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TOPIC HIGHLIGHT

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How expensive is inflammatory bowel disease? A critical analysis

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Abstract

Economic analysis of chronic diseases is required for proper allocation of resources and understanding cost-effectiveness studies of new therapies. Studies on health care cost of ulcerative colitis (UC) and Crohn's disease (CD) are reviewed here. These studies were carried out in various countries with disparate health care systems. In the United States, data were often modeled or retrieved from large insurance schemes. Surgery and in-patient hospitalization accounted for over half the outlay on UC and CD. Fistulous disease in CD and parenteral nutrition were very costly. In Canada, overall charges were lower than in the United States, but there too, surgical costs were relatively high. In European studies, economic data were abstracted directly from patients' files. One pan-European study examined the outlay on UC and CD in a community-based prospective inception cohort followed for 10 years. Overall costs in Europe were lower than in the United States. Surgery, hospitalization, year of follow-up, disease phenotype in CD and ASCA-positivity impacted significantly on costs. In all studies, the cost data were right skewed, aminosalicylates were expensive drugs, and biological agents the most expensive; moreover indirect costs were not calculated. Infliximab raised costs considerably in CD, but there were no long-term follow-up studies, so that the cost-benefit of biological agents remains unknown. In conclusion, costs of managing UC and CD vary by country, surgery, genotype and several other factors. The most important question for further research is whether the biological therapies are cost-effective in the long-term.

INTRODUCTION

The science of medical economics, as a branch of welfare economics, is concerned with providing quality health care to patients while streamlining costs. In the current age of escalating health care charges and growing constraints on national health budgets, formal economic analysis of chronic diseases is essential for the proper allocation of resources and the design of cost-effectiveness studies of novel therapeutic agents and diagnostic modalities that are invariably more expensive than existing methods. The fundamental requirements of good economic studies are given in Table 1. Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). These are idiopathic chronic inflammatory conditions that affect the intestines in particular, with a high rate of extraintestinal manifestations[1]. CD and UC present predominantly in young adults, whose concerns relate to their higher education, careers and establishing their families. These persons then find themselves having to cope with illnesses that have life-time morbidity. Life-long medical treatment is required, and often surgery. CD has been shown to have an increased mortality even in its early course[2], but this was not found for UC[3]. Patients spend variable time periods in transition states, which depend on the severity of disease, type of

pharmacotherapy given, need for surgery, and apparently also geographical origin[4,5]. Additionally, there is the risk of intestinal and extraintestinal malignancies, and extraintestinal manifestations in the joints and other systems. There is evidence for a rising incidence of these maladies in many countries, including in Asia and Africa, where cases were scarce until recently[6]. For all the foregoing reasons, the direct health care costs of UC and CD are expected to place a considerable and increasing burden on national health care resources. In addition, there is the large burden of indirect health costs engendered by decreased work productivity and disability[7,8]. This is quite difficult to estimate and no suitable method exists.

There have been a number of studies published on the health care costs of UC and CD and these are reviewed in this article. IC will not be discussed in detail because it is rarer and has been seldom the subject of economic analysis. A MEDLINE search was conducted using the terms ulcerative colitis, Crohn's disease, indeterminate colitis, inflammatory bowel disease, infliximab (and other biological agents), health care cost, economics, charges, cost-benefit, cost-utility, cost-effectiveness, and Markov model, to find pertinent original research articles published after 1990, excluding letters, commentaries and reviews. The studies selected for inclusion will be reviewed by country. Of note, there have been few actual investigations (as opposed to speculative models) attending to the issue of the cost-utility of modern biological agents that are becoming so widely used in CD, and now more recently, in UC. Furthermore, there are new expensive technologies for the investigation of patients with CD and UC. These matters have considerable economic importance.

