Chapter

Pharmacoeconomical Impacts of Crohn's Disease

Stjepan Rudan, Rudika Gmajnić and Sanda Pribić

Abstract

Provide an overview of Crohn's disease and its cost assessment options, establish the need for implementing Croatian national Crohn's Disease Registry to precisely quantify the costs and the outcomes, and establish model to evaluate values of treatment options for Crohn's disease.

Keywords: Crohn's disease, farmacoeconomical impact

1. Introduction

Crohn's disease is a chronic, progressive inflammatory bowel disease (IBD). Although mortality is rare, Crohn's disease significantly impacts quality of life as it causes significant disabilities related to the debilitating symptoms and complications of the disease and its treatment. As such, IBD exerts physical, social, sexual, emotional, educational, and job-related limitations. Therefore Crohn's disease produces a huge burden on patients, families, and societies.

While it is clear that new biological therapies have raised the bar for what is an acceptable symptomatic response in Crohn's disease, the key pharmacoeconomical and humanical questions are whether TNF antagonists can reduce hospitalization and surgery rates or can, if applied in earlier stages, modify the course of the disease by means of fistula healing, mucosal healing, and overall improvement in QOL [1].

Novel therapies and alternative treatment algorithms require that healthcare providers evaluate the value of these treatments. Pharmacoeconomic analyses aim to assess whether new technologies are superior to existing treatments by relating costs to outcomes.

In the absence of the national registry, in Croatia, we do not have national data on Crohn's disease; therefore in this paper, we can only apply epidemiological models to project Crohn's disease costs and pharmacoeconomically evaluate treatment options.

2. How to evaluate CD therapies: clinical indexes and endpoints

Traditional primary endpoints in clinical trials (i.e., Crohn's Disease Activity Index (CDAI)) quantify physical symptoms, without incorporating overall "illness experience."

Therefore, QOL measures are commonly used as secondary endpoints in clinical trials, and several QOL tools are available. Since the first being created in 1985, the development of IBD questionnaires has substantially advanced studies

of HRQOL. In addition to the common physical complaints associated with CD, IBDQ also measures social, functional, and psychological factors, and it has strong correlation to CD (Shah 1). A total of 32 items comprise the questionnaire, being grouped into 4 major domains (bowel function, social function, emotional functional, and systemic function). Total score ranges from 32 to 224 points, higher score indicating better QOL (Shah 2). Several validation studies of IBDQ were performed in different populations confirming its validity (Shah 3). A score above 170 is considered desirable [2–4].

To better address patient concerns in regard to the effects of the disease and their health status, rating form of IBD patient concerns was developed [5].

However, review study assessing several HRQOL tools led to the conclusion that IBDQ was simple, reliable, and accurate in disease activity assessment and therefore more favorable than other instruments [6].

3. Medical treatments: outcomes

Corticosteroids have long been used in the management of Crohn's disease. They demonstrate rapid onset of action and efficacy while having significant side effect profile and lack of maintenance benefit [7]. The need for corticosteroids' use is a significant indicator of future disabling disease and complications, including mortality [8, 9]. One analysis has shown that Crohn's disease patients using corticosteroids had 38% risk for surgery in 1 year [10].

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ACCENT I trial has clearly demonstrated efficacy of infliximab maintenance treatment in patients with fistulizing Crohn's disease [11]. Further subgroup analysis has shown that in patients randomized to maintenance infliximab treatment following successfully induction therapy, the mean number of hospital days per 100 patients treated was significantly reduced in the group of patients assigned to infliximab compared with those who received placebo [12]. Significant reductions in the rates of surgery and procedures were also demonstrated [12].

CHARM trial [13] confirmed adalimumab efficacy and safety in moderate to severe Crohn's disease. Based on CHARM data, the effect of ongoing adalimumab treatment on the risk for hospitalization was evaluated [14]. It showed a significant difference between placebo and adalimumab group, demonstrating relative risk reduction of 57% and absolute risk reduction 8%, showing the difference between the treatment groups early in the course of the therapy. Multivariable analysis confirmed that assignment to adalimumab therapy was inversely correlated with the risk of hospitalization and surgery.

