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A comparison between on-demand usage of rFVIIa vs prophylaxis use of emicizumab in high titer inhibitory hemophilia A patients in Iran

A cost–utility analysis

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Abstract

Background: Hemophilia A (HA) is an inherited X-linked bleeding disease with costly treatment, especially for high titer inhibitory patients. Emicizumab, a new humanized bispecific antibody, has been approved for use to prevent or reduce the frequency of bleeding episodes in HA patients with inhibitors. This study evaluated the cost-utility of emicizumab prophylaxis (EP) in comparison with recombinant factor VII activated on-demand treatment in HA patients with inhibitors.

Methods: A life-time Markov model with payer and societal perspectives was developed in different age groups with different annual bleeding rates (ABR). Efficacy of treatments were extracted from HAVEN trials. Utilities were retrieved from published evidence. Costs were calculated based on Iran food and drug administration official website, national tariff book for medical services and hospital data. One-way deterministic sensitivity analysis was performed.

Results: EP was dominant choice in comparison with on-demand administration of recombinant factor VII activated in all age groups with ABR 20 and 25, and it remained dominant in patients with age 2 and age 12 at start point with ABR 16 and 17. The reported incremental cost-effectiveness ratio for the group with ABR 18 at the age 20, was 12,936 United States Dollars which is lower than the acceptable threshold of cost-effectiveness in Iran (1–3 gross domestic product per capita) and EP can be considered as cost-effective choice in this scenario.

Conclusion: EP was found to be a dominant and cost-effective choice for Iranian HA patients with factor VIII inhibitors with ABR 18 and above with considerable cost saving.

Abbreviations: ABR = annual bleeding rate, BPAs = bypassing agents, CUA = cost–utility analysis, EP = emicizumab prophylaxis, FDA = Food and Drug Administration, FVIII = factor VIII, HA = hemophilia A, ICER = Incremental Cost-effectiveness Ratio, IFDA = Iran Food and Drug Administration, MCCH = Mofid Comprehensive Care Center for Children with Hemophilia, OD = on-demand, QALY = quality-adjusted life-years, rFVIIa = recombinant factor VII activated, RR = risk ratio, SV/RSV = synovectomy/radio-synovectomy, TJ = target joint, USD = United States dollars.

Keywords: antibodies, anti-inhibitor coagulant complex, bispecific, emicizumab, Hemlibra, hemophilia A, recombinant recombinant factor VII activated

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1. Introduction

Hemophilia A (HA) is an X-chromosome-related congenital defect that disrupts the production of coagulation factor VIII (FVIII) and affects the coagulation cascade, which is seen in men with a prevalence of 1 in 5000 male births.[1] Patients with a severe type of hemophilia who have 1% or less clotting factor in their blood are more likely to have recurrent spontaneous and post-traumatic bleeding in joints and muscles.[1,2]

The treatment strategies in HA management, are on-demand (OD) FVIII infusion to manage bleeding, or prophylactic treatment to prevent bleeding.[3] However, FVIII replacement therapy is less effective in patients who produce FVIII antibodies, also known as inhibitors. Inhibitors develop in up to one-third of patients with severe HA, complicating management and leading to considerable morbidity and mortality.[3–5] Management of bleeding in these patients is based on OD or prophylaxis therapy with bypassing agents (BPAs) including, activated prothrombin complex concentrates and recombinant factor VII activated (rFVIIa).[6,7] Despite the use of BPAs, the risk of uncontrolled bleeding, subsequent disability, and devastating damage is high in patients with high titer inhibitors, leading to poor quality of life.[8,9] In most healthcare systems, the main costs of management of HA patients with inhibitors are attributable to the direct costs of clotting factor concentrates, which constitute more than 98% of costs.[10] The high cost and low quality of life of these hemophiliacs have made it a substantial issue for healthcare systems.[11]

In 2017, the U.S. Food and Drug Administration (FDA) approved emicizumab (Hemlibra, Genentech, Inc.) prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric HA patients (ages newborn and older) with FVIII inhibitors.[12] An additional indication was approved in October 2018 for prophylactic treatment of HA patients without FVIII inhibitors.[13] Promising results of trials have drawn the attention of medical staff in field and health sectors to emicizumab. The clinical trials in adolescent and adult patients (HAVEN1) and pediatrics (HAVEN2) have shown a decrease in the annual bleeding rate (ABR) in patients treated with a weekly emicizumab prophylaxis (EP), compared with OD or prophylactic treatment with BPAs.[14,15]

Current standard of care for high titer HA patients with inhibitors in Iran primarily involves OD administration of BPAs.[16] By introducing emicizumab prophylactic treatment for HA patients with inhibitors, comparative studies should be performed that can evaluate the clinical and economic value of this method with existing standard of care. So far, no economic evaluation study has been conducted in Iran to compare OD use of rFVIIa as standard care of healthcare vs newer therepeutic option (prophylaxis therapy with emicizumab) in high titer inhibitory HA patients.

