Original Article

Economic Evaluation of Infliximab for Treatment of Refractory Ulcerative Colitis in Iran: Cost-Effectiveness Analysis

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Abstract

The aim of this study is to assess cost-effectiveness of infliximab, compared with conventional treatments in patients with moderate to severe Ulcerative Colitis (UC) in Iran. We developed an analytical decision model with a 5-year-time horizon to follow up 1000 hypothetical patients, in order to estimate treatment costs and outcomes. Hypothetical patients were individuals with moderate to severe UC that are resistant to conventional treatments. Remission rate, clinical response, and surgery were selected as clinical outcomes. For estimating QALY, utility value related to each state, was derived form published paper. We also estimated associated probabilities by using patients 'medical records and specialists' opinion. Costs of treatment such as Physician visit fee, laboratory tests, hospitalizations, surgery, and drugs were estimated based on the public sector tariffs and drug price list set by pricing committee of food and drug administration. Infliximab costs at dosage of 5 mg /kg were considered for UC patients with average weight of 75 kilogram. Incremental Cost-Effectiveness Ratio (ICER) of infliximab treatment in UC patients were 240,903 USD dollars per QALY gained, compared with conventional treatments. According to recommendation of World Health Organization for choosing cost-effective intervention, interventions with relative cost-effectiveness value less than 3 times of Gross Domestic Production (GDP) per capita, are cost–effective. Our result showed that the ICER value of infliximab is approximately 51 times of Iran's local GDP per capita, in 2014 – i.e. more than 3 time GDP per capita. Thus, for UC patients, our finding indicates that infliximab is not a cost-effective treatment.

Keywords: Conventional treatments, Cost-effectiveness analysis, Economic evaluation, Incremental cost-effectiveness ratio, Infliximab, Ulcerative colitis.

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1. Introduction

One of the two major types of Inflammatory
Bowel Disease (IBD), known as Ulcerative
Colitis (UC), is a chronic gastrointestinal
disorder that occurs in colon and rectum, and
characterized by mucosa inflammation and
periods of exacerbations and remissions [1]. The
pathogenesis of this disease is unknown, but it
assumed that combination of genetic and
environmental factors are efficacious [2]. The
symptoms of disease are different, depending on
the extent and severity of the inflammation
including diarrhea with blood, abdominal
cramps, bloody stool, fever, fatigue, weight loss,
and decrease in appetite [3]. According to the
extent and severity of disease, patients are
classified from mild, moderate to severe state.
At diagnosis stage, most of the patients have
mild to moderate symptoms, and less than 10%
have severe disease [4].
Patients with UC experience a lower quality of
life than general public [5].Among different
affecting variables on patients' health related
quality of life, the disease severity is the
strongest predictor, and accordingly lower
quality of life is related to severer symptoms [6].

More health care costs and impairment in daily
activity and work are associated to greater
disease activity [7].

The researches have shown that the incidence
of UC is continuous to grow in the world,
involving developed and developing countries
[8]. However, the UC is more prevalent in
Europe and North America and less common in
Asian countries [9]. The results, in line with
recent systematic review, indicate that in Iran,
the incidence and prevalence of UC is
increasing. The incidence and prevalence of UC
in Iran was estimated 3.04 and 3.25 per 100000
persons and, 15 per 1000000 persons,
respectively. It was also indicated that the milder
forms of the UC are common in Iran and also, it
is more common in women and people in their
fourth decade of life [10].

The economic burden of UC in Iran has not
been investigated. The results of a systematic
review on economic burden of UC in western
countries showed that UC is a costly disease,
and hospitalization costs plays a significant role
in direct medical costs [11]. Approximately, half
of the direct costs are associated with
hospitalization which is in turn related to more
severe therapy- resistant UC patients, i.e. with
worsening disease severity its costs were
increased [7]. Therefore, to decrease the cost of
disease, those treatments which are capable of
reducing disease severity rates of UC-related
hospitalization and surgeries are preferable.