These studies confirmed that TNF antagonists can reduce the risk of hospitalization and surgery in Crohn's disease. Together with Lemann trial on infliximab [15], both trials confirmed that anti-TNF agents are effective steroid-sparing agents.

In the provocative trial inverting the treatment pyramid [16], newly diagnosed patients with symptomatic disease were randomized either to infliximab + azathioprine combination (top-down group) or to steroids initially (step-up group), which were increased if patients flared during taper, or azathioprine and a second course of steroids if patients flared after the initial steroid course was completed. If symptoms recurred, or the response was inadequate, infliximab was given. Remission of steroids without surgery was achieved in 60% of patients in top-down group

vs. 36% of patients in step-up group at 26 weeks and 62% vs. 42% of the patients, respectively, at 56 weeks.

As approximately one third of the patients with Crohn's disease will develop fistulas at some point in the disease course [17], it is important to underline that both infliximab [18] and adalimumab [13] were proven effective for the partial or complete healing of fistulas in patients with Crohn's disease, maintaining the effect among responders in majority of patients at 1 year.

Mucosal healing as a potential disease-modifying point was reported superior in patients receiving infliximab in an endoscopic sub study of the ACCENT I trial [19]. This is even more important knowing that mucosal healing findings have not correlated well with clinical remission by CDAI: 56% of patients in remission by CDAI did not have mucosal healing. The reasons for this remain unclear.

In a sub study of step-up was top-down trial [20], 44 patients were endoscopically evaluated at year 2 from initiation of the treatment, and results were compared with endoscopy findings at the diagnosis. For the comparison, five ileal and colonic segment lesions were scored for each patient. Complete ulcer disappearance was observed in 71% of patients who received top-down vs. 30% of patients who received step-up treatment. Mucosal healing was more pronounced in top-down group, with ulcer reductions observed in 88% of patients in top-down vs. 47% of patients in step-up group. The results indicate that infliximab is effective for the induction of mucosal healing. Effects of adalimumab have not been reported.

Finally, both infliximab and adalimumab were associated with improvements in QOL scores:

ACCENT I studied HRQOL [21], suggesting substantial impairment HRQOL at baseline scores and substantial improvements throughout the infliximab maintenance therapy.

CLASSIC II trial [22] demonstrated that patients on maintenance adalimumab therapy achieving remission have demonstrated improvements in IBDQ that were maintained throughout 1 year.

It can be concluded that both infliximab and adalimumab are significantly more effective in improving both CDAI and HRQOL than other treatment options. Also, it is suggested that reverting the treatment algorithm and introducing infliximab earlier on (top-down approach) may result in better mucosal healing and therefore modify the course of the disease.

4. Costs of the disease

Crohn's disease patients are typically diagnosed at their young age, and the treatment is generally lifelong.

Patients require chronic drug therapy due to the recurrent episodes of abdominal pain, diarrhea, and bleeding. Conventional therapies (glucocorticoids and immunosuppressives) are effective but associated with considerable side effects. Biological therapies have been introduced into routine clinical use, improving the disease outcomes over the past decade [11–14]; however, the costs related to novel options are substantially higher.

Hospitalization and surgeries are often needed to manage complications such as abscesses, perforations, and obstructions. Bowel resections are associated with considerable morbidity and, infrequently, death.

It is clear that both symptoms and the treatment of Crohn's disease reduce patients' health-related quality of life (HRQOL).

Cost of illness studies has showed that hospitalization and surgery are major factors of the total societal costs of Crohn's disease [23–25].

But above these obvious disease management costs, work loss and impaired HRQOL increase the humanistic and economic burden in Crohn's disease.

4.1 Direct costs: disease management costs—course and prognosis related

Direct costs are easily identifiable and quantifiable. The costs of Crohn's disease include outpatient care costs (medications, tests, procedures) and inpatient care costs (hospitalization).

In a prospective study [26], 33% of patients with chronic or intermittently active disease required hospitalization and surgery after developing complications in the first year following diagnosis, and 13% required hospitalization and surgery in the second year and 3% in each following year.

