Review paper

Economic implications of biological therapy for Crohn's disease

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Abstract

In the early 90s American authors estimated that if a theoretical new drug was introduced that was capable of changing the natural course of the disease and reducing direct non-drug medical costs (including hospitalisation and surgery) by 20%, despite doubling the overall drugs bill, there would still be a reduction in total direct medical costs of Crohn's disease by 13%. Infliximab proved to be efficacious in reducing and maintaining remission in moderate to severe active Crohn's disease and/or fistulising Crohn's disease. A higher acquisition cost still remains its major limitation. Currently only the use of infliximab in case of treatment for flares seems to be cost-effective. However, this statement may be modified in the near future.

Introduction

Crohn's disease (CD), together with ulcerative colitis being referred as to inflammatory bowel diseases, is characterised by transmural inflammation, which may involve each segment of the gastrointestinal tract from mouth to anus. The majority of patients experience abdominal pain and diarrhoea, and in some cases symptoms of malabsorption syndrome are observed. In 30–40% of cases there is spontaneous formation of fistulas, both external and internal. Other intestinal complications of CD include abdominal abscesses adjacent to inflamed bowel loops and strictures, i.e. narrowing of the intestinal lumen. The typical course in patients with CD is one of intermittent exacerbations followed by periods of remission. At the present stage there is no causal treatment for CD, albeit symptomatic and anti-inflammatory treatment may be necessary for the rest of the patient's life. During flares immunosuppressive drugs and antibiotics should be applied additionally, but many patients are hospitalised. Within 10 years of diagnosis, 60% of patients require surgical treatment. One year after surgery endoscopic signs of relapse are present in 70% of patients, and clinical manifestations are back within 4 years in 40–50% of patients. Forty-five percent of patients will require reoperation. Mortality is low, although the long-term course of the disease and, not rarely, the permanent presence of symptoms can cause disability [1–7].

The review of the literature made by the authors clearly shows that the main component in the direct medical costs of inflammatory bowel disease, irrespective of the country in which they have been calculated, are the costs of hospitalisation, which range from 49% to 80% of the total cost. The implication from this is that the new therapies that result in a reduction in the need for hospitalisation and/or surgical treatment, will not only contribute to the improvement of the quality of life of patients with inflammatory bowel diseases, but will also reduce the costs of their medical treatment. Infliximab is a chimeric monoclonal antibody that binds to and blocks the activity of tumour necrosis factor α (TNF-α) [8]. Intravenous administration of infliximab turned out to be more effective than a placebo in the induction of remission and maintenance treatment in moderate to severely active CD and/or fistulising CD [9–11]. Recently, the tendency to start infliximab early in the course of the disease prevails [12]. The efficacy of infliximab in ulcerative colitis has also been proven [13]. Since

December 1, 2007 the following therapeutic programs have been carried out in Poland: treatment of CD in adults with the use of budesonide, infliximab, and adalimumab and treatment of CD in children with the use of infliximab.

Infliximab is characterised by a relatively high acquisition cost compared with other medications in CD. In the UK the cost of a single infusion of infliximab is £1469 (at a dose of 5 mg/kg, for a person weighing 70 kg). This is much more than the cost of 8-week treatment with prednisone orally with a gradual reduction in dose (less than £5) and 8-week treatment with azathioprine (£100–150) [14]. It is known, however, that the expenditure on drugs in inflammatory bowel diseases is only 10–25% of their direct medical costs [15, 16]. Hay and Hay applied regression analysis for the calculation of the potential impact on the total cost of the theoretical new drug that significantly would change the natural course of the disease. If such a "magic" drug led to a decrease in direct medical costs but except for drug therapy (including the costs of hospitalisation and surgical treatment) by 20% and at the same time doubled the total expenditure on drugs, then its use would result in a reduction of the direct medical cost of CD by 13% [17]. Is infliximab such a "magical" medicine? There is another aspect that should be raised. It is known that at least half of patients with CD require surgical treatment within 10 years of diagnosis, and approximately 70–80% in their life. The use of a drug that would reduce the need for surgery could prove economically beneficial, but it is important to question whether this drug would prevent the operation or only postpone it, and for how long it should be used. Treatment with infliximab requires the repetition of doses in order to maintain remission, while surgical treatment often produces long-lasting remission, without the need for expensive infusions. It is possible, therefore, that in some cases, especially when the lesions are localised, the decision to operate on may be considered the most effective economically [15, 16]. In order to answer the question about the cost-effectiveness of infliximab one should seek properly designed randomised clinical trials that would compare two alternatives: infliximab and previously used treatment, and that would evaluate as primary endpoints both the results and the costs. Unfortunately, so far such research has not been carried out.

