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Cost-effectiveness analysis of infliximab versus CinnoRA in the treatment of moderate to severe ulcerative colitis in Iranian patients

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Abstract

Introduction: As two biological agents, infliximab (IFX) and biosimilar adalimumab (CinnoRA®) are routinely used in the clinical management of ulcerative colitis (UC) in Iran.
Objectives: This study was done to evaluate the cost-effectiveness of IFX versus CinnoRA for the treatment of moderate-to-severe UC patients.
Patients and Methods: To accomplish this, we developed a hybrid decision-tree/microsimulation (MS) approach for modeling UC's natural history. We populated our model with available data on probabilities, costs, utilities / disutilities, and emergent adverse effects. Costs were reported in Iranian Rial (IRR) and in April 2021 US dollars ($). One-way and multiple sensitivity analyses were used to determine the uncertainty of the model's parameters.
Results: For five, 10, and lifetime horizon times, patients on IFX received slightly more quality-adjusted life-year (QALY) per year in remission and experienced about 3 to 5 times less surgery than CinnoRA patients. With willingness-to-pay (WTP) thresholds of 1800 ($7826.08), 820($3565.21), and 520 ($2260.86) million IRR for these horizon times, IFX was cost-effective with 100% certainty. Our findings were highly sensitive to the number of adverse effects.
Conclusion: Our results demonstrated that IFX is more effective and more costly than CinnoRA, and if we ignore the predicted surgeries, CinnoRA is nearly as effective as IFX. However, these findings should be cautiously interpreted without a robust clinical trial of CinnoRA in UC patients. Since the impact of CinnoRA may have been over/underestimated.
Keywords: Cost-effectiveness, infliximab, CinnoRA, Ulcerative colitis, Microsimulation
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Introduction

Ulcerative colitis (UC) and Crohn's disease are two forms of inflammatory bowel disease (IBD) that affected nearly 40.67 people per 100 000 in Iran in 2012 (1). These incurable and long-lasting diseases can engage people of any age (2), lowering their quality of life and incurring high costs (3, 4). As a result, inducing remission and its sustaining over time is crucial in IBD treatment (5). The treatment of IBD has revolutionized the era of biological medicine; therefore, the importance of surgery and hospitalization has diminished in the costs of IBD (6).

Two biological agents of infliximab (IFX) and CinnoRA (a biosimilar version of adalimumab), are routinely administered in the clinical management of UC in Iran. However, their effectiveness has not been thoroughly investigated using optimized approaches such as microsimulation. Several studies have compared the efficacy of these two and other biological agents and most have shown that IFX and adalimumab (ADA) are almost equally effective in medical practice (7-9). Since the information of economic studies is related to the region or/and nation-specific, its generalization to a specific country is debatable (10). In addition, the ADA biosimilar form "CinnoRA" is widely administered in Iranian medical centers as a non-inferior substitute for ADA.

Furthermore, microsimulation models have improved the limitations of state-transition models based on the Markov assumption (memoryless models). Therefore, we can adopt these models to consider the individual clinical course, baseline differences, people heterogeneity and memory. These features pave the way for studying diseases such as IBD with a heterogeneous and unpredictable clinical course.

Objectives

Overall, we aimed to assess and compare the effectiveness of IFX and CinnoRA in moderate-to-severe UC patients in an Iranian environment. This is the first microsimulation research in Iran to test the cost-effectiveness of two commonly used biological drugs. We hope our findings will be useful in selecting funding sources, incorporating research results, and determining treatment options.

