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Management for severe Crohn's disease: A lifetime cost-utility analysis

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Objectives: Infliximab is a costly therapy for active Crohn's disease resistant to corticosteroids and immunosuppressive medication. The purpose of this study was to examine whether a treatment including infliximab (episodic re-infusions for relapse or maintenance therapy every 8 weeks) was relevant compared with conventional management (surgery and medical treatment without infliximab) for nonfistulizing resistant Crohn's disease.
Methods: We performed a life-time cost-utility analysis with an analytic Markov decision model from the perspective of the third-party payer system. Utility measurement using Standard Gamble was used to adjust the survival time for each health state of the disease. Direct costs were estimated from standard management based on expert opinion. A sensitivity analysis was conducted to gauge the effects of uncertainty in the values assigned to variables.
Results: The incremental effectiveness with infliximab therapy is .761 Quality-Adjusted Life Years (QALYs) for an added cost ranging from 48,478.79 euros to 596,990.35 euros, depending on treatment procedure. The incremental cost utility ratio expressed in euros per QALYs saved varied from 63,700.82 euros (episodic re-infusions) to over 762,245.09 euros (maintenance therapy).
Conclusions: Infliximab therapy could be cost-effective in the case of relapse treatment only, whereas the marginal cost-utility ratio exceeds conventional benchmarks for maintenance therapy. This analysis will be supplemented by conducting further randomized controlled trials and prospective observational study, focused on the costs of illness (direct and indirect), patient preferences, the disease's clinical course, and infliximab safety.

Keywords: Cost of illness, Quality of life, Crohn's disease

Even if not life-threatening for most patients, active Crohn's disease (CD) disrupts the physical, social, and emotional well-being of patients because of the physical symptoms, hospitalization, surgery, and adverse effects of treatment (20). Health-related quality of life, therefore, is a relevant outcome to consider. Other outcomes such as early retirement, lengthy absence from work, and permanent disability can have an economic impact and must be considered too. Neither medical intervention nor surgery are curative. Existing treatments (corticosteroids, immunosuppressive agents,

aminosalicylates, surgery, and so on), although effective for most patients, are associated with a high incidence of relapse and particularly morbidity because of side effects.

Since 1999, infliximab (Remicade®) is currently indicated for the treatment of patients with moderately to severely active CD resistant to conventional therapy and with fistulizing CD (24;22). It is a chimeric monoclonal antibody directed against tumour necrosis factor-alpha (TNF-α), which is a major factor in the pathogenesis of CD. It leads to control of those forms in approximately 50 percent of cases. Infliximab is, therefore, a promising new therapy in terms of efficacy: its development provides an opportunity to improve significantly health outcomes and patient quality of life, and seems to have the potential to help avoid surgery and admission to the hospital. Nonetheless, additional clinical studies should document the long-term toxicities associated with intermittent or long-term infliximab therapy. Its cost, attributed to hospital budget is substantial, approximately 2,439.18 euros per injection. Because societal resources are limited, governments and third party health-care purchasers will have to make choices about implementing new drugs like Remicade®. For this purpose, economic appraisals provide useful information to aid in decision making and financial negotiations. With this aim in mind, we conducted a cost-utility analysis with a Markov model to compare two therapeutic options for a patient with active CD resistant to conventional therapy: the first was medical care including Remicade®, the second was surgery followed by conventional therapy for CD. Outcomes were measured in terms of health-related quality of life (HRQOL), and costs were estimated from the perspective of the third-party payer system.

METHODS

Study Design

Two alternative strategies have been compared for management of patients with a moderate to severe active ileocolonic CD for at least 6 months, with a Crohn's Disease Activity Index (CDAI) between 220 and 440, resistant to conventional medical therapy (oral corticosteroids for 2 months or more; immunosuppressive agents mercaptopurine or azathioprine for 6 months or more, methotrexate for more than 3 months). We considered that patients entering in the model cohort were 38 years old.