The aim of this study was to evaluate the cost-utility of emicizumab (Hemlibra, Genentech, Inc.) compared with locally manufactured rFVIIa (AryoSeven, Aryogen Co. Iran) in high titer HA patients with inhibitors from societal and payer perspective in the Iran healthcare system. The similar efficacy[17–19] and lower price of AryoSeven vs original brand of rFVIIa, makes this study challenging to evaluate emicizumab cost-effectiveness. The study designed based on Iran Food and Drug Administration (IFDA) request.

2. Methods

A Markov state transition model was designed in Excel-2010 based on different ABRs for different age categories to perform a cost–utility analysis (CUA) of EP compared to rFVIIa OD administration in HA patients with inhibitors. The CUA was performed using payer and societal perspectives, in the Iran healthcare system. The incremental cost per quality-adjusted life-years (QALY) was considered as an outcome of the analysis.

2.1. Model description and inputs

All details about the construction of Markov model were considered in terms of defining states, transition probabilities, time horizon, discount rate, etc.[20]

A lifetime Markov model has been run for 3 different hypothetical cohorts of patients with different age groups. The cost and clinical outcomes of treating the cohort patients were followed using model through 3 states, EP, OD rFVIIa, and death. Each cycle was 1 year. At the end of every cycle each patient either remained in the states OD and EP or was moved to the absorbable state "Death". The model was re-run multiple times (9 times for 3 age group and 3 ABRs) to simulate different scenarios. Model diagram is summarized in Figure 1.

The age categorization was designed based on patient pools in HAVEN 1 & 2 as starting from 2 to 12, 12 to 20, and >20 years-old.[14,15] The clinical information for base-case was taken from Mofid Comprehensive Care Center for Children with Hemophilia (MCCH) in Tehran. Based on IFDA Pharmacoeconomics Committee Guideline, the discount rate of 5% and 3% was applied for cost and outcomes, respectively. Clinical efficacy, safety, route of administration, and dosage considerations were extracted from literature for both EP and rFVIIa. Locally manufactured form of rFVIIa selected as the comparison arm claimed to have the same efficacy with the original brand at a lower cost.[21] The Iranian adjusted life table was used to calculate the age-dependent weight.

The model was run based on the following assumptions

- Individuals were entered at the ages of 2, 12, and 20-year-old.
- Surgical events rate and costs were assumed the same in both arms.
- No target joint (TJ) bleedings in EP arm starts from 2-year-old (in the designed model, due to the significant effectiveness of emicizumab in children, it was assumed that children who receive this medication from the age of 2 do not get involved in the TJ, and their few bleeds were considered as maximum joint bleeding).
- No arthroplasties were included in EP arm according to the hemophilia treatment guideline and the high effectiveness of this drug, which leads to a 95% reduction in bleeding of the TJs.
- Base case utility was assumed constant in all ages (no decrease for elderly patients).
- After age 20, the weight was supposed to be constant.
- Two arthroplasties and 2 revisions were calculated for patients with TJs.
- No transportation fees were supposed for spontaneous bleedings (managed at home).
- It was assumed that there was no waste in dosing in both arms.
- Compliance was considered to be 100% for both arms.
- Adverse effects were not included in costs and utility calculation for both arms.

