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# Cost Assessment of Implementation of Immune Tolerance Induction in Iran

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A B S T R A C T

**Objective:** A number of hemophilia A patients who receive clotting factors may develop antibodies (inhibitors) against clotting factors. The immune tolerance induction (ITI) method has proved to be a very cost-effective alternative to bypassing agents. Iran's national health authority is interested in implementing the ITI method for the management of hemophilia patients with inhibitors. The objective of this study was to calculate the breakeven point between costs attributed to the ITI method and the use of bypassing agents for the management of high-responder hemophilia patients with inhibitors. **Methods:** This study assessed costs attributed to the implementation of ITI for the management of Iranian hemophilia patients with costs of high-titer and high-responding inhibitors from the perspective of the national health system. The main objective was to find the breakeven point for the ITI method in comparison with the use of bypassing medicine, recombinant factor VIIa (Novoseven). **Results:** Based on the sensitivity analysis performed, the breakeven point mainly depends on costs of factor VIII, Novoseven, and the success rate of the ITI intervention. According to this analysis, the breakeven point of ITI and Novoseven methods varies between 16 and 34 months posttreatment. The optimized point is about 17 months posttreatment. **Conclusions:** Iran's national health system spends more than 24 million euros for providing bypassing agents to about 124 hemophilia patients with inhibitors. Because of limited resources available in Iran's health sector, this is a huge burden. Results of this study show that the implementation of the ITI method for the management of Iranian hemophilia patients with inhibitors is a cost-saving method and Iran's health system will recover all the expenditure related to the implementation of ITI in less than 2 years and will make a considerable saving along with providing standard care for these patients.

*Keywords:* cost assessment, hemophilia patients, immune tolerance induction, Iran.



## Introduction

Hemophilia is a rare inherited blood disorder that normally affects males. About 1 in 10,000 newborns may have this congenital disorder. These patients lack sufficient clotting factors VIII, IX, or, in rare cases, other clotting factors. Efficient management of hemophilia patients and their complications require appropriate administration of clotting factors. Otherwise, these patients may face massive internal and external bleeding. However, some of these patients may develop antibodies against clotting factors during the course of treatment. This is mainly due to an immune response against clotting factor concentrates. This will ultimately produce neutralizing antibodies, which are named "inhibitors." Inhibitors could occur in 15% to 35% of patients with severe hemophilia A. In addition to immune system response, factors such as severity of the disease, age, type of mutation, genetics, and previous exposure to clotting factors may play roles in developing inhibitors. Inhibitor titer is measured by Bethesda units (BU). Patients are categorized to low titer (<5 BU) and high titer (≥5 BU). Although high doses of factor VIII (FVIII) concentrate could mange patients with low titer of inhibitors, high-titer patients require other types of medicines named "bypassing" agents. Otherwise, their bleeding cannot be controlled and will lead to severe complications or death [1,2].

Patients with inhibitors may face serious bleeding episodes that of course do not respond to regular clotting factor replacement therapy. Bleeding into muscles and joints may cause permanent joint damage. Currently, there are two main approaches for managing hemophilia patients with inhibitors. These patients could be treated by using bypassing agents such as recombinant FVIIa and activated prothrombin complex concentrate. These medicines stop the bleeding by providing activated or partially activated forms of FVII and/or factor X. However, these medicines are very expensive and for many patients, especially those living in developing countries, unaffordable. Data reported show that the use of bypassing agents for the management of these patients may even increase costs of treatment up to 12 times [3,4].

The second approach for managing hemophilia patients with inhibitors is immune tolerance induction (ITI). For three decades ITI has been used with promising efficiency for the management of hemophilia patients with inhibitors. With recent scientific con-

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sensus, however, ITI became a practical modality for hemophilia patients with inhibitors [5]. ITI could eliminate FVIII inhibitors and restore normal clinical response to FVIII in these patients. Recent published reports indicate the efficiency and cost-effectiveness of the ITI intervention in patients with inhibitors [4–7]. These reports clearly explain the benefits of this method, especially in young children who have recently developed inhibitors against FVIII.