Aim of study

The aim of the study is the economic evaluation of health programs with the use of infliximab in the treatment of CD on the basis of a review of the available literature.

Types of pharmacoeconomic analyses, measurement of utility, decision rules, and modelling

In the economic evaluation of health programs one can use the following types of analysis:
a) cost-minimisation analysis (CMA),
b) cost-effectiveness analysis (CEA),
c) cost-utility analysis (CUA),
d) cost-benefit analysis (CBA).

Cost-effectiveness analysis and its special cases, cost-minimisation analysis and cost-utility analysis, enable assessment of the relative value of comparable health programmes, and thus answer the question: which one is more cost effective? Cost-benefit analysis allows further assessment of the absolute value of such programs.

Cost-effectiveness analysis measures, evaluates, and compares the cost of obtaining the outcomes expressed in natural units in different alternative therapies and indicates which among them provides the best value for money. To be conducted, the same unit of measurement of outcome should be applied in the programs being compared.

In cost-utility analysis the results are presented in QALYs – quality adjusted life years. This unit includes not only improving survival (quantitative score), but also improving the quality of life (quality score). We calculate it as the product of the life-years gained and the quality of life index, on a scale from 0 (death) to 1 (full health).

Quality-of-life index used for the calculation of QALY can be measured both in a direct and indirect way, taking account of preferences. The most commonly used direct methods to measure the preferences are: standard gamble, time trade-off, and rating scale.

An alternative to the method of direct measurement of preferences are multi-attributable utility functions used to score utility on the basis of questionnaires assessing health states, such as: Quality of Well-Being, the Health Utility Index I, II, and III, and EQ-5D. EQ-5D is a general evaluation system of health states, made up of five domains (mobility, self-service, usual daily activities, pain/discomfort, anxiety/depression).

If program A costs less and gives a better outcome than B, we recognise it as a dominant and we accept it. If program A costs more and gives a worse outcome than B, we recognise it as dominated and we reject it. In the case when program A costs more and gives a better outcome than B or, if program A costs less and gives a worse outcome than B, the decision about its acceptance or rejection can be made only after having performed an incremental analysis. Incremental analysis is the calculation of the additional cost incurred due to

the introduction of the new programme, and a comparison of it with an additional outcome obtained thanks to the new programme. The result of an incremental analysis is presented in the form of the incremental cost-effectiveness ratio (ICER), which tells us how much it costs to get an additional unit of outcome by replacing the old programme with the new one: ICER = Δ costs A and B/Δ outcomes A and B.

In order to determine whether the program is cost effective, it is necessary to designate a so-called cost-effectiveness threshold, i.e. society's willingness to pay (WTP) for an additional outcome unit. This threshold in highly developed countries was set at US$50,000/life-year gained or QALY, which is equivalent to the annual cost of renal replacement therapy. If ICER does not exceed this limit, the programme is considered cost effective, but if it exceeds it the programme is deemed not cost effective.

In the economic evaluation of health programs a key role is played by modelling, enabling the integration of clinical and economic data in a result that can then be used in medical decision-making. The model should be replenished with the best available data. The Markov model contains a finite number of mutually exclusive health states, representing events that are important from a clinical and economic point of view. The patient may be present at any given time in only one state. For a change from one state to another, transition probabilities need to be determined (the patient remains in the same state or moves to other states), which constitutes the so-called Markov cycle. An important limitation of the Markov model is the independence of the transition probability in any given cycle from what was happening in the past. The Markov model is particularly useful with regard to chronic diseases. The entire medical process may be combined in the form of cyclical changes in health states, and by assigning each a cost and utility one can estimate the long-term costs and outcomes associated with the disease and various therapeutic programs [18–25].