2.2. Mortality rate

The probability of death in each year for individuals treated OD or as EP was based on WHO life-table of Iranian male which was

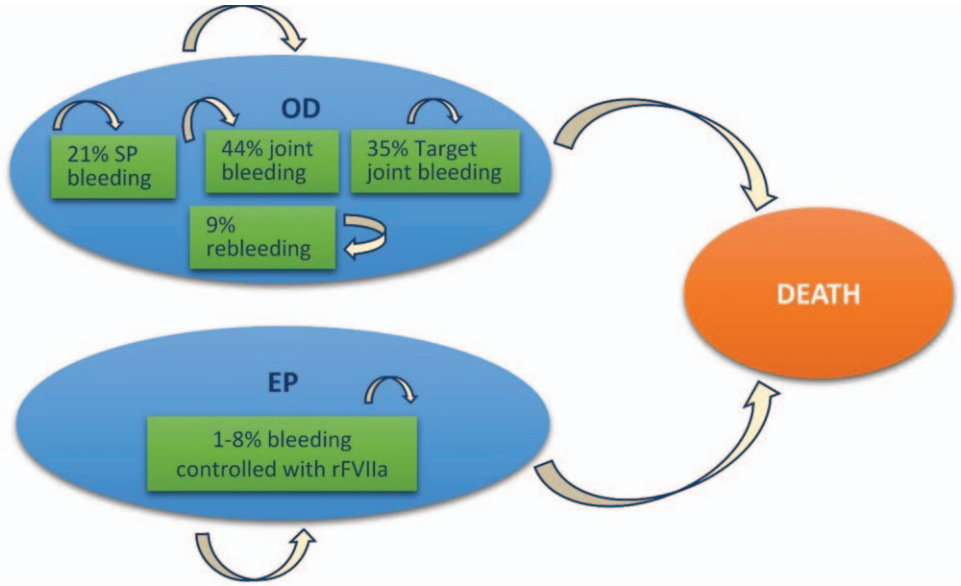

Figure 1. States and sub-states of the Markov model. EP = emicizumab phrophylaxis, OD = on demand.

adjusted by risk ratio (RR) extracted from published literature.[22] The RR for individuals in OD treatment was considered 2.69 and for those in EP arm, was considered 1.16.[21] Also, for individuals who entered EP arm with the age range from 12 to 20, we assumed direct relationship between duration of treatment method until about 40 years and death RR (if a patient receives OD treatment for about 40 years his death RR would be 2.69), then for age 12 the RR was calculated relatively 67% for EP and 33% for the OD ratio ($0.67 \times 1.16 + 0.33 \times 2.69 = 1.67$). Subsequently, for individuals who entered EP arm from age 20, the RR was calculated relatively 50% as the EP and 50% as the OD ($0.50 \times 1.16 + 0.50 \times 2.69 = 1.92$).

2.3. Dosing

EP was defined as 3 mg/kg/wk for the first 4 weeks and 1.5 mg/kg/wk for the maintenance therapy based on HAVEN1 and HAVEN2 studies.[12,15]

On the other hand, the required dose of rFVIIa OD treatment was defined for those types of bleeding mentioned in the HAVEN1 study. Different dose of rFVIIa was calculated for patients suffering from TJ bleedings with or without synovectomy (SV) or radio-synovectomy (RSV).[23] In addition, based on literature the rFVIIa dose needed for general operations or arthroplasty was considered 9.24 mg/kg.[24]

2.4. Effectiveness and bleeding rate

Based on HAVEN1/2 results, in the EP arm 99% reduction was considered for all types of bleedings (including joint, TJ and, spontaneous bleedings) for start age 2-year-old group.[15] The effectiveness of emicizumab in reducing bleeding in the age group of 12-year-old and above in HAVEN1 study was 92%, 85%, and 95% for spontaneous, joint and, TJ bleedings, respectively.

2.5. Utilities

The utility of different states was adapted from Noone et al[25] which is a multinational study calculated utilities in 3 basic states

1. OD treated HA patients with high titer of inhibitors: 0.619.
2. HA patients with high titer of inhibitors who have received prophylaxis treatment throughout life: 0.866.
3. HA patients with high titer of inhibitors who have received half-life of prophylaxis treatment: 0.812.

2.6. Costs analysis

To analyze costs, direct medical, direct non-medical and indirect expenses were considered with a societal perspective; however, with a payer perspective just direct medical costs were calculated. In both arms, the patients' weight was the main factor in calculating the cost of treatment as dosing is based on weight, which was calculated based on the average male weight of different ages.[26] Available data were used only to estimate the paradigms and proportions of patients' bleedings and the number of visits.

According to the information collected from Mofid hospital, the ABR was considered 25 for base-case, which was close to 23, the ABR calculated in the HAVEN1 study; however, in this study, the Markov model was run for other hypothetical ABRs, and the results were reported. The proportion of each type of bleeding was reported in Table 1.