The two options differed first in initial treatment: an intravenous infusion of infliximab 5 mg/kg for strategy 1, surgery for strategy 2; and second in the further treatments including Remicade® for strategy 1 and not for strategy 2. We also tested two approaches to the use of infliximab in strategy 1: the first one was an intravenous infusion of infliximab 5 mg/kg with retreatment when patients relapse or do not respond (option 1); and the second was maintenance infusions of infliximab 5 mg/kg every 8 weeks (option 2). We supposed that these two options were exclusive so that they could not be simultaneously implemented for the same indication. We performed a cost-utility analysis with a Markov model (2;14). We used CD states based on intensity of medical or surgical treatment. Seven states of increased severity, therefore, were individualized as well as death:

- **Remission not following surgery:** no corticosteroids, possible treatment with aminosalicylates, immunosuppressive medications as maintenance treatment, or infliximab.
- **Mild disease:** treatment with aminosalicylates, antibiotics, oral corticosteroids, or immunosuppressive medications.
- **Moderate to severe disease, drug refractory:** treatment with oral corticosteroids (>2 months), immunosuppressive medications (>6 months), or infliximab (one infusion) with no clinical improvement.
- **Moderate to severe disease, drug dependent:** treatment with oral corticosteroids or immunosuppressive medications lasting more than 6 months or infliximab with documented improvement provided that drugs are maintained.
- **Moderate to severe disease, drug responsive:** treatment with oral corticosteroids or immunosuppressive medications or infliximab with documented improvement.
- **Surgery:** state including the hospitalization and 6 weeks of convalescence.
- **Postsurgical remission:** no corticosteroids, possible treatment with aminosalicylates, immunosuppressive medications as maintenance treatment, or infliximab.

The primary measure of effect was survival time adjusted for the quality of life expressed in Quality Adjusted Life Years (QALYs) (26). The time horizon of the analysis was lifelong, and the Markov cycle length was 2 months.

Probability of Events

Transition probabilities from the initial cycle were derived from published data and expert opinion. Targan et al. showed the effectiveness of a single infliximab infusion in a randomized, placebo-controlled trial (24). We assumed a clinical response rate (reduction of 70 points or more in the score on the CDAI) at 8 weeks equal to 65 percent. We considered that patients in clinical response could be in the following health states:" Remission not following surgery," "Mild disease," "Drug-responsive or—dependent moderate to severe disease." The rate of remission (score of less than 150 on the CDAI) at 8 weeks was set to 40 percent. Patients without clinical response could enter to the "Surgery" or "Moderate to severe disease drug refractory" states. These remaining probabilities were also estimated using expert opinion. After initial surgery, we considered that patients could enter "Postsurgical remission," "Mild disease," and "Death" states. The early postoperative mortality rate reported in the literature varies between 0 and 2 percent (8;12;13). We used a 1 percent rate for analysis. Patient repartition into the states "Postsurgical remission" and "Mild disease" reported in the literature is, respectively, 95 percent and 5 percent (25). Transition

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probabilities for subsequent cycles for strategy 2 (initial surgery) were derived from Olmsted County data (23). For strategy 1 (infliximab), we assumed a 5 percent diminution of probability to enter the state "Drug refractory moderate to severe disease" or "Surgery" whereas probabilities to switch to "Remission not following surgery" and "Mild disease" were increased accordingly.

Utility Data

We used the utility measurement assessing quality of life using the Standard Gamble (SG), published by Gregor et al. (9) in a prospective study involving 180 patients with CD. The state "Surgery" is assumed to result in a decreased quality of life comparable to the effects of 1 month with "Severe disease" (great impact of the acute symptoms just before surgery and of the surgical stress on HRQOL) and 1 month with "Moderate disease" (symptoms improvement but weight loss, reduced working capacity, anxiety about future disease activity) as defined by Gregor et al. The utility weight for the "Postsurgical remission" was considered to be equal to that of "Remission not following surgery" (4). Utility score for "Drug-dependent moderate to severe disease" was assimilated with the one for "Moderate disease" described by Gregor et al. (9). Effects and utility were discounted at a rate of 5 percent.

Cost Data

This analysis was conducted from the perspective of third-party payer system. The average cost of 2 month's care per patient, for each modeled health state and for the two strategies evaluated was estimated from standard management based on expert opinion. The following direct cost sources related to CD were considered in our cost-utility analysis: hospitalizations, outpatient care (physicians' visits, nursing care, laboratory), medications, and patient transportation. The cost of inpatient hospitalizations was calculated from the French Diagnosis Related Group system with their quantitative scale: ISA points. Physicians' visits, medications, and patient transportation costs were determined by the negotiated price list. Initial management (daily hospitalizations for an intravenous infusion of infliximab 5 mg/kg or surgery) was taken into account and added in the first cycle for each modeled health state when the transition probabilities were different from 0. Costs were discounted at a rate of 5 percent.