Infliximab-assessment of the costs and outcomes

The aim of the ACCENT I study was to compare a single infusion of infliximab at a dose of 5 mg/kg at week 0 with the following treatment schemes: infliximab at a dose of 5 mg/kg at week 0, 2, and 6 and then in the same dose every 8 weeks and infliximab at a dose of 5 mg/kg at weeks 0, 2 and 6, and then at a dose of 10 mg/kg every 8 weeks in 573 patients with moderate to severe active CD. In both scheduled groups, significantly fewer hospitalisations and abdominal surgeries associated with CD were reported compared with the group treated in an episodic way (single dose) [26]. By analysing the results of the ACCENT I study Lichtenstein *et al.* noticed that the number of hospitalisations and abdominal operations significantly depends on the time that patients spend in disease remission (CDAI, Crohn's Disease Activity Index < 150): the longer it is, the smaller the percentage of patients requiring hospitalisation or surgery. Among the group of patients who were unemployed at baseline, 31% of those patients who achieved CDAI remission at week 54 were employed, compared to 16% who were not in CDAI remission at week 54 ($p < 0.05$). Patients who achieved remission also achieved a higher score in both components of the questionnaire SF-36, physical and mental [27].

Jewell *et al.* assessed the use of resources in a group of 205 patients with CD treated with infliximab in seven centres in the UK. Most of the patients had chronic active disease and received a single infusion of infliximab. Data on resource consumption was obtained retrospectively for the 6 months prior to the inclusion of infliximab and 6 months after the first infusion. In the period after administration of infliximab 21 fewer ambulatory visits, 99 fewer diagnostic procedures, 1093 fewer inpatient days, 7 fewer surgeries, and 33 fewer examinations under anaesthetic were reported compared with the period before the treatment. Savings in direct medical costs were calculated at £591,006. A total of 353 infliximab infusions were applied, which cost £719,562. Thus, there was a net reduction of £28,287 or £138 per patient [28].

Similarly, the resource use by an average of 9.8 years before infliximab and an average of 4.3 years after its inclusion into the therapy of 34 patients with CD was evaluated by the Spanish authors Saro *et al.* Direct medical costs before infliximab were calculated at €4464/patient/year, of which the costs of hospitalisation were 62.4%. Direct medical costs after infliximab inclusion were €10,594/patient/year, of which drug acquisition costs and costs of 1-day hospitalisation in order to administer the medicine accounted for 75.5%. These results remain at odds with the results of the previous investigation. Despite the fact that as a result of the application of infliximab there was a reduction in the number of man-days, the cost of its acquisition and administration was high enough that the overall balance sheet did not result in savings [29].

Arseneau *et al.* performed cost-utility analysis for infliximab to be used in the medical treatment of perianal fistulas in patients with CD. The study was conducted from the payer's perspective. A Markov model composed of 12 one-month cycles was employed. Four alternative treatment schemes were compared:

a) 6-mercaptopurine and metronidazole, b) 3 infusions of infliximab and then 6-mercaptopurine and metronidazole, c) infliximab administered intermittently, d) 6-mercaptopurine and metronidazole and then infliximab. Utilities were elicited from patients with CD and healthy volunteers by standard gamble. Schemes including infliximab were slightly more effective and much more costly when compared to the schema of 6-mercaptopurine and metronidazole (alternative reference). Incremental cost-utility ratio was as follows: b) US$355,450/QALY, c) US$360,900/QALY, and d) US$377,000/QALY and exceeded the limit value of societal WTP for QALY. High ICER value was the result primarily of a high acquisition cost of infliximab (the cost of a single infusion at a dose of 5 mg/kg for a person weighing 70 kg in 1999 amounted to US$2140). Sensitivity analysis showed that a reduction of the infliximab acquisition cost by 85% (i.e. to US$304 for a single infusion) would result in the reduction of ICER in the case of schema c) to US$54,050/QALY [30].

