

## INFLAMMATORY BOWEL DISEASE

# Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery

J Cosnes, I Nion-Larmurier, L Beaugerie, P Afchain, E Tiret, J-P Gendre

*Gut* 2005;54:237–241. doi: 10.1136/gut.2004.045294

See end of article for authors' affiliations

Correspondence to:  
Pr Jacques Cosnes, Hôpital Saint-Antoine, 184 rue du Faubourg St-Antoine, 75571 Paris cedex 12, France; jacques.cosnes@sat.ap-hop-paris.fr

Accepted for publication  
3 June 2004

**Background/Aim:** Immunosuppressants are now used much earlier in the course of Crohn's disease; however their effect on the natural history of the disease, especially on the need for surgery, is not known. The aim of this study was to assess the evolution of the need for surgery in Crohn's disease during the last 25 years.

**Patients and Methods:** The medical charts of 2573 patients were reviewed retrospectively. The use of immunosuppressants (azathioprine or methotrexate), the need for intestinal resection, and the occurrence of intestinal complications were assessed using Kaplan-Meier analysis in five consecutive cohorts of patients defined by the date of diagnosis of Crohn's disease (1978–82; 1983–87; 1988–92; 1993–97; 1998–2002).

**Results:** In 565 patients seen in the authors' unit within the first three months after diagnosis, characteristics of Crohn's disease at diagnosis did not differ from one cohort to another. The five year cumulative probability to receive immunosuppressants increased from 0 in the 1978–82 cohort to 0.13, 0.25, 0.25, and 0.56 in the 1983–87, 1988–92, 1993–97, and 1998–2002 cohorts, respectively ( $p < 0.001$ ). Concomitantly, the cumulative risk of intestinal resection remained unchanged (from 0.35 to 0.34 at five years;  $p = 0.81$ ). The cumulative risk of developing a stricturing or a penetrating intestinal complication remained also unchanged. Similar results were obtained in the 2008 patients seen during the same period who were referred to us more than three months after diagnosis.

**Conclusion:** Although immunosuppressants have been used more frequently over the last 25 years, there was no significant decrease of the need for surgery, or of intestinal complications of Crohn's disease.

The treatment strategy for Crohn's disease (CD) is evolving.<sup>1</sup> Steroids and 5-aminosalicylates are still commonly used; however, during recent years there have been some significant changes. Firstly, the remarkable efficacy and the overall good tolerance of immunosuppressants were recognised<sup>2–5</sup> and when compared with the morbidity of untreated disease,<sup>6</sup> led to their wider greater use. Some authors even proposed using immunosuppressants from the very beginning of the disease, with the objective to modify its natural history,<sup>7</sup> and this strategy has been shown to improve disease course and to avoid steroids in children with moderate to severe disease.<sup>8</sup> Secondly, anti-tumour necrosis factor therapy became available in the late 1990s. Infliximab was shown to be able to induce clinical remission in patients unresponsive to standard treatment,<sup>9</sup> to clear anatomic damage, and, when used as maintenance treatment, to maintain clinical remission<sup>10</sup> and fistula closure.<sup>11</sup>

However, the impact of an increasing use of immunosuppressants and novel therapies on the natural history of CD remains poorly evaluated. An important and unbiased criterion for assessing the overall severity of CD is the need for surgery: for decades there has been a consensus to limit surgery to complications and refractory intractable forms.

The aim of our study, performed in a large series of patients with CD, was to evaluate the effect upon the need for surgery of an increasing use of immunosuppressants over the last 25 years.

## PATIENTS AND METHODS

### Patients

Patients with CD who were seen consecutively in our unit between January 1978 and December 2002 were included retrospectively. In January 2003, our unit moved from Rothschild hospital to St-Antoine Hospital and recruitment for this study was interrupted. Diagnosis of CD was based on Lennard-Jones criteria.<sup>12</sup> Two groups of patients were analysed. The first group consisted of 565 patients who were seen in our unit early in the course of their disease—within the first three

months following diagnosis of CD. The time of diagnosis was defined as the date of first detection of unequivocal inflammatory abnormalities of the intestine, as assessed from radiological, endoscopic, or peroperative observations. Patients in the second group ( $n = 2008$ ) were seen more than three months after diagnosis, being referred to us for various reasons. Within each group, patients were divided into five consecutive five year cohorts, according to the date of diagnosis: cohorts 1978–82, 1983–87, 1988–92, 1993–97, and 1998–2002.

