$ patients), or 80 μg FVIIa per kg ($n = 297$ patients) within four hours after the onset of stroke. The primary endpoint was severe disability or death after the stroke. The authors concluded that treatment with rFVIIa

Table 1.—The labeled and unlabeled indications approved by Ministry of National Guard Health Affairs, Central Region (MNGHA-CR)

Labeled indications at MNGHA:
- ☐ Treatment or prevention of bleeding episodes in adults:
  1. Patients with hemophilia A (factor VIII deficiency) or B (factor IX deficiency) with inhibitors to factor VIII or factor IX
  2. Patients with congenital/acquired factor VII deficiency
- ☐ Treatment of inherited disorders of platelet function, for example, Glanzmann thrombasthenia

Unlabeled indications (approved at MNGHA):
- ☐ Preventing peri- and postoperative hemorrhage due to body (not brain) trauma* or surgery
- ☐ Management of patients with massive* uncontrolled life-threatening bleeding

Unlabeled indications (not approved at MNGHA):
- ☐ Treatment or prevention of refractory bleeding after:
  1. Cardiac surgery in non-hemophiliac patients
  2. Brain trauma
  3. Liver transplantation
  4. Gastrointestinal bleeding associated with end-stage liver disease
  5. Pulmonary hemorrhage (e.g., diffuse alveolar hemorrhage or massive hemoptysis)
  6. Thrombocytopenia
  7. Factor XI deficiency
  8. Von Willebrand disease
  9. Prostatectomy
  10. Anticoagulant-related intracerebral hemorrhage
  11. Coagulopathy of liver dysfunction

reduced the growth of the hematoma but did not improve survival or functional outcome after ICH.[4]

Recombinant FVIIa was the most expensive medication at the Ministry of National Guard Health Affairs (MNGHA) up until 2015. Its use has been associated with expenditures of more than Saudi riyal (SR)30 million ($8 million) annually at MNGHA. Recombinant FVIIa used under conditions considered an off-label use outside the terms of the drug license has been constrained by high costs and limited clinical efficacy data. Therefore, we conducted a retrospective cohort MUE of rFVIIa at King Abdul-Aziz Medical City-Western Region (KAMC-WR) in 2015 in an effort to address the off-label use pattern and the cost associated with inappropriate use of rFVIIa in KAMC-WR, which is one of the leading healthcare facilities in Saudi Arabia.

MATERIALS AND METHODS

This study was an observational retrospective cohort study conducted to assess the off-label usage pattern and the direct cost of rFVIIa over one year at MNGHA-WR. All adult patients more than 18 years old who received rFVIIa from January to December 2014 were included.

In 2006, the institutional Corporate Pharmacy and Therapeutic Committee at MNGHA, Saudi Arabia, approved rFVIIa for refractory life-threatening hemorrhage (LTH) either for patients with hemophilia or for non-hemophiliac patients and spontaneous intracerebral hemorrhage (SICH). The Regional Pharmacy and Therapeutic Committee at the Ministry of National Guard Health Affairs, Central Region (MNGHA-CR), had expressed concern about possible overutilization of rFVIIa medication in MNGHA. Hence MUE of rFVIIa was conducted by the Drug Use Policy and Economic Center (DPEC) at MNGHA-CR to assess the utilization pattern of rFVIIa in December 2012. This evaluation included 147 patients; 2.04% of the patients who received rFVIIa were patients with hemophilia; 94.56% were non-hemophiliac patients with LTH, and 3.4% were patients with SICH. The drug use policy of rFVIIa was developed and approved by Corporate Pharmacy and Therapeutic Committee in September 2014 based on the MUE mentioned above, which was conducted by DPEC at MNGHA-CR. Table 1 shows the labeled and unlabeled indications approved by MNGHA. This policy was used to evaluate the pattern of off-label use of rFVIIa in our MUE.

Table 2.—Characteristics of patients who received recombinant human factor VIIa ($n = 27$)

Characteristics	Value
Age, mean ± SD	54 ± 25
Weight, mean ± SD	72 ± 23
Male, *n* (%)	14 (52%)

Our primary objective was to evaluate the appropriate use of rFVIIa according to our MNGHA-CR rFVIIa guidelines approved in 2014, and the secondary objective was to evaluate the cost impact of inappropriate use of rFVIIa at KAMC-WR.

Descriptive statistics were used to present baseline characteristics and demographic data for participants as deemed necessary, mean ± SD, and percentages for categorical variables. The proposal was approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC) on September 1, 2015.