The same study showed that 20% of CD patients were unable to work at full capacity 20 years after the time of diagnosis. Another long-term follow-up study showed that approximately 74% of all patients with CD will eventually be hospitalized and ultimately require surgical intervention for their disease [27].

4.2 Indirect costs: total economic loss experienced by patients, caregivers, and society/HRQOL-related costs

Indirect costs are more subjective than direct costs. In Crohn's disease, sources of indirect costs include absence from work, premature retirement, and the social and psychological effects of chronic disease on patients and their families.

As a consequence of the Crohn's disease course and prognosis, HRQOL is diminished and directly correlates with a higher likelihood of unemployment [28]. In a case-controlled study [29], adult patients with CD were reported to have more long-term unemployment than controls. Furthermore, in the same study, up to 30% of CD patients were reported to concealed their illness from their employers.

As determined in ACCENT I [30], there were high unemployment rates of 27% in males and 44% in females among Crohn's disease patients. However, only 25% of patients received disability benefits. This further strengthens economic burden of Crohn's disease to society.

5. How to evaluate CD therapies: costs vs. outcomes

As societal resources for healthcare are limited, sound methodology for resource allocation is needed. Pharmacoeconomic analyses address this issue, considering costs (currency) and the consequences of the therapy. In 2007 Feagan [31] posted an effective overview of the methodology, commonly classified into four categories: cost-minimization, cost-effectiveness, cost–benefit, and cost-utility analyses. The differences between methodologies are based on the outcome to which costs are related.

When two competing interventions have equivalent clinical outcomes, it is logical to use *Cost-minimization analysis*. Being the most simple analysis, it favors less costly treatment when no clinical difference has been demonstrated.

In more often, real-life cases, when we are faced with new therapies that are both more effective and more expensive, we have to relate different costs and different outcomes. Therefore other more sophisticated methodologies are needed [32].

Cost-effectiveness analysis relates costs to clinically meaningful differences in outcomes: per beneficial outcome attained, the incremental cost of a novel therapy is then expressed in terms of currency expended. It can be used in indications where

robust endpoints exist (i.e., myocardial infarction prevention) and the incremental costs are easily understood by patients and providers [32].

Cost-benefit analysis translates differences in outcomes into monetary terms, as they are for the costs. This brings two inputs into the same units, and the comparison between the treatments is easily interpreted. Logically, the strategy that maximizes net value for the society (net currency gained) is preferred. Relevance of this technique in terms of healthcare applicability is challenged: it requires value judgments, which are usually inappropriate [33].

Cost-utility analysis expresses currency expended per incremental improvement in HRQOL achieved. It evaluates well chronic diseases with serious impact on HRQOL, but without causing excess mortality or frequent complications. The HRQOL measure used is utility. This is a generic metric placing a value on HRQOL, ranging from 1 (perfect health) to 0 (death). Quality-adjusted life years (QALYs) are then derived by multiplying the time in a health state by the appropriate utility score. Logically, differences between treatments are expressed as the incremental costs per QALY gained [34].

Cost of illness studies identify where efficacies can be realized. These studies are descriptive evaluations that (1) assess the total economic burden of the disease; (2) define the relative proportions of total costs allocated to diagnostic tests, healthcare professionals, institutions, and drugs; and (3) generate hypotheses regarding the economic consequences of treatment alternatives.

Only a few such studies have been reported for Crohn's disease.

A cost model for IBD was created in the early 1990s using data from a California health maintenance organization [23]. Reducing the charges obtained from a teaching hospital in San Francisco by 35%, the mean annual medical cost of Crohn's disease was estimated to be 6561$ per person. It was demonstrated that approximately 20% of patients generate 80% of healthcare costs. Surgery and hospitalization were associated with 79.9% of the average costs of medical services. Drug therapy was responsible for 10.2% of the total costs. By extrapolating these data to the US population, using published prevalence estimates and 1990 census data, the total direct cost of Crohn's disease was estimated to be 1–1.2 billion annually, compared to 0.4–0.6 billion for ulcerative colitis. The indirect costs of the disease were estimated based exclusively on lost labor productivity and calculated 0.4–0.8 billion annually. Therefore, the total (direct + indirect) economic burden for IBD (Crohn and UC) was estimated to be 1.8–2.6 bio $ yearly [23].

