

# Cost-utility analysis of immune tolerance induction therapy versus on-demand treatment with recombinant factor VII for hemophilia A with high titer inhibitors in Iran

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**Background:** In developing countries, the treatment of hemophilia patients with inhibitors is presently the most challenging and serious issue in hemophilia management, direct costs of clotting factor concentrates accounting for >98% of the highest economic burden absorbed for the health care of patients in this setting. In the setting of chronic diseases, cost-utility analysis, which takes into account the beneficial effects of a given treatment/health care intervention in terms of health-related quality of life, is likely to be the most appropriate approach.

**Objective:** The aim of this study was to assess the incremental cost-effectiveness ratios of immune tolerance induction (ITI) therapy with plasma-derived factor VIII concentrates versus on-demand treatment with recombinant-activated FVIIa (rFVIIa) in hemophilia A with high titer inhibitors from an Iranian Ministry of Health perspective.

**Methods:** This study was based on the study of Knight et al, which evaluated the cost-effectiveness ratios of different treatments for hemophilia A with high-responding inhibitors. To adapt Knight et al's results to the Iranian context, a few clinical parameters were varied, and cost data were replaced with the corresponding Iranian estimates of resource use. The time horizon of the analysis was 10 years. One-way sensitivity analyses were performed, varying the cost of the clotting factor, the drug dose, and the administration frequency, to test the robustness of the analysis.

**Results:** Comparison of the incremental cost-effectiveness ratios between the three ITI protocols and the on-demand regimen with rFVIIa shows that all three ITI protocols dominate the on-demand regimen with rFVIIa. Between the ITI protocols the low-dose ITI protocol dominates both the Bonn ITI protocol and the Malmö ITI protocol and would be the preferred ITI protocol. All of the three ITI protocols dominate the on-demand strategy, as they have both a lower average lifetime cost and higher quality-adjusted life-years (QALYs) gained. The cost per QALY gained for the Bonn ITI protocol compared with the Malmö ITI protocol was \$249,391.84. The cost per QALY gained for the Bonn ITI protocol compared with the low-dose ITI protocol was \$842,307.69.

**Conclusion:** The results of data derived from our study suggest that the low-dose ITI protocol may be a less expensive and/or more cost-effective option compared with on-demand first-line treatment with rFVIIa.

**Keywords:** cost-utility analysis, immune tolerance induction, on-demand, rFVIIa

## Introduction

Hemophilia A is a bleeding disorder caused by a functional absence, or reduced levels, of factor VIII (FVIII). In the developed world, prophylaxis for hemophilia

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A uses infusions of virus-attenuated plasma-derived FVIII or recombinant (rFVIII) clotting factor replacement. Such treatment has substantially improved the quality of life (QoL) of persons with severe (FVIII > 1%) and moderate (FVIII 1%–5%) hemophilia A by avoiding bleeding episodes and their long-term consequences, particularly in the joints.<sup>1</sup> However, we are still grappling with issues of cost-effective care of the disease and its other complications. The most serious of these complications is the development of a neutralizing antibody, or inhibitor, to FVIII.

In developed countries, where economic resources are available for high-cost products, the development of antibodies neutralizing the hemostatic effect of therapeutically administered clotting factor concentrates (inhibitors) is the key problem of treating hemophilia.<sup>2</sup> In the presence of an inhibitor, especially if at high titer, the standard safe and effective replacement treatment is hampered, and high rates of morbidity and mortality are reported.<sup>3</sup> In addition, this challenging treatment is associated with a very high economic burden.<sup>4,5</sup> At variance with other settings of chronic disease, costs of treatment in hemophilia are mainly related to direct costs of replacement clotting factor concentrates.<sup>5,6</sup> When patients with inhibitors are evaluated, these costs account for more than 98% of the strikingly high amount of medical and economic resources absorbed for their care.<sup>5</sup>

Development of inhibitors to transfused FVIII is currently the most severe and challenging complication of hemophilia treatment<sup>6</sup> and represents the highest economic burden for a chronic disease.<sup>7</sup> Inhibitors occur in up to one-third of patients with severe hemophilia A (FVIII, 1 u/dL).<sup>8</sup> The presence of an inhibitor complicates treatment and increases disease-related morbidity,<sup>9</sup> because it renders factor replacement ineffective.<sup>6,10</sup> Consequently, hemophiliacs with inhibitors, particularly those with high-titer inhibitors (over five Bethesda units), are at increased risk of uncontrollable hemorrhage, devastating joint damage, and subsequent disability, although they are usually under treatment with bypassing agents.<sup>10–13</sup>

To reduce these risks and improve QoL, immune tolerance induction (ITI), eg, the regular infusion of FVIII concentrates over a time period ranging from months to years, is usually attempted to overpower high responding (anamnesis) FVIII inhibitors of recent onset and restore normal factor pharmacokinetics.<sup>10,14,15</sup>

ITI is nowadays usually started in connection with, or early after development of, an inhibitor. The regimen used often comprises very high doses of factor concentrate, and the treatment course spans over several months or even years.