Methods

Model design

In this research, we established a hybrid decision-tree/microsimulation (MS) approach to modeling the natural history of UC (Figure 1), as illustrated by Wilson et al (7) study. We modified the MS model suggested by Krijkamp et al (11) for UC and then combined it with the decision tree. In this way, the induction phase was modeled by the decision tree (Figure1a) and the maintenance phase by the MS approach (Figure1b). We employed the Mayo clinic classification system to describe UC's natural history, in which remission (Mayo score 0-2), mild (Mayo score 3-5) and moderate to severe (Mayo score 6-12) health states

Key point

To evaluate the cost-effectiveness of infliximab versus biosimilar adalimumab (CinnoRA) for the treatment of moderate-to-severe ulcerative colitis, we found that infliximab is more effective and more costly than CinnoRA.

for UC were established. Accordingly, we first consider a hypothetical cohort of 10 000 patients with moderate to severe UC. Then, during the induction period, we enter our cohort into the tree separately for different drugs. According to Figure1a, the person entering the model is classified based on response to treatment and the presence or absence of adverse effects from drug administration. Depending on the level of response during the induction period, these individuals are assigned to remission, mild, and/or moderate to severe states. We consider the number of individuals in the terminal nodes of the decision tree to determine the distribution of individuals in the MS health states for the first cycle. Then, individuals either switch between different model states or remain in the same state, depending on transition probabilities provided in the model over each cycle. The discount rate was assumed to be 3% for the cost and quality-adjusted life-year (QALY). We set the research horizon at five years and the length of each cycle at two months (eight weeks). It is worth noting that CinnoRA is the Iranian equivalent of ADA, produced by the CinnaGen Company (12). To estimate the model parameters, we employed information from the literature about ADA for CinnoRA, assuming the two drugs were equivalent. However, as demonstrated below, a portion of the probability of transition between states was derived

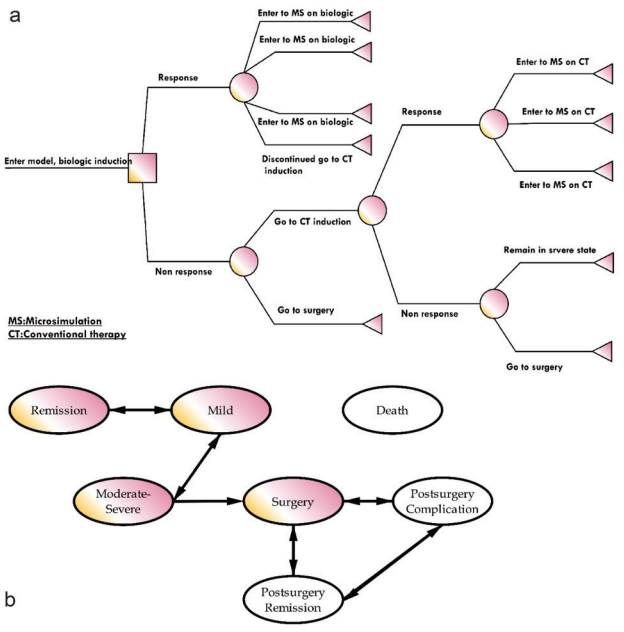

Figure 1. Schematic representation of the hybrid decision tree/microsimulation model in patients with UC, a: decision tree (induction phase), b: microsimulation (maintenance phase) (as illustrated by Wilson et al (7)).

from an analysis conducted in our clinic.

Biological agents

In this study, we simulated our cohorts for two biological agents as follow:

- IFX, intravenous infusion of 5 mg/kg of patient weight for weeks 0, 2 and 6 (induction period) and every eight weeks (maintenance period) thereafter;
- CinnoRA, subcutaneous injection of 160 mg at week 0, 80 mg at week two (induction phase) and 40 mg every two weeks thereafter (maintenance phase).

Transition probability

Our previous study retrieved the transition probability between various UC disease states (like remission, mild, moderate to severe and surgery). This was planned to describe the natural history of IBD using two separate multi-state and ordered logistic regression methods (Table 1). We also found that the possibility of transition between surgery and two post-surgery states reported previously by Wilson et al (7). However, to convert the annual probabilities to eight weeks, we did not use the simplistic approach applied in the study by Wilson et al. Instead, we conducted the eigendecomposition method provided by the correct methodological research (13) to minimize bias.