### Study design

The study analysed the evolution of surgical requirements over 25 years by comparing the need for excisional surgery in relation to the use of immunosuppressants among the five chronologic cohorts. Only excisional intestinal surgery was taken into account. Appendectomy, stricturoplasty, bypass, and elective surgical treatment of abscess were not considered. The time to first intestinal resection was the main outcome criteria. In addition were noted the time to first large intestinal resection—either alone or cumulative, defined by a post-surgical index equal or superior to 20,<sup>13</sup>—and the time to establishment of a definitive stoma. The post-surgical handicap index has been developed to predict the functional consequences of intestinal resection for CD. It is calculated from operative records, taking into account the location and extent of intestinal resection. An index score equal or superior to 20 has a high predictive value of diarrhoea following intestinal resection.<sup>13</sup> Intestinal complications of CD were defined according to the Vienna classification: intestinal strictures as the occurrence of constant luminal narrowing demonstrated by radiological, endoscopic, or surgical examination combined with prestenotic dilatation and/or obstructive signs or symptoms but without evidence of penetrating disease.<sup>14</sup> Perforations were intra-abdominal fistulas, inflammatory masses, and/or abscesses.<sup>14</sup> First morphological

**Abbreviations:** CD, Crohn's disease; HR, hazard ratio.

demonstration of narrowing or penetrating complication was used to date the occurrence of the complication.

### Treatment of Crohn's disease

Our treatment policy has been described elsewhere.<sup>15</sup> Flare up episodes were treated with mesalamine (3–4 g daily) or prednisolone (1 mg/kg per day, progressively tapered after four weeks), according to their clinical severity. When steroid therapy failed, patients seen before 1999 were given a three week course of enteral or parenteral nutrition; those seen after June 1999 (when infliximab became available in France) received infliximab 5 mg/kg.

As maintenance treatment, we used aminosaliclates (sulphasalazine, olsalazine, or mesalamine, 2–3 g daily) for asymptomatic or moderately active forms of the disease, and immunosuppressive drugs for severe forms (patients who were steroid dependent or poorly responsive to steroids). Azathioprine 2 mg/kg per day was used as the first line immunosuppressive drug. In case of repeated flare-ups or chronic active disease in a patient receiving azathioprine, its dosage was increased to 2.5–3 mg/kg per day. Intramuscular methotrexate (20–25 mg weekly) was used in patients unresponsive or intolerant to azathioprine. Its dosage was tapered progressively to 10–15 mg, and re-augmented in case of clinical relapse.

Although the overall strategy remained mostly unchanged, over time there was a clear tendency to initiate immunosuppressants earlier in the disease course.

Surgery was reserved for stenotic and extraparietal complications, or intractable forms after a well conducted medical management.

### Statistical analysis

Continuous data are expressed as median (interquartile range), and differences between cohorts were tested for significance by ANOVA. Discrete data are given as percentages, and comparisons were made with Pearson  $\chi^2$  test. Kaplan-Meier survival analysis was used to estimate the cumulative probability of needing immunosuppressants or surgery after diagnosis. Survival curves were compared by means of a two sided log rank test. A Cox proportional hazards regression model with a backward variable elimination procedure was used to assess the strength of the associations while controlling for possible confounding variables. All baseline variables suspected to be possible predictors of intestinal surgery (age, sex, initial disease location (upper GI tract, jejunal, ileal, colonic, rectal, or anoperineal lesions), smoking status,

appendectomy, familial history, ethnicity (White, North-African non-Jewish ancestry), geographic origin outside Paris area, and calendar period of diagnosis (before or after 30 June 1990)), were entered into the model. Results of analysis are presented as hazard ratios (HRs) with 95% confidence intervals. Calculations were performed using GB-STAT statistical software (Silver Spring, MD, USA).