Although, for UC patients, combinations of
intervention such as nutritional, medical, and

surgical treatments are used, the medical treatment is the basis [4]. Conventional medical treatments are 5-aminosalicylic acid (5-ASA) derivatives, immunosuppressant drugs (azathioprine, cyclosporine, mercaptopurine, and methotrexate), and corticosteroids and monoclonal antibodies to Anti-Tumor Necrosis Factor Alpha (Anti-TNF-α) as a biological treatment(12).The biological therapy has changed therapeutic approaches to the inflammatory bowel diseases particularly in the case of refractory UC. Although their costs are higher, they work more quickly than traditional medicines in reducing symptoms [13-15].

Infliximab was the first biologic treatment approved for treatment of adults with moderate to severe, which is unresponsive to conventional therapies [16]. Published researches indicated that that Infliximab is an effective treatment in these patients via achieving high clinical response rate, faster remission rate, and improving health related quality of life [16-18]. It was found that infliximab reduced the need for surgery and hospitalization in severe acute and refractory UC patients [19]. However, in spite of demonstrated effectiveness of Infliximab in patients with UC, it is an expensive treatment option and sometimes not cost-effective. Also, some of recent economic evaluations showed that Infliximab maintenance treatment in moderate to severe UC patients is cost-effective [20, 21].

To date, to best our knowledge, no study has ever examined the cost-effectiveness of infliximab in Refractory UC patients in Iran. The present economic evaluation was performed to evaluate the costs, effects, and cost-effectiveness of infliximab treatment compared with conventional treatments, in patients with moderate to severe UC.

2. Materials and Methods

2.1. Study Design

To assess cost-effectiveness of infliximab in UC patients, we developed a decision model with a 5-year-time horizon, to follow up 1000 hypothetical patients for estimating treatment costs and outcomes of infliximab compared with conventional treatments. Costs of treatment were estimated based on the local tariff and prices. Clinical outcomes were obtained from available literature.

2.2. Conventional Treatment

Conventional treatment in UC patients is a medical treatment which is prescribed according to the severity and extent of disease. It includes aminosalicylates, corticosteroids, azathioprine/6-mercaptopurine, cyclosporine, and anti-tumor necrosis factor therapy, Antibiotics, and Methotrexate [12]. Surgery is the last treatment option which is considered when drug therapy fails or when an urgent surgery occurs such as colon perforation. Surgical procedures are total colectomy (panproctocolectomy) and ileostomy, total colectomy, and ileoanal pouch reconstruction or ileorectal anastomosis [22].

2.3. *Infliximab*

Infliximab is a monoclonal antibody, that by blocking TNF, reduces the inflammation associated with UC. It is available in vial of 100 milligram (mg) and used for remission induction or maintenance in UC patients. The most effective dose which is recommended, is 5 mg/kg with prescription at weeks 0, 2 and 6 by intravenous injection for induction therapy, and repeated it every eight weeks to keep the remission period as maintenance therapy [23].

Infliximab was the first medicine that approved by US Food and Drug Administration (FDA) for the UC patients in remission, considered as the induction and long-term maintenance in 2006 [24]. Also, according to the updated guidance of National Institute for health and Care Excellence (NICE), Infliximab has been recommended to treat adults with moderate to severe active UC that don't have adequate clinical response to conventional treatments, including Corticosteroids and mercaptopurine or azathioprine, or the patients who are intolerant, or to whom have medical contraindications for such therapies [25, 26].

2.4. *Clinical Outcome*

UC is a chronic disease with recurrent inflammation [27].The clinical course of UC is characterized by exacerbation and remission [28]. Almost 30% of patients need surgery [8], but evidences showed that there is no difference in mortality rate between UC patients and general population [29-31]. Therefore, we selected remission rate, clinical response, and surgery as clinical outcomes. We also estimated probabilities and transitional probabilities associated with each clinical outcome, using patients 'medical records and specialists' opinion. Then, for estimating QALY- as an effectiveness measure, utility value related to each state is derived from published paper by Arseneau et al [32].

2.5. *Cost of Outcome*

Direct medical costs of treatment were extracted based on the treatment process for all three clinical outcomes at 5-year follow-up. It includes physician visit fee, laboratory tests, hospitalizations, surgery, and drugs. Public sector tariffs and drug price list set by pricing committee of Food and Drug Administration in 2014, were used to estimate associated costs. Indirect costs are costs related to loss productivity caused by disease such as absent from work and premature retirement or death. Due to the obstacles in measuring these costs, they are not included in this analysis.