Iran is a country with a population of more than 74 million and has a very well-defined and comprehensive national program for the management of hemophilia. According to a global survey by World Federation of Hemophilia, Iran has the second highest number of hemophilia cases in the Eastern Mediterranean region. According to Iran's Ministry of Health (MOH) statistics, currently there are about 7300 patients with congenital bleeding disorders registered in Iran, with 4100 of them having hemophilia A [8]. Two separate studies have reported that about 3.8% to 4% of Iranian hemophilia patients may develop high-titer antibodies against FVIII [9,10]. According to Iran's MOH, currently there are about 124 registered hemophilia A patients with inhibitors in Iran. Costs of hamophilia care in Iran are fully covered by the government of Iran through payment of direct subsidy for the medicines and costs of other cares used by these patients. The per-capita consumption of FVIII in Iran is reported to be 1.8 IU [11]. Despite the presence of such a comprehensive national program, however, it seems that the Iranian society has been faced by some social consequences that have arisen from this program [12].

Despite the low number of hemophilia patients with inhibitors in Iran, the cost attributed to the management of bleeding episodes through the administration of bypassing agents is huge. It is estimated that every year Iran's national health system spends more than 24 million euros for the importation of bypassing agents. However, it seems that because of direct payment of the government subsidies to the importing pharmaceutical companies, which results in a very low price of bypassing agents in Iran's market and very low surveillance regarding the administration and use of these medicines in Iran's market, some parts of these medicines are either wasted or used in other clinical applications such as hemostatic agents in nonhemophilia patients.

The per-capita expenditure on health in Iran is about US $700 [12]. Therefore, despite the presence of very few number of hemophilia patients with inhibitors, costs of treatment of these patients with bypassing agents place a huge burden on Iran's health sector. It is clear that overall high costs of treating patients with inhibitors are largely attributed to only very small number of patients who use large amounts of bypassing agents. Recently, Iran's MOH decided to establish a trial on the implementation of ITI for the management of hemophilia patients with inhibitors. Although one of the objectives of this initiative was to evaluate the clinical efficacy of ITI in Iranian hemophilia patients with inhibitors, Iran's MOH was also interested in estimating the costs of this treatment compared with the costs of current traditional use of bypassing agents. This study was designed to compare costs attributed to the implementation of ITI for the management of high-responder Iranian hemophilia patients with costs of administration of on-demand therapy using bypassing agents.

## Methods

The objective of this study was to calculate costs attributed to the implementation of ITI for the management of Iranian hemophilia patients with high-titer and high-responding inhibitors from the perspective of the national health system. The main objective was to find the "breakeven" point for the ITI method in comparison with the use of bypassing agents. Recombinant factor VIIa (Novoseven) as the most used bypassing medicine for the management of these patients in Iran was used for the purpose of cost comparison with the ITI method. To measure the costs of the ITI method in Iranian hemophilia patients with inhibitors, Iran's MOH decided to set up a trial including 10 patients in each arm of the study. Peak historical titer less than 200 BU and pre-ITI titer less than 10 BU were considered as the inclusion criteria for including good risk patients in the ITI arm [5]. Patients should also have an interval of fewer than 5 years between inhibitor diagnosis and the start of ITI. National consensus of expert panel was used as treatment protocol for both arms of the study. The ITI regimen in this model was defined as 100 IU/kg/d of FVIII. Bleeding events of the patients were divided into three categories as follows [5,7]:

1. Mild events, which could be treated with a standard dose of medicines at home;
2. Moderate events, which could be managed by the administration of a double dose of medicines; and
3. Severe events, which need hospitalization for their management.

Presumptions for both groups of this study are summarized in Tables 1 and 2. Complete response was defined as no detectable level of inhibitors, in vitro recovery of more than 66%, along with half-life of FVIII of more than 6 hours. Partial response was defined as decrease in inhibitor to less than 5 BU, without in vitro recovery, and half-life improvement, and no response was defined as not able to reduce inhibitor titer to less than 5 BU after completing the treatment course [13]. Iran's MOH was interested in finding out how long it will take to reach a breakeven point following the implementation of the ITI intervention. Therefore, to simplify the calculations, except for medicine costs, we assumed identical costs for utilized resources in both groups. A simple cost comparison method was used to find out the breakeven point for these two groups. The breakeven point was defined as the intersection of costs versus time graphs of these two methods. Costs of medicines for second and third years post treatment were discounted on the basis of a discount rate of 7.5% [14].