Other regimens are also in use with lower doses or combined with immunosuppressive agents and extracorporeal inhibitor adsorption.<sup>16</sup> The high cost of the treatment makes it controversial, and a comparison between two different regimens using different dose levels is now ongoing.<sup>17</sup>

Three primary therapeutic regimens have been developed for inhibitor eradication. The high-dose Bonn protocol currently calls for the administration of FVIII at a dosage of 150 IU/kg twice daily.<sup>18</sup> The Bonn protocol is intensive for patients and families and very costly because of high FVIII consumption.

In the low-dose Van Creveld (Dutch) regimen, FVIII is administered every other day at a dose of 25 IU/kg.<sup>19</sup> The dose is decreased each time the absolute FVIII recovery exceeds 30%. These reductions are continued until a prophylactic FVIII dose of 10–15 IU/kg three times weekly is reached.

The Malmö protocol utilizes extracorporeal immunoadsorption with protein A columns as needed to remove high-titer inhibitory antibodies (over ten Bethesda units).<sup>20,21</sup>

Two bypassing agents are currently available: the activated prothrombin complex concentrate (APCC) FEIBA® (Baxter AG, Vienna, Austria) and recombinant-activated FVII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark). Both products have been shown to control at least 80% of bleeding episodes associated with high-titer inhibitors, including perioperative bleeding.<sup>22–27</sup>

rFVIIa was first approved in Europe in 1996. It has proved to be an effective and safe therapeutic agent for the management of bleeding in hemophiliac patients with inhibitors, with adverse thrombotic events occurring in less than 1% of patients.<sup>28</sup> Data collected in a database demonstrated that rFVIIa dosed in a range of less than or equal to 200 µg/kg had a bleeding cessation rate of 84% compared with 97% for those receiving over 200 µg/kg. The median total dose over 72 hours was 360 µg/kg (range 40–4280 µg/kg).<sup>29</sup>

Currently, there are about 7000 hemophilia patients in the Islamic Republic of Iran.<sup>30</sup> The Iranian national health care system allocates more than 31% of total subsidized funds on hemophilia. This amounts to \$103 million of total subsidized. Out of this figure, 38% of this figure is dedicated to hemophilia patients with either inhibitors or FVII-deficient patients. In other words, Iran spends \$39 million for only 450 patients (175 with inhibitors and 276 with FVII deficiency) annually. Average per capita consumption of FVIII clotting factor is rising in the country and, in 2010, it was about 2.0, but there is a lack of economic evaluation studies to measure the cost-effectiveness of this spending.<sup>30</sup>

The high initial cost of ITI has led some to question the cost-effectiveness of this strategy, and long-term data on the costs and efficacy of any individual ITI regimen are sparse.<sup>31,32</sup> We therefore conducted a cost-effectiveness analysis to determine the optimal strategy for the management of patients with inhibitors by estimating the lifetime costs and survival for ITI followed by the use of FVIII concentrates, compared with a strategy using other hemostatic agents without ITI.

## Materials and methods

Our analysis is based on the study of Knight et al,<sup>33</sup> which evaluated the cost-effectiveness of different treatments for hemophilia A with high-responding inhibitors. To adapt Knight et al's results to the Iranian context, a few clinical parameters were varied, and cost data were replaced with the corresponding Iranian estimates of resource use. The time horizon of the analysis was 10 years. The foreign exchange rate used in the analysis was 10,620 Iranian Rial = 1US\$ (May, 2011).

The analysis conducted is a cost-utility analysis, ie, an economic evaluation that estimates the cost per quality-adjusted life-year (QALY) gained from undertaking one intervention instead of another.<sup>8</sup> The QALY is a potential measure of health and is obtained by multiplying the duration of a health state (in years) by a factor representing the quality ("utility") of that health state. A QALY value of 1 is equivalent to a year of "perfect health," whereas a value of 0 corresponds to "death."

## Utilities

Because of a lack of suitable Iranian data on the effect of the different treatment regimens on health-related QoL of individuals with hemophilia A with high-responding inhibitors, the number of QALYs gained for different strategies were derived from Knight et al.<sup>33</sup> All input data used in the study are reported in Table 1.