Feagan's study [24] evaluated reimbursement charges from patients enrolled in a health benefit claims program serving 50 largest US employers. Eligible patients were enrolled in their health plan for a minimum of 3 years and had at least 1 CD-related claim over a 1-year interval (1994/1995). The study retrospectively classified patients into three mutually exclusive status: mild (patients in remission or those requiring less than 6 months of active treatment during the observation period), moderate (patients who required chronic treatment for more than 6 months with prednisone or antimetabolites), and severe disease (patients requiring admission to hospital for treatment). A total of 607 patients generated average annual charges of 12.417$ per patient: 6.277$ being the average for the mild, 10.033$ for the moderate, and 37.135$ for the severe form of the disease.

These studies suggest that treatments that reduce the need for hospitalization or surgery may result in important cost savings.

As quoted earlier on, two subgroups of large randomized clinical trials have strongly indicated that the use of TNF antagonists reduces the rate of hospitalization and surgery in Crohn's disease [12, 14].

It is important to evaluate in economic models whether the potential offsets that result from reduced rates of hospitalization and surgery justify the high price of biological.

Lindsay et al. [35] used Markov models to simulate the disease progression and track associated costs and outcomes as QALYs over 5 years of treatment in hypothetical cohort of patients with active luminal or fistulizing CD, during treatment with infliximab (5 mg/kg). Transitions were estimated from published clinical trials of infliximab. Standard care, comprising immunomodulators, and seven corticosteroids were used as a comparator. An average weight of 60 kg was used to estimate the dose of infliximab. Authors discounted the costs and outcomes 3.5% over 5 years. The primary effectiveness measurement was quality-adjusted life years estimated using EQ-5D. One-way and probabilistic sensitivity analyses were used by varying infliximab efficacy estimates, costs, and utilities. The incremental costs per QALY gained were 26.128P in luminal and 29.752 in fistulizing CD at 5 years. Results were robust, remaining in the range of 23.752–38.848 for luminal and 27.047–44.206 for fistulizing CD. Not surprisingly, the most important factor affecting cost-effectiveness was patients' body weight. The authors concluded that 8-week scheduled maintenance treatment with infliximab is a cost-effective treatment for adult patients suffering from active luminal or fistulizing CD.

6. Where we are in Croatia and how we should move forward

In Croatia there is no national registry of Crohn's disease. Therefore, we are lacking precise epidemiological data that are essential for high-quality cost-utility/HRQOL assessments.

Consequently, we do not have exact data on the total incidence and prevalence of the disease. We cannot precisely conclude how many of Croatian patients are suffering from the mild, moderate, or severe form of the disease. We also cannot confirm precise age or weight distribution of the patients. We also do not know the educational distribution or the rate of unemployment among Crohn's disease patients.

As it concerns outpatient care costs, while we can find IMS data or HZZO data on total cost of biological therapies, we do not have the access to cost split per indication. Also we are not aware on how much resources are allocated to other outpatient care elements.

Furthermore, we cannot define essential resource allocation inputs for Crohn's disease. There is no available source to confirm the exact number of hospital days/related costs due to Crohn's disease or to provide exact number of surgery procedures/related costs undertaken for Crohn's disease. We do not know how much is spent on side effect management. Also we cannot define the disease costs per mild, moderate, and severe form of the disease.

Related to the lack of the national registry, we cannot quantify DASS and IBDQ improvements related to treatments applied; therefore we cannot define price per HRQOL improvement.

What we can do at this point is to improvise: to extrapolate epidemiological data [36, 37] and estimate the incidence and the prevalence of the disease in Croatia. Then we can apply international data to estimate patients' split and treatment outcomes and average cost per patient group. Then we can use Markov models and analyses as implemented by Lindsay et al. [35].