Based on the official IFDA website, AryoSeven was 208.3 United States dollars (USD) per milligram.[27] Also, based on the Roche product price list, Hemlibra was 1835 Euros/30 mg, which was calculated 97.39 USD/mg (based on the Euro exchange rate of Iran central bank website at February 5, 2020).

To calculate other direct medical costs, the official national tariff price list of the year 2020, and the 80:20 ratio for the public–private sector was administered (Table 1).

The costs of durable medical equipment such as walking aid and wheelchairs were omitted due to the low likelihood of consumption and low price. In accordance to Knight et al[28] and based on the data from Imam Khomeini Hospital complex in Tehran, the number of arthroplasties and revision arthroplasties for patients with ABR > 20 were considered 2 (for each one) first one at the age of 30 and second at 40 years. Due to the temporary

Table 1

Model inputs.

	Parameters	Values	Ref.
Costs (USD)	Emicizumab price per mg	97	Company data on file
	rFVIIa (local manufactured) price per mg	208	IFDA
	Arthroplasty	3438	Calculated
	Revision arthroplasty	7010	Calculated
	Synovectomy	635	Calculated
	Other surgeries	687	Calculated
	Annual physiotherapy cost	100	Calculated
	Transportation costs	3.5	Estimated
	Each day productivity lost	14.5	Official salary
Emicizumab efficacy	Bleeding categories (age > 12)	ABR reduction (RR)	Ref.
	Treated spontaneous bleeds	0.92 (0.08)	[14]
	Treated joint bleeds	0.89 (0.11)	[14]
	Treated target joint bleeds	0.95 (0.05)	[14]
	Bleeding categories (age 2–12)	ABR reduction (RR)	Ref.
	All bleeds	0.99 (0.01)	[15]
Utility	State		QALY Ref.
	On-demand		0.619 [27,33]
	Prophylaxis	Whole life	0.866 [27,33]
		>50% life on prophylaxis	0.812 [27,33]
Mortality rate	State	HR	Ref.
	On-demand	2.69	[21]
	Prophylaxis whole life	1.16	[21]
	Prophylaxis from 12 years old	1.6	Calculated
	Prophylaxis from 20 years old	1.9	Calculated
rFVII a (AryoSeven) dosing	Bleeding conditions	mg/kg	Ref.
	Spontaneous bleeding (other than joint bleeding)	0.18	Local guidelines
	Joint bleeding	0.45	[24]/specialist
	Target joint bleeding without RSV/SV	8.1	Specialists
	Target joint bleeding with RSV/SV	3.94	Specialists
	Surgical events (arthroplasty, routine surgery)	9.24	[25]/calculation
Emicizumab dosing	Time	mg/kg/week	Ref.
	First month	3	[14]
	The second month onwards	1.5	[14]
Bleeding rate in complicated patients	Bleeding conditions	%	Ref.
	ABR	Vary (base-case 25)	Different scenarios
	Treated spontaneous bleeding	21.6%	MCCH data
	Treated joint bleeding	43.9%	MCCH data
	Treated target joint bleeding	34.5%	MCCH data
	Re-bleeding	9%	[31]

ABR = annualized bleeding rate, IFDA = Iran food and drug administration, rFVIIa = recombinant activated factor VII, RR = risk ratio, HR = hazard ratio, SV/RSV = synovectomy, radio synovectomy, USD = United States Dollar, MCCH = Mofid Comprehensive Care Center for Children with Hemophilia.

elimination of the problem of a TJ in patients undergoing joint replacement, a 10-year linear model was considered to take the joint problem of these patients into consideration. According to HAVEN 1/2 study, the average ABR per TJ was considered 3 times a year.[12] It was also assumed that 50% of the extensive TJ bleedings have been reduced after joint replacement.

Another assumption was to consider 9.1% re-bleedings probability in patients with mild to moderate bleedings treated by rFVIIa.[29] Also, SV/RSV costs were considered the same. According to the data from MCCH, the SV/RSV rate was calculated 30%; however, it was considered 25% in Iran, due to limited access to radioisotope medicines. The number of annual physiotherapy sessions was estimated at 10 (Table 1).

The transportation costs were calculated as 3.5 USD for each visit. The number of visits for each joint bleeding was considered 1, and for patients with TJ bleedings was estimated at 10. The indirect costs included the productivity loss of patients (or one of their parents) for the visit days; which was calculated based on the minimum annual wage at 2020.[30]

According to Iran central bank statistics, currency exchange rate was considered 42,000 Iranian Rial/1 USD.

