

## A cost evaluation of treatment alternatives in mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Turkey

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### Summary

A decision-analysis model was constructed to assess total direct health care costs of four current first-line treatment options for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Turkey: recombinant activated Factor VII (rFVIIa); high-dose Factor VIII; prothrombin complex concentrate (PCC); and activated PCC (aPCC). Resource utilisation was based on a retrospective analysis of 105 bleeding episodes treated during the period January 1996 to December 2002. Clinical outcomes were

derived from a combination of the retrospective patient data and literature review, both validated by an expert panel of Turkish haematologists. rFVIIa was more effective and resolved bleeds more quickly than any of the alternatives. rFVIIa and PCC were associated with similar direct treatment costs that were relatively lower than those compared with the other options. Given the better efficacy, rFVIIa should be considered the preferred treatment option in the management of haemophilia patients with inhibitors in Turkey.

*Key words: bleeding episodes, haemophilia, inhibitor, costs, recombinant activated Factor VIIa*

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## Introduction

Haemophilia is an inherited bleeding disorder affecting males, with females as carriers. It affects approximately 10–20 in 100,000 live births<sup>1–3</sup>. Haemophilia A is due to Factor VIII disorder, whereas haemophilia B (also referred to as Christmas disease) is due to Factor IX disorder. Severe haemophilia is characterised by recurrent and spontaneous bleeding of the joints, and the treatment of choice is Factor VIII replacement therapy. However, some patients develop antibodies to Factors VIII and IX (inhibitors), and the management of such individuals is more difficult and more expensive than that of those patients without inhibitors<sup>4,5</sup>.

According to the latest domestic data, there are 1,059 patients with haemophilia A and 252 patients with haemophilia B in Turkey<sup>6</sup>. The following agents are used to treat acute bleeding episodes in patients with inhibitors in Turkey:

- high-dose Factor VIII/IX;
- prothrombin complex concentrates (PCCs);
- activated PCCs (aPCCs);
- recombinant activated Factor VII (rFVIIa).

In general, management of bleeding episodes in haemophilia patients is costly, particularly so in patients who have developed inhibitors to Factor VIII. Therefore, a cost analysis is considered of value to determine and to support adoption of lower-cost treatment options.

## Materials and methods

Our aim was to compare direct costs only for the management of mild-to-moderate bleeding episodes in patients with haemophilia with inhibitors from the perspective of the Turkish Reimbursement Institutions using a decision-analysis model.

### Decision-analysis model

A decision-analysis modelling technique was used to sequentially follow patients initially treated with either rFVIIa, PCC, aPCC or high-dose Factor VIII. Data<sup>TM</sup> 3.5 (TreeAge Software, Williamstown, MA, USA) was used to develop the model. It was assumed that all bleeds would eventually cease regardless of treatment and thus the model was one of cost minimisation. The model consisted of:

- initial treatment for a bleed;
- further treatments for a bleed;
- the probability of switching from one treatment to another;
- the duration of each treatment;
- the effectiveness of each treatment;
- the probability of a re-bleed;
- treatment of a re-bleed.

Resource-utilisation data incorporated into the model included costs for haemostatic agents, outpatient visits, hospital stay and concomitant medications. Costs were provided by staff of Novo Nordisk in Turkey from the Ministry of Health; costs of haemostatic agents were those negotiated

with the health authorities. The decision model (Figure 1) was validated with input from a panel of Turkish experts.

