Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

Costs of Crohn's Disease According to Severity States in France: A Prospective Observational Study and Statistical Modeling over 10 Years

Gilles Boschetti, MD, PhD,[1,2] Stephane Nancey, MD, PhD,[1,2] Fady Daniel, MD,[3,4] Benjamin Pariente, MD, PhD,[5] Eric Lerebours, MD, PhD,[6] Bernard Duclos, MD, PhD,[7] Arnaud Bourreille, MD, PhD,[8] Guillaume Cadiot, MD, PhD,[9] Mathurin Fumery, MD,[10] Jacques Moreau, MD,[11] Philippe Marteau, MD, PhD,[12] Yoram Bouhnik, MD, PhD,[13] Edouard Louis, MD, PhD,[14] and Bernard Flourié, MD, PhD,[1,2] the GETAID[15]

From the Service de Gastroentérologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France; Université Claude Bernard Lyon 1, Lyon, France; [3]Service de Gastroentérologie, Hôpital Lariboisière, AP-HP, Paris, France; [4]Service de Gastroentérologie, American University of Beirut Medical Center, Beirut, Lebanon; [5]Service de Gastroentérologie, Hôpital Claude Huriez, Lille, France; [6]Service de Gastroentérologie, Hôpital Charles Nicolle, Rouen, France; [7]Service de Gastroentérologie, Hôpital Haute-Pierre, Strasbourg, France; [8]Institut des Maladies de l'Appareil Digestif, CHU de Nantes, CIC Inserm 1413, Université de Nantes, Nantes, France; [9]Service de Gastroentérologie, Hôpital Robert Debré, Reims, France; [10]Service de Gastroentérologie, CHU d Amiens, Amiens, France; [11]Service de Gastroentérologie, Hôpital de Rangueil, Toulouse, France; [12]Service d'Hépatologie, AP-HP, Hôpital Saint-Antoine, Paris, France; [13]Service de Gastroentérologie, Hôpital Beaujon, AP-HP, Clichy, France; [14]Depart-ment of Gastroenterology, University Hospital of Liège, Liège, Belgium; and Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du tube Digestif, Service de Gastroentérologie, AP-HP, Hôpital Saint-Louis, Paris, France.

ABSTRACT

Background: To describe the medico-economic characteristics of Crohn's disease (CD), we implemented a multicenter study in France.

Methods: From 2004 to 2006, disease severity states, direct (hospital and extra hospital) and indirect costs were prospectively collected over 1 year in patients with CD naive from anti-tumor necrosis factor alpha (infliximab) at inclusion. Economic valorization was performed from the French Social Insurance perspective, and a statistical modeling over 10 years was performed.

Results: In 341 patients, the mean total costs of management were €6024 per year (€4675 for direct costs). As compared to patients in remission, costs were 4 to 6 times higher in patients in an active period and 19 times higher for patients requiring surgery (SURG). The most important expense items were medical and surgical hospitalizations (56% of total costs), including cost of infliximab (36% of hospitalization costs, i.e., 20% of total costs), indirect costs (22%), and drugs (11%). The statistical modeling over 10 years showed that most of the clinical course was spent in drug-responsive state (54%) with 26% of costs or in remission (32%) with 11% of costs; time spent in a SURG state was small (3.2%) but generated 48% of total costs.

Conclusions: Before the introduction of self-injectable anti-tumor necrosis factor alpha, the most important expenses were supported by hospitalizations, explaining why the most costly states were for patients requiring SURG or dependent on inhospital administrated drugs. Projected data show that most time is spent in a stabilized state with appropriate treatments or in remission, and that costs associated with SURG are high.

Key Words: Crohn's disease, costs, severity states, clinical course, health economics

Given its chronicity and the early onset of its symptoms, Crohn's disease (CD) accounts for substantial costs to the health care system and society.[1] However, because of the variable clinical evolution of each patient and to the variability of the available types of management, CD leads to very different costs depending on patients. Moreover, because of its impact during their most economically productive life period on patient ability to work, this pathology implies significant indirect costs for society. Some previous studies have evaluated the costs of CD management. However, most of them were retrospective[2-7] or based on statistical modeling.[7-10] In addition, they primarily focused on direct costs by leaving off indirect costs, and a few of them included the costs because of anti-tumor necrosis factor alpha (TNFα).[11,12] Finally, they were implemented in other health care systems in Europe or North America, but the understanding of the costs of CD in France has not been evaluated yet.

Therefore, we conducted an observational study of CD to describe prospectively the medico-economic characteristics of this pathology within the French health system. The study was performed before the introduction of self-injectable anti-TNFα and in the setting of a classical step-up care.

Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

PATIENTS AND METHODS

From November 2004 to April 2006 a medico-economic observational study (OCEMIC, Observatoire Clinique et Economique de la Maladie de Crohn) was conducted in 10 French teaching hospitals from the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif to assess the costs of management according to disease severity states and the clinical evolution of CD. Patients included in the study had to be between 18 and 80 years, to have ileal, ileocolonic, or colonic CD, with or without perianal lesions, to be anti-TNFα-naive and to accept a regular follow-up once every 3 months over 1 year. Patients included in another clinical research protocol (which might modify the costs or the clinical history of the disease), having cancer or for whom follow-up seemed difficult to implement (living far from University hospital or referred by a gastroenterologist in private practice), were not included in the study. Patients were included on a consecutive basis during a routine consultation or hospitalization after they had given their written informed consent to the protocol, which had been approved by the Ethics Committee of Lyon's Hospices Civils.