Model inputs are presented at Table 1.

2.7. Sensitivity analysis

One-way sensitivity analysis performed to investigate the effect of main variables changes. The variables selected include the medications acquisition cost, discount rate for cost and utility, percentage of patients with TJ bleedings who have an SV/RSV procedure, physician visits, re-bleeding incidence, patients' weight, utility, effectiveness and therapeutic dose of each treatment strategy, and public/private share for cost calculation.

2.8. Budget impact

To calculate the budgetary impact of EP in management of hemophilia, it is necessary to estimate the number of patients consume this medication. This number can be estimated according to the ABR threshold. However, since the reliable

statistics on the condition of patients in the country were not available, to maintain the accuracy of the results, the budgetary impact of using emicizumab in a patient with different ABRs and different weight was calculated. By multiplying the number of eligible people to the estimated impact on a patient, the policymaker can achieve the overall budget impact.

2.9. Ethical approval

The study was done according to the IFDA pharmacoeconomic committee request and the ethical approval was gotten from this committee.

3. Results

3.1. Incremental cost effectiveness ratio for different categories

The Markov model was run using the inputs mentioned in Table 1. The results of CUA were reported for the societal and payer perspective in Table 2. EP was dominant choice in comparison with OD administration of rFVIIa in all age groups with ABR 20 and 25, and it remained dominant in patients with age 2 and age 12 at start point with ABR 16 and 17. Also, the EP arm was cost-effective option for the group with ABR 18 at start age of 20-year-old based on the reported incremental cost effectiveness ratio; 12,936 USD, which was lower than the 3 gross domestic product (GDP) per capita ($3 \times 5520 = 16{,}560$ USD) as acceptable threshold of cost-effectiveness in Iran.

3.2. Sensitivity analysis

Sensitivity analysis was performed for all age groups. At the start age 2- and 12-year-old, with changing of the mentioned variables, EP was dominant; with the exception of a 20% decrease in the price of AryoSeven, which indicates dominancy of OD.

The results of the sensitivity analysis in all ages by applying the changes were provided in Tables 2–5.

Based on the results of sensitivity analysis, change in dominancy were mostly reported as the result of assuming a decrease in the price of AryoSeven, an increase in the price of Hemlibra, a decrease in the effectiveness of Hemlibra, no application of RSV, and reduction in the discount rate.

Changes in variables, including weight, 100% calculation of the public-sector tariff, the assumption of no re-bleeding, a wide range of rFVIIa dosing (0.09 mg/kg–0.27 mg/kg), or reduction in the utility of the emicizumab arm up to 15%, could not significantly affect the results of the analysis.

3.3. Budget impact

The difference between the average cost for a patient in the case of EP or OD treatment of AryoSeven provides a budgetary impact for a patient per year. The results of the budget impact for each patient in ABR 16, 20, and 25 showed the cost saving of 8253, 80,934, and 130,036 USD, respectively. This amount in each ABR is equal to 2%, 16%, and 23% annual cost saving of treatment with emicizumab for each patient, respectively.

4. Discussion

Based on the results, EP in HA patients with high titer inhibitor with ABR more than 18, is the dominant option for all ages from both societal and payer perspectives.

The difference in treatment costs between the 2 arms is substantial, for example, for a patient with ABR 25, using EP can save more than 1,426,022 to 1,808,599 USD for different age groups in the life-long run with a 5% discount, which is a significant amount.

On the other hand, in patients with ABR less than 16 in all ages, AryoSeven OD treatment is preferred to PE; so, we can identify the hemophilia patients who are advised to use PE as their treatment, based on age and ABR in Iran.

Although primary prophylaxis is recommended by international guidelines such as the World Health Organization and the World Federation of Hemophilia,[31] still many patients in different countries receive OD treatment. There is also a review in 2009 which acknowledged the prophylactic use of both FVIII and rFVIIa in HA patients with inhibitors.[31] The reason that the primary prophylaxis is believed to be important is the fact that it protects against the development of hemophilic arthropathy; That's why there is an agreement on starting prophylaxis at an early age before arthropathy develops.[31] However, there are some reasons that prophylaxis is not yet being used widely; one of the most important reasons is the cost of treatment.[32]

Colombo et al[33] evaluated the cost-effectiveness of primary prophylaxis with FVIII concentrates versus secondary prophylaxis and OD treatment in Italy healthcare system on Jul 2011. They demonstrated that prophylaxis is a cost-effective option compared with OD treatment, even though it is a costly treatment. Also, Farrugia et al[34] study included a model which was applied to a single provider national health system exemplified by the United Kingdom's National Health Service and a third-party provider in the United States on July 2013 showed the undoubted benefits for prophylaxis with FVIII versus OD treatment. Zhou et al in 2020 and Patel et al in 2018 showed Hemlibra resulted in lower costs for all patients with hemophilia of any ages with or without inhibitors as well.