### Clinical outcomes

Patient data were obtained from a retrospective analysis of 105 bleeding episodes in 24 patients between January 1996 and December 2002 provided by three representative centres (Hacettepe University Medical Faculty, Ankara; Istanbul University Oncology Institute, Istanbul; Ege University Medical Faculty, Izmir). These bleeding episodes comprised 66 cases of haemarthrosis, 28 haematomas, 1 submandibular bleeding, 3 oral-cavity bleedings, 2 minor bleedings due to surgery for insertion of a central catheter, 4 cases of haematuria, and 1 bleeding due to fracture. Of the 66 cases of haemarthrosis, 24, 14, 23

and 5 cases were treated using first-line rFVIIa, PCC, high-dose Factor VIII concentrate and aPCC, respectively. Of the 28 haematomas, 3, 5, 17 and 3 cases were treated using first-line rFVIIa, PCC, high-dose Factor VIII concentrate and aPCC, respectively. The case of submandibular bleeding was treated using rFVIIa; the four cases of haematuria were treated using PCC; the bleeding due to fracture was treated with aPCC; one minor bleeding due to surgery was treated using high-dose Factor VIII and the other using PCC; one of the oral-cavity bleedings was treated using PCC and the other two were treated using high-dose Factor VIII as first-line treatment. For this analysis, treatments were considered effective if pain or swelling were absent within 24 h and were considered ineffective if pain or swelling persisted for more than 24 h.

**Table 1. Treatment, outcomes and resource-utilisation data from a retrospective analysis of 105 bleeds in 24 patients**

|  | rFVIIa<br>(n = 28) | PCC<br>(n = 25) | aPCC<br>(n = 9) | High-dose<br>Factor VIII<br>(n = 43) |
|--|--------------------|-----------------|-----------------|--------------------------------------|
| Mean number of doses per episode                         | 3.6                | 3               | 4.8             | 10.6                                 |
| Mean treatment dose per bleeding episode per body weight | 0.204<br>mg/kg     | 132.5<br>IU/kg  | 166.8<br>IU/kg  | 232.6<br>IU/kg                       |
| Mean time to resolution of bleeding episode (h)          | 17.3               | 40.2            | 43.6            | 23.0                                 |
| Effectiveness* (%)                                       | 89.3               | 75.0            | 79.0            | 71.4                                 |
| Episodes treated on a home basis (%)                     | 32.1               | 0               | 33.3            | 2.3                                  |
| Episodes treated on an outpatient basis (%)              | 42.9               | 84.0            | 42.9            | 81.4                                 |
| Episodes treated on an inpatient basis (%)               | 25.0               | 16.0            | 23.8            | 16.3                                 |
| Mean number of days hospitalised per bleeding episode    | 1.12               | 0.72            | 1.89            | 1.16                                 |

\* Defined as absence of pain or swelling within 24 h.

rFVIIa, recombinant activated Factor VII; PCC, prothrombin complex concentrate; aPCC, activated PCC.

**Table 2. Effectiveness of therapy based on a retrospective analysis of 105 bleeds in 24 patients — comparison with expert opinion and published literature**

| <i>First-line treatment</i> | <i>Effect of therapy</i> | <i>Patient-outcome percentage (%)</i> | <i>Expert-opinion percentage (%)</i> | <i>Literature percentages (%)</i>                          |
|-----------------------------|--------------------------|---------------------------------------|--------------------------------------|--|
| rFVIIa                      | Effective                | 89.3*                                 | 89.3*                                | 92 <sup>7</sup><br>85 <sup>8</sup><br>86 <sup>9</sup>      |
|                             | Ineffective              | 10.7                                  | —                                    | —  |
| High-dose FVIII             | Effective                | 71.4*                                 | 70                                   | 80 <sup>10</sup><br>33.3 <sup>11</sup>                     |
|                             | Ineffective              | 28.6                                  | —                                    | —  |
| aPCC                        | Effective                | 66.7                                  | 70–90                                | 79 <sup>12</sup><br>60 <sup>13</sup><br>81.3 <sup>14</sup> |
|                             | Ineffective              | 33.3                                  | —                                    | —  |
| PCC                         | Effective                | 80.0                                  | 75*                                  | <70 <sup>15,16</sup>                                       |
|                             | Ineffective              | 20.0                                  | —                                    | —  |

rFVIIa, recombinant activated Factor VII; PCC, prothrombin complex concentrate; aPCC, activated PCC.