Risk and duration of adverse effects

We extracted the risk of serious infections, acute infusion reactions, skin site reactions and adverse sinusitis effects from previous literature for IFX and ADA, as documented in Table 2. We considered only acute reactions related to IFX infusion and not delayed reactions, as approximately 90% of cases are acute (14). Table 3 shows the course of treatment for each of the adverse effects. However, treatment duration for severe infections is not explicitly defined in the literature and it varies from person to person and also the risk of recurrence. For instance, this time is usually 7-14 days for urinary tract infection (15), 5 days for pneumonia (16), 1-3 weeks for bronchitis (a self-limited illness) (17), 7-10 days for sepsis (18) and 3-14 days for upper respiratory infections. These common five infections were considered in our study. Therefore, in general, we assumed one month of treatment for serious infections (Table 2).

Table 1. Two months (8 week) transition probabilities for IFX and CinnoRA

From/to	Remission	Mild	Moderate to severe	Surgery
IFX				
Remission	0.869	0.131	0	0
Mild	0.172	0.712	0.116	0
Moderate to severe	0	0.193	0.804	0.003
CinnoRA				
Remission	0.870	0.130	0	0
Mild	0.174	0.711	0.115	0
Moderate to severe	0	0.186	0.801	0.013

Utility and disutility

The utility of health states related to the natural history of the UC and the reduction of utility associated with the adverse effects of biological agents are summarized in Tables 2 and 4. Since most of the adverse effects of IFX infusion are anaphylactoid reactions, we have only considered anaphylactoid-based utility decrement (19).

Costs

In this study, we considered only the direct costs for UC patients, including drug costs, surgery, complication, emergent adverse effects, hospital admission and different diagnostic costs (Tables 2 and 4). Costs were reported in Iranian Rial (IRR) and in April 2021 US Dollars ($). The costs of drugs were obtained from the Android app TTAC (https://play.google.com/store/apps/details?id=ir.ttac.IRFDA&hl= en&gl= US), developed by the Food and Drug Administration (FDA). We also obtained the cost of other

Table 2. Adverse effects related risks, treatment duration, costs and disunities

	IFX	CinnoRA (ADA)	Ref.
Discontinuation [% per cycle]			
Induction	0.00	0.06	(20)
Maintenance	0.08	0.124	(20)
Adverse events [% per cycle]			
Serious infections	0.38	0.23	(5,27)
Acute infusion reactions	0.25	0.00	(5)
Skin site reactions	1.52	1.85	(5,27)
Sinusitis	1.01	0.00	(5)
Adverse events duration			
Serious infections	4 weeks	4 weeks	(15-18)
Acute infusion reactions	1 months	1 months	(28)
Skin site reactions	3-5 days	3-5 days	(29)
Sinusitis	10-14 days	10-14 days	(30)
Adverse events unit cost, thousand IRR ($)			
Serious infections	7511454 (32.65)	7511454 (32.65)	
Acute infusion reactions	280000 (1.21)	280000 (1.21)	
Skin site reactions	50000 (0.21)	50000 (0.21)	
Sinusitis	614600 (2.67)	614600 (2.67)	
Adverse events disutility			
Serious infections	−0.218	−0.218	(31)
Acute infusion reactions	-0.00082	-0.00082	(32)
Skin site reactions	−0.004	-0.004	(33)
Sinusitis	-0.0022	-0.0022	(34)

Table 3. Remission and response rates in two apprised biologic agents

	Induction phase		Maintenance phase	
	Response	Remission	Response	Remission
IFX	0.686	0.313	0.583	0.221
CinnoRA (ADA)	0.504	0.147	0.531	0.311

Table 4. Costs, used services % for each health state per cycle and health states utilities