### RESULTS

The characteristics of CD at diagnosis in the five cohorts of group 1 are given in table 1. Patients were very similar at diagnosis from one cohort to another, with a predominance of females, a mean age about 30 years, a large proportion of smokers (half the patients), and a similar disease location. Table 2 gives the cumulative characteristics of the disease at the end of 2003. No attempt was made to contact the patients at that time and 31% of them had been lost to follow up. Because patients from the oldest cohorts had a longer disease duration, they developed more stricturing or penetrating complications and were classified so according to Vienna classification.<sup>16</sup> Similarly, the respective proportions of patients needing steroids or immunosuppressants, and operated on, should be interpreted in relation to different durations of follow up. Azathioprine was maintained for a prolonged period in most cases but had to be stopped within the first month because of adverse events in 16 patients (11%). It was switched to methotrexate in eight of those latter patients.

### Changes in the use of immunosuppressants over 25 years in group 1 patients

Figure 1 shows the cumulative use of immunosuppressants in the five cohorts. Data of patients for whom immunosuppressants had to be stopped early are included. As expected, immunosuppressants have been used more and more early over the last 25 years, with a five year cumulative probability of prescription of zero in the 1978–82 cohort to 0.56 (95% CI 0.31 to 0.78) in the 1998–2002 cohort.

### Cumulative need for excisional surgery in the five group 1 cohorts

One hundred and ninety patients (34%) were operated on at least once. Excisional surgery was performed in 41 cases before first admission in our unit and thereafter in 149 cases. Figure 2 gives the cumulative need for first excisional surgery. The curves were superimposed, with no significant difference from one curve to another (log rank,  $p = 0.81$ ). Excluding the 80 patients who had had surgery within the

**Table 1** Characteristics at diagnosis of the five consecutive chronological cohorts of patients seen in our unit within the three months following diagnosis (group 1)

	Cohort 1978–82	Cohort 1983–87	Cohort 1988–92	Cohort 1993–97	Cohort 1998–2003
Patients (n)	34	46	102	176	207
Males	15 (44)	24 (52)	38 (37)	71 (40)	73 (35)
Median age (interquartile range)	25 (21–35)	27 (21–38)	27 (20–37)	29 (22–38)	27 (20–36)
Disease location					
Ileocolonic	13 (38)	19 (41)	41 (40)	60 (34)	72 (35)
Small bowel	11 (32)	16 (35)	32 (31)	59 (34)	70 (34)
Colon	7 (21)	10 (22)	27 (26)	52 (30)	60 (29)
Other	3 (9)	1 (2)	2 (2)	5 (3)	5 (2)
Appendectomised	13 (38)	20 (43)	35 (34)	49 (28)	63 (30)
Familial history	4 (12)	13 (28)	10 (10)	30 (17)	33 (16)
Smokers	18 (53)	31 (67)	51 (50)	86 (49)	100 (48)
Caucasian	30 (88)	40 (87)	93 (91)	153 (87)	167 (81)
North-African non-Jewish ancestry	2 (6)	6 (13)	8 (8)	16 (9)	26 (13)
Living outside Paris area	13 (38)	19 (41)	26 (25)	57 (32)	65 (31)

Numbers in parentheses are percentages.  
Intergroup comparisons showed no significant differences.

**Table 2** Cumulative characteristics of the five consecutive chronologic cohorts of patients seen in our unit within the three months following diagnosis (group 1)

	Cohort 1978-82	Cohort 1983-87	Cohort 1988-92	Cohort 1993-97	Cohort 1998-2003
Patients (n)	34	46	102	176	207
Deceased	4	2	3	3	0
Lost to follow up	14 (41)	20 (43)	42 (41)	70 (40)	24 (12)
Median disease duration, months (interquartile range)	188 (23-256)	181 (64-207)	123 (43-144)	59 (10-91)	14 (3-35)
Vienna classification					
Inflammatory	15 (44)	17 (37)	42 (41)	95 (54)	130 (63)
Stricturing	9 (26)	4 (9)	17 (17)	22 (13)	11 (5)
Penetrating	10 (29)	25 (54)	43 (42)	59 (34)	66 (32)
Medical treatment					
No steroids, no IS	6 (18)	7 (15)	20 (20)	57 (32)	60 (29)
Steroids, no IS	22 (65)	29 (63)	51 (50)	80 (45)	81 (39)
IS	6 (18)	10 (22)	31 (30)	39 (22)	66 (32)
Early withdrawal of IS	0	1 (2)	2 (2)	1 (1)	4 (2)
Infliximab	0	1 (2)	1 (1)	7 (4)	13 (6)
Cumulative number of intestinal resections					
0	18 (53)	23 (50)	53 (52)	120 (68)	161 (78)
1	11 (32)	17 (37)	42 (41)	50 (28)	45 (22)
2	2 (6)	5 (11)	5 (5)	6 (3)	1
>2	3 (9)	1 (2)	2 (2)	0	0