Table 1 Requirements of good cost-of-disease studies

Requirements
Economic analysis is carried out from the societal perspective
The cohort is community-based
The study provides knowledge of
Total direct cost of a disease
Inclusion of diagnostic costs and treatments until diagnosis
Inpatient and outpatient costs
Resources that drive costs
The analysis
Accounts for the skew of cost data
Provides for time-based discounted downstream costs
The result
Is applicable to patient cohorts from other countries
Provides a basis for cost–utility analysis

COST STUDIES

United States

In the 1990s, the initial cost studies in IBD were carried out in the United States. Hay *et al*[9,10] produced the first reports. They described an economic evaluation of UC and CD using a medical decision algorithm costing methodology, based on examination of 1988-1989 claims data from a major United States commercial medical insurer. They calculated a mean annual direct cost per patient with CD as $6561 (1990 US dollars), and for UC $1488. Surgery accounted for the majority of these sums. The distribution of annual medical expenses was right-skewed. The top 2% of CD patients accounted for 28.9% of total charges and 34.3% of the total amount paid; for UC, the corresponding estimates were 36.2% and 39.0%. Surgery and inpatient costs accounted for some 56% of costs; outpatient care 3.0%-7.1%; initial diagnostic workup 1.5%-7.8%, and medications 10%.

Feagan *et al*[11] used a commercial claims database serving employees of about 50 large companies in the US, to determine the payer costs of CD. Charge claims from 607 patients were analyzed and the results expressed in 1995 US values. The mean annual cost of medical care per patient was determined to be $12417 (95% CI, $10226-$14607). In a sub-set of 117 hospitalized CD patients, the mean annual cost per patient was $37135 (95% CI, $28227-$46043). Pharmacy charges amounted to about 4% of this outlay. The cost data were again right-skewed, with 25% of patients accounting for 80% of total costs. Thus, in 607 CD patients, the median annual cost was $3668 (95% CI, $1417-$12107), and in the sub-set of hospitalized patients the median annual cost per patient was $21671 (95% CI, $11738-$35535). The major determinants of cost, in descending order of magnitude, were inpatient hospitalization, outpatient services, physician office visits and prescription medications. Twenty-seven of the CD patients had a fistula, and these individuals encountered 2.5-fold higher mean total medical care costs, $31370 per patient per year, of which amount, inpatient services contributed 71%.

Silverstein *et al*[4] performed a Markov model analysis of the costs of health care; the utilization/time profile in this study was based largely on assumed conditions. They examined direct health care costs in a population-based inception CD cohort (174 patients, time period 1970-1993), who were residing in Olmsted County, southeastern Minnesota. Clinical information was abstracted retrospectively and sometimes from original medical records, and data on direct medical charges (the payer's perspective) were obtained from a county database. Medical expenses of matched non-CD subjects were subtracted from the health care expenses of the CD patients to derive charges that were then attributed solely to their CD illness. Results were given in 1995 US prices. The estimated life-time direct cost of health care in the CD cohort (with a 5% annual discount rate applied) was $125404. Taking the projected follow-up period of the disease to be 42.6 years (mean age at diagnosis 32.1 years plus assumed 42.6 years of life after diagnosis in a representative patient), the mean cost of health care can be calculated to be $2944 per patient per year of disease. In appreciation of the skew of health care cost data, calculations using median values can be performed instead. The predicted median life-time cost of health care was $39906. Again, using the authors' assumed median follow-up period of 46.4 years (28.1 median age at diagnosis plus 46.4 projected life years),

the median cost can be calculated at $860 per patient per year of disease. Alternately, using the figure of 10 years median follow-up time of the cohort, as stated by the authors, the cost of disease becomes $3991 per patient per follow-up year (or roughly $12 504 mean cost per patient per disease year). Surgery and aminosalicylate therapy accounted for 44% and 30% of the total cost, respectively. The mean cost of surgery was $9109 per patient per month, compared with medical costs up to $1000 per patient per month for cases in remission or with mild disease, or up to $1500 per patient per month for those on steroids and immunosuppression. Charges for physician services constituted the largest component of services for non-surgical patients. CD patients in remission after medical or surgical treatment had health care expenses that were substantially higher than those of the matched controls.

Cohen *et al*[12] looked at the cost of hospitalization in CD patients hospitalized in Chicago. There were 147 patients with 175 hospitalizations, mostly surgical, in a 1-year period ending in June 1997. Duration of hospitalization was: overall, 8.7 d; medical, 7.5 d; and surgical, 9.6 d. The mean overall hospitalization charges, excluding physicians' fees, totaled $12 528, with medical and surgical admissions being $10 020 and $14 409, respectively. The mean charges including physicians' fees amounted to: overall, $35 378; medical, $20 744; and surgical, $46 354. High-cost items were surgery and total parenteral nutrition.