Cost-Utility Analysis

Alternative strategies were compared with the incremental cost-utility ratio, defined as the incremental cost to achieve 1 QALY more.

Sensitivity Analysis

One-way and two-way sensitivity analyses were conducted on influential variables with regard to expected cost and utility (5;15). It was performed on utilities' estimates, transition probabilities from the initial cycle, transition probabilities for subsequent cycles for strategy 1, and the infliximab cost. They were analyzed over a range of values in likelihood interval estimated from the literature or expert opinion. This was done to determine the stability of our results and to gauge the effects of uncertainty in the values we assigned to these variables.

RESULTS

Utility and Cost Data

The strategy including conventional therapies generated the fewest QALY (29.62 QALYS) compared with the strategy involving infliximab (30.38 QALYs). The average costs of 2 months of care per patient, for each modeled health state and for the two strategies are summarized in Tables 1 and 2. The comparator is much less costly than the strategy with infliximab: 71,296.44 euros against 119,801.60 euros or 687,086.96 euros, respectively, when infliximab administration is through episodic reinfusion or maintenance therapy every 8 weeks. Then, no strategy was dominant.

Cost-Utility Analysis

In the first option to the use of infliximab in strategy 1 (intravenous infusion of infliximab 5 mg/kg with retreatment when patients relapse or do not respond), the incremental cost-utility ratio was 63,700.82 euros versus strategy 2 involving conventional therapies. In the second option (maintenance infusions of infliximab 5 mg/kg every 8 weeks), this ratio was 784,057.49 euros versus strategy 2.

Sensitivity Analysis

Utility weights for the states "Postsurgical remission" and "Remission not following surgery" in strategy 2 were identified on a Tornado diagram as influential variables in this model for both approaches to the use of infliximab. However, variation in the cost of infliximab infusion did not lead to a change in our model findings. Concerning the one-way sensitivity analysis on the utility weight assigned to the state "Postsurgical remission," when the "Postsurgical remission" utility score increases, the effectiveness of strategy 2 increases too and becomes greater than the one of strategy 1, so that dominance of strategy 1 is shown with a value of 0.92, for options 1 and 2. Concerning the results of the one-way sensitivity analysis on the utility score of the state "Remission not following surgery," in the same way, the effectiveness of strategy 2 increases when this value becomes higher, but strategy 1 is not dominated within the accepted variation interval between 0.69 and 0.92. The two-way sensitivity analysis was not informative.

DISCUSSION

The evaluation of two options of infliximab prescription as systematic maintenance therapy or re-infusions for relapse

Table 1. Estimated Health State Costs of Two Month Care for Infliximab Treatment Strategies (Euros)

Health state	Medications	Hospitalizations	Outpatient care	Patient transportation	Total
Remission not following surgery (option 1[a])	66.77	126.69	125.62	4.73	323.8
Remission not following surgery (option 2[b])	2,245.12	596.53	125.62	110.22	3,077.49
Mild disease (option 1[a])	66.77	0	113.57	0	180.35
Mild disease (option 2[b])	2,245.12	469.85	113.57	105.49	2,934.03
Drug refractory moderate to severe disease	2,365.7	1,600.71	320.75	105.49	4,392.67
Drug-dependent moderate to severe disease	2,245.12	469.85	113.57	105.49	2,934.03
Drug responsive moderate to severe disease (option 1[a])	201.39	0	270.44	0	471.83
Drug responsive moderate to severe disease (option 2[b])	2,379.58	469.85	270.44	105.49	3,225.36
Surgery	393.62	5,599.76	207.64	121.20	6,322.21
Postsurgical remission (option 1[a])	66.77	126.69	125.62	4.73	323.8
Postsurgical remission (option 2[b])	2,245.12	596.53	125.62	110.22	3,077.49

[a] Option 1: intravenous infusion of infliximab 5 mg/kg with retreatment when patients relapse or do not respond.
[b] Option 2: maintenance infusions of infliximab 5 mg/kg every 8 weeks.