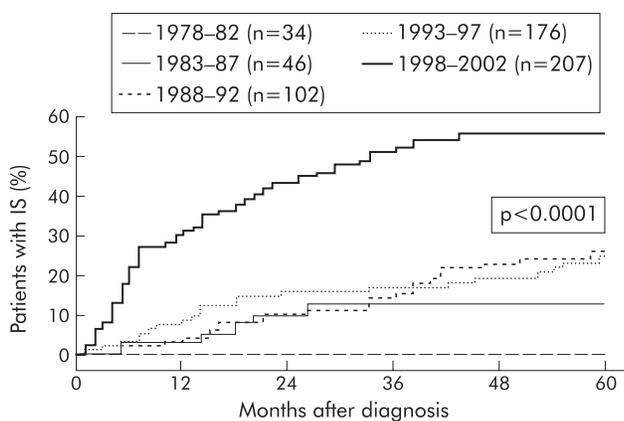
Numbers in parentheses are percentages. IS, immunosuppressants.

first three months following diagnosis yielded the same result (log rank,  $p = 0.49$ ), although immunosuppressants were used in that group much earlier over the years (log rank,  $p < 0.0001$ ). In the whole group of 565 patients, Cox analysis confirmed that the year of diagnosis had no significant effect upon the need for surgery. Factors associated with surgery were ileal involvement (HR 2.78; 95% CI 2.19 to 3.51) and absence of rectal involvement (HR 0.34; 95% CI 0.27 to 0.43). In the cohorts 1978-82, 1983-87, 1988-92, 1993-97, and 1998-2002, the five year cumulative probabilities of having a large intestinal resection, defined by a post-surgical handicap index  $\geq 20$ , were 0.29 (0.15-0.50), 0.20 (0.10-0.36), 0.24 (0.16-0.35), 0.13 (0.07-0.22), and 0.17 (0.04-0.49), respectively. The curves were not significantly different according to log rank test ( $p = 0.23$ ). The five year cumulative probability of having a definitive stoma varied not significantly between 0 and 0.03 from one cohort to another ( $p = 0.33$ ).

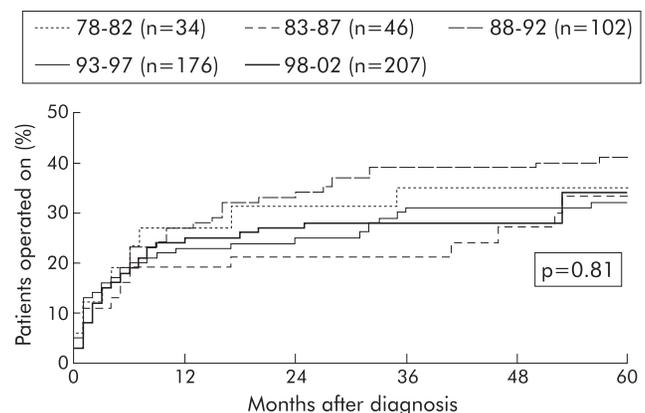
**Indications for first intestinal resection in group 1 patients**

Table 3 gives the indications for the first intestinal surgery in the five cohorts. The proportion of patients being operated on

for medical failure, stricture, and perforation, respectively, did not change significantly between the five cohorts, although in the most recent cohort there was a clear reduction of operations for medical failure (13% v 22-38% in the other cohorts). Kaplan-Meier analysis of the cumulative probability of intestinal stricture and perforation did not show significant differences between cohorts. In the cohorts 1978-82, 1983-87, 1988-92, 1993-97, and 1998-2002, the five year cumulative probabilities of intestinal stricture were 0.23 (0.11-0.43), 0.14 (0.06-0.29), 0.19 (0.12-0.30), 0.17 (0.11-0.26), and 0.10 (0.02-0.42), respectively (log rank  $p = 0.12$ ), and the five year cumulative probabilities of intestinal perforation were 0.03 (0-0.19), 0.22 (0.12-0.37), 0.18 (0.11-0.29), 0.19 (0.12-0.29), and 0.18 (0.05-0.47), respectively (log rank  $p = 0.22$ ). When analysing the time relation between prescription of immunosuppressants and first intestinal surgery, we found that in all the cohorts a great majority of patients were operated on without having received immunosuppressants, because surgery was performed early in the course of the disease (within the first three months following diagnosis ( $n = 80$ , 43% of operations)), or because surgery preceded or followed the prescription of immunosuppressants for less than three



**Figure 1** Kaplan-Meier estimates of the cumulative risk of receiving immunosuppressants in five chronologic cohorts of patients with Crohn's disease.