Canada

Bernstein *et al*[13] investigated the direct hospital costs from the payer perspective for a cohort of 187 CD and 115 UC patients at a tertiary care hospital in Manitoba, in 1994-1995. Charts were reviewed to validate that the admissions were for CD or UC only. There were 275 hospital admissions entered in the analysis. Resources used were documented and priced (Canadian $, 1994-1995) according to the hospital billing database. Cases were classified as medical or surgical admissions. Data are shown here for the costs that were related to CD or UC and not non-digestive disease admissions. The mean cost of hospital admission per medical case was C$2571 (95% CI, C$1801-C$3340) for CD and C$2186 (95% CI, C$1449-C$2922) for UC. The mean cost per hospitalized surgical case was higher, with C$3427 (95% CI, C$2728-C$4126) for CD and C$4635 (95% CI, C$3549-C$5726) for UC. Using the median values per hospitalized patient, the medical cost was C$1664 for CD and C$1262 for UC; the surgical cost was C$2546 for CD and C$3341 for UC. Surgery accounted for 50% of all hospital admissions, 58% of all hospital days, and 61% of all costs. Patients with multiple admissions were more costly than those with only a single admission. Patients receiving total parenteral nutrition demonstrated escalated costs. IC was more costly for surgical hospitalization (mean C$6898) than CD or UC.

Europe

Cost studies were reported from Europe in the present decade. Bassi *et al*[14] reported retrospectively the inpatient and outpatient costs, from the payer perspective (UK National Health service), of patients with CD (160 prevalent cases, 12 incident cases), UC (253, 31) and IC (20, three) at a university hospital in north-west England, over a 6-mo period, ending in December 2000. Charges for hospitalization, surgery, outpatient services, investigations and medications were documented. IC was included with UC in the paper. Values were expressed in 2000-2001 values. Costs are re-calculated here to represent a period of a calendar year. The cost for treating CD was £3416 per patient per year, and for UC, £3021 per patient per year. Fourteen percent of the patients were hospitalized during the study period. Inpatient and surgery costs accounted for over half of the costs for CD and UC. Patients not requiring hospitalization had less than 10% of the costs of patients who were admitted. The outlay on oral 5-aminosalicylates exceeded that of all other medications. Cost data were highly skewed: the 10% most costly patients in CD and UC accounted for 59% and 62% of total costs. Variables driving up the cost of disease care were a diagnosis of CD, hospitalization, and severity of illness, but not age, sex or disease extent.

Ebinger *et al*[15] assessed retrospectively the cost of outpatient care in CD (390 patients) and UC (158 patients) in a German university hospital in Ulm from 1997 to 2000, using the payer perspective and the current hospital fee schedule. The mean annual cost for outpatient care was €3171 in all 548 patients, with drugs accounting for 85% of this outlay. The mean cost for one outpatient visit was €162, of which diagnostic procedures accounted for 82% of charges. Costs were higher in patients with disease duration of less than one year. Variables driving the cost of care were frequent visits to outpatient clinics, complications and corticosteroid therapy. Costs were no different between patients with CD or UC.

Odes *et al*[16] carried out a cost analysis in a community-based inception cohort with 10 years of follow up. There were 425 CD patients and 896 UC patients from eight European countries and Israel (the European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD) inception cohort, established 1991-1993) followed through to 2004. Extensive measures were taken to assure the highest rate of case ascertainment. All patients met the exacting diagnostic criteria of Lennard-Jones[1]. Data on consumption of resources were obtained retrospectively from electronic patient questionnaires (in nine languages) and electronic physician-per-patient follow-up questionnaires. The mean annual expenditure (2004 monetary values) on total health care (outpatient care, diagnostics, hospitalization, surgery, medication) in IBD was €1871 (SD €4884) per patient per year over the decade of follow up. The mean outlay on total health care for CD (€2548 per patient-year) was appreciably higher than that for UC (€1524 per patient-year). Mean costs varied considerably between countries, being highest in Denmark at €3705 per patient-year and lowest in Norway at €888 per patient-