Services	Unit cost, thousand IRR ($)	Remission	Mild	Moderate to severe	Surgery	Postsurgery remission	Postsurgery complications
Hospitalization	5817000 (25.29)	0.05	0.05	0.05	-	-	
Blood tests	1532350 (6.66)	0.5	0.6	1	-	0.23	
Endoscopy	6696900 (29.11)	0.03	0.08	0.13	-	0.18	
Non-elective endoscopy	15804684 (68.71)	-	0.04	0.12	-	0.08	
Specialist visits	624000 (2.71)	0.31	0.69	1	-	0.23	
Surgery	196052470 (852.40)	-	-	-	1	-	
Per-cycle cost, thousand IRR ($)	-	1451372 (6.31)	2808759.3 (12.21)	5214359 (22.67)	196052470 (852.40)	6760430 (29.39)	28007495.7 (121.77)
Utility		0.86	0.80	0.68	0.42	0.6	0.42

services from real data recorded at Taleghani hospital of Shahid Beheshti University of Medical Sciences. The price of each unit of IFX 100 mg was 9970 IRR thousand ($43.33), while the cost of each unit of CinnoRA 50 mg was 7730 IRR thousand ($33.60).

Clinical Outcomes

In IBD-related clinical trials, response and remission rates are considered treatment efficacy markers for induction and maintenance periods. In this regard, the response is defined by a decrease of three or more (≥30%) in the Mayo score from the baseline. Remission is also known as a Mayo score of two or less and neither of the sub-items has a score higher than one. To this end, we derived information on remission and response for IFX and ADA based on the latest network meta-analysis (NMA) (20) that examined the indirect relationship of biological drugs in UC treatment (Table 2). In this way, we employed the following formula:

$$p_{treatment} = \frac{OR * p_{control}}{1 + OR * p_{control} - p_{control}}$$

OR is the odds ratio in the case group relative to the comparison group in the NMA. $p_{control}$ is the probability of the occurrence of the desired event in the reference group that we calculated by the meta-analysis of the event ratio for all of the included studies (Table 3), using meta-package of R software (version 3.6.1) (21).

Sensitivity analysis

To evaluate the validity of our model, the influence of some predetermined parameters was explored by one-way deterministic sensitivity analysis and multiway probabilistic sensitivity analysis (PSA) in R software dampack package (version 3.6.1).

In one-way sensitivity analysis, we first entered all of the variables into the model, considering the decrease and increase of 20% of their initial values. Then, variables with the largest effect on the incremental cost-effectiveness (ICER) were reported.

We applied Monte Carlo simulation with 500 replications to perform multiway sensitivity analysis.

Similarly, we utilized the beta distribution for utilities/disutilities and probabilities and the gamma distribution for the costs and effects frequency of the emergent adverse.

The cost-effectiveness acceptability curve (CEAC) and the ICER scatter plot were used to present the result of multiway sensitivity analysis. There is more detail about how to use and interpret these two plots elsewhere (22). The willingness-to-pay (WTP) threshold was expected to be twice as Iran's per capita for 2020.

Scenario planning

In this section we assume that CinnoRA is not an equivalent substitute to its original "Humira", and, as a non-inferior version. Hence, we repeated our analysis by doubling the number of adverse effects for CinnoRA over a five-year horizon. Furthermore, to compare the findings with other related studies and evaluate the long-term cost-effectiveness of two drugs, we extended the research horizon to ten and lifetime years (50 years), respectively.

Results

Base case

IFX and CinnoRA had mean costs of 880 million IRR and 700 million IRR, respectively. Patients on IFX gained more QALYs than those who received CinnoRA, which is almost negligible (Table 5). These patients were also in remission for a longer time (less than a month) than CinnoRA. Likewise, patients on CinnoRA experienced approximately 4.5 times more surgery compared to IFX (Table 5).