**Figure 2** Kaplan-Meier estimates of the cumulative risk of intestinal resection in five chronologic cohorts of patients with Crohn's disease.

**Table 3** Indications for the first intestinal resection in the five consecutive chronologic cohorts of patients seen in our unit within the three months following diagnosis (group 1)

	Cohort 1978-82	Cohort 1983-87	Cohort 1988-92	Cohort 1993-97	Cohort 1998-2002
Resections (n)	16	23	49	56	46
Diagnosis	1 (6)	0	0	1 (2)	1 (2)
Stricture	6 (38)	3 (13)	11 (22)	8 (14)	7 (15)
Perforation	3 (19)	15 (65)	21 (43)	25 (45)	31 (67)
Failure of medical treatment	6 (38)	5 (22)	16 (33)	19 (34)	6 (13)
Other*	0	0	0	2 (4)	1 (2)
Unknown	0	0	1	1	0

Numbers in parentheses are percentages.

\*Other included mesenteric infarction, haematochezia, and small bowel adenocarcinoma, respectively.

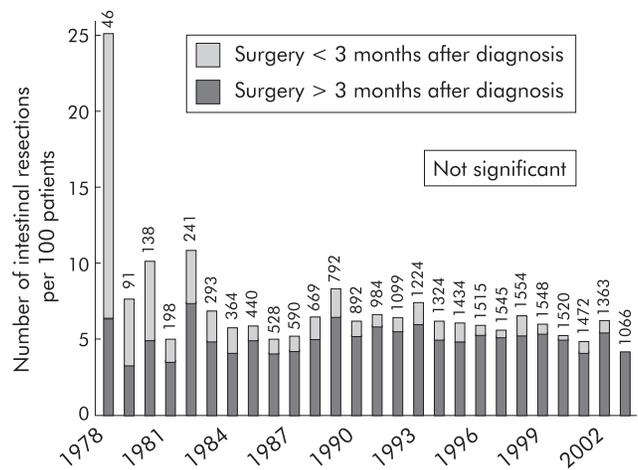
months (n = 92, 49%). Only 16 patients (9%) had to be operated on having received immunosuppressants for more than three months, and this proportion was not significantly different between cohorts (0–17%).

**Referred patients (group 2)**

Of the 2008 patients referred to us more than three months after diagnosis, 880 (44%) were operated on at least once. Excisional surgery was performed in 490 cases (56%) before first admission in our unit and after in 390 cases. Thus compared with the first group of patients, a higher proportion of referred patients had had surgery before admission in our unit (p<0.001). Otherwise, results observed were similar to those of group 1 regarding an increased use of immunosuppressants but a stable need for excisional surgery over the years (table 4). The risk of having a definitive stoma remained also stable. However, in that group, the risk of having a large intestinal resection decreased significantly with time.

**Evolution of the need for surgery 1978–2003**

In the total cohort of 2573 patients from groups 1 and 2, 1070 underwent 1426 intestinal resections from January 1978 to December 2003 (22 928 patient years). Two hundred and seventeen resections (15%) were performed within the first three months following diagnosis. Except for the year 1978 (46 patients only), the percentage of patients who were



**Figure 3** Evolution of the annual rate of intestinal resections from 1978–2003 in 2573 patients with Crohn’s disease. The numbers above the columns indicate the number of patients at risk for intestinal resection at the beginning of the year.

operated on during the first three months remained less than 5% (fig 3). After the first three months, the operative rate (number of operations performed per year) fluctuated within a narrow range (3.3–7.5%), without any significant change over 26 years (fig 3).

**DISCUSSION**

This study shows that although immunosuppressants were initiated much earlier during the course of CD, the need for intestinal resection remained stable over 25 years. The percentage of patients requiring intestinal surgery each year remained equal. The probability of having a definitive stoma appeared also to be unaffected from 1978 to 2002. However, large intestinal resections became more unusual.