\*Values used in model.

### **Resource utilisation**

Data on resource utilisation were obtained from a review of the records of the 24 patients from whom outcome data were obtained.

Costs assigned to the resource-utilisation data for each component of the analysis were obtained from Turkish sources and extrapolated to 2003 values.

### **Sensitivity analysis**

Sensitivity analysis was conducted on the values of key variables that were likely to vary between hospitals or for which there were uncertainties. These include the efficacy of first-line therapy, the length of hospital stay and the probability of a re-bleed.

## **Results**

### **Patient data**

In total, 16 of the 24 patients were considered adults (aged  $\geq 17$  years). Mean weight was 49.0 kg. Of the 105 bleeding episodes that could be evaluated, 9 were initially treated with aPCC, 28 with rFVIIa, 43 with high-dose Factor VIII and 25 with PCC. Treatment, outcomes and resource-utilisation data are shown in Table 1. The analysis showed that rFVIIa was more effective and provided a faster time to resolution of bleeding than the other agents. No safety issues were reported with any treatment.

Clearly, the outcomes data have great potential to affect the cost analysis; therefore,

**Table 3. Baseline model results — total direct health care costs (from initiation to cessation)**

| <i>Model (initial haemostatic agent)</i> | <i>Overall cost/million TRL (US\$)</i> |
|--|--|
| Model I (rFVIIa)                         | 13,348 (9,113)                         |
| Model II (aPCC)                          | 18,370 (12,542)                        |
| Model III (high-dose Factor VIII)        | 22,080 (15,075)                        |
| Model IV (PCC)                           | 13,369 (9,128)                         |

rFVIIa, recombinant activated Factor VII; PCC, prothrombin complex concentrate; aPCC, activated PCC.

these data were discussed with experts and, where necessary, were compared with published findings to establish the outcomes data to be used in the model (Table 2). It was concluded that the effectiveness of rFVIIa and high-dose Factor VIII could be based directly on the patient data (89.3% and 71.4%, respectively), as these were in line with published findings<sup>7-11</sup> and were validated by expert opinion. In the case of aPCC, the patient outcomes data gave a lower value (66.7%) than estimates from expert opinion (between 70% and 90%) and the literature<sup>12-14</sup>. Thus, it was decided that the figure of 79% from the literature should be used for the model<sup>12</sup>. The patient outcomes data of 80% for PCC compared with an expert opinion of 75% and literature values of less than 70%<sup>15,16</sup>. The value of 80% for PCC was considered to be unrealistic in light of the literature value, so the expert-opinion value of 75% was used for the model.

#### Unit costs

An inpatient day in a university hospital costs approximately 60,000,000 TRL (US\$41.0), compared with approximately 15,000,000 TRL (US\$10.2) for an outpatient day. In Turkey, 1.2 mg and 2.4 mg versions of rFVIIa are available. The price used in this analysis was 2,925,470,000 TRL (US\$1997) for the 2.4 mg dose. Costs

for the other agents per 500 IU were: aPCC, 744,844,000 TRL (US\$509); high-dose Factor VIII, 706,113,500 TRL (US\$482); and PCC, 594,394,000 TRL (US\$406).