RESULTS

A total of 27 patients who received rFVIIa were included in this study; 52% of patients were male (Table 2). Two patients out of 27 had hemophilia A with inhibitors (7%); one out of 27 had congenital factor VII deficiency (4%); one out of 27 had ICH (warfarin-related) (4%), and 23/27 received rFVIIa with off-label indications (85%) (Table 3). The average number of doses per patient for all non-hemophiliac patients was two doses compared with an average of 2.24 similar MUE conducted by DPEC in MNGHA-CR in 2012.

The cost of one vial (1 mg/mL) of rFVIIa was SR3700 in 2015 ($986.7). Total cost associated with use of rFVIIa at KAMC-WR was SR18.61 million ($4.96 million). The cost of the rFVIIa used for the appropriate purpose of rFVIIa was SR17.83 million ($4.75 million), which represented 95.8% of the total expenditures associated with use of rFVIIa in one year at KAMC-WR. The direct cost of rFVIIa

Table 3.—Indications for patients who received recombinant human factor VIIa based on policy developed and approved by Ministry of National Guard Health Affairs, Central Region

Indications	No. of Patients *n* (%)	Appropriateness According to Own Policy	No. of 1 mg Vials	Cost in Saudi Riyal, SR ($)
Bleeding episodes in hemophilia A with inhibitors	2 (7%)	Appropriate	4794	17.74 million (4.73 million)
Bleeding episodes in congenital factor VII deficiency	1 (4%)	Appropriate	19	70,300 (18.747)
Off-label use				
Intracerebral hemorrhage (warfarin-related)	1 (4%)	Appropriate	6	22.200 (5.920)
Total appropriate use	4 (15%)	Appropriate	4819	17.83 million (4.75 million)
Others				
Warfarin-related bleeding				
× Refractory hemoptysis	1 (4%)	Inappropriate	3	111.000 (29.600)
× Refractory permacath bleeding	2 (7%)		10	
× Upper gastrointestinal bleeding	2 (7%)		12	
× hemothorax	1 (4%)		5	
Non-warfarin related bleeding				
× Treatment of refractory bleeding after abdominal surgery	1 (4%)	Inappropriate	8	669.700 (178.587)
× Treatment of refractory bleeding after biopsy	1 (4%)		7	
× Aortic aneurysm	1 (4%)		5	
× Refractory vaginal bleeding	2 (7%)		7	
× Refractory rectal bleeding	1 (4%)		5	
× Intracerebral hemorrhage	4 (15%)		111	
× Intraventricular hemorrhage	1 (4%)		5	
× Refractory upper gastrointestinal bleeding	3 (11%)		19	
× Pulmonary hemorrhage + hemoptysis	1 (4%)		3	
× Extra-axil hemorrhage + hemoptysis	1 (4%)		6	
× Hemothorax	1 (4%)		5	
Total inappropriate use	23 (85%)		211	780.700 (208.187)
Total use	27 (100%)		5030	18.61 million (4.96 million)

for inappropriate use of rFVIIa was SR780,700 ($208,187), which represented only 4.2% of the total expenditures. The cost of the rFVIIa used for the management of two hemophilia patients with inhibitors was SR17.74 million ($4.73 million), which represented 95.4% of the total cost. Table 4 shows the consumption of rFVIIa for patients with hemophilia associated with the cost on a monthly basis.

DISCUSSION

One of the most severe complications in the management of patients diagnosed with hemophilia is the development of neutralizing antibodies (inhibitors). Generally, antibodies are formed in response to the presence of foreign substances to protect the body from them. In a person with hemophilia A or B, neutralizing antibodies or inhibitors directed against either factor VIII or IX, respectively, may be created by the immune system as a response against harmful foreign substances to proteins in factor concentrates following treatment. When this happens, it stops the factor concentrates from being able to fix the bleeding problem.[5] Among patients with severe (less than 1% factor level) or moderately severe (1% to 5% factor level) hemophilia A, incidence of antibody development is around 20% and 33%. On the other hand, inhibitor development is much less frequent in patients with hemophilia B, affecting only 1% to 6%.[6,7]

Medication-use evaluation served as a trigger tool to continuously improve the quality and safety of hemophilia patients having inhibitors and provided us opportunities for finding cost-effective treatment options in these patient population. This happened in a cyclic fashion whereby our MUE which has guided us and pharmacy and therapeutic committees to make formulary management decisions for the prevention and management of bleeding associated with hemophilia having inhibitors in a cost-effective manner during the past five years. So we are showing cyclic improvement strategies in a cost-effective manner. Our MUE suggested that major use of rFVIIa has been for the management of hemophilia A with inhibitors whereas rFVIIa is much more expensive in comparison with other bypassing agents such as factor eight inhibitor bypassing activity (FEIBA) and emicizumab.