**Table 1 – Presumptions for the ITI arm.**

| | |
|---|---|
| Success rate of ITI | 80% |
| Dose of FVIII | 100 IU/kg/d |
| Mean time to success | 12 mo |
| Dose of Novoseven to control bleeding events in the first year | |
| Minor events | 270 μg/kg |
| Intermediate events | 540 μg/kg |
| Major events | 5400 μg/kg |
| No. of bleeding events in the first year (during ITI implementation) | |
| Minor events | 1.5 |
| Intermediate events | 1 |
| Major events | 0.1 |
| No. of bleeding events in second and third years (for on-demand therapy with FVIII in patients managed with the ITI method in the first year) | |
| Minor events | 27 |
| Intermediate events | 3 |
| Major events | 0.2 |
| Dose of FVIII to control bleeding events in second and third years | |
| Minor event | 40 IU/Kg/d |
| Intermediate event | 80 IU/Kg/d |
| Major event | 100 IU/Kg/d |
| Price of FVIII in Iran's market* | 3000 rials/IU |
| Mean estimated patient's weight of a 6-y-old child | 20 kg (with annual 10% increase) |

FVIII, factor VIII; ITI, immune tolerance induction.
* Based on the official exchange rate: 1 US $ =12,260 rials.

**Table 2 – Presumptions for the bypassing agent group.**

| | |
|---|---|
| Success rate of Novoseven | 95% |
| Dose of Novoseven to control bleeding events | |
| Minor events | 270 μg/kg |
| Intermediate events | 540 μg/kg |
| Major events | 5400 μg/kg |
| No. of bleeding events per year in on-demand therapy method | |
| Minor events | 27 |
| Intermediate events | 3 |
| Major events | 0.2 |
| Price of Novoseven in Iran's market* | 7750 rials/μg |

* Based on official exchange rate US $1 = 12,260 rials.

### *Treatment protocol and outcomes*

#### *The ITI group*

It was assumed that following the receipt of 100 IU/Kg/d of FVIII for 1 year, 80% of patients with inhibitors will respond to the treatment (success rate of 80%) and in following years they will only need FVIII as on-demand therapy for the management of their bleeding episodes. However, it was assumed that this group of patients in the first year of treatment will also need bypassing agents for the management of their bleeding episodes. The number of minor, intermediate, and major bleeding events in these patients will be 1.5, 1, and 0.1 episodes annually, respectively [5,15]. However, these patients will face 27, 3, and 0.2 minor, intermediate, and major bleeding events after the first year of treatment. Subsequently, their bleeding would be treated on demand with FVIII similar to that in other hemophilia patients without inhibitors. This pattern will also continue in the third year and in the following years of their life.

Twenty percent of patients who are assumed not to respond to ITI even after 1 year of treatment with 100 IU/Kg/d of FVIII still need Novoseven for the management of their bleeding episodes. The incidence of minor, intermediate, and major bleeding events in these patients is estimated similar to that of other on-demand treated hemophilia patients without inhibitors. The number of events is considered to be 27, 3, and 0.2 episodes, respectively, in the next years.

#### *On-demand therapy with bypassing agent (Novoseven) group*

This group also consisted of 10 patients. These patients will receive Novoseven for the management of their bleeding events. The incidence of minor, intermediate, and major bleeding events in these patients will be 27, 3, and 0.2 episodes, respectively, similar to that in other on-demand treated hemophilia patients without inhibitors. The dose of Novoseven for these patients is summarized in Table 2.

**Table 3 – Variables used for sensitivity analysis on the breakeven point of ITI and Novoseven methods.**

| Variable | Range |
|---|---|
| ITI success rate | 60%–80% |
| Price* of factor VIII | 2000–4000 rials/IU |
| Price* of Novoseven | 6000–8000 rials/μg |

ITI, immune tolerance induction.
* Based on official exchange rate US $1 = 12,260 rials.

