Long-term Outcome After Admission for Acute Severe Ulcerative Colitis in Oxford: The 1992–1993 Cohort

D. Bojic, MD,,† Z. Radojicic, PhD,‡ M. Nedeljkovic-Protic, MD,† M. Al-Ali, MD,* D.P. Jewell, MD,* and S.P.L. Travis, MD**

Background: To determine the long-term outcome of patients admitted with acute severe colitis (ASC) who avoided colectomy on the index admission, a retrospective cohort study was performed.

Methods: Patients admitted for intensive treatment of ASC in 1992–1993 previously described for a predictive index of short-term outcome in severe ulcerative colitis (UC) were followed for a median 122 months (range 3–144). Complete responders (CR) to intensive therapy had <3 nonbloody stools/day on day 7 of the index admission; incomplete responders (IR) were all others who avoided colectomy on that admission. Main outcome measures were colectomy-free survival, time to colectomy, and duration of steroid-free remission.

Results: In all, 6/19 CR (32%) came to colectomy compared to 10/13 IR ($P = 0.016$; relative risk 3.33, 95% confidence interval [CI] 1.12–9.9). The median ± interquartile range time to colectomy was 28 ± 47 months (range 6–99) for CR who came to colectomy versus 7.5 ± 32 (3–72) months for IR ($P = 0.118$). Among the IR, 7/13 came to colectomy within 12 months, and all within 6 years from the index admission. The longest period of steroid-free remission was 42 ± 48 (0–120) months for CR, but 9 ± 20 (1–35) months for IR ($P = 0.011$).

Conclusions: One week after admission with ASC in the prebiologic era, IRs had a 50% chance of colectomy within a year and 70% within 5 years, despite cyclosporin and azathioprine where appropriate. The maximum duration of remission in CRs was almost 5 times longer than IRs. It is unknown whether biologics change the long-term outcome.

(*Inflamm Bowel Dis 2009;15:823–828)*

Key Words: severe ulcerative colitis, colectomy, cyclosporin, steroids

Acute severe ulcerative colitis (UC) requiring hospital admission affects about 15% of patients during the course of their illness.[1] The mortality from severe attacks of UC has declined from 7% after the introduction of steroids in 1955[2] to <1% in specialist centers today.[3] Nevertheless, the response to intensive treatment with steroids has remained unchanged for almost 50 years. A systematic review of 32 studies of severe UC involving 1991 patients shows that the colectomy rate did not change between 1974 and 2006 (29%, 95% confidence interval [CI] 28–31).[4]

With the advent of cyclosporin, first used to treat intravenous steroid-refractory UC in 1984,[5] 70%–80% of such patients show a short-term response, but by 12 months 65% have relapsed and by 7 years 58%–88% have come to colectomy.[6,7] Alternative rescue therapies include tacrolimus[8] and infliximab,[9] which makes the difficult decision between continued medical therapy and colectomy yet more challenging. The long-term outcome of patients presenting with a severe attack, who either respond completely or incompletely to therapy, remains unclear.

In 1992–1993 a prospective study was performed on 49 patients admitted with 51 episodes of severe UC to examine clinical and biochemical factors that might predict short-term outcome.[10] It was found that the simple measures of a C-reactive protein (CRP) >45 mg/L and stool frequency 3–8/day, or a stool frequency >8/day on day 3 of intensive treatment were associated with an 85% chance of colectomy on that admission. The short-term outcome was defined according to the treatment response on day 7 of the index admission: complete responders, incomplete responders, and colectomy on that admission. In this patient cohort, 14/51 episodes were treated with cyclosporin in addition to intravenous steroids. The purpose of the current study was to use this cohort to examine the long-term outcome of those making a complete or incomplete response to medical therapy for severe UC. This provides a measure of the burden of disease among patients admitted with severe colitis.

MATERIALS AND METHODS

Patients and Follow-up Data

All patients who avoided colectomy on the index admission out of a consecutive series of 49 patients receiving intensive treatment for severe UC (1992–1993)[10] represent

Received for publication October 27, 2008; Accepted November 4, 2008.

From the *Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK, †Gastroenterology Department, University Clinical Center Zvezdara, Belgrade, Serbia, ‡Institute for Statistics, University of Belgrade, Belgrade, Serbia.