Emicizumab received its first approval in 2017. To date, there are a few studies been published reflecting an economic evaluation of this medication. A report was released by Institute for Clinical and Economic Review on January 2018 and found that according to U.S. acceptable thresholds (50,000–250,000 USD/QALY) the prophylactic administration of emicizumab was 100% cost-effective in both age groups over and under 12-year-old compared to the prophylactic use of BPAs. In addition, EP compared to OD treatment with BPAs was 96% and 92% likely to be cost-effective in age groups over and under 12-year-old, respectively. These results are in the same line with the results of the present study. Both studies indicate acceptable cost-effectiveness and significant savings from the use of emicizumab in HA patients.

The results of a study that assessed the short and long-term clinical and economic outcomes of EP treatment for HA patient compared to FVIII prophylaxis, shown a significant cost saving (over 7,500,000 USD) with EP treatment over life-long time horizon.[35]

Another economic evaluation of EP therapy for HA patients in comparison with OD or prophylaxis of BPAs from the Italian National Health Service perspective on December 2019 has reported consistent results. Compared with BPAs prophylaxis, EP was reported as dominant option in a cohort of 4-year-old patients with inhibitory HA who failed immune tolerance induction.[36]

Despite of the lower costs of the healthcare services in Iran compared to other countries, which would make more benefits

Table 2

The results of the model for different age groups with the societal/payer perspective in 100 cohort patients (costs in USD).

	ABR25/age 2		ABR25/age 12		ABR25/age 20		ABR20/age 2		ABR20/age 12		ABR20/age 20		ABR 18/age 2		ABR 18/age 12		ABR18/age 20	
	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY	Cost	QALY
Emicizumab (Hemlibra) prophylaxy									Societal perspective									
	6.6E+8	2290.5	8.7E+8	1893.4	8.8E+8	1589.3	6.5E+8	2290.4	8.6E+8	1893.4	8.7E+8	1589.3	6.5E+8	2290.4	8.6E+8	1893.4	8.7E+8	1589.3
									Payer perspective									
	6.56E+08	2290.44	8.69E+08	1893.42	8.79E+08	1589.29	6.55E+08	2290.44	8.65E+08	1893.42	8.73E+08	1589.29	6.5E+08	2290.44	8.6E+08	1893.4	8.7E+08	1589.29
OD rFVIIa (AryoSeven)									Societal perspective									
	7.9E+8	1428.2	1.1E+9	1268.4	1.0E+9	1104.1	7.3E+8	1428.2	9.6E+8	1268.4	9.3E+8	1104.1	6.7E+8	1428.2	9.1E+8	1268.4	8.6E+8	1104.1
									Payer perspective									
	7.93E+08	1428.19	1.0E+09	1268.43	1.0E+09	1104.12	7.3E+08	1428.19	9.6E+08	1268.43	9.3E+08	1104.13	6.94E+08	1428.19	9.1E+08	1268.4	8.63E+08	1104.13
ΔCost & ΔQALY									Societal perspective									
	−1.4E+8	862.2	−1.8E+8	625.0	−1.4E+8	485.2	−7.7E+7	862.2	−9.8E+7	625.0	−5.6E+7	485.2	−4.0E+7	862.2	−4.7E+7	625.0	6.2E+6	485.2
									Payer perspective									
	−1.38E+08	862.25	−1.8E+08	624.98	−1.4E+08	485.16	−7.3E+07	862.25	−9. 6E+07	624.98	−5.46E+07	485.16	−3.87E+07	862.25	−4.5E+07	624.98	7.9E+07	485.16
ICER									Societal perspective									
	Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		12936	
									Payer perspective									
	Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		Dominant		16413	
Each patient saving in life									Societal perspective									
	1,409,115		1,808,599		1,426,022		768,511		977,332		558,644		408,781		467,867		–	
									Payer perspective									
	1,376,115		1,780,662		1,493,312		741,801		954,451		539,654		384,825		447,416		–	

ABR = annualized bleeding rate, ICER = incremental cost effectiveness ratio, OD = on-demand, QALY = quality adjusted life years, USD = United States Dollar.