The above mentioned leaves calculation table empty at basic input level. Our first conclusion is that there is an essential need to implement national IBD registry to summarize the data needed for an economic analysis model.

Our second conclusion taken from CD example is that if we want to better drive our HC resources, *Cost-effectiveness analysis* needs to become the key method for assessing costs and benefits of alternative ways of allocating resources to assist

decisions aiming to improve efficiency. An efficient allocation of resources implies that no further health gains can be achieved by allocating the same resources differently. The analysis is based on maximizing health effects subject to a cost constraint, where costs are measured in monetary units and health effects in non-monetary units, such as life years or quality-adjusted life years. QALYs are constructed by adjusting life years for the quality of life in which they are spent. To achieve this, the number of years in a health state is multiplied by utility weight between 0 (dead) and 1 (full health). To determine whether a treatment is cost-effective compared to alternative, the cost per gained unit of effectiveness (i.e., cost per QALY gained) must be compared with the willingness to pay (WTP) for a gained unit of effectiveness (i.e., the value of QALY gained). WTP can be defined as the price the payer is willing to pay for a QALY. If the price per unit increase in effectiveness exceeds the target price, then the program is cost-effective. Without the information about the price per unit increase in effectiveness, CEA gives no information on whether an intervention is cost-effective. The value of a QALY differs between courtiers and is logically related to the level of GDP.

7. CD example/Markov models: how to implement it in Croatia

The model characterizes the disease severity by two discrete "on-treatment" health states: (1) remission (DAI </=150) and (2) response but no remission/active state (CDAI >150). All patients started in the active state and remained as such for the first model cycle. At the end of the first and each subsequent model cycle, patients either remained in the active state or moved to a different health state. In the illustration of the model bellow, two separate numbers denote different transitions in standard care and infliximab* treatment arm. If single number, there were no differences between the arms.

Patients responding to treatment and achieving CDAI </= 150 moved to the remission and remained on treatment. Patients responding but not achieving remission remained in the active state and continued treatment [11]. Nonresponders or discontinuing-from-treatment patients moved to the nonresponding active state. Once patients failed the treatment and discontinued from the treatment, they could not go back to the on-treatment status, but they were followed up to capture costs and outcomes.

As obvious from diagrams, both on-treatment and off-treatment patients could transition to surgery. Following surgery, patients could either undergo repeat surgery due to immediate complications, therefore remaining in surgery state, or they could move to a post surgery health state (remission or post surgery complications). Patients in post surgery remission could continue in the same health state, enter surgery for repeated procedure, enter post surgery complication state, or have CD recurrence and move to a nonresponsive active state. Infliximab failures were not re-treated, and also patients with post surgery complications could continue in the same health state, enter surgery, respond to treatment for their complications and enter post surgery remission, or have recurrence of CD and enter nonresponding active state.

In model adjusted for fistulizing DC, on-treatment health states of remission were further sub classified as with or without failure. This gives four on-treatment health states as shown in the diagram. The rest of the model was identical to the active luminal CD model.

The patient and treatment parameters (sources of efficacy estimation, treatment regimen, comparators, treatment strategy) in Markov models are based on standard treatment protocols and ACCENT trial evidence [11, 18]. Treatment horizon was 5 years.

Before establishing national registry, as suggested in Lindsay trial [35], transition probabilities for different health states could be taken from published randomized placebo-controlled induction studies [38].

Consequently, before establishing the national registry, probability of surgery, postsurgical states, and CD recurrence are to be obtained from the literature [39–44].

Costs resulting from the impact of CD on QOL and productivity and overall burden to the Croatian society are difficult to estimate based on international trial findings [45, 46] and might be disregarded at this initial point of establishing CEA model.

Drug costs per indication are drug acquisition costs (price per pack), drug administration costs (price per infusion in the case of infliximab), and price of concomitant drugs (immunomodulators, aminosalisylates, corticosteroids).