Data collection was jointly performed by practitioners, clinical research associates, and patients with their own data collection notebook which they were to keep and fill out during the entire follow-up. Practitioners or clinical research associates collected the hospitalizations and prescriptions data while patients focused on the drugs they actually purchased and the procedures they underwent. The data notebook consisted in 2 parts: collection of costs and clinical evolution of the disease.

During each 3-month period, the following information regarding 2 types of costs was collected: direct hospital and extra hospital costs and indirect costs. Regarding direct costs, the following data were collected: conventional hospitalizations, day hospitalizations, ambulatory care performed either in hospital or in practice (consultations, laboratory, endoscopic and x-ray examinations), transportation costs (personal car, taxi, or medical transport that were reimbursed by the French Social Insurance), and treatments delivered in practice or after the patient's discharge from hospital. Indirect costs included daily and disability compensations, if any.

Identified and quantified consumptions for various expense items were then valorized in money units (euro) from the French Social Insurance perspective. Stays were classified into diagnosis-related groups. Consultations and ambulatory care were quantified using the French medical classification for clinical procedures. Ambulatory biology procedures were quantified using the French list of medical biology procedures and valorized using the National Table for Biology and the applicable fees as of December 2006. Drug consumption was quantified using the daily or the prescription amount for nondaily drugs. It was valorized from the 2006 rate negotiated between the pharmaceutical industry and the pharmacy of the study hospitals regarding molecules used in a hospital setting. Valorization also included the marketing price of molecules delivered in ambulatory care. Drug cost excluded drugs used in hospital, as in France these were included in the cost of hospitalization. If a drug is considered as being innovative, it may qualify for special funding outside hospital budgets, which is the case for anti-TNFα. Among anti-TNFα, only infliximab (IFX) was used because the study was performed before the introduction of adalimumab, which was registered only in 2007 for CD; costs for inhospital administration of IFX were therefore not incorporated in drug cost, but it was possible to extract IFX cost from the cost of hospitalization. Transportation costs were quantified as the number of return trips between the patient's home and the hospital, and they were valorized from the 2006 convention rates of ambulance companies and other compensation rates.

The number of sick leave days and the assignment of a disability pension were noted. They were valorized using an average daily amount of compensations calculated from the total amount settled by the French Social Insurance over 1 year for sick leave and disability across all pathologies.

Every 3 months for 1 year, information regarding the evaluation of the disease and treatments were systematically collected by physicians at each visit. Depending on the treatments followed during the elapsed period and responses to these treatments, patients were categorized in a disease severity state according to the classification of Silverstein et al[7] excluding mortality. These severity states are presented in Table 1. The categorization of patients in a given severity state was determined both by the heaviest treatment they underwent and the way they responded to it, whatever the treatment duration. For patients who underwent surgery (SURG) state, if clinical symptoms were still present after surgery, the following period was categorized according to the response to the postoperative treatment. On the contrary, when symptoms disappeared, the following period was systematically classified as postsurgical remission state (REMPS), whatever the drugs received by patients.

Data Analysis

Cost analyses were performed for the 8 severity states of CD. Quarterly costs were presented with their mean values and 95% confidence intervals (CI). Mean costs were compared among the various health states with the

Kruskal-Wallis test.

The nonparametric Mann-Whitney test was used to compare states by pairs when the Kruskal-Wallis test was significant with Bonferroni correction.

A Markov model analysis, adapted from Silverstein et al,[7] was performed. The model allowed comparisons with earlier publications of probability analysis of the outcomes in CD. For these analyses, remisssion without treatment (REM0), remission with mild treatment (REM1), and postsurgical remission (REMPS) states were analyzed as an aggregated severity state called "remission". A matrix of transition probabilities was created that provided the probability of transitioning from one disease state to any other from one 3-month period to the next period. Transition probabilities between consecutive 3-month periods were calculated as the number of patients in one disease state in a 3-month period divided by the number of patients in the disease state they came from in the previous 3-month period. According to Silverstein et al,[7] the median costs for each state were applied over the entire cohort. Using the transition probability matrix and then running the model over a large number of cycles (40 quarters), the total time spent in each severity state and the related costs were predicted over 10 years. We assumed that the course of the disease over a relatively short period (10 years) could be modeled with observations from 1 year of patients with CD with different severity states, and that transitions recorded in serial 3-month cycles during 1 year of a thorough follow-up remained constant. We assumed that transitions were not affected by age, smoking, and duration of the disease. Finally, we assumed that costs did not change and that 10 years costs reflected the costs in each health state observed over 1 year.

The database was created using the ACCESS 2000 software. Data were analyzed using the following software: SAS Version 6 (SAS, Cary, NC); SPSS version 11 (SPSS, Chicago, IL); and R ("The msm package") version 0.7.6 (December 2007; Revolution Analytics, Mountain View, CA).

TABLE 1. Disease Severity States over the Past 3 Months

REM0	Patients in remission with no treatment (except for antidiarrhea drugs, if any)
REM1	Patients in remission with a mild treatment (either general or topical: 5-ASA, antibiotics, topical corticosteroids)
MILD	Patients with mild symptoms and treatment (either general or topical: 5-ASA, antibiotics, topical corticosteroids)
RESP	Patients with either oral corticosteroids and/or an immunosuppressive therapy and/or anti-TNFα who responded to these treatments
DEP	Patients with either oral corticosteroids and/or an immunosuppressive therapy and/or anti-TNFα who responded to these treatments but who also grew dependent to these drugs
REF	Patients with either oral corticosteroids and/or an immunosuppressive therapy and/or anti-TNFα but who were refractory to these treatments
SURG	Patients who underwent inpatient surgery
REMPS	Patients in postsurgical remission

5-ASA, 5-aminosalicylates.