This study has some limitations. Firstly, the retrospective nature of the study may have led to bias in the interpretation of the data—however, it was necessary to obtain an observation period long enough to ascertain the long term effect on surgery of changes in the medical strategy of CD. In addition, intestinal resection can be considered as an unbiased and solid criterion, even retrospectively, as it is performed only when necessary. Besides, during a period of

**Table 4** Five year cumulative rates (95% CI) of therapeutic intervention in the patients referred to our unit more than three months after diagnosis of Crohn’s disease (group 2, n = 2008)

	Cohort 1978-82	Cohort 1983-87	Cohort 1988-92	Cohort 1993-97	Cohort 1998-2002	Log rank p value
Patients (n)	218	342	486	563	399	
<i>IS therapy</i>						
Cumulative probability (95% CI)	0.04 (0.02–0.08)	0.14 (0.10–0.18)	0.27 (0.23–0.32)	0.45 (0.40–0.50)	0.63 (0.49–0.76)	<0.00001
Patients at risk (n)	195	278	296	203	17	
<i>Intestinal resection</i>						
Cumulative probability (95% CI)	0.36 (0.29–0.48)	0.30 (0.25–0.35)	0.32 (0.28–0.37)	0.31 (0.27–0.36)	0.36 (0.22–0.53)	0.528
Patients at risk (n)	137	227	274	263	21	
<i>Large intestinal resection</i>						
Cumulative probability (95% CI)	0.29 (0.23–0.35)	0.22 (0.18–0.27)	0.19 (0.16–0.23)	0.15 (0.11–0.19)	0.12 (0.05–0.28)	<0.00001
Patients at risk (n)	145	250	321	310	27	
<i>Definitive stoma</i>						
Cumulative probability (95% CI)	0.01 (0–0.03)	0.02 (0.01–0.04)	0.02 (0.01–0.04)	0.02 (0.01–0.04)	0.02 (0–0.13)	0.72
Patients at risk (n)	202	315	387	355	33	

20–25 years, many factors other than the treatment strategy may have influenced the indications for surgery. However, all patients seen from the beginning were followed up in the same unit by the same small group of physicians, who used homogeneous guidelines and took collegial decisions. Moreover, comparison of cohorts at inclusion showed that they were very similar regarding demographic characteristics and disease location. In particular there is no reason to believe that CD became more severe with time while other disease characteristics did not change. Secondly, it should be noted that a relatively large proportion of patients were lost to follow up. We made no attempt to contact the patients or physicians to update the data. We do not believe this may have minimised the need for surgery of the oldest cohorts because patients who are lost to follow up are usually those doing well and not requiring further surgery. The cumulative probability of surgery in our patients was very similar to those reported in two unbiased and complete series of the literature, the NCCDS<sup>17</sup> and the Copenhagen County cohort study.<sup>18</sup> Finally, our unit is a tertiary referral centre and referral bias is unavoidable. To limit this bias, we restricted the analysis to patients seen during the first three months of the disease course. This precaution was not sufficient to eliminate such a referral bias because an important proportion of these patients came to surgery during that period. However, when we excluded these latter patients, analyses gave similar results and, in particular, the discrepancy between an increased use of immunosuppressants and a stable need for surgery remained unchanged. These results were confirmed in a second large group of patients.

The occurrence of stricturing and perforating complications was the main reason for excisional surgery. The frequency of these complications did not change significantly from one cohort to another. This is a disappointing result because it could be expected that immunosuppressants could have an anatomic effect and prevent these complications. Indeed, D'Haens *et al* reported that in 74% of patients with colonic or ileocolonic disease who were clinically responders to azathioprine, endoscopic lesions had healed completely or nearly completely after a mean of two years of treatment. Histologically there was disappearance of the inflammatory infiltrate, with only a degree of architectural disturbance remaining.<sup>19</sup> In the present study there was, over the most recent years, a clear decrease of intestinal resection for medical failure, which represented only 13% of surgical indications in the 1998–2002 cohort. This result may be related to immunosuppressants, but also to infliximab even though it was used sparingly in very few patients. In any case, the absence of a decrease in the need for surgery over the last 25 years questions the efficiency of our medical strategy. In fact, there is the possibility that in this study immunosuppressants had no impact on complications and the need for surgery because they were given too late during the course of the disease. Supporting this hypothesis, a large majority of patients came to surgery while not having received immunosuppressants, or were operated on early (within the first three months), while the mean time of response to purine analogues is three months.<sup>20</sup> By contrast, if we make the hypothesis that immunosuppressants are able to change the natural history of CD, nearly half the patients who were operated on more than three months after diagnosis could have avoided surgery. Thus we can extrapolate that in our series immunosuppressants were given too late and too scarcely to have a significant impact on the need for surgery. Such an assertion is not in accordance with the anatomic effect observed by D'Haens *et al*,<sup>19</sup> that immunosuppressants, even when given early, may have no preventive effect on the occurrence of stricturing and penetrating complications.