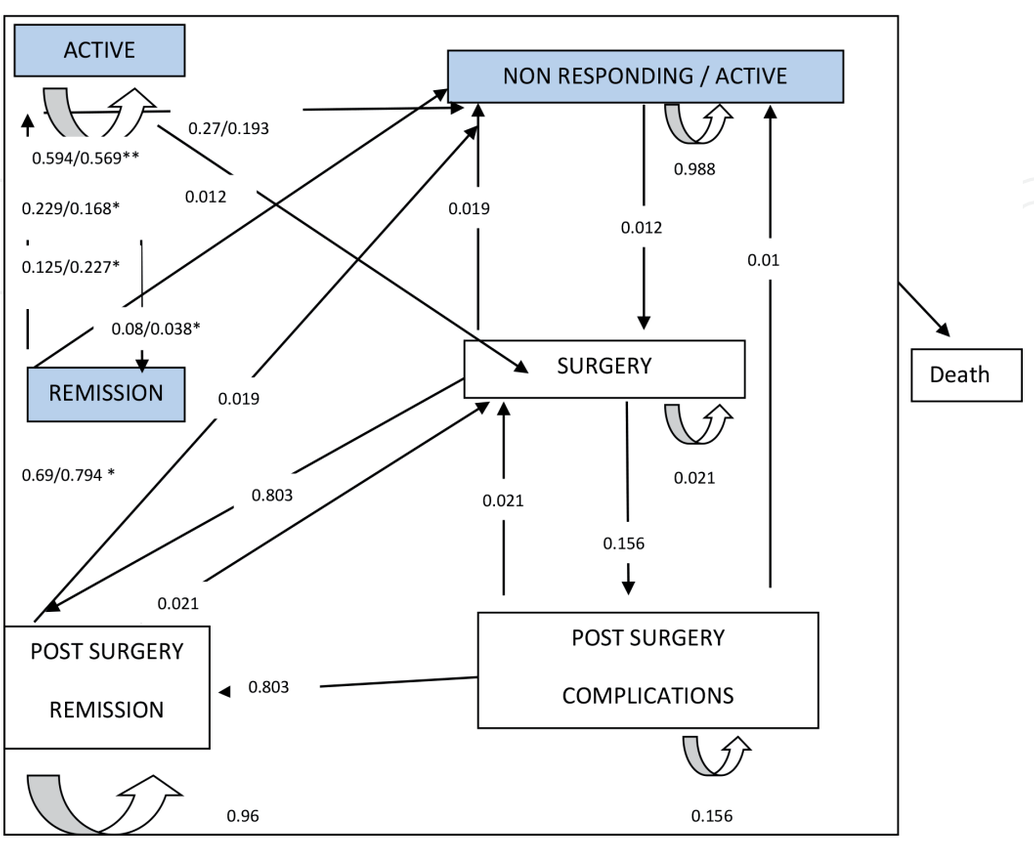
These drug costs can be obtained from HZZO or from the national CD registry.

Alternatively we can calculate drug acquisition costs assuming an average body weight of 60 kg based on NICE guidance for infliximab case.