RESULTS

Three hundred seventy-four patients were included in the study over a period of 17 months; 33 were excluded of the analysis for the following reasons: 18 lost to follow-up, 1 cancer, 7 dropouts,

2 doubles, and 5 included in another protocol. A total of 341 patients were therefore followed up enabling to obtain 1364 follow-up quarters. The characteristics of patients are described in Table 2.

Distribution of Costs According to Expense Items over the Entire Cohort and to Severity States

Quarterly total mean costs, across severity states, were €1506 (95% CI €1365 to €1648) per patient. Table 3 describes the distribution of total costs according to expense items. In this cost distribution, the "Hospitalizations" item ranked first with 56.0% of expenses. The expense items are as follows: "Disability" (13.2%), "Drugs" (11.2%), and "Sick leave" (9.2%).

Figure 1 describes the quarterly total, direct, and indirect mean costs (and their 95% CI) according to disease severity states. The surgery (SURG) and dependent (DEP) states had the highest mean total costs. These were significantly higher ($P < 0.001$) than the mean total costs of all other states. The refractory (REF) state also showed high mean total costs, which were significantly higher ($P < 0.05$) than the responsive (RESP), mild

Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

(MILD), remission without (REM0), and with mild treatment (REMI) states. The REMO and REMI states had the lowest mean total costs, which were significantly lower ($P < 0.001$) than all others states, excepted for the MILD state.

The quarterly mean costs according to both expense items and severity states are given in a Table (see Supplemental Digital Content, http://links.lww.com/IBD/B380). The SURG quarters showed the highest mean score expense ($P < 0.05$) for hospitalizations as compared with the quarters of all other severity states.

TABLE 2. Characteristics of Patients at Baseline

	Patients (n = 341)
Male	120 (35.2%)[a]
Age at baseline	35 (18-72)[b]
Age at diagnosis	26 (4-66)[b]
No. years of evolution at baseline	9 (0-46)[b]
Weight (kg)	61 (38-112)[b]
Height (cm)	167 (131-200)[b]
Familial form of the disease	14.1%
Extradigestive manifestations	30.8%
Articular manifestations	25.8%
Skin manifestations	9.1%
Ocular manifestations	2.3%
Bowel disease without perianal lesion	61.9%
Bowel disease and perianal lesions	38.1%
Smoking history	59.2%
Smoking at baseline	37.8%
History of bowel surgery	44.6%
History of surgery for perianal lesions	19.1%
History of surgery for bowel disease and perianal lesions	8.5%
Associated pathologies	18.2%

[a]n (%).
Mean (range).

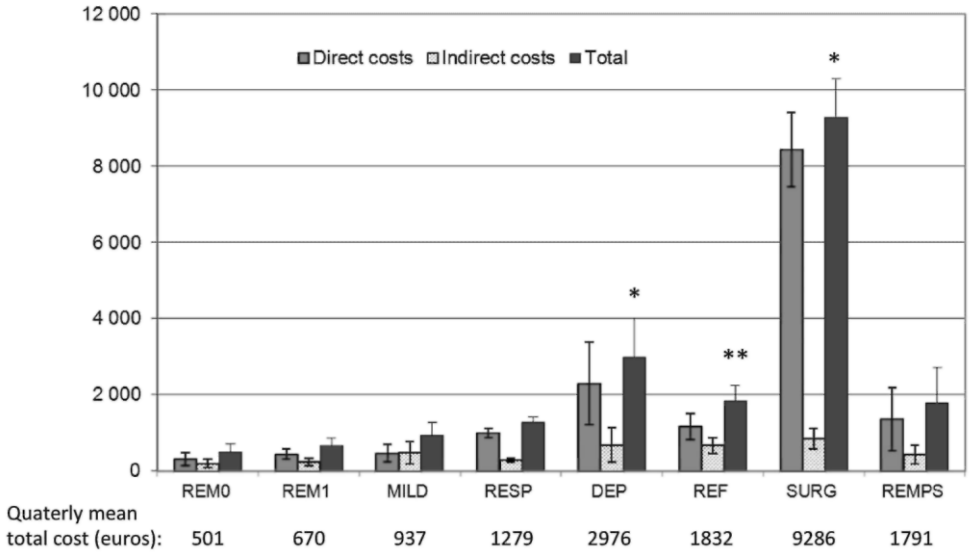
TABLE 3. Distribution of Total Costs According to Expense Items

Hospitalizations	56.0%[a]
Disability	13.2%
Drugs	11.2%[b]
Sick leave	9.2%
Consultations	3.4%
Transportations	3.0%
Biology	2.4%
Nursing care	0.8%
Examinations[c]	0.8%

[a]Cost of IFX accounting for 36% of hospitalization cost. [b]Excluding IFX. [c]Radiology and endoscopy.

Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

FIGURE 1. Quarterly mean direct, indirect, and total costs and 95% confidence intervals in euros according to severity states. Remission without (REMO) and with mild treatment (REM1) states; mild (MILD), responsive (RESP), dependent (DEP), refractory (REF), surgery (SURG) and postsurgical remission (REMPS) states. *P < 0.001 vs other severity states; **P < 0.05 vs REM0, REM1, MILD, and RESP states.