One-way sensitivity analysis

We used a tornado plot to report the findings of a one-way sensitivity analysis. As depicted in Figure 2, serious infections that emerged in patients on IFX had the highest impact on the ICER. Subsequently, CinnoRA related serious infections had the highest impact on the ICER. Other emergent adverse effects have a smaller impact on ICER, hence the IFX-induced infusion reaction had the lowest impact. In general, these findings suggest that

Table 5. Base case models results, before and after scenario analysis, in five, 10 and lifetime (50 years) horizon times

Drug	Cost million IRR ($)	QALYs	Incremental Costs million IRR ($)	QALYs Gained	ICER, million IRR ($)	Year in remission	No. of surgeries per 1000 people
Before, five-year horizon time							
IFX	886980710 (3856.43)	4.258	184081840 (800.35)	0.118	1555825700 (6764.45)	1.35	0.96
CinnoRA	702898870 (3056.08)	4.14				1.33	4.30
Before, 10-year horizon time							
IFX	1229071100 (5343.78)	6.173	259450740 (1128.04)	0.299	867537340 (3771.90)	2.67	1.45
CinnoRA	96962036 (4215.74)	5.874				2.56	6.09
Before, lifetime horizon time							
IFX	1465650410 (6372.39)	14.116	314792330 (1368.66)	0.549	573515600 (2493.54)	1.23	4.9
CinnoRA	1150858080 (5003.73)	13.567				0.95	17.3
After five-year horizon time							
IFX	886980710 (3856.43)	4.258	183671660 (798.57)	0.128	1437441470 (6249.74)	1.35	0.96
CinnoRA	703309060 (3057.86)	4.131				1.33	4.30
After 10-year horizon time							
IFX	1229071100 (5343.78)	6.173	258883330 (1125.57)	0.312	829219990 (3605.30)	2.67	1.45
CinnoRA	970187770 (4218.20)	5.86				2.56	6.09
After, lifetime horizon time							
IFX	1465650410 (6372.39)	14.116	314128340 (1365.77)	0.564	556678850 (2420.34)	1.23	4.9
CinnoRA	1151522070 (5006.61)	13.551				0.95	17.3

adverse events have a substantial effect on economic analysis.

Multi-way sensitivity analysis

The ICER scatter plot (Figure 3) and CEAC plot (Figure 4) were both used to report the results of the multiway PSA. In Figure 3, 50% and 100% of the outcomes are located in the right of 1650 ($7173.91) million IRR and 1800 ($7826.08) million IRR vertical lines in quadrant I, respectively. As a result, IFX dominance CinnoRA and is more cost-effective if patients spend an additional 1650 ($7173.91) million IRR and more (Figure 3). As seen in Figure 4, for a WTP value of 1650 ($7173.91) million IRR per QALY, there is a 50% probability that IFX would be cost-effective and, with a 100% probability, IFX is cost-effective for any WTP greater than 1800 ($7826.08) million IRR. In other

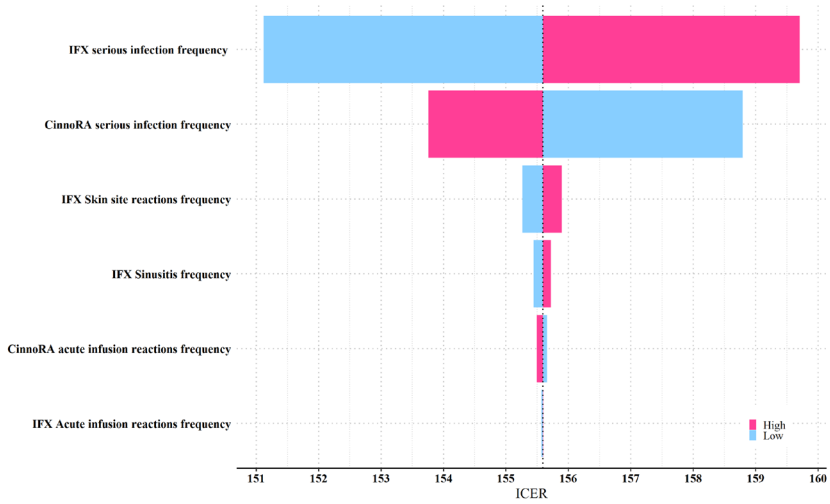

Figure 2. One-way sensitivity analysis results for IFX vs. CinnoRA.