was relevant to anticipate potential therapeutic management changes (11). The relapsing and quiescent lifelong course of Crohn's disease justified Markov modeling. For this Markov process, we used a previously published health state classification defined by type of medical or surgical therapy and by patients' response (23) We introduced some changes because of therapeutic management evolution. First, treatment with salicylates or immunosuppressive medications could be used in the "Remission" and "Mild disease" states as maintenance therapy. In the case of infliximab therapy, no prospective studies to date have shown a change in the clinical course of patients, who either received this maintenance therapy or not. In the case of conventional management, however, it is, now established that salicylates (19) and immunosuppressive therapy (21) prescriptions may have a great impact on clinical history. Nonetheless, transition probabilities entered in the model did not quantify it. Second, for each health state, we considered that infliximab could be used in the case of systematic re-infusion every 8 weeks.

Transition probabilities for strategy 2 (not including infliximab) were derived from a cohort of 174 patients with CD, all stages mixed, with a median duration of follow-up of 10 years (23). However, our base-case is particular, and we can suppose that the real transition probabilities after surgery for a patient already in a severe stage will be different from those observed generally. Unfortunately, the published data were insufficient for making this assumption more accurate. Because of the lack of long-term data about infliximab impact on the disease's clinical history, we assumed, for strategy 1, a 5 percent decrease of probabilities to enter in the state "Drug refractory moderate to severe disease" or "Surgery." In contrast, probabilities to switch in "Remission not following surgery" and "Mild disease" were increased accordingly. Even if reducible, this hypothesis was meant to take into account the potential impact of infliximab on disease course. Clearly, further research is needed to better define the benefit related to treatment with infliximab on clinical course.

An analytic Markov decision model makes it feasible to consider the chronic disease's clinical course with a long time horizon. Therefore, outcome measures should be given for each health state introduced in the model. That is the reason why the length of life adjusted for the quality of life appeared to be the most suitable outcome. It is also the approach used recently by Arseneau et al. (1) in a study examining the economic aspects of infliximab treatment in CD with perianal fistula. Moreover, HRQOL is probably the most relevant outcome to consider, because the burden of chronic symptoms, treatments, and their potential toxicities leads more often to a psychological morbidity and impaired quality of life (6). Furthermore, even if optimally treated,

Table 2. Estimated Health State Costs of Two Months of Care for Conventional Therapeutic Management (Euros)

Health state	Medications	Hospitalizations	Outpatient care	Patient transportation	Total
Remission not following surgery	126.53	68.30	19.51	2.59	216.93
Mild disease	250.78	0	235.23	0	486.01
Drug refractory moderate to severe disease	281.27	3414.10	380.97	131.72	4,208.05
Drug-dependent moderate to severe disease	100.46	0	219.53	0	319.99
Drug responsive moderate to severe disease	232.33	2731.73	219.98	105.49	3,289.54
Surgery	66.77	5529.63	201.99	105.49	5,903.89
Postsurgical remission	84.30	46.80	19.06	1.68	151.84

patients with CD suffer poor HRQOL compared with age- and sex-matched controls (16). Therefore, the goals of therapy are rather to improve quality of life than to increase life expectancy. Existing measures of disease activity, such as the CDAI, laboratory markers, or endoscopic findings are inadequate to fully encompass the patient's illness experience (10;16). One of the strengths of the QALY approach is that it combines gains in duration of survival and gains in corresponding quality of life into a single parameter. To be appropriate for use in cost-utility analysis, measures of HRQOL must be preference-based, interval-scaled, and referenced to death (7). Utilities are a particular approach to the measurement of HRQOL. They can be measured directly by means of techniques such as visual analog scaling, standard gamble, or time trade-off, which provide cardinal preferences measures suitable for cost-utility analysis. We used utility scores derived by the standard gamble method and reported in a prospective study of 180 patients with Crohn's disease. Utility weights used for this analysis were the same in the two arms of our analytic model. These were reported in a study performed before infliximab marketing and distribution. That is one of the limitations of our study that highlights the opportunity to perform a prospective study with the particular aim of determining patient preferences when infliximab is used.

Clinical pattern of disease has been recognized as a major determining factor for recurrences and surgical indications (17;27). Therefore, our base-case was a patient with disease involving both colon and ileum, because it is the most frequent clinical feature, so that we could use the transition probabilities derived from the Olmsted County cohort of 174 patients with CD, all stages mixed (18;23). Moreover, our base-case patient was estimated to be 38 years old to reflect the population enrolled in published trials for treatment-resistant CD (22;24).