Most of the use of the rFVIIa has been observed in patients having hemophilia A with inhibitors. At MNGHA, our hematology department has been using rFVIIa as a prophylaxis for prevention of bleeding in patients having hemophilia A with inhibitors at the dose of 90 mcg/kg three times per week, which is an off-label indication that is evident in our MUE. We know that rFVIIa is a short-acting medication, and effective dose and frequency of its use have not been established in the

Table 4.—Consumption of recombinant human factor VIIa for patients with hemophilia, total doses, and number of vials associated with cost on monthly basis

Parameters	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Patient A:													
Total No. of doses	14	9	10	13	51	89	8	139	10	9	10	15	377
Doses, mg	70	45	53	65	255	445	40	691	50	45	50	75	1884
No. of vials	70	45	53	65	255	445	40	691	50	45	50	75	1884
Cost	259,000	166,500	196,100	240,500	943,500	1,646,500	148,000	2,556,700	159400	166,500	185,000	277,500	6,970,800
Patient B:													
Total No. of doses	4	43	26	38	9	42	4	115	79	4	53	45	462
Doses, mg	24	297	222	209	45	289	23	677	518	26	265	315	2910
No. of vials	24	297	222	209	45	289	23	677	518	26	265	315	2910
Cost	88,800	1,098,900	821,400	773,300	166,500	1,069,300	85,100	2,504,900	1,916,600	96,200	980,500	1,165,500	10,767,000

literature. Therefore, rFVIIa is neither approved for prevention of bleeding in patients having hemophilia A with inhibitors nor effective for this indication. However, rFVIIa is useful only for the management of bleeding in patients having hemophilia A with inhibitors.

For prophylaxis and bleeding episodes, the person with hemophilia and a high-responding inhibitor will have to rely on an alternative treatment (bypass therapy) selected and dosed on the basis of circumstances such as inhibitor characteristics, nature and severity of the bleed, age, and treatment response pattern of the individual, whether or not the person is eligible for or on immune tolerance induction and, for many individuals, has access to the various therapeutic products. For both hemophilia A and B, the choice of products within the global hemophilia community includes FEIBA, rFVIIa, and emicizumab.

FEIBA is a key therapeutic option for controlling acute bleeding in patients with high-titer inhibitors or low-titer inhibitors refractory to replacement therapy. It has been used in the treatment of inhibitor bleeding since the late 1970s. It is useful for 60% to 90% of musculoskeletal bleeds as well as for major and minor surgery prophylaxis.[8] A phase 3 prospective study evaluated the safety and efficacy of prophylaxis with FEIBA in hemophilia A and B with inhibitors. Over one year, 17 subjects were treated prophylactically with a dose of 85 U/kg every other day, while 19 were treated on demand. The median annual bleeding rate (ABR) during prophylaxis was 7.9 compared with 28.7 during on-demand treatment, which amounts to a 72.5% reduction and a statistically significant difference in ABRs between arms ($p = 0.0003$).[9,10]

Recombinant FVIIa also bypasses the requirement for factor VIII or IX in persons with hemophilia A or B and inhibitors. Recombinant FVIIa has been found to be effective in the treatment of joint bleeding and the treatment of life-threatening bleeding, as well as in the prevention of surgical bleeding. Because this product is very short-acting, multiple doses of 90 μg/kg or more are infused every two to six hours to stop bleeding.[8] In a multi-center, randomized, parallel-group study,[11] 22 subjects having hemophilia A with inhibitor treated with a bypassing agent were randomized to receive rFVIIa 90 or 270 mcg/kg per day for three months. The rate of bleeding during the pre-prophylaxis period was 5.6 and 5.3 bleeds per month in the two groups, respectively. Over the three months of prophylaxis, this decreased to 3 bleeds per month in the 90 mcg/kg group and 2.2 bleeds per month in the 270 mcg/kg group, with corresponding reductions in target joint bleeds of 43% and 61%, respectively. According to this study, when rFVIIa was used as prophylaxis in hemophilia patients with inhibitors with a dose of 90 mcg/kg daily, the monthly bleeding rate was three bleeds per month. If we extrapolate this to one year, then ABR was 36, which is much more in comparison with FEIBA. Hence, rFVIIa neither is useful in the prevention of bleeding episodes in patients having hemophilia with inhibitors nor is approved for this indication by any regulatory authority. Therefore, the use of rFVIIa for this indication is not cost-effective.[11]

Both rFVIIa and FEIBA have been studied across various clinical scenarios with similar overall efficacy and rates of adverse events.[12–14] However, more frequent use of rFVIIa imposed by its short half-life is practically demanding and costly when used for extended periods, and that favors FEIBA over rFVIIa for routine prophylaxis in hemophilia patients with an inhibitor.[15] Table 5 shows a cost comparison of rFVIIa versus FEIBA in 2015 when used as a prophylactic agent in patients with hemophilia A with inhibitors.