Descriptive Analysis of Care Consumption

The "Hospitalization" item represented 7%-84% of all expenses depending on the severity state; most significantly for the SURG (84%) and DEP (62%) states (Fig. 2). Among all 434 hospitalizations noted during the follow-up of study patients, most were day hospitalizations (56%), especially in the DEP (100%), REF (87%), and RESP (69%) states. As expected, the SURG state had the lowest proportion (2%) of day hospitalization, which most often consisted in conventional hospitalization. Furthermore, within hospitalization-related management costs, cost of IFX accounted for 36% of costs, i.e., approximately 20% of total costs.

Indirect costs represented a notable proportion of the overall patient management, accounting for 9% to 50% of the management costs across severity states (Fig. 2). Over the entire cohort (341 patients), 87 patients (25.5%) benefited from at least one sick leave. The longest sick leaves were in the SURG (24.1 days per quarter), REF (11.3 days), and REMPS (10.6 days) states. At baseline, 35 (10.3%) of 341 patients were disabled, and 10 patients were recognized as disabled during the study, i. e., 45 patients (13.2%) disabled after the follow-up.

The "Drugs" item, which was the third overall expense item (Table 3), included all prescribed treatments except for the molecules administered in hospital (in particular IFX) whose expense was included in "Hospitalizations" expense item. Across severity states, the proportion which can be attributed to therapeutic prescriptions remained notable (>10%), except for the DEP and SURG quarters (Fig. 2). Figure 3 shows the percentage of quarters with each prescription type according to severity states. 5-ASA and antibiotics prescriptions were recorded in all severity states, even if there were more prescribed for the REM1 (83% and 8%, respectively) and MILD (41% and 53%, respectively) states, and 16% of all costs related to the "Drugs" item came from 5-ASA. An immunosuppressive therapy was prescribed in more than half periods of the SURG and REMPS states and for most patients in the RESP (94%) and REF (93%) states. A systemic Fifty-three of 341 patients received at least one infusion of anti-TNFα (IFX in all patients). Anti-TNFα were prescribed in 50% of DEP quarters, which was more than the immunosuppressive prescription. They were also prescribed in 18% of SURG quarters, 15% of REF quarters, 13% of RESP quarters, and 7% of REMPS quarters. However, for these latter states, most prescriptions were for immunosuppressive therapies (Fig. 3).

Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

FIGURE 2. Quarterly contribution of each expense item according to severity states. Remission without (REM0) and with mild treatment (REM1) states; mild (MILD), responsive (RESP), dependent (DEP), refractory (REF), surgery (SURG) and postsurgical remission (REMPS) states.

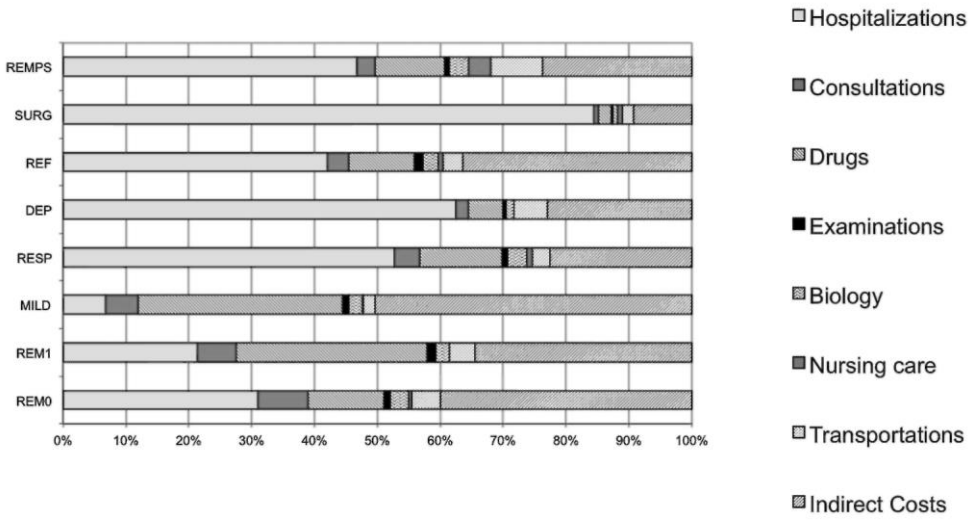
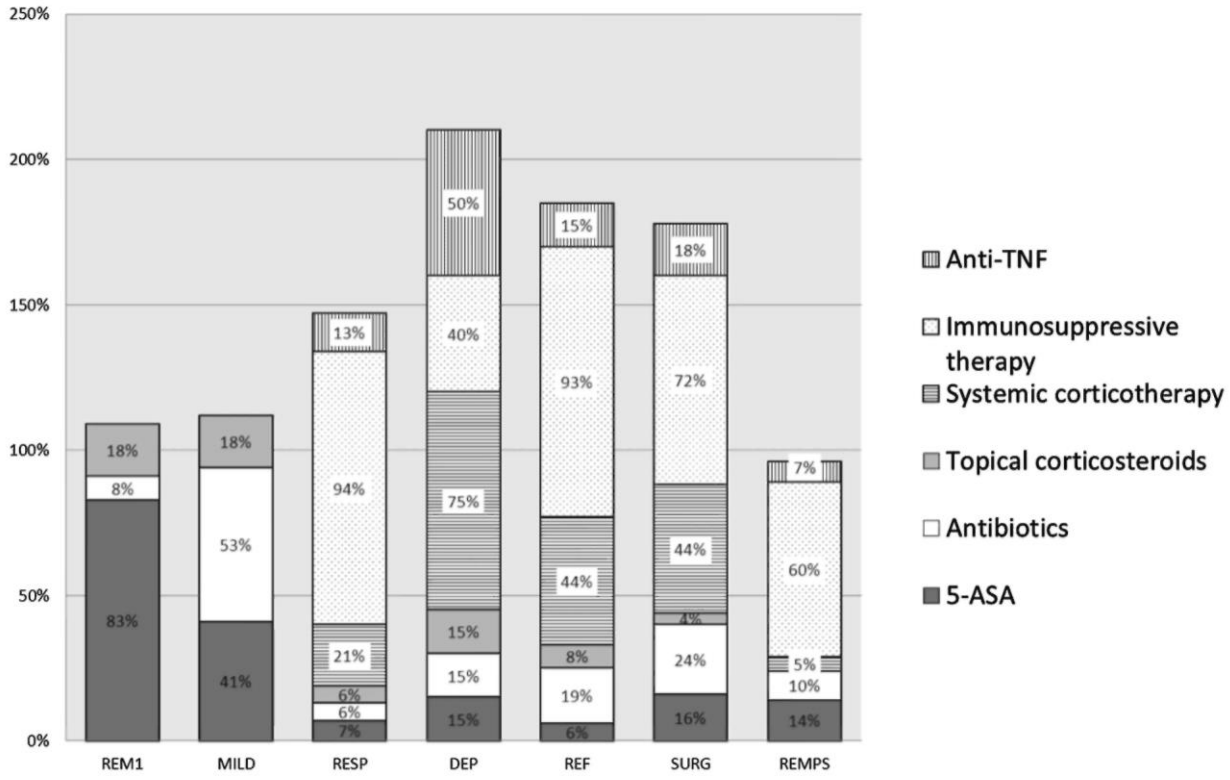