As mentioned above, Infliximab is a weight-based drug with dosage of 5 mg/kg. In the case of weight-based dosing drug, patient's body weight is an important parameter which influences ICER value, and result is sensitive to it. In this study, in consultation with clinicians, patient's weight of 75 kg was used to estimate Infliximab costs at dosage of 5 mg /kg.
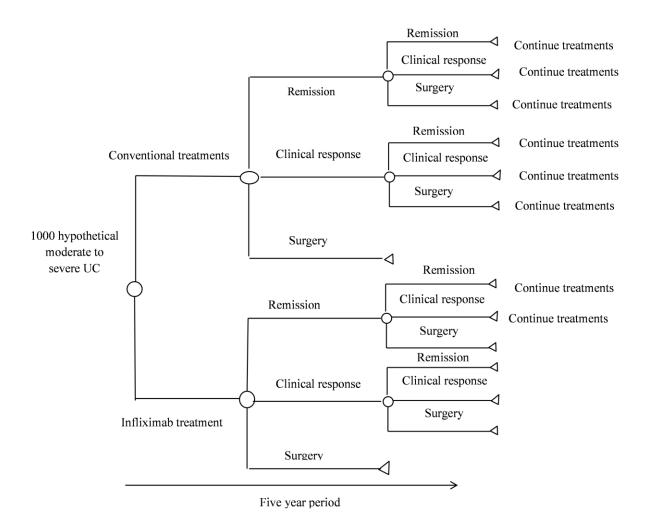
Figure 1. The structure of the decision model used in analysis.

2.6. Model structure

Figure 1 shows the structure of the decision model that is used to track the progression of disease in 1000 hypothetical UC patients that received different treatments to estimate associated costs and outcomes during 5 years. This model, which is simple Markov model, was developed and ran using Microsoft Excel 2010.

Patients were hypothetical individuals with moderate to severe UC, whom were resistant to conventional treatments. They were treated with infliximab or conventional treatment, either responded to treatment and achieved remission, clinical response or failed treatment, and underwent surgery.

2.7. Data Analysis Methods

The analysis took in the form of a cost-effectiveness analysis, using analytical decision model in 5-year-time-horizon. All assumptions related to the clinical pathway and alternative treatments were developed in consultation with a group of Iranian gastroenterologists. The parameters were

used to estimate costs and outcomes of infliximab and conventional treatment including Patient's weight, probability of achieving remission, clinical response, and surgery for each treatment option, and utility values for each health states. The Data were obtained from a published literature, patients' medical records and specialists' opinion. This means that in cases that patients' medical records were incomplete and didn't have enough information, the physicians were interviewed.

QALY was chosen as a well-accepted effectiveness measure [33]. It was estimated for UC patients with both treatment options, with considering two assumptions: first, there is no difference in survival rate of patients who were treated with infliximab and patients who were treated with conventional treatments. Second, the time horizon is too short to capture the risk of death. Hence, only quality of life is affected by type of treatment. Costs are discounted at 5%. A one-way sensitivity analysis was conducted to assess the impact of change in price of Infliximab on results of evaluation.

3. Results and Discussion

3.1. Clinical Efficacy

Literature review showed that Infliximab in patients with moderate to severe UC is an effective treatment. This effectiveness was confirmed by increasing in clinical response and remission rate on induction and maintenance therapy, compared to placebo. In addition, it was found that infliximab reduced the need for surgery and hospitalization, in severe acute and refractory UC patients. The findings also showed that remission is achieved faster in patients who have used infliximab early stage of disease than patients who began Infliximab treatment later [15].

3.2. Outcomes- Health Status

The utility value for each health state, extracted from Arseneaus 'study conducted with time trade off method. The utility value for the remission, clinical response –active UC, and surgery outcomes were considered equal to 0.79, 0.32, and 0.68 respectively [32, 34].