FEIBA was added to the MNGHA formulary for both prevention and management of bleeding episodes in patients having hemophilia A with inhibitors after the findings of our MUE as a cost-saving strategy in 2017, which had resulted in cost savings of around SR20 million ($5.33 million) annually.

Recently, emicizumab was also approved by the U.S. FDA for prevention of bleeding in hemophilia patients with inhibitors on November 16, 2017 and without inhibitors on October 4, 2018. It has been associated with significantly less ABR. One phase 3 randomized controlled trial looked at the efficacy, safety, and pharmacokinetic profile of once-weekly subcutaneous emicizumab prophylaxis in patients with hemophilia A with inhibitors. The ABR was 2.9 with emicizumab

Table 5.—Cost comparison of rFVIIa versus FEIBA in 2015 when used as a prophylactic agent in patients with hemophilia A with inhibitors with an average weight of 80 kg

Bypassing Agent with Prophylactic Dose	Unit Cost	Total Vials Required per Year	Cost per Year per Patient	Annual Bleeding Rate (ABR) in the Published Literature
rFVIIa (90 mcg/kg three times per week)	SR3700 ($986.7) per 1 mg vial	1092 vials	SR4.04 million ($1.077 million)	More than 25[11] Similar to placebo. Each bleeding episode costs around SR250,000 to 1,000,000 ($66,667–266,667)
FEIBA (85 U/kg three times per week)	SR1500 ($400) per 500 U vial	2028 vials	SR3.04 million ($0.81 million)	7.9[10] Each bleeding episode costs around SR50,000 to 150,000 ($13,333–40,000)

rFVIIa, recombinant human factor VIIa; FEIBA, factor eight inhibitor bypassing activity.

prophylaxis (group A) versus 23.3 events with no prophylaxis (group B), representing a significant difference of 87% favoring emicizumab prophylaxis ($p < 0.001$).[16]

We evaluated emicizumab at the Corporate Pharmacy and Therapeutic Committee in MNGHA and found that it was much more cost-effective than FEIBA and rFVIIa when used as prophylaxis for prevention of bleeding in patients having hemophilia with inhibitors. Our conclusion at the Corporate Pharmacy and Therapeutic Committee was based on the published literature demonstrating better efficacy and lower cost of emicizumab in comparison with other bypassing agents using the Saudi Food and Drug Authority (SFDA) price list. Moreover, emicizumab has a very convenient administration pattern as it is administered subcutaneously once weekly or once every two weeks or even once every four weeks. It has better efficacy than other bypassing agents with ABR of around 2 to 3. Moreover, emicizumab is much cheaper than FEIBA and rFVIIa with a direct cost saving of around SR1 million ($266.6667) per patient per year when used for prophylaxis in patients with hemophilia with inhibitors. Therefore, we have added emicizumab to the MNGHA formulary for prevention of bleeding in hemophilia patients with inhibitors replacing FEIBA in November 2019. In contrast, rFVIIa will stay in the formulary for the management of bleeding episodes in these patients.

We have recommended modifying the institutional guidelines for the use of rFVIIa at MNGHA, deleting the prophylactic use indication of rFVIIa for prevention of bleeding in patients having hemophilia with inhibitors. Hence, our MUE helped us in the formulary management of bypassing agents used for hemophilia patients with inhibitors in a cost-effective manner.

Limitations

There are several limitations of this study, as it was retrospective and could not clearly differentiate prophylactic use of rFVIIa from the FDA-labeled hemophilia indication such as on-demand use of rFVIIa for management of bleeding episodes or perioperative use of rFVIIa for management in patients with hemophilia A or B with inhibitors. The ABRs were not reported in the study, which is a major limitation.

CONCLUSIONS AND FUTURE DIRECTIONS

Recombinant FVIIa is one of the most expensive medications in our hospital. It has been used mostly in patients having hemophilia A with inhibitors. Our MUE suggested that we evaluate other bypassing agents such as FEIBA and emicizumab as a cost-saving strategy.

A multi·center retrospective study is going on at MNGHA, comparing the cost-effectiveness of using FEIBA versus rFVIIa in the management of hemophilia patients with inhibitors. This study will determine the ABR per patient in patients having hemophilia A with inhibitors using FEIBA as a prophylaxis and will compare this with historical control of patients receiving rFVIIa at MNGHA as prophylaxis, comparing the cost-effectiveness of two bypassing agents.

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