#### Total direct health care costs

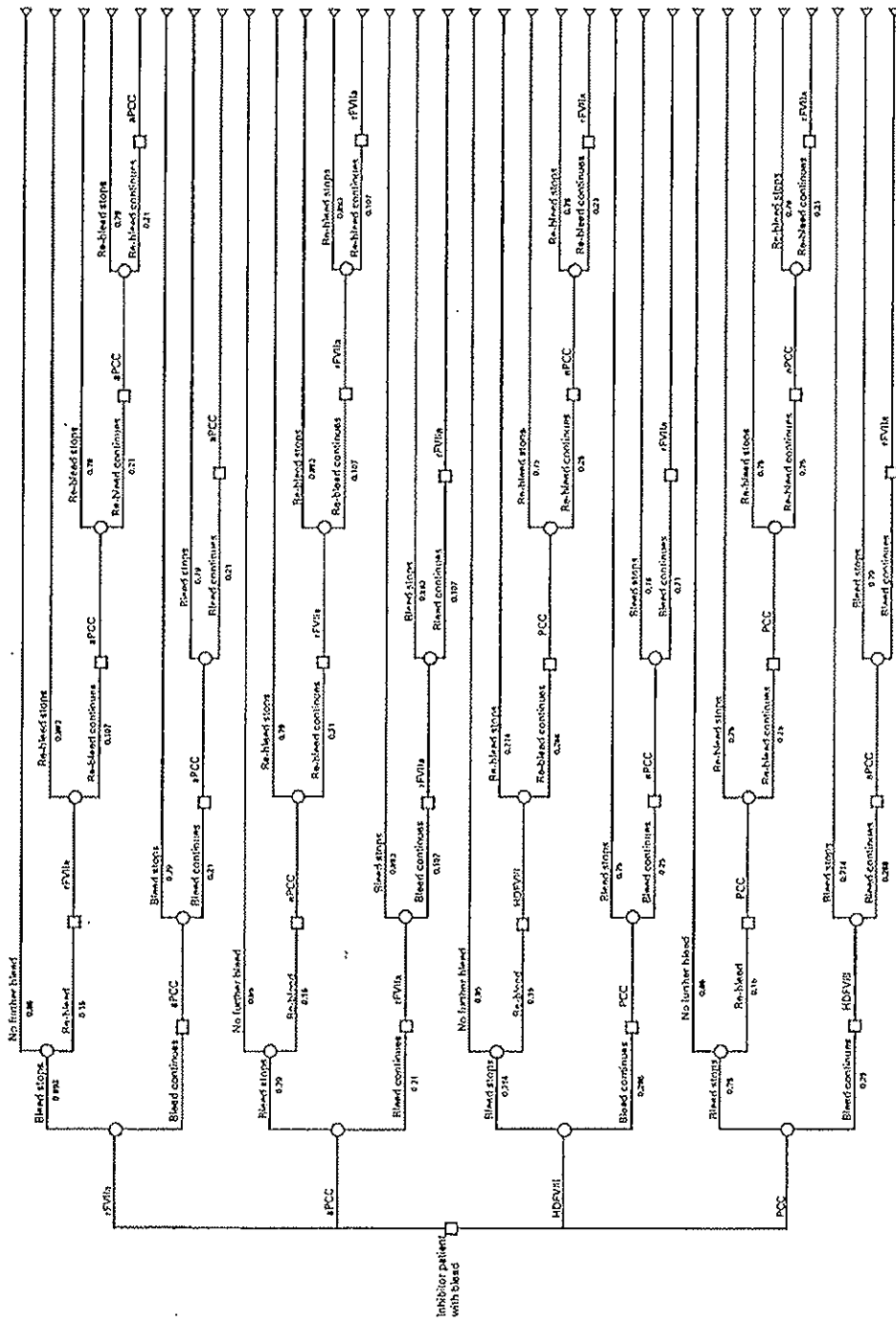
Table 3 shows the total direct health care costs based on the model. Total costs were similar for rFVIIa and PCC as initial treatments. Initial treatment both with rFVIIa and PCC were associated with lower costs than initial treatment with aPCC or high-dose Factor VIII.

In all cases, more than 97% of the total cost was attributable to the drug (rFVIIa, aPCC, high-dose factor VIII or PCC) being considered. Concomitant medications represented less than 1% of total costs.