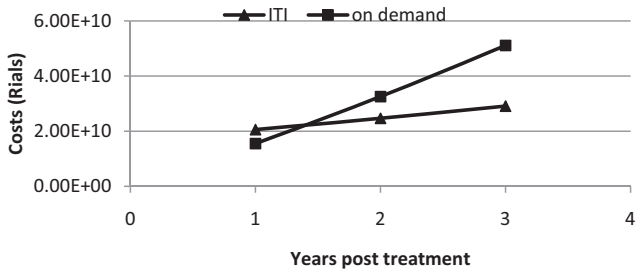


**Fig. 1 – Breakeven analysis for the ITI group and on-demand therapy with Novoseven. US $1 = 12,260 rials. ITI, immune tolerance induction.**

### *Sensitivity analysis*

The sensitivity analysis was performed for important variables related to this study. Costs calculation for both methods was repeated for different values of variables mentioned in Table 3. The results showed that the breakeven point was sensitive to a number of variables including cost of medicines, dose, and the success rate of the treatment protocols. The breakeven point was calculated as cross point of lines represented for total costs attributed to ITI and on-demand therapy with bypassing agent regimen (Fig. 1).

## Results

Results of a sample cost calculation for ITI and bypassing agent are summarized in Table 4. This table has been created on the basis of the assumption of 80% success rate for ITI and current prices of medicines in the Iranian market. The management of 10 patients with the ITI method (100 IU/Kg/d of FVIII) in the first year will cost 21,900,000,000 rials. On the other hand, in this year Iran's MOH will need to pay 2,301,750,000 rials for the management of bleeding episodes of these patients using Novoseven. Therefore, the total costs of the ITI arm of this study will reach 24,201,750,000 rials in the first year. Based on the success rate of 80% for the ITI method and therefore need of 20% of patients for Novoseven, the costs of the management of patients in the second year in this group will be 4,209,150,000 rials. Cumulative costs of first and second years will be 28,410,900,000 rials. Costs attributed to this group in the third year will be 4,591,800,000 rials. However, total costs for the management of 10 patients using on-demand therapy with Novoseven will be 15,484,500,000, 17,032,950,000, and 18,581,400,000 for first, second, and third year post treatment, respectively. To calculate the breakeven point, costs versus time for each arm were graphed. The breakeven point was defined as the intersection of these two graphs (Fig. 1).

Based on sensitivity analysis, the breakeven point very much depends on costs of FVIII, Novoseven, and the success rate of the ITI intervention. Ranges of variables used for sensitivity analysis are summarized in Table 3. According to this analysis, the breakeven point of ITI and Novoseven methods varies between 16 and 34 months post treatment. However, based on current price of medicines in the Iranian market and the assumption of 80% success rate for the ITI method, the breakeven point was calculated at about 17 months post treatment.

## Conclusions

The main objective of this study was to calculate the breakeven point for the implementation of ITI versus on-demand therapy with Novoseven in high-responder hemophilia patients with inhibitors from Iran's MOH perspective. Iran's health system pro-