**Table 1** Immune tolerance induction and on-demand default protocols

| Protocol         | Dose                    | Success rate (%) | Average patient weight (kg) | QALY |
|------------------|-------------------------|------------------|-----------------------------|------|
| Bonn (high dose) | 300 U/kg/day pdFVIII    | 72.8             | 60                          | 33.0 |
| Low dose         | 50 U/kg/day             | 43.0             | 60                          | 29.1 |
| Malmö            | 207 U/kg/day            | 53.3             | 60                          | 28.1 |
| On-demand        | 90–120 rFVIIa µg/kg/day | 92               | 60                          | 25.1 |

**Abbreviations:** pdFVIII, plasma-derived factor VIII; QALY, quality-adjusted life-year; rFVIIa, recombinant-activated factor VIIa.

## Resource use

### Management of patients with inhibitors in Iran

APCC and rFVIIa are available for the treatment of these patients. APCC (Feiba) is used in doses of 50–100 U/kg/dose for treatment of bleeds every 12 hours until resolution. rFVIIa is given at 90–120 µg/kg per dose every 2 to 4 hours until bleeding resolves. ITI is occasionally attempted with 50–100 U/kg of the appropriate factor concentrate three times a week.<sup>24</sup>

All local costs associated with the administration of clotting FVIII during ITI and on-demand with rFVIIa are shown in Table 2.

## Cost analysis

This study was conducted with the perspective of the Iranian Ministry of Health. Due to the unavailability of other medical resources unit costs, study was focused on treatment costs and excluded outpatient and inpatient costs associated with the bleeding episodes. The direct costs (\$) included are only those related to using clotting factors. The total cost per year and per patient was estimated by multiplying the price per unit (2011) by the number of units used per year during hospitalization and/or outpatient treatment. It has been reported that when patients with inhibitors are evaluated, their medication costs account for more than 98% of medical and economic resources absorbed for their care (Table 3). Gringeri et al<sup>5,7</sup> also reported that clotting factors accounted for 99% of the medical cost associated with hemophilia patients. Based on this information, indirect costs were not taken into account in this analysis.

## Sensitivity analysis

One-way sensitivity analyses were performed, varying the cost of the clotting factor, the drug dose, and the administration frequency, to test the robustness of the analysis.

## Results

To compare the cost-effectiveness of one treatment over another is to calculate the incremental cost-effectiveness ratio (ICER). The traditional decision rule is that one treatment should be funded over another when the ICER is better than the societal value of a QALY. This is represented by the

**Table 2** Cost of hemostatic agent in Iran (May, 2011)

| Factor                  | Price per unit (\$) |
|-------------------------|---------------------|
| Factor VIII             | 0.3 per IU          |
| Recombinant factor VIIa | 684.0 per mg        |

**Table 3** Cost and benefit of the immune tolerance induction (ITI) protocols and on-demand therapy with recombinant factor VIIa

| Protocol     | Average cost of managing bleeding episodes for 10 years (\$) | Quality-adjusted life-years |
|--------------|--|-----------------------------|
| Bonn ITI     | 5,528,649.60   | 33.0                        |
| Low-dose ITI | 2,243,649.60   | 29.1                        |
| Malmö ITI    | 4,306,629.60   | 28.1                        |
| On-demand    | 6,205,248.00   | 25.1                        |

formula  $ICER = (\text{cost T1} - \text{cost T2}) / (\text{QALY T1} - \text{QALY T2})$ . Table 4 compares the ICERs between the three ITI protocols and the on-demand regimen.

When cost-utility analysis is considered, the on-demand protocol has the worst QALYs (25.1), whereas ITI is associated with better values. The Bonn protocol obtains the best value (33.0) in this setting, intermediate values being expressed by the Malmö (28.1) and the low-dose (29.1) protocols. On the whole, the comparison of ICERs (cost per QALY) made the low-dose ITI protocol the most cost-effectiveness approach in a lifetime perspective, followed by the Malmö and then by the Bonn protocol.

Comparison of the ICERs (Table 4) between the three ITI protocols and the on-demand regimen with rFVIIa shows that all three ITI protocols dominate the on-demand regimen with rFVIIa. Between the ITI protocols the low-dose ITI protocol dominates both the Bonn ITI protocol and the Malmö ITI protocols and would be the preferred ITI protocol.

Both the low-dose ITI protocol and the Bonn ITI protocol generate more health benefit (more QALYs) than both the Malmö ITI protocol and the on-demand protocol with rFVIIa but at a different cost.

All of three ITI protocols dominate the on-demand strategy, as they have both a lower average lifetime cost and higher QALYs gained. The cost per QALY gained for the Bonn ITI protocol compared with the Malmö ITI protocol was \$249,391.84. The cost per QALY gained for the Bonn ITI protocol compared with the low-dose ITI protocol was \$842,307.69.