#### Sensitivity analysis

As effectiveness for rFVIIa increases, rFVIIa as first-line therapy rapidly becomes the lowest-cost option (compared with PCC), and is so whenever the effectiveness of rFVIIa is greater than 89% (Table 4). Table 4 also shows the effect of changing the efficacy (by up to 10%) or cost (by up to 20%) of the other agents. Within a realistic range of effectiveness and cost values, first-line treatment with rFVIIa will always be the

**Figure 1. Baseline decision tree structure for comparing recombinant activated Factor VII (rFVIIa) high-dose Factor VIII (HDFVIII), prothrombin complex concentrate (PCC) and activated PCC (aPCC) in first-line therapy**



lowest-cost option compared with first-line treatment with aPCC or high-dose Factor VIII. In the case of PCC, small differences in total process costs are observed.

## Discussion

The results of this model analysis suggest that the total direct health care costs of

treating a mild-to-moderate bleeding episode (from initiation to resolution) in patients with haemophilia with inhibitors are lower using rFVIIa or PCC as the initial treatment compared with other options. Given that PCC is not recommended for such treatment in Turkey and that rFVIIa appears to be more effective, rFVIIa may be considered as the optimum first-line treatment in most patients. Our cost

**Table 4. Sensitivity analysis: costs in Turkish Lira (billions) (and in US\$ (thousands) in parenthesis)**

| Scenario 1            | Effectiveness of rFVIIa                   |                |                |                |                |                | Threshold value |
|-----------------------|---|----------------|----------------|----------------|----------------|----------------|-----------------|
|                       | 0.8                                       | 0.84           | 0.88           | 0.92           | 0.96           | 1.0            |                 |
| rFVIIa                | 14.5<br>(9.9)                             | 14.0<br>(9.6)  | 13.5<br>(9.2)  | 13.0<br>(8.9)  | 12.5<br>(8.5)  | 12.0<br>(8.2)  |                 |
| aPCC                  | 18.7<br>(12.8)                            | 18.5<br>(12.6) | 18.4<br>(12.6) | 18.3<br>(12.5) | 18.2<br>(12.4) | 18.1<br>(12.4) |                 |
| PCC                   | 13.4<br>(9.1)                             | 13.4<br>(9.1)  | 13.4<br>(9.1)  | 13.4<br>(9.1)  | 13.4<br>(9.1)  | 13.4<br>(9.1)  | 0.892%          |
| High-dose Factor VIII | 20.1<br>(13.7)                            | 20.1<br>(13.7) | 20.1<br>(13.7) | 20.1<br>(13.7) | 20.1<br>(13.7) | 20.1<br>(13.7) |                 |
| Scenario 2            | % change in effectiveness of other agents |                |                |                |                |                | Threshold value |
|                       | -10                                       | -6             | -2             | 2              | 4              | 6              |                 |
| rFVIIa                | 13.5<br>(9.2)                             | 13.4<br>(9.1)  | 13.4<br>(9.1)  | 13.3<br>(9.1)  | 13.3<br>(9.1)  | 13.2<br>(9.0)  |                 |
| aPCC                  | 19.3<br>(13.2)                            | 18.9<br>(12.9) | 18.6<br>(12.7) | 18.2<br>(12.4) | 17.8<br>(12.2) | 17.4<br>(11.9) |                 |
| PCC                   | 15.1<br>(10.3)                            | 14.4<br>(9.8)  | 13.7<br>(9.4)  | 13.0<br>(8.9)  | 12.4<br>(8.5)  | 11.8<br>(8.1)  | 0.14%           |
| High-dose Factor VIII | 23.4<br>(16.0)                            | 22.9<br>(15.6) | 22.3<br>(15.2) | 21.8<br>(14.9) | 21.4<br>(14.6) | 20.9<br>(14.3) |                 |
| Scenario 3            | % change in price of other agents         |                |                |                |                |                | Threshold value |
|                       | -20                                       | -12            | -4             | 4              | 12             | 20             |                 |
| rFVIIa                | 13.0<br>(8.9)                             | 13.1<br>(8.9)  | 13.3<br>(9.1)  | 13.4<br>(9.1)  | 13.6<br>(9.3)  | 13.7<br>(9.4)  |                 |
| aPCC                  | 15.3<br>(10.4)                            | 16.5<br>(11.3) | 17.7<br>(12.1) | 19.0<br>(13.0) | 20.2<br>(13.8) | 21.5<br>(14.7) |                 |
| PCC                   | 10.7<br>(7.3)                             | 11.8<br>(8.1)  | 12.8<br>(8.7)  | 13.9<br>(9.5)  | 15.0<br>(10.2) | 16.0<br>(10.9) | -0.16%          |
| High-dose Factor VIII | 17.7<br>(12.1)                            | 19.5<br>(13.3) | 21.2<br>(14.5) | 23.0<br>(15.7) | 24.7<br>(16.9) | 26.5<br>(18.1) |                 |