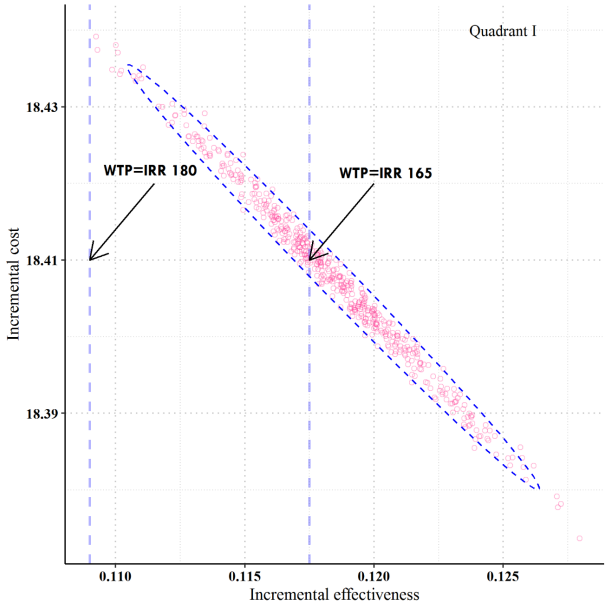

Figure 3. The incremental cost-effectiveness scatterplot. Horizontal lines represent WTP thresholds at 165 and 180 IRR million.

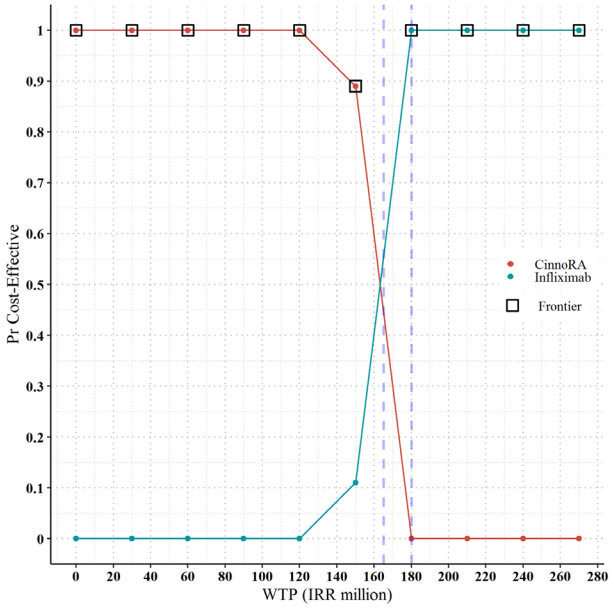

Figure 4. The cost-effectiveness acceptability plot for comparison of IFX vs. CinnoRA. Two dotted lines reflect the 50% and 100% assurance for IFX cost-effectiveness, respectively.

words, IFX is cost-effective across all thresholds of over 180 million tomans.

Scenario analysis

In this study, years gained for QALYs on ten-year and lifetime horizons increased to nearly six and thirteen years, respectively. The ICER decreased as the study horizon extended, and it ultimately reached about 550 ($2391.30) million IRR (Table 5). In this respect, the number of surgeries increased, but it was still 3 to 5 times higher in patients on CinnoRA (Table 5). In the five, ten and lifetime years horizon, we observed a relatively higher gained QALYs for patients on IFX after doubling the number of adverse effects for CinnoRA (Table 5). These findings suggest that, over time, the QALYs obtained from the two drugs are almost similar and equivalent. Although the average cost of IFX is higher, the number of surgeries needed for CinnoRA users is also high.