FIGURE 3. Percentages of quarters with each prescription type according to severity states. Patients could have several drug prescriptions. Remission with mild treatment (REM1) states; mild (MILD), responsive (RESP), dependent (DEP), refractory (REF), surgery (SURG) and postsurgical remission (REMPS) states.



Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

TABLE 4. Maximum Likelihood Estimates of 3-Month Probabilities of Transition Between Disease States

Initial State	Subsequent State: Remission	MILD	RESP	DEP	REF	SURG
Remission	0.7785078	0.0588951	0.1272685	0.0054279	0.0151610	0.0147398
MILD	0.5471048	0.3214273	0.1121997	0.0028207	0.0085554	0.0078920
RESP	0.0490997	0.0055976	0.8584385	0.0075244	0.0530859	0.0262539
DEP	0.0840664	0.0046121	0.4875960	0.1441640	0.2157691	0.0637924
REF	0.1026554	0.0051480	0.4285063	0.0541496	0.3305341	0.0790066
SURG	0.5394939	0.0288836	0.1993706	0.0064110	0.0413200	0.1845209

corticotherapy was frequently prescribed in the DEP (75%), REF (44%), and SURG (44%) states.

Statistical Modeling over 10 Years

The maximum likelihood estimates of the 3-month probabilities of transition between the initial to the subsequent state are shown in Table 4. The vast majority of patients with CD in remission (without or with minor medications) or considered as drug-responders to a treatment with oral steroids, immunosuppressants, or IFX at the onset of the follow-up stayed either in remission (78%) or in response to their therapy (86%) during the following 3 months (Table 4). In addition, half of the patients who experienced a CD-related drug-DEP state and 43% of patients considered as a drug-REF state became drug-responders (RESP state) during the 3 following months. Whereas, only 22% patients with a drug-DEP CD moved to a drug-REF state; one-third of the patients with a severe disease associated with a drug-REF continued with the same state during the following quarter. Although 18% of patients who underwent a CD-related surgery were reop-erated during the 3 following month period, as expected the majority of them (54%) achieved disease remission upon surgery.

Figure 4 shows the observed and projected time spent in each severity state over 1 and 10 years depending on the application of transition probabilities. Over 10 years, the proportions of time spent were a little higher in remission and lower in RESP state than over 1 year. Patients will spend most of the 40 quarters in the RESP state (i.e., responsive to treatments with steroids, immunosuppressants or IFX) with 54.0% of the total time spent in this severity state or in the remission state with 32.0% of the total time. On the contrary, the DEP, MILD, REF, and SURG were more transient states with only 1.2% to 6.0% of the total time spent in these severity states. Over 10 years, the RESP and remission states represented 26% and 11% of costs, respectively (Table 5). The MILD, DEP, and REF states represented from 3% to 8% of costs. Time spent in the SURG state, even if it represented only 3.2% over 10 years, had a major economic impact because it represented approximately 48% of costs (Figure 4 and Table 5).

DISCUSSION

Our medico-economic study was performed outside any standardized research protocol, which enabled to evaluate direct and indirect costs as well as clinical course in a real life practice condition. Moreover, on the contrary to most previous studies, which were retrospective and based on medical reports or insurance databases, this study design was prospective with a 1 -year follow-up and the cost data were directly collected taking into account the different disease severity states. Our study also included an original aspect: it was based on an observation collection notebook managed by the patients themselves. This notebook was introduced to obtain the most comprehensive collection of ambulatory care data and to evaluate real patient care consumption.