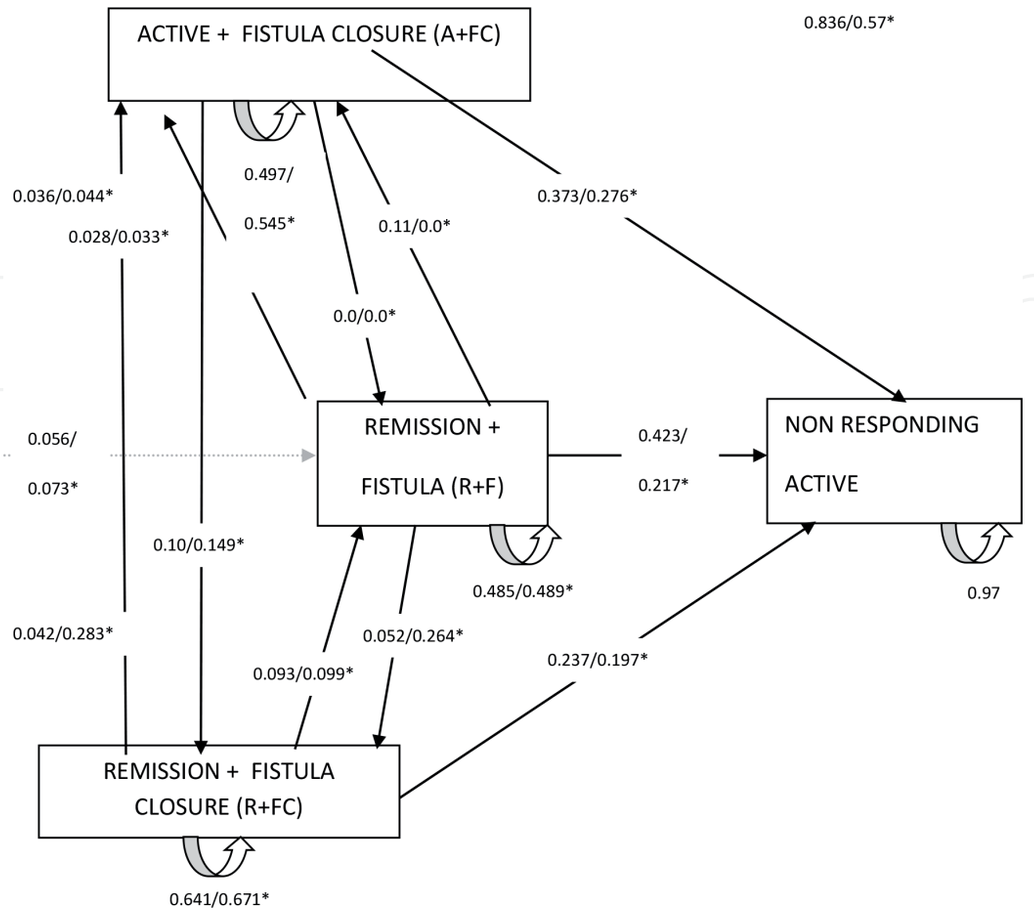
Surgery, hospitalization, and other assessment costs should be obtained from HZZO [47].

The primary efficacy measure of Croatian CD model should be QALY, gains being driven by quality-of-life benefits. Utility as a measure places a value on HRQOL, ranging from 1 (perfect health) to 0 (death). Quality-adjusted life years are then derived by multiplying the time in a health state by the appropriate utility score. Cost-utility analysis represents incremental cost per QALY gained. Logically, differences between treatments should be expressed as the differences in incremental costs per QALY. Cost and outcomes are to be calculated in accordance with NICE guidelines, separately for the entire cohort of patients in treatment arms, regardless of their response rates, and discounted to present values at 3.5% per annum.

7.1 Markov model for active luminal CD



7.2 Markov model modified for fistulizing CD



8. Conclusions

Based on international trials, TNF antagonists' maintenance therapy may bring significant improvements in patients' HRQOL in adult patients with severe active luminal or fistulizing CD.

Based on international cost-utility analyses, it can be concluded that a substantial part of TNF antagonist acquisition costs could be offset by savings on other disease-related costs in patients not responding to or intolerant to steroids and immunomodulators.

It is essential to establish Croatian National Registry of Crohn's disease to prospectively evaluate epidemiology, clinical subgroups, transition from states, treatment outcomes, and costs.

Markov models combined with registry data and findings from international trials represent solid frame to calculate pharmacoeconomic impacts of Crohn's disease treatments.

From the payers perspective, it seems to be a must to establish a QALY-based process of assessment of new therapeutic options and HC technologies in Croatia. Using this methodology, payers would develop comparable data even in different indications/treatment options, evaluate objectively contributions for incremental costs per QALY, and allocate HR resources accordingly.

Author details

Stjepan Rudan[1], Rudika Gmajnić[2,3*] and Sanda Pribić[1,3]

1 Faculty of Dental Medicine and Health Osijek, Croatia

2 Medical Faculty of Osijek, Croatia

3 European University Brčko District, Bosnia and Herzegovina

*Address all correspondence to: rudika.gmajnic01@gmail.com

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