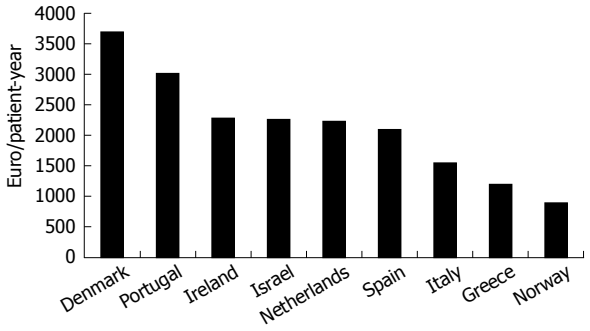

Figure 1 Mean annual cost of health care for IBD patients in the EC-IBD countries with 10-year follow-up. Data provided by EC-IBD.

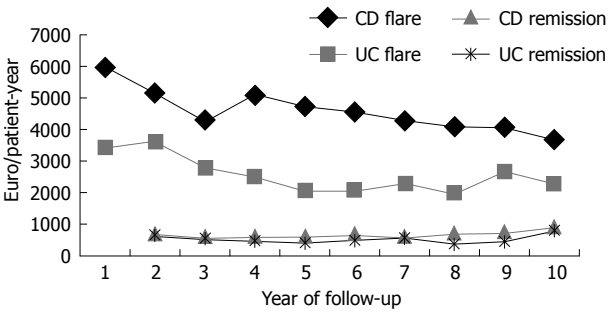

Figure 2 Mean annual expenditure in CD and UC in remission and with flares in the EC-IBD countries during 10 year follow-up. Data provided by EC-IBD.

year (Figure 1). Median costs were lower than mean costs, which confirmed the right skew of the mean cost data. The most expensive resources were hospitalization, which accounted for 63% of the cost in CD and 45% in UC. Total and hospitalization costs were much higher in the first year after diagnosis than in the follow-up period. The significant variables driving the cost of care were country, year of follow-up [year 1: odds ratio (OR) = 3] and diagnosis (CD: OR 1.5); sex and age had no incremental effect on cost. Patients with flares were more expensive than those without during the entire follow-up period (Figure 2). 5-Aminosalicylate was the most expensive drug category; this was the result of a high price and long duration of use. There were too few patients receiving infliximab in this study to greatly affect cost. The extent of disease was found to affect the cost significantly in UC but not CD patients; the cost in CD varied significantly according to the Vienna classification phenotypes. Of importance in this context is the finding that the extent of UC is known to be changeable over time in about half of patients, with extension as well as regression being noted[17].

Juan *et al*[18] reported a cost study on CD in Spain in 2003. It was based on questionnaires to gastroenterologists to obtain disease-related information, and phone interviews to patients to obtain drug utilization data. The annual cost per patient was estimated at between €2104 to €6808 for direct medical costs, and €4704 for indirect costs. Hospitalization and loss of productivity were the items driving these respective costs.

INFLIXIMAB AND COST

Infliximab entered widely into the management of CD over the last decade or so, and since 2006 for UC as well. Recently, other biological therapies have entered the market. Infliximab is an antibody to tumor necrosis factor α which has revolutionized therapy in over 50% of patients who receive this treatment, and who were non-responders to standard medical therapies[19]. There is a developing trend to introduce infliximab earlier into the therapeutic regimen, in the hope that prolonged unresponsive illness, steroid side-effects and surgery may be avoided, and health-related quality of life improved. The use of maintenance therapy with biological agents is gaining acceptance, as it reduces hospitalization and surgery[20]. However, these are expensive agents, and assessment of their impact on short- and long-term health care costs is required. Such studies lead to disease activity scores and outcomes of biological treatments as reported in clinical trials. Not all reports fulfill these criteria. Modeling can only approximate real patient documentation but does provide a useful indicator of costs. To date, there have been few reports published in this area.