The mean quarterly management costs of CD in our cohort (across all severity states) were €1506 per patient, i.e., €6024 per year (€4675 for direct costs and €1349 for indirect costs). According to severity states, the mean quarterly costs ranged from €501 to €9286. These costs were presented using mean values, as in some severity states (especially for patients in remission) more than 50% of quarters did not lead to any costs and medians were often equal to zero. Our results are actually consistent with the patients' health status degradation and therapeutic needs. Indeed, as compared with patients in the REMO state, direct costs were 4 and 6 times higher in patients in REF and DEP states, respectively, and 19 times higher in the SURG state requiring hospitalization. The literature review by Yu et al[13] also concluded that patients with a severe form led to costs 3 to 9 times higher than for patients in remission. Other retrospective studies had already objectified and quantified that an active period of the disease increased the ambulatory costs by 2 or 4, and that in case of hospitalizations, costs were multiplied by at least 20.[2,14,15] Odes et al[16] who were interested in economic outcomes in a retrospective CD cohort showed also highly significant differences in mean costs between 7 severity states which were close to ours.

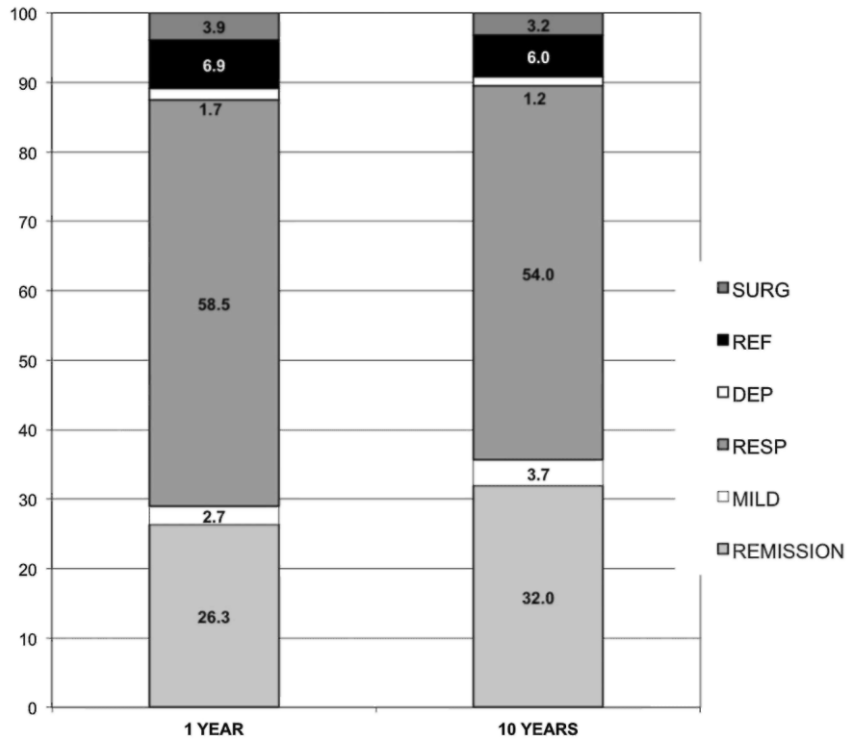
Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

Particularly, as compared to patients in remission (medical or surgical), annual health care costs were 4 to 10 times higher in patients in "drug" states (drug-RESP, drug-DEP, or drug-REF) and more than 30 times higher in the SURG state.

In France, before the introduction of self-injectable anti-TNF*α* agents, inpatient stays including IFX-related costs represented the most significant expense item in CD management with 56% of total costs and 72% of direct costs. This explains why the most costly states were for patients requiring SURG and DEP to drugs in whom inhospital infusions of IFX were more frequent. A retrospective study published in 2006[5] on direct medical costs performed in a large cohort from 8 European countries and Israel before the wide use of anti-TNF*α* concluded that the most significant expenses were related to medical or surgical hospitalizations, accounting for 63% of CD costs. Our results are consistent with this study, even though they are in the top range, probably because of IFX-related costs (≈16% of patients received at least one perfusion of IFX), which were included in "Hospitalizations" expense item. Cost of IFX was quite significant because it represented 20% of total costs and 26% of direct costs. This result is therefore close to those found in the Kappel-man et al[17] case-control study (in which 10% of patients with CD received IFX infusions) and during the first year after CD diagnosis in the EpiCom cohort[18] (in which 15% of patients with CD received anti-TNFα, mainly IFX), where anti-TNF*α*-related costs represented ≈20% of direct costs. Interestingly, in a recent study[19] after the introduction of IFX and adalimumab and including a large cohort of patients with CD (23% on anti-TNF*α* therapy, mainly adalimumab) invited to fill in a 3-month web-based follow-up questionnaire, the traditional cost profile has changed and health care costs are now mainly driven by anti-TNF*α* (64%), hospitalization accounting for a minor part of the health care cost (20%). Similar results were found in a cross-sectional German study; anti-TNF*α* and hospitalizations accounting for respectively 58% and 21% of the direct costs, even though only 8% of patients were treated with anti-TNF*α*.[20]

In our cohort, the "Drugs" item, which excluded anti-TNFα, also represented a significant expense item in the management of patients with CD because it was the third item after the "Hospitalization" and "Disability" items, with 11% of total costs and 14% of direct costs. Among the costs related to drug prescriptions, 16% are due to 5-ASA. This proportion was close to that reported in studies performed in the biological era.[17,18]

FIGURE 4. Proportion of time spent in each severity state observed over 1 year and projected over 10 years (40 quarters). Remission without and with mild treatment and post-surgical states (remission); mild (MILD), responsive (RESP), dependent (DEP), refractory (REF), surgery (SURG) states.