rFVIIa, recombinant activated Factor VII; PCC, prothrombin complex concentrate; aPCC, activated PCC.

findings are supported by results from a study undertaken in the UK<sup>17</sup>, which also showed higher first-line costs with rFVIIa than with aPCC, but equivalent or lower overall costs. The main difference between the current study and the UK study is that actual resource-utilisation data were made available for patients treated in Turkey, as opposed to the almost exclusive expert-panel approach used in the UK.

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. Such information also helps to address questions regarding the allocation of limited resources<sup>18</sup>. Indeed, it has also been suggested that models of cost-effectiveness ranking be used in certain countries to set budgets for specific areas of health care intervention<sup>19</sup>.

Ideally, cost data should be obtained in prospective studies. However, the limited number of haemophilia patients with inhibitors in Turkey makes such a study impractical and thus we chose to use a decision-analysis model. Various resource elements were identified, measured and included in the analysis: hospitalisation, outpatient administration and concomitant medication. However, the analysis showed that the key economic drivers are the cost of the study medications (rFVIIa, aPCC, high-dose Factor VIII and PCC), the dose used and the probability of first-line effectiveness. This last component was based on a combination of the analysed data, results from published clinical trials and expert opinion. By ensuring

that baseline effectiveness values could be supported by the results from established clinical trials, it was intended to avoid possible bias that could be attributed to any of the agents being compared.

We found that only a minority of bleeds were treated in an inpatient setting in Turkey and thus hospitalisations contribute less to the overall costs than in similar studies in other countries, for example the UK<sup>17</sup>.

Considering direct health care costs alone, there is clearly little difference between rFVIIa and PCC. However, the greater efficacy of rFVIIa, shown by the larger percentage of bleeds stopped (as evidenced by resolution of pain and swelling) within 24 h and the much faster time to bleed resolution, must be considered when choosing treatment options. In addition, this greater efficacy is likely to have an impact in terms of quality of life and, potentially, societal costs. It is interesting to note that similar numbers of bleeding episodes were initially treated with rFVIIa and PCC, for which the perceived low cost of PCC may have been a contributory factor. One of the implications of our study is that the decision to use rFVIIa or PCC should be based on clinical criteria rather than the cost per vial or the cost per individual bleed.

It must be noted that comparison of the high-dose Factor VIII data with that of the other agents may not be of great value. High-dose Factor VIII is expected to be used predominantly in patients with low-titre inhibitors, whereas the other agents will be used more in patients with high-titre inhibitors.

In comparing PCC, aPCC and rFVIIa, it is important to note that no safety issues were identified with any first-line treatment.

## Conclusion

Our study shows that rFVIIa and PCC are associated with similar direct treatment costs that are lower than those associated with other first-line options. However, rFVIIa has higher efficacy than PCC and may therefore be considered the agent of choice for the management of haemophilia patients with inhibitors in Turkey. This result is relevant for the development of clinical guidelines that would ensure optimum management of haemophilia patients in Turkey, as well as in other countries in the region with similar treatment options.

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