**Table 4** Incremental cost-effectiveness ratios: comparison between all four protocols (cost per quality-adjusted life-year)

| Protocol     | On-demand | Malmö ITI    | Low-dose ITI | Bonn ITI |
|--------------|-----------|--------------|--------------|----------|
| On-demand    |           |              |              |          |
| Malmö ITI    | Dominates |              |              |          |
| Low-dose ITI | Dominates | Dominates    |              |          |
| Bonn ITI     | Dominates | \$249,391.84 | \$842,307.69 |          |

**Abbreviation:** ITI, immune tolerance induction.

## Sensitivity analyses

The sensitivity analyses performed show that the results were sensitive to a number of variables, including the cost of the clotting factor, which is a cost driver in this study, and the drug dose.

## Discussion

The aim of this study was to conduct a cost-effectiveness analysis of ITI versus on-demand rFVIIa treatment for hemophilia A individuals with high-responding inhibitors in an Iranian clinical setting. The results of the current study are in compliance with those reported by Kessler and Aledort,<sup>31</sup> Knight et al,<sup>33</sup> Lippert et al,<sup>34</sup> and Colowick et al.<sup>35</sup>

Patients with hemophilia and inhibitors are a challenge to treat, requiring high costs over their lifetimes for effective management. The drug acquisition costs of various treatment options must be considered in the context of patient QoL and management of the entire bleeding episodes. Well-designed studies are needed to compare recombinant and plasma-based agents for the treatment of hemophilia patients with inhibitors. In the meantime, decision makers are left to determine which therapies are most cost-effective based on the best information available. The costs and cost-effectiveness of rFVIIa versus ITI are controversial and are primarily dependent on dosing requirements to control bleeds. The total dose used to manage a bleeding episode may have profound effects on the overall cost of treatment.<sup>36</sup>

As hemophilia with inhibitors is rare, an individual clinician may manage only one or two patients at a time. The problem of a small sample size with this rare disease population is unavoidable, though these patients may have up to 20 bleeds per year and few are lost to follow-up as patients usually stay with a hematologist/hemophilia center because of the frequent need for care. Thus, using economic evaluation to understand the larger impact across a health system or country might be helpful in understanding the broader cost-effectiveness issues associated with selection of a preferred drug treatment strategy.<sup>36</sup>

Additional studies are needed to determine the impact of different treatments on the QoL of hemophilia patients with inhibitors. In summary, the future direction of outcome assessment for hemophilia with inhibitors will probably focus on bleeding time comparisons among available treatments and how recurrent joint bleeds affect long-term joint status, QoL, and cost-effectiveness.

Perhaps one of the most important observations of inhibitor economics, also demonstrated by several authors,

is that the higher overall costs of treating inhibitor patients can be largely attributed to only a small number (1%–2%) of patients who use huge amounts of bypassing agents.<sup>37,38</sup>

To our knowledge, this is the first attempt to undertake a cost-effectiveness analysis of ITI versus on-demand treatment for hemophilia A individuals with high-responding inhibitors in an Iranian clinical setting.

Our study had a number of limitations mainly due to its structure, the wide time horizon, the assumptions made, and the data used, some of which were derived from different sources. Clinical outcomes were derived from a literature review. Therefore, in a further economic evaluation it could be interesting to compare clinical effectiveness among different alternatives used in an Iranian setting, but data on costs and outcomes for different clotting factors would need to be collected over a longer period of time. Moreover, most published guidelines for pharmacoeconomic evaluations recommend the adoption of a societal perspective.<sup>38</sup> The societal perspective, in addition to direct medical costs, includes direct nonmedical costs and potential indirect costs.<sup>38</sup> However, because it has been reported<sup>15,7,39</sup> that clotting factor concentrates account for 98% of total costs, this study only limited the information to the direct medical costs.

In spite of all the limitations of pharmacoeconomic study, these instruments have a key role when priorities in resource allocation have to be established.<sup>37</sup> In fact, they provide decision makers in the health care system with useful tools to make more rational and effective decisions.

In countries with limited resources available to the health care sector, a strategy of lower-cost treatment and a holistic approach to patient care with cost-effective utilization of limited resources provide a viable standard of care, especially in the expensive field of hemophilia treatment.<sup>35</sup> The current study can provide the Iranian Ministry of Health with an effective tool to allocate its limited resources on more cost-effective interventions for hemophilia.

## Conclusion

The results of data derived from our study suggest that the low-dose ITI protocol may be the most cost-effective option compared with on-demand first-line treatment with rFVIIa.

## Disclosure

This independent study was financially supported by Shahid Beheshti University of Medical Sciences. The authors state that they have no conflict of interest.

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