**Table 4 – Samples of costs calculations for the ITI method versus on-demand therapy with Novoseven.**

| First year | FVIII (IU/kg/d) | Patient Wt. (kg) | Time length (d) | Total FVIII (IU) | Price of FVIII/IU* | Cost/patient* | No. of patients | Total costs*/year | |
|---|---|---|---|---|---|---|---|---|---|
| | 100 | 20 | 365 | 730,000 | 3000 | 2,190,000,000 | 10 | 21,900,000,000 | |
| | Novoseven ($\mu$g/kg/event) | Patient Wt. (kg) | No. of events | Price* of rFVII/$\mu$g | Total Novoseven | Cost/patient | No. of patients | Total costs | Total costs* (first year cumulative) |
| | 270 | 20 | 1.5 | 7750 | 8100 | 62,775,000 | 10 | 627,750,000 | |
| | 540 | 20 | 1 | 7750 | 10,800 | 83,700,000 | 10 | 837,000,000 | |
| | 5400 | 20 | 0.1 | 7750 | 10,800 | 83,700,000 | 10 | 837,000,000 | 2,301,750,000 |
| | | | | | | | | | 24,201,750,000 |
| Second year | FVIII (IU/kg/d) | Patient Wt. (kg) | No. of events | Total FVIII (IU) | Price of FVIII/IU* | Cost/patient* | No. of patients | Total costs | Total costs* (first year cumulative) |
| | 40 | 22 | 27 | 23,760 | 3000 | 71,280,000 | 8 | 570,240,000 | |
| | 80 | 22 | 3 | 5280 | 3000 | 15,840,000 | 8 | 126,720,000 | |
| | 1000 | 22 | 0.2 | 4400 | 3000 | 13,200,000 | 8 | 105,600,000 | 802,560,000 |
| | Novoseven ($\mu$g/kg/event) | Patient Wt. (kg) | No. of events | Price* of rFVII/$\mu$g | Total Novoseven | Cost/patient | No. of patients | Total costs | |
| | 270 | 22 | 27 | 7750 | 160,380 | 1,242,945,000 | 2 | 2,485,890,000 | |
| | 540 | 22 | 3 | 7750 | 35,640 | 276,210,000 | 2 | 552,420,000 | |
| | 5400 | 22 | 0.2 | 7750 | 23,760 | 184,140,000 | 2 | 368,280,000 | 3,406,590,000 |
| | | | | | | | | | 4,209,150,000 |
| | | | | | | | | | 28,410,900,000 |
| Third year | FVIII (IU/kg/d) | Patient Wt. (kg) | No. of events | Total FVIII (IU) | Price of FVIII/IU* | Cost/patient | No. of patients | Total costs | Total costs* (third year cumulative) |
| | 40 | 24 | 27 | 25,920 | 3000 | 77,760,000 | 8 | 622,080,000 | |
| | 80 | 24 | 3 | 5760 | 3000 | 17,280,000 | 8 | 138,240,000 | |
| | 1000 | 24 | 0.2 | 4800 | 3000 | 14,400,000 | 8 | 115,200,000 | 875,520,000 |
| | Novoseven ($\mu$g/kg/event) | Patient Wt. (kg) | No. of events | Price* of rFVII/$\mu$g | Total Novoseven | Cost/patient | No. of patients | Total costs | |
| | 270 | 24 | 27 | 7750 | 174,960 | 1,355,940,000 | 2 | 2,711,880,000 | |
| | 540 | 24 | 3 | 7750 | 38,880 | 301,320,000 | 2 | 602,640,000 | |
| | 5400 | 24 | 0.2 | 7750 | 25,920 | 200,880,000 | 2 | 401,760,000 | 3,716,280,000 |
| | | | | | | | | | 4,591,800,000 |
| | | | | | | | | | 33,002,700,000 |

FVIII, factor VIII.
* Unit price; US$1=12,260 rials.

vides free of charge treatment for hemophilia patients [11]. Therefore, Iran's MOH currently spends considerable resources for the management of patients with rare coagulating disorders.

Because of numerous reports indicating both clinical efficacy and cost-effectiveness of ITI for the management of hemophilia patients with inhibitors against FVIII [16], Iran's MOH decided to implement the ITI method for the management of high-responder hemophilia patients. A recently published report evaluated the cost utility of ITI versus on-demand therapy with Novoseven in Iranian hemophilia patients with high-titer inhibitors. The report concluded that low-dose ITI protocol (50 U/kg/d) is a cost-effective option compared with on-demand treatment with Novoseven in a 10-year period of time [17].

To finance the ITI intervention, Iran's MOH was interested in finding out the breakeven point of this method versus the management of patients using on-demand therapy with Novoseven. Results of our calculations show that Iran's MOH will be able to recover earlier higher expenditure on ITI, because of high doses of FVIII in first and second years of post treatment, in less than 2 years. Despite the sensitivity of the breakeven point to some variables (Table 3), a most realistic scenario for the price of FVIII and Novoseven in the Iranian market and the assumption of 80% success rate for the ITI method (Table 4) show that the breakeven point for these two methods will be at about 17 months post treatment (Fig. 1). Therefore, Iran's MOH will recover all costs attributed to the ITI method in 17 months of starting the ITI program and will have substantial saving on the management of these patients in coming years afterward. The money saved could also be allocated to other priorities of Iran's health sectors.

However, this study had one important limitation, which is the exchange rate for Iran's national currency (rial). As is already mentioned, the estimation of the breakeven point is very sensitive to the price of medicines. Both medicines used for the management of these patients (FVIII and Novoseven) are imported medicines, and the exchange rate plays a major role in their final price. Although we used the official exchange rate for rial versus international currencies, in recent months, rial has experienced a substantial devaluation. Rial has lost about 30% of its value in recent months, and this might affect the final result and the conclusion of this study. Otherwise, the results of this study clearly show that the ITI method is a cost-saving method for the management of high-responder inhibitor hemophilia patients when compared with on-demand therapy with Novoseven.

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