Published in: Inflammatory Bowel Diseases (2016), vol.22, pp. 2924-2932. DOI 10.1097/MIB.0000000000000967
Status : Postprint (author's version)

TABLE 5. Projected Time Spent in Each Severity State and Costs in Euros over 10 Years

Disease State	Course (Quarter)	%	Median Costs	%	Mean Costs	%
Remission	12.8	32.0	2620	10.6	9483	16.8
MILD	1.5	3.7	656	2.6	1377	2.4
RESP	21.6	54.0	6366	25.8	27,601	49.1
DEP	0.5	1.2	1219	4.9	1488	2.6
REF	2.4	6.0	2002	8.1	4397	7.8
SURG	1.3	3.2	11,845	47.9	11,886	21.1
Total	40	100	24,707	100	56,232	100

Sick leave and disability (indirect costs) represented the second most significant expense item in our cohort after hospitalization, with 22% of total costs. However, the financial impact of disability was more significant (13%), with 13.2% of patients disabled at the end of the study, a rate which varies widely in the literature depending on the setting in which disability was measured and on how it was defined.[22] Bassi et al[2] and van der Valk et al[20] estimated that indirect costs (corresponding to loss of employment days) accounted for 16% to 18% of total costs. In our study, we took into account only the daily compensations for sick leave and disability, which underestimate the total significance of indirect costs. Taking into account the labor force nonparticipation resulting from early retirement or unemployment and the reduced productivity ("absenteeism" and "presenteeism") in the evaluation of indirect costs goes further than our study by adopting a societal perspective (contrary to our French Social Insurance perspective). [12,22-24]

The results of the statistical modeling over 10 years show that patients will spend most of the 40 quarters in the RESP state (i.e., responsive to major treatments) with 54.0% of the total time spent in this severity state or in the remission state with 32.0% of the total time. On the contrary, the DEP, MILD, and REF are more transient states with only 1.2% to 6.0% of the total time spent in a severity state. There are 2 earlier publications of probability analysis of the outcomes in CD, including economic analysis. From a direct cost estimation study retrospectively performed over 46 years in a cohort of 174 patients with CD diagnosed from 1970 to 1993, Silverstein et al[7] concluded that patients would spend most of their time in the remission (REM: 23.9% or REMPS: 40.7%) and MILD states (27.3%). More recently, Odes et al[16] established similarly that most time was spent in mild (51%) or remission (24%) states in the European Cohort (EC)-IBD cohort (318 patients with CD) during 10 years of follow-up with data inclusion ending in 2004. These discrepancies with our results may result from the evolution of therapeutic strategies in CD, especially regarding the use of immunosuppressive therapies,[25] which used to be limited to the most severe disease forms. The results are actually quite consistent: most time is spent in a remission state or stabilized using appropriate treatments. The SURG state represents few quarters over our 10-year projection, but is very costly.

Our study has some limitations. It may be argued that patients were included in reference centers thus not representing the whole population of patients with CD. However, we wanted to enroll a large number of patients allowing us to capture patients accessing care for a wide variety of purposes, ranging from patients requiring hospitalization through consulting patients whose only contact with the hospital might have been a routinely scheduled surveillance visit. Therefore, key cost drivers such as expensive biological therapies are included and important patient subgroups, such as the most severely ill, are accounted for. We included patients naive of anti-TNFα, which may lead to underestimate IFX cost by excluding patients already treated by IFX. Indirect costs were underestimated because we aimed to collect only objective data and did not measure labor force nonparticipation (resulting from early retirement or unemployment) and reduced productivity. We can also mention some limitations regarding the statistical model. First, the chosen health status was the worst over the period, but it might not be the most representative of the most present state over the quarter. The treatment received by the patient defined both the disease severity state and the factor leading to a change into the following severity state. Second, transition probabilities were accurately measured over 1 year, and we considered that they were not modified over time; consequently, extrapolation from 1 year to 10 years may be somewhat inaccurate. The relatively short follow-up limited our ability to detect outcomes with long periods of induction-latency, such as cancer or death. Although factors, such as disease history or localization, smoking, behavior phenotypes or therapy by anti-TNFα, could affect CD outcome, our study was not designed and powered to analyze the impact of such factors on transition probabilities. Third, the model did not identify the usual binary nature of surgery and recorded these as successive surgery cycles. This may have overestimated the costs associated with surgery. Concerning costs, sensitivity analysis was not performed to assess any impact of changes in the discount rate of medication or in other health care costs. Finally, our results are somewhat

outdated because self-injectable anti-TNFα, such as adalimumab, has not been evaluated in our study performed before these products came on the market in France. These new therapies have proven to be less costly than IFX.[26] However, our results are always valid for IFX. Moreover, in France, there exists no CD reference study that can be used as a comparator to assess improvements or impairments over time with the introduction of self-administrable anti-TNFα or intravenous biosimilars and innovative biological agents requiring hospitalization.