Discussion

We correctly assessed the cost-effectiveness of IFX and CinnoRA in the Iranian clinical setting, by a micro-simulation approach. Our results suggest that over a five-year time horizon, IFX is more effective but more costly than CinnoRA, by a slight improvement over QALYs years and remission time. However, the occurrence of surgery was almost five times lower. In a five-year horizon time, if people were willing to pay around 1800 ($7826.08) million IRR for one year of QALYs, with 100% certainly IFX is more cost-effective than CinnoRA or dominates it. The WTP thresholds for ten-year and lifetime horizons were about 820 ($3565.21) million IRR and 570 ($2478.26) million IRR with 100% certainty that IFX is most cost-effective, respectively. As a result, IFX is more likely to be cost-effective than CinnoRA over time. Except for surgery, these results may suggest that the effectiveness of two treatments are comparable, while there is no discernible difference over a five-year time horizon. Thereby, IFX eventually dominance CinnoRA in a longer horizon time.

Previous studies have shown that IFX and ADA have comparable efficacy. In a recent modeling study(23), patients taking IFX received higher QALYs than patients taking ADA, by around 0.43, over a ten-year horizon. The costs in this group were about 1.26 times higher. These findings approve our results, with 0.312 incremental QALYs and 1.26 times higher cost in a ten-year horizon time (Table 5). In another similar study by former researchers in 2017 (24), IFX showed a similar pattern to ADA, but with a larger effect size, 0.9 increments for QALYs, and 1.65-time higher cost. Aside from the time gap between the two studies, the difference in drug costs and the number of drugs evaluated. In these studies, the discrepancy between the estimates derived from the models can be due to differences in the kinds of adverse effects included in the models. As a result, it seems that the 2020 report of these authors is more reliable when serious infections are considered. Since our study's findings were particularly sensitive to the number of serious infections (Figure 2). Moreover, it should be noted that the microsimulation model enabled us to consider the number and length of treatment for clinical complications in this study.

The cost-effectiveness of the biological agents was recently assessed in Japan (25) authors used a lifetime horizon. In such a way, we are technically not permitted to compare our findings during this long time. Hence, we set

our model's time horizon to a lifetime of years. As a result, patients on IFX gained 0.549 more QALYs (IFX=13.55, ADA=13.28) and the ICER was 57351560 IRR million, which was nearly three times less than the five-year time horizon and 1.6 times less than the ten-year time horizon (Table 5). A recent study at a UK university (7) evaluated the efficacy of vedolizumab compared to other anti-TNFα drugs (IFX, ADA and golimumab) in moderate to severe UC patients during their lifetime. Patients on ADA gain slightly more QALYs, remission time and even required surgery than IFX, confirming our results (Table 5). These findings, however, indicate that the effectiveness of these two drugs is comparable. Nevertheless, since QALYs and year in remission were more significant for IFX, and the number of surgeries was higher for CinnoRA, these findings could mean that CinnoRA is the unequal substitute to Humira (ADA) and we are dealing with an overestimating the CinnoRA effect size. Non-modeling research validated our findings and noted the two drugs' comparability during the maintenance phase (26).

On the other hand, the rising pattern of cases requiring surgery from the time horizon of five to ten years, followed by an increase in the number of cases over the lifetime horizon, demonstrates the following issue. Therefore more patients will require surgery over time, at periods of more than two decades per 1000 people (Table 5), which is usual. Unfortunately, most studies with five- to ten-year horizons have not reported data on the number of surgeries and years spent in remission. Lifetime horizon studies have also not reported information from past years. Consequently, no explicit comparison can be made in this context (7, 23-25). However, in our analysis, the number of IFX related surgeries for the lifetime horizon exceeded the number of surgeries predicted in Japan and the UK (7, 25). Hernandez et al, report a similar pattern in terms of years in remission (25). Thus, the years of further improvement were related to IFX. However, the result of the UK study was inconsistent with both studies since long years of remission were associated with ADA (7). On the other hand, this difference could mean the importance of utilizing more local data in economic models since the transition probabilities used in this research differed slightly from information applied in other analysis, such as the UK study, especially for the transition probability to surgery in IFX patients.