An interesting and more encouraging result of our study was the decrease of the probability of having a large intestinal resection over the last 25 years in the group of referred patients. A similar trend, although not significant, was observed in patients who were seen early after diagnosis and were, for the most part, operated on in our surgical unit. The reason for such a decrease, from 29% to 12% five years after diagnosis, may be linked to a greater use of immunosuppressants, but may also be a change in the surgical strategy favouring segmental and limited resections in the most recent years.

In summary, this study shows that immunosuppressants have been used increasingly over the years. However, this evolving therapeutic strategy was not associated with a decrease in the need for surgery or in a decrease of the occurrence of intestinal complications. This result does not question the efficacy of immunosuppressants for achieving and maintaining remission,<sup>21</sup> sparing steroids,<sup>22</sup> and improving quality of life, but it does questions the timing of starting immunosuppressants in patients with moderate to severe Crohn's disease.

#### Authors' affiliations

J Cosnes, I Nion-Larmurier, L Beaugerie, P Afchain, J-P Gendre, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, Paris, France  
E Tiret, Service de Chirurgie, Hôpital Saint-Antoine, Paris, France

#### REFERENCES

- Hanauer SB, Dassopoulos T. Evolving treatment strategies for inflammatory bowel disease. *Annu Rev Med* 2001;**52**:299–318.
- Lennard-Jones JE. Azathioprine in the treatment of Crohn's disease. *Proc R Soc Med* 1972;**65**:291–3.
- Feagan BG. Standard immunosuppression in IBD: current practice. *Acta Gastroenterol Belg* 2001;**64**:182–8.
- Korelitz BI, Present DH. A history of immunosuppressive drugs in the treatment of inflammatory bowel disease: origins at the Mount Sinai Hospital. *Mt Sinai J Med* 1996;**63**:191–201.
- Pearson DC, May GR, Fick GH, *et al*. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995;**123**:132–42.
- Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology* 2000;**118**:1018–24.
- Hanauer SB. Crohn's disease: step up or top down therapy. *Best Pract Res Clin Gastroenterol* 2003;**17**:131–7.
- Markowitz J, Grancher K, Kohn N, *et al*. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;**119**:895–902.
- Targan SR, Hanauer SB, van Deventer SJ, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029–35.
- Hanauer SB, Feagan BG, Lichtenstein GR, *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
- Sands BE, Anderson FH, Bernstein CN, *et al*. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
- Lennard-Jones JE. Classification of IBD. *Scand J Gastroenterol* 1989;**170**:2–4.
- Cosnes J, de Parades V, Carbonnel F, *et al*. Classification of the sequelae of bowel resection for Crohn's disease. *Br J Surg* 1994;**81**:1627–31.
- Gasche C, Scholmerich J, Brynskov J, *et al*. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;**6**:8–15.
- Cosnes J, Carbonnel F, Beaugerie L, *et al*. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;**110**:424–31.
- Cosnes J, Blain A, Beaugerie L, *et al*. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244–50.
- Mekhjian HS, Switz DM, Melnyk CS, *et al*. Clinical features and natural history of Crohn's disease. *Gastroenterology* 1979;**77**:898–906.
- Munkholm P, Langholz E, Davidsen M, *et al*. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;**30**:699–706.
- D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999;**50**:667–71.
- Present DH, Korelitz BI, Wisch N, *et al*. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;**302**:981–7.
- Pearson DC, May GR, Fick G, *et al*. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000:CD000067.
- Present DH. 6-Mercaptopurine and other immunosuppressive agents in the treatment of Crohn's disease and ulcerative colitis. *Gastroenterol Clin North Am* 1989;**18**:57–71.