Table 3

The results of the sensitivity analysis from 2 years old for ABR 25 in 100 patients.

Parameters	ΔCost (USD)	ΔUtility	ICER	ΔCost changes	ΔUtility changes
20% Hemlibra price up	−1.0E+7	862.25	Dominant	1.3E+8	0
20% Hemlibra price down	−2.7E+8	862.25	Dominant	−1.3E+8	0
20% AryoSeven price up	−3.0E+8	862.25	Dominant	−1.6E+8	0
20% AryoSeven price down	1.7E+7	862.25	19631	1.6E+8	0
Utility discount 0%	−1.4E+8	2113.17	Dominant	0	1250.92
Utility discount 6%	−1.4E+8	477.67	Dominant	0	−384.58
Cost discount 0%	−7.4E+7	862.25	Dominant	6.7E+7	0
Cost discount 7%	−1.1E+8	862.25	Dominant	2.2E+7	0
50% TJ with RSV	−2.1E+8	862.25	Dominant	−7.2E+7	0
None of TJ with RSV	−3.7E+7	862.25	Dominant	1.0E+8	0
No transportation in JB	−1.4E+8	862.25	Dominant	155,687	0
No re-bleeding	−1.3E+8	862.25	Dominant	8.7E+6	0
30% weight increase	−1.5E+8	862.25	Dominant	−9.3E+6	0
EP surgery preparation cost 50%	−1.4E+8	862.25	Dominant	−1.4E+6	0
Prophylaxis utility −10%	−1.4E+8	633.20	Dominant	0	−229.04
Prophylaxis utility −15%	−1.4E+8	518.68	Dominant	0	−343.57
EP 15% lower efficacy	1.2E+8	862.25	Dominant	1.7E+7	0
100% public share for costs	−1.4E+8	862.25	Dominant	3.4E+5	0
8.16 mg/kg dosing AryoSeven in surgery	−1.4E+8	862.25	Dominant	1.1E+6	0
SB management dose 90 μg/kg	−1.3E+8	862.25	Dominant	8.3E+6	0
SB management dose 270 μg/kg	−1.5E+8	862.25	Dominant	−8.3E+7	0

EP = emicizumab prophylaxis, ICER = incremental cost effectiveness ratio, JB = joint bleeding, RSV = radio synovectomy, SB = spontaneous bleeding, TJ = target joint, USD = United States Dollar.

for OD treatment arm, the results of this study was shown the dominance of PE strategy in both societal and payer perspectives. As an example, the cheapest type of arthroplasty was 30,000 USD for inpatient in 2019,[37] while the calculated arthroplasty cost was 3438 USD in Iran. Also, there are some other assumptions in this study that could benefit the OD arm, for example, the omission of other costs due to low probability, like the expenses of wheelchair, hand sticks, and other probable costs.

As we used local manufactured rFVIIa which has lower price than Novoseven and FEIBA, the result could be supportive for comparing emicizumab with Novoseven and FEIBA too.

Limitations of the study included the lack of comprehensive information about the controlled trials of efficacy and side effects of studied medications in Iran. Also, the utility of various states were not measured in Iranian HA patients.

Table 4

The results of the sensitivity analysis from 12 years old for ABR 25 in 100 patients.