In a five-year horizon time, the clinical adverse effects of the medications had the most influence on the economic model (Figure 2). Severe infections associated with the use of IFX and CinnoRA were the most effective. However, there was an interesting point in the war on drugs cost. Thus, the fewer adverse effects from CinnoRA, the higher the ICER, while the higher the adverse effects, the lower the ICER. The opposite was true for IFX. This pattern was also present at higher time horizons. However, the adverse effects of CinnoRA had the highest impact on the scenario analysis, followed by the complications induced by IFX, but the previously described pattern persisted. These findings may indicate the need for a CinnoRA clinical trial in UC patients as selecting the appropriate model parameters can be very effective. Our comparative modeling researches have not provided a greater impact of clinical adverse effects on ICER, which is perfectly normal and should not come as a surprise, as none of them have compared the efficacy of IFX and ADA or/and CinnoRA by Tornado plot.

The following are limitations of the current work. First, we were unable to utilize local evidence on response and remission rates and the number of adverse effects in our model, given the lack of relevant clinical trials. Furthermore, we know, no clinical trials have been conducted to assess the efficacy and safety of CinnoRA to its original form (Humira) in patients with UC. So far, it is only available phase three clinical trial for people with rheumatoid arthritis that showed the not-inferiority of the CinnoRA to Humira. The current situation may have led to an under/ overestimation of our economic model, especially concerning CinnoRA. However, we have tried to minimize it as much as possible by scenario analysis based on the number of emergent adverse effects related to CinnoRA. First, the number of adverse effects has the most influence on ICER (Figure 2). While micro-simulation models can adhere to treatment, the impact of stress and other influential variables on economic models is possible (second adverse effects). Several local research pieces have been published in this respect, but none of them gave the details required to construct the model. Lastly, we only consider the direct costs of treating the disease in our model, not indirect and direct non-medical costs such as food and transportation.

Conclusion

Overall, these findings suggest that if we ignored the most CinnoRA related surgeries, CinnoRA be as effective as IFX, but with a minor variation. In other words, if CinnoRA is equivalent to ADA, this conclusion appears to be correct; otherwise, it cannot be explicitly expressed. However, in the absence of a robust clinical trial of CinnoRA in UC patients, these findings should be interpreted cautiously to upgrade model parameters. Since the impact of CinnoRA may have been over/underestimated. Furthermore, our results prove that the cost-effectiveness of drugs should be tested employing local evidence to obtain the desired outcome. However, as a general remark, insurance providers and healthcare decision-makers seem to choose between CinnoRA, which is less expensive but has more surgery, and IFX, which is more expensive but more efficient.

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Authors' contributions

Conceptualization: MO, MRZ, MAP, SHN, ShSh, MI, PI, SKH, HAA, SS, SKh, MR, BH, HM and GHSH. Data curation: MO and HB. Formal analysis: MO, MAP, MI, PI, SHN, SS, AHD and SRP. Methodology: MO, PR, GhM, MR, BH, HM and GHSH. Project administration: MO, MRZ, HAA, SS, HB, GhM, AHD and SRP. Writing—original draft: MO and HB. Writing—review and editing MRZ, MAP, HB, MI, PI, SHN, ShSh, SS, SKh, HAA, PR, GhM, MR, BH, HM and GHSH.

Conflicts of interest

The authors have no conflicts of interest to declare for this study. In addition, none of the authors of this study are members of pharmaceutical companies, and none of them received funding from pharmaceutical companies.

Ethical issues

This project has been ethically approved by the Ethics Committee in Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran (NO. IR.SBMU.RCGLD.REC.1399.057). Because this is a simulation study based on available data, no intervention was performed on actual patients.

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