Arseneau *et al*[21] were the first to determine the cost-utility of treatment with infliximab in CD with perianal fistulae. Using a Markov model, and with a given cost of a three-course infusion of infliximab of $6420 (2000 prices), the cost of achieving one quality-adjusted life-year exceeded US $350 000. This result was highly dependent on the cost of the medication. Since 2001, the cost of infliximab has decreased somewhat, and several of the disease-course assumptions have changed. A more recent retrospective audit by Jewel *et al*[22], based on 205 patients who received infliximab in seven hospitals in the UK, showed that the mean total health care costs in the 6 mo before the initial infliximab infusion (£2883 per patient) exceeded the mean costs in the 6 mo following the infusion (£2744 per patient), by an average of £139 per patient (a saving of 5%), which suggests that this biological agent is potentially cost-effective. There was a 76% reduction in the number of hospitalization days and 79% of patients reduced or stopped taking corticosteroids. Lindsay *et al*[23] used this study as a basis for determining the cost-effectiveness of scheduled maintenance treatment with infliximab for moderate/severe luminal and fistulizing CD in hypothetical patients in a commercially funded study. Markov models were constructed to simulate the progression of adult CD patients, using transition states estimated from published clinical trials of infliximab, particularly the ACCENT trial. The respective incremental costs per quality-adjusted life year gained were £26 128 and £29 752 in severe luminal and fistulizing CD at a 5-year time horizon. The body weight of patients had the most important impact on the incremental cost-effectiveness ratio, since dosing of infliximab is weight-based. A 10% increase in body weight raises the cost per quality-adjusted life year by some £7000. The reduction in surgery predicted in this

study was similar to that documented by Saro *et al*[24] and the time of follow up was similar. Dose-escalation in patients losing their response to infliximab was very expensive[25].

Jaisson-Hot *et al*[26] carried out a life-time cost-utility analysis with an analytic Markov decision model in non-fistulizing resistant CD patients treated with infliximab (episodic re-infusions for relapse, or scheduled maintenance therapy), compared with conventional surgery and medical treatment. The perspective was that of the third-party payer system. Utility measurement using Standard Gamble was employed to adjust the survival time for each transition state of disease. The incremental cost-utility ratio per quality-adjusted life years saved varied from €63 701 (episodic re-infusions) to over €762 245 (scheduled infusions). The analysis suggested that infliximab could be cost-effective only in the case of treatment for flares of disease.

Saro *et al*[24] reported the impact of infliximab on health care costs in CD patients in northern Spain. There were 34 patients in the study with a mean disease duration of 13.6 years. The mean follow-up time was 9.8 years before and 4.3 years after the first infliximab treatment. About 53% of the patients had penetrating and/or perianal disease, and 41% had extraintestinal manifestations. Following the introduction of infliximab (which was always given as 5 mg/kg body weight) to the treatment regimen, mean hospitalization costs were reduced from €2783 to €679 per patient-year, and the mean surgical cost dropped from €139 to €79 per patient-year. However, the cost of infliximab treatment amounted to a mean €7996 per patient-year. Therefore, the total annual cost of health care increased considerably, from a mean €4464 per patient-year before to a mean €10 594 per patient-year after the introduction of infliximab. This study contradicts that of Jewell *et al*[22]. It must be stressed that all the foregoing studies did not account for the innate fluctuations of disease activity and the so-called placebo-response of the disease, so that future studies need to take these factors into consideration in the interpretation of outcomes and costs after therapeutic interventions.