The increasing use of new expensive technology (magnetic resonance imaging and capsule endoscopy) will increase the outlay on diagnostics and regular assessments in CD in the coming years. However, the growing use of anti-TNFα and newer biological therapies, although quite expensive, may keep patients out of the hospital, avoid surgery, and reduce direct as well as indirect costs.[27-29] From our results, the latter cost savings could exceed the additional treatment costs, reducing spending on CD care overall. Some limited evidence exists to support the existence of this effect.[20]

In conclusion, this is the first study that evaluated costs of CD from the perspective of the French Social Insurance shedding insight on direct and indirect CD costs in France, outside any standardized research protocol. The analysis according to disease severity states confirms the major economic impact of the active periods and complications of the disease, whereas the impact of indirect costs is significant whatever the disease state. In addition, our prospective study provides an estimate of the clinical course of patients with CD taking into account newer therapeutic modalities. However, the presented picture highlights the architecture of the cost of CD management in the setting of a classical step-up care and without subcutaneous biologies; it could allow sensitivity analyzes on the impact of new agents and/or therapeutic strategies.

ACKNOWLEDGMENTS

The authors thank P. Guerre, I. Jaisson-Hot, S. Bastide, A. Belot, M. Rabilloud, and C. Colin for their help in collecting and entering the study data.

Supported by grant from the Plan Hospitalier de Recherche Clinique (Hospices Civils de Lyon), by the Association François Aupetit, and by the grant from Schering-Plough.

G. Boschetti, S. Nancey, B. Pariente, G. Cadiot, J. Moreau, and E. Louis report receiving lecture fees and travel support from MSD and AbbVie; A. Bourreille, Y. Bouhnik, and B. Flourié from MSD, AbbVie, and Ferring; P. Marteau from MSD, AbbVie, Ferring, and Hospira; The remaining authors have no conflict of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

REFERENCES

1. Burisch J, Jess T, Martinato M, et al. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis.* 2013;7:322-337.

2. Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut.* 2004; 53:1471-1478.

3. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med.* 2008;50:1261-1272.

4. Feagan BG, Vreeland MG, Larson LR, et al. Annual cost of care for Crohn's disease: a payor perspective. *Am J Gastroenterol.* 2000;95: 1955-1960.

5. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology.* 2006;131:719-728.

6. Cohen RD, Larson LR, Roth JM, et al. The cost of hospitalization in Crohn's disease. *Am J Gastroenterol.* 2000;95:524-530.

7. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology.* 1999;117:49-57.

8. Malone DC, Waters HC, Van Den Bos J, et al. A claims-based Markov model for Crohn's disease. *Aliment Pharmacol Ther.* 2010;32:448-458.

9. Hay AR, Hay JW. Inflammatory bowel disease: medical cost algorithms. *J Clin Gastroenterol.* 1992;14:318-327.

10. Buchanan J, Wordsworth S, Ahmad T, et al. Managing the long term care of inflammatory bowel disease patients: the cost to European health care providers. *J Crohns Colitis.* 2011;5:301-316.

11. Bernstein CN, Longobardi T, Finlayson G, et al. Direct medical cost of managing IBD patients: a Canadian population-based study. *Inflamm BowelDis.* 2012;18:1498-1508.

12. van Deen WK, van Oijen MGH, Myers KD, et al. A nationwide 2010-2012 analysis of US health care utilization in inflammatory bowel diseases. *Inflamm Bowel Dis.* 2014;20:1747-1753.

13. Yu AP, Cabanilla LA, Wu EQ, et al. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin.* 2008;24:319-328.

14. Mesterton J, Jönsson L, Aimer SHC, et al. Resource use and societal costs for Crohn's disease in Sweden. *Inflamm Bowel Dis.* 2009;15:1882-1890.

15. Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. *J Gastroenterol Hepatol.* 2007; 22:1306-1312.

16. Odes S, Vardi H, Friger M, et al. Clinical and economic outcomes in a population-based European cohort of 948 ulcerative colitis and Crohn's disease patients by Markov analysis. *Aliment Pharmacol Ther.* 2010;31:735-744.

17. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology.* 2008;135:1907-1913.

18. Burish J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom study. *Inflamm Bowel Dis.* 2015;21:121-131.

19. van der Valk ME, Mangen MJJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. *Gut.* 2014;63:72-79.

20. Prenzler A, Bokemeyer B, von der Schulenburg JM, et al. Health care costs and their predictors of inflammatory bowel diseases in Germany. *Eur J Health Econ.* 2011;12:273-283.

21. Büsch K, da Silva SA, Holton M, et al. Sick leave and disability pension in inflammatory bowel disease: a systematic review. *J Crohns Colitis.* 2014;8:1362-1377.

22. Juan J, Estiarte R, Colomé E, et al. Burden of illness of Crohn's disease in Spain. *Dig liver Dis.* 2003;35:853-861.

23. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scand J Gastroenterol.* 1997;32:1134-1139.

24. Stark R, König HH, Leidl R. Costs of inflammatory bowel disease in Germany. *Pharmacoeconomics.* 2006;24:797-814.

25. Cosnes J, Nion-Larmurier I, Beaugerie L, et al. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut.* 2005;54:237-241.

26. Sussman DA, Kubiliun N, Mulani PM, et al. Comparison of medical costs among patients using adalimumab and infliximab: a retrospective study (COMPAIRS). *Inflamm Bowel Dis.* 2012;18:2043-2055.

27. Lichtenstein GR, Yan S, Bala M, et al. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol.* 2004;99:91-96.

28. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology.* 2008;135:1493-1499.

29. Feagan BG, Reilly MC, Gerlier L, et al. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECISE 2 study. *Aliment Pharmacol Ther.* 2010;31:1276-1285.