French authors Jaisson-Hot *et al.* conducted a cost-utility analysis, which compared the two regimens of infliximab treatment (intermittent infusions in the case of flares and 8-week maintenance therapy) with a standard medical and surgical treatment in patients with non-fistulising severe active CD [31]. The study was done from the payer's perspective. A Markov model was used, in which the individual health states (remission, surgical remission, mild disease, moderate to severe disease, responding to medical therapy, moderate to severe disease, drug-tolerant, moderate to severe disease, drug-resistant, surgery, death), and the transition probabilities were adopted from the study made by Silverstein *et al.* in Olmsted County [32]. Health outcomes were quantified as utility by extrapolating data about the utility measured by the standard gamble in the Canadian study [33]. Cost data for each of the health states in the model were based on expert opinion. The model, consisting of 2-month cycles, was designed for the entire further life of the patient, on the assumption that the patient entered a model at the age of 38 years. ICER for treatment with infliximab used only in case of flares amounted to €63,700/QALY, and it fitted within the range established for the other commonly accepted medical interventions (US$50–100,000). ICER for maintenance treatment with infliximab was €784,057/QALY and substantially exceeded the limit value of societal WTP for QALY [31]. However, when indicated, infliximab infusions repeated every 8 weeks are more effective compared to the infusion of the drug only in the case of flares, in terms of mucosal healing and prevention of immunisation. There is a consensus that they shall become the primary objectives for therapy in CD, and the intervention allowing to achieve these objectives – the intervention of choice [34].

Lindsay *et al.* carried out a cost-utility analysis in two groups of patients with moderate to severe CD, with and without fistulas, comparing the treatment with infliximab given in infusions repeated every 8 weeks with the standard treatment without infliximab [35]. The source of data on health states and the corresponding transition probabilities in a Markov model constructed by the authors were primarily the ACCENT and ACCENT II studies [9, 11], while the data on QALYs gained was estimated on the basis of the Spanish study, which assessed preferences for health states in CD with the use of EQ-5D [36]. The average dose of infliximab was calculated for a patient weighing 60 kg. ICUR in the case of disease without fistulas was £26,128/QALY and £29,752/QALY in the case of disease with fistulas (at a 5-year horizon). Sensitivity analysis showed that the patient's body weight is the factor with the greatest impact on the end result. An increase in body weight up to 80 kg results in an increase in ICUR for the disease without and with fistulas to £38,848/QALY and £44,206/QALY, respectively [35].

Conclusions

The inclusion of infliximab more than 10 years ago for treatment of CD meant significant progress in dealing with the disease, acting as the transition from the interventions exclusively symptomatic to interference in the pathomechanism of inflammatory bowel disease. Its high acquisition cost is still a major limitation to the use of the drug. Currently there are only a few studies in which some treatment schemes using infliximab have undergone pharmacoeconomic evaluation. Since they mainly use a Markov model, it must be borne in mind that the inevitable source of error in this case will be the simplified initial assumptions and uncertainty about the input data of the model. It can be seen that although infliximab substantially reduces the number and duration of hospitalisations and the number of surgical procedures, due to its high cost of acquisition and administration, it seems to be economically justified the use of the drug only in case of flares. The drug allows for disease remission, evaluated as a decrease in CDAI, which translates to improvement in the quality of life and the reduction of indirect costs. It allows us to achieve new therapeutic goals, where, except for other newer biological drugs, there is no alternative. So, one can expect that appropriately designed cost-effectiveness analysis, in which the costs and the outcomes are evaluated in a way that is real, and in which account is taken of indirect costs, will show the profitability of the use of infliximab in the

maintenance treatment as well. Further reduction of the acquisition cost of infliximab will undoubtedly will play a part in this.

Conflict of interest

The authors declare no conflict of interest.

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