We report a detailed assessment of direct costs in CD from standard management based on expert opinion. We are aware of the lack of validity of the data generated by this approach because underestimation of clinical features and clinical management heterogeneity. But this is the first stage of our project, which would be continued with the prospective gathering of cost data during the course of an observational study. Indirect costs are of great interest in chronic diseases such as CD because of decreased earnings, early retirement, and absence from work, but are more difficult to assess. In only one study published, indirect costs of CD were determined in Sweden to be approximately twice the direct costs in 1994 (3). However, detailed data on productivity changes with CD particularly with infliximab are not currently available in a French setting. This analysis will require updates to inform this parameter as far as costs related to long-term adverse events experienced with infliximab treatment.

The added cost of using infliximab in treatment-resistant patients ranged from 48,478.79 euros to 596,990.35 euros, according to treatment procedure: episodic reinfusion or maintenance therapy every 8 weeks. Nonetheless, the incremental effectiveness of 0.761 QALYs was slight in comparison with gain in life expectancy for other interventions such as interferon therapy in a 35-year-old with chronic hepatitis B without cirrhosis with 37 months gained (29). The incremental cost utility ratio expressed as euros per QALY saved varied from 63,700.82 euros to over 762 K euros, respectively, for options 1 and 2 of infliximab therapy use. Although there is no currently accepted absolute standard by which the effectiveness of a medical intervention can be judged to be worth its cost, many widely accepted medical interventions or drugs have marginal cost-effectiveness ratios between $50,000 to $100,000 (56,085 to 112,170 euros) per discounted QALY gained. Thus any new medical intervention with comparable ratio can be considered to be "cost-effective." The marginal cost-utility ratio of option 1 falls within this range, whereas option 2 exceeds conventional benchmarks. A study published in abstract form reports a cost-utility analysis of infliximab therapy in chronic active CD (28). This preliminary analysis suggested that infliximab treatment is cost-effective if infliximab-induced remission is equivalent to medically induced remission or mild disease (US $14,200/QALY and US $40,000, respectively) and should be cost-saving if equivalent to surgical remission. Another study has been published recently by Arseneau et al. (1). Three strategies for infliximab administration were compared with a Markov process to treatment with 6-mercaptopurine (6-MP) and metronidazole alone (comparator strategy) for resistant CD with perianal fistula for a 1-year treatment: the first was three infliximab infusions (0, 2, 6 weeks) and 6-MP/metronidazole for failures; the second was three infliximab infusions (0, 2, 6 weeks) with infliximab reinfusions for failures; and the last was 6-MP/metronidazole with infliximab for failures. The infliximab and 6-MP/metronidazole treatment strategies had quite similar effectiveness values but the incremental cost-utility of infliximab for treating CD perianal fistulae remains above $350,000/QALY for each method of infliximab administration. Indirect costs were not included in this analysis either, because they were considered to be consistent among the different strategies evaluated. The question raised was whether society would be willing to pay the added costs for infliximab treatment when other practices, already proved to be more cost-effective have not yet been made universally available.

Our model is most sensitive to the utility weight for the "Postsurgical remission" in strategy 2, insofar as strategy 1 becomes strongly dominated for a value up to 0.92. Even if not generating a strong dominance of strategy 1, an increase in the utility score of the state "Remission not following surgery" has been shown to generate an increase in the incremental cost-utility ratio. It highlights the great significance of utility estimates in our model; therefore, further examinations should be performed to make them more accurate, in particular when infliximab therapy is used.

CONCLUSIONS

Our cost-utility analysis showed that infliximab therapy could be cost effective in the case of relapse retreatment after the first infusion, whereas the greatest utility afforded by maintenance infusions every 8 weeks may not justify the increase cost. Results that emerge from our study are sufficiently robust, nonetheless they incompletely reflect the real clinical and economical impact of infliximab therapy because of the lack of prospective data. This analysis using medical decision costing algorithms will be supplemented by conducting a multicenter observational study focused on costs of illness (direct and indirect), patient preferences, disease's clinical course, and infliximab safety. Further randomized controlled trials and prospective observational study will also complete the information available on infliximab efficiency for severe resistant CD and help to develop guidelines for more responsible use of expensive medical practice.

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