GENOTYPES AND PHENOTYPES DRIVING COSTS

It would be very useful to identify patients whose genotypes and phenotypes predicted higher health care costs, since aggressive treatment might reduce morbidity as well as cost. Alternatively, genotypes and phenotypes with a better prognosis would be a reassuring finding. It was reported recently that the expenditure on patients with CD was greatly influenced by the disease phenotypes. In a cohort of 418 patients with CD and 10 years of follow-up, the total cost of health care for the Montreal classification[27] behavior phenotypes was €1690 for non-stricturing/non-penetrating, €2081 for stricturing, €3133 for penetrating, and €3356 for penetrating-with-perianal-fistula ($P < 0.001$); all values given as means per phenotype-patient-year[28]. Taking these phenotypes in the same order, the cost of surgical hospitalization was €215, €751, €1293 and €1275 per patient-phenotype-year ($P < 0.001$). Surgical hospitalization costs differed significantly by the location phenotypes: ileum, €558, €209, €492 and €542, expressed as means per patient-phenotype-year ($P < 0.001$). Younger age at diagnosis predicted greater surgical expenses. Estimates of the proportion of CD patients with the various phenotypes of disease vary in different reports[28]. Notably, there is a change in phenotype with length of follow-up, with structuring and penetrating disease becoming more frequent[29]. Unlike behavior, location of disease was shown to be relatively stable over time[29]. Additionally, smoking appears to influence disease location in CD, with current smokers having a lower rate of colonic disease, fewer strictures and fistulae, and a lower rate of surgery[30]. CD patients with stricturing and penetrating disease were more likely to be positive for anti-*Saccharomyces cerevisiae* antibody[31]. CD patients with the NOD2/CARD15 mutation Gly908Arg or positive serology to ASCA had higher health care costs, in particular for surgery, and prolonged hospitalization[32]. However, the mutants Leu1007fsinsC and Arg702Trp had little effect on disease course in that study. ASCA-positive patients were significantly younger at diagnosis than ASCA-negative patients, and Gly908Arg-positive patients showed a trend towards younger age at diagnosis of CD. In another study, NOD2/CARD15 variants in CD patients aged under 16 years were strongly associated with jejunal and ileal involvement, stricturing disease and early recourse to surgery[33]. ASCA is an established serological marker for CD. Moreover, ASCA is frequently detected in CD patients with NOD2/CARD15 allele mutations[34]. NOD2/CARD15 variants constitute a risk factor for ileal site of disease, development of intestinal strictures and fistulae, occurrence of more severe disease, and an increased requirement for surgery[35]. It is possible that measurements of Gly908Arg and ASCA at onset can be used to foretell increased health care costs in CD patients.

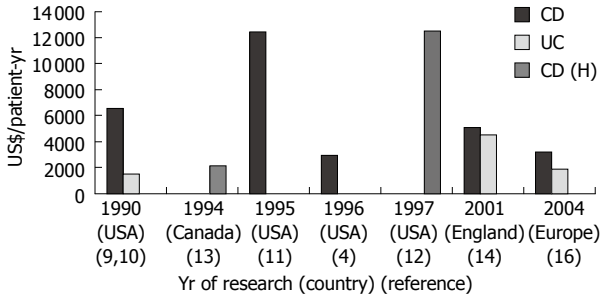

Figure 3 Mean annual total direct cost of health care in selected countries, discounted[36] to year 2004, and expressed as US$ (currency conversions from http://www.oanda.com/convert/fxhistory, accessed 10 May 2008). H: Hospital costs only.

CONCLUSION

CD and UC are serious diseases with considerable health care costs. The studies reviewed above however

displayed considerable disparity of outcomes (Figure 3). These differences clearly cannot be resolved by simply applying a discount rate (currently reckoned to be 2.5%-3.0%[36]) to the costs derived at different time periods. Some of these discrepancies can be attributed to variations of methodology, selection of cohorts, locality, and whether the health care system is private or public. In these studies, the costs were computed from the payer (third party) perspective or from economic data abstracted directly from patients' files, according to the nature of the research. Differences of medical practice would seem to play a role as well. There are also wide differences in the health care price structure within and between countries[9,16]. This could explain some of the differences in health care expenditure between the various European countries that participated in the EC-IBD study. In all the studies, the charges for hospitalization, surgery and biological therapy comprised a large percentage of costs. Despite the trend to do as much care as possible on an outpatient basis, it appears that the rate of hospitalization is increasing[37]. The benefits of keeping patients in remission include a significant drop in the rate of medical as well as surgical hospitalization[38], and therefore a reduction in cost. A new issue in recent years is the welcome development of biological therapies for CD and UC; these drugs have profoundly improved the treatment of these diseases, but with a large price tag. Available economic modeling exercises and the study from Spain imply that infliximab has a relatively high incremental cost per quality-adjusted life year compared with standard care, but this requires further investigation, preferably with real patient data. Comparison of the costs of biological agents with established treatments in trials is complicated by the need to assess the downstream effects of an intervention. In those situations, modeling is a quicker method to obtain cost data, but has its limitations. More data of health cost in CD and UC are certainly required.

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