3.3. Measurement Costs

For this purpose, treatment costs related to conventional treatments and Infliximab were estimated for a one-year period, based on the approved tariffs in the public sector at 2014. Conventional treatments include induction treatment (prednisone 1 mg/kg, azathioprine 50 mg, mesalazine 500 mg, methronidazol 250mg) and maintenance treatment (azathioprine 50 mg and mesalazine 250 mg). Surgical procedures include total colectomy, partial colectomy, and ileal pouch anal anastomosis. Table 1 presents the resource and costs used in our model.

Table1. Resource use and costs used in the model for a one year period.

Healthcare use	costs
Specialist visit [a]	2.4
hospitalized /day [b]	19
Surgical procedure [a]	1341.7
Diagnostic tests [a] (laboratory tests and X-rays)	20.5
Infliximab [a](a vials of 100 mg)	587.4
induction therapy with Infliximab at 0,2, and 6 weeks	6608.5
maintenance therapy with infliximab at every 8 week	14318
Current treatments including induction and maintenance therapy	39

a =Number of units, b Number of days of treatment, dollar exchange rate: 1US Dollar=25,535 Iranian Rials (IRR)

Table 2. The result of cost-effectiveness analysis of Infliximab compared with conventional treatment in UC patients.

Strategy	Cost($)	Utility	QALY*	Cost/QALY	ICUR($)
conventional treatments	985.1	0.65	3.24	295.6	-
Infliximab	77137.7	0.71	3.56	21679.9	240902.6

*=After 5 years with the same life expectancy, USD 1= IRR 30.000

3.4. Cost –Utility Analysis

Table 2 shows the result of analysis based on associated costs, utility, QALY gained, and Incremental Cost-Effectiveness Ratio (ICER) for each treatment option in hypothetical UC patients.

As the table shows, the estimated ICER value of infliximab treatment in UC patients was 240,903 US dollars per QALY gained, compared with conventional treatments. According to the World Health Organization (WHO) guidelines for choosing cost –effective intervention, it is not cost –effective treatment option. It will be discussed as follow:

As we mentioned later, the aim of this analysis was to evaluate cost-effectiveness of infliximab treatment in refractory UC patients, compared with conventional treatments.

Although a meta–analysis of placebo- controlled trials showed that infliximab treatment is an effective strategy for these patients in terms of mucosal healing, remission rate, and decrease in hospitalization and colectomy [35]; yet, it is an expensive treatment option. The high cost of infliximab in comparison with cost of conventional therapy affects the result of analysis. There are conflicting results on cost-effectiveness of infliximab in UC patients [13]. Some CEA analyses reported that Infliximab is not a cost-effective treatment while the others mentioned that Infliximab is a cost –effective treatment [20, 21, 36, and 37].

Results of the present study indicate that ICER value of infliximab is more than 3 time of Iran's local GDP per capita at 2014, namely 50.6. According to the World Health

Organization (WHO) guidelines for choosing cost –effective intervention, an intervention with ICER value less than one GDP per capita, would be considered very cost- effective, between one to three times of GDP per capita, will be cost- effective and more than three times of GDP per capita, considered as not cos – effective (38). Therefore, by considering ICER value of analysis as 50.6 GDP per capita, infliximab treatment is not cost–effective option in comparison with conventional treatments. According to the Published literature on sensitivity analysis in this case, ICER value would be affected by some factors such as patient's weight, time horizon, treatment effect, and utility value [20, 21, and 37]. In this study, we performed a one-way sensitivity analysis via change in price of infliximab, as we believe that cost of infliximab is the most important factor that affects ICER value. Our result indicated by 90% decrease in price of infliximab, the ICER value will be less than 3 time of GDP per capita and infliximab could be cost-effective treatment option.

Closing point is that current analysis has several limitations. First, information on some parameters such as the survival of UC patients and their quality of life associated with each health state were not available in Iran and therefore, the results of related studies in this area were used. Moreover, in cases where the required information were not extracted from the literature, the expert opinions were used such as probability rate, which may have caused bias in the analyses; impact of adverse effects on cost and health status, and indirect costs were not included in the study because of difficulties in measuring costs.

4. Conclusion

We concluded that in comparison to conventional treatment, infliximab treatment is not cost-effective intervention in moderate to severe refractory UC patients at a 5-year-time-horizon. This study is done at the short-long time, future studies at longer time horizon is suggested.

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