Parameters	ΔCost (USD)	ΔUtility	ICER	ΔCost changes	ΔUtility changes
20% Hemlibra price up	−1.46E+7	570.85	Dominant	1.7E+8	0
20% Hemlibra price down	−3.4E+8	570.85	Dominant	−1.7E+8	0
20% AryoSeven price up	−3.8E+8	570.85	Dominant	−2.0E+8	0
20% AryoSeven price down	2.0E+7	570.85	35,869	2.0E+8	0
Utility discount 0%	−180,859,925	1153.64	Dominant	0	582.79
Utility discount 6%	−180,859,925	346.61	Dominant	0	−224.24
Cost discount 0%	−1.8E+8	570.85	Dominant	4.6E+6	0
Cost discount 7%	−1.6E+8	570.85	Dominant	2.2E+7	0
50% TJ with RSV	−2.5E+8	570.85	Dominant	−7.2E+7	0
None of TJ with RSV	−5.6E+7	570.85	Dominant	1.2E+8	0
No transportation in JB	−1.7E+8	570.85	Dominant	131,909	0
No re-bleeding	−1.7E+8	570.85	Dominant	1.1E+7	0
30% weight increase	−2.0E+8	570.85	Dominant	−2.3E+7	0
EP surgery preparation cost 50%	−1.8E+8	570.85	Dominant	−1.8E+6	0
With payer perspective	−173,273,169	570.85	Dominant	2,793,741	0
Prophylaxis utility −10%	−176,066,910	386.92	Dominant	0	−183.93
Prophylaxis utility −15%	−176,066,910	294.95	Dominant	0	−275.89
EP 15% lower efficacy	9.7E+7	570.85	Dominant	8.4E+7	0
100% public share for costs	−1.8E+8	570.85	Dominant	3.0E+5	0
8.16 mg/kg dosing AryoSeven in surgery	−1.8E+8	570.85	Dominant	1.9E+6	0
SB management dose 90 μg/kg	−1.7E+8	570.85	Dominant	1.0E+7	0
SB management dose 270 μg/kg	−1.9E+8	570.85	Dominant	−1.0E+7	0

EP = emicizumab prophylaxis, ICER = incremental cost effectiveness ratio, JB = joint bleeding, RSV = radio synovectomy, SB = spontaneous bleeding, TJ = target joint, USD = United States Dollar.

Table 5

The results of the sensitivity analysis from 20years old for ABR 25 in 100 patients.

Parameters	ΔCost (USD)	ΔUtility	ICER	ΔCost changes	ΔUtility changes
20% Hemlibra price up	2.02E+7	485.24	41726	1.6E+8	0
20% Hemlibra price down	−3.0E+8	485.24	Dominant	−1.6E+8	0
20% AryoSeven price up	−3.3E+8	485.24	Dominant	−1.9E+8	0
20% AryoSeven price down	4.7E+7	485.24	98,566	1.9E+8	0
Utility discount 0%	−135,168,075.1	861.33	Dominant	0	376.1
Utility discount 6%	−135,168,075.1	316.95	Dominant	0	−168.3
Cost discount 0%	−1.7E+8	485.24	Dominant	−3.3E+7	0
Cost discount 7%	−1.3E+8	485.24	Dominant	1.6E+7	0
50% TJ with RSV	−1.6E+8	485.24	Dominant	−1.8E+7	0
None of TJ with RSV	−3.6E+7	485.24	Dominant	1.0E+8	0
No transportation in JB	−1.3E+8	485.24	Dominant	123,410.6	0
No re-bleeding	−1.32E+8	485.24	Dominant	1.1E+7	0
30% weight increase	−1.8E+8	485.24	Dominant	−4.1E+7	0
EP surgery preparation cost 50%	−1.4E+8	485.24	Dominant	−11.4E+6	0
Prophylaxis utility −10%	−135,168,075.1	326.31	Dominant	0	−158.9
Prophylaxis utility −15%	−135,168,075.1	246.84	Dominant	0	−238.4
EP 15% lower efficacy	1.7E+7	485.24	36051	1.6E+8	0
100% public share for costs	−1.4E+8	485.24	Dominant	2.5E5	0
8.16 mg/kg dosing AryoSeven in surgery	−1.4E+8	485.24	Dominant	2.9E+6	0
SB management dose 90 μg/kg	−1.3E+8	485.24	Dominant	1.0E+7	0
SB management dose 270 μg/kg	−1.5E+8	485.24	Dominant	−1.0E+7	0

EP = emicizumab prophylaxis, ICER = incremental cost effectiveness ratio, JB = joint bleeding, RSV = radio synovectomy, SB = spontaneous bleeding, TJ = target joint, USD = United States Dollar.

5. Conclusion

To our knowledge, this is the first attempt to undertake a CUA on HA patients with inhibitors considering EP versus OD treatment with rFVIIa in the Iranian healthcare system. The results of our analysis showed that EP is a cost-effective treatment strategy compared with OD rFVIIa for HA patients with inhibitors and ABR more than 18, as demonstrated by the QALY values obtained.

Author contributions

All authors contributed in the design and preparation of the manuscript. PS reviewed the analyzed data and drafted the paper and finalized the manuscript. ARD drafted the paper. JK implemented the project and data analysis. PE reassess the results and apply his expert perspective on the method. MS designed the method, data analysis, and supervised the project. All authors read and approved the final manuscript.

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