Reprints: Dr. Simon Travis, DPhil, FRCP, Gastroenterology Unit, John Radcliffe Hospital, Oxford, OX3 9DU, UK (e-mail: simon.travis@ndm.ox.ac.uk).

DOI 10.1002/ibd.20843

Published online 14 January 2009 in Wiley InterScience (www.interscience.wiley.com).

TABLE 1. Original Patient Data Prior to Index Admission (with Regard to Patients Included in the Follow-up Study)

	Complete Responders	Incomplete Responders	Nonresponders
Number of patients	19	13	14
Age (y) (SD)	46.2 (18.7)	48.2 (12.6)	45.9 (15.3)
First episode (%)	53	7	20
Duration of last remission prior to index admission (months, range)	15 (5–38)	14 (5–240)	9 (3–54)
Previous admission (%)	47	38	50
Time since last admission (months, range)	64 (24–185)	62 (8–240)	5 (1–103)
Disease duration before index admission (median, range) (y)	2 ± 12 (0–42)	10 ± 16 (0–32)	1 ± 10 (0–25)

the patient cohort. Criteria for the index admission were a bloody stool frequency ≥6/day and just 1 or more of the additional Truelove & Witts' criteria (tachycardia >90 bpm, or temperature >37.8°C, or hemoglobin <10.5 g/dL, or erythrocyte sedimentation rate (ESR) >30 mm/hr). Patient data prior to index admission are shown in Table 1. In 2004–2005 the long-term outcome of the index admission was assessed by review of hospital notes, confirmed by telephone contact. Although a referral center, Oxford has a large secondary care population and hospital-based follow-up system with rapid access clinics. The convention has been to treat a relapse of UC decisively with steroids and it would be exceptional for steroids to be prescribed in primary care without a hospital visit. Relapse was defined as any worsening of symptoms and/or an inflamed mucosa at sigmoidoscopy requiring a change of treatment.

Demographic information, discharge summaries, pathology and operative reports, as well as follow-up notes were extracted and a database constructed. Patients were stratified according to treatment response on day 7 of the index admission. Complete response was defined as ≤3 stools/day without visible blood on day 7. Incomplete response was defined as all others who did not come to colectomy on that admission. It should be noted that the CRP formed part of the predictive index on day 3 of treatment and was not used to define response to intensive treatment at day 7. Nonresponders were those who underwent colectomy during the index admission.

Database

Eleven parameters reflecting disease behavior were evaluated: disease duration before index admission, disease extent prior to the index admission according to Montreal classification[11]; disease activity, presented as number of relapses since index admission, median number of relapses per year for each individual patient, number of hospital readmissions for a severe attack (independent of elective surgery), and maximum duration of remission (the longest interval between relapses); number of steroid courses since index admission; treatment with azathioprine; time from index admission to index surgery; time from index diagnosis to index surgery; total number of operations (defined as the sum of initial colectomy followed by stoma closure and ileal pouch anal anastomosis or permanent ileostomy, or complications requiring surgery).

Statistics

All results are expressed as median ± interquartile range (IQR), since the data were not normally distributed. Statistical analysis was performed between the groups using Mann–Whitney test, chi-square test, Fisher's exact test, or Moses extreme reaction test (discussed in text) where appropriate. In spite of the small sample size, multivariant binary logistic regression analysis was performed along with backward conditional methods. Since this showed the same results as univariate analysis, only the results derived from univariate analysis are presented for the sake of clarity. Kaplan–Meier plots were constructed and log rank value calculated to present the time to colectomy for complete and incomplete responders. The statistical package SPSS v. 16 (Chicago, IL) was used to analyze all data.

RESULTS

Patients

The outcomes from 32 patients were analyzed, 19 complete responders (CRs) and 13 incomplete responders (IRs). In all, 46/49 original patients (94% follow-up rate) remained under hospital follow-up for a median 122 ± 63 months (range 3–144). Two patients were excluded due to lack of documentation after they moved abroad and were untraceable (1 CR, 1 nonresponder). One original IR was excluded due to incomplete documentation. For the entire cohort, 30/46 had a colectomy at some time from index admission to the end of follow-up period, so the cumulative colectomy rate was 65%. Indications for colectomy are shown in Table 2.

The diagnosis of UC was changed to Crohn's disease in 2 patients and to indeterminate colitis in 3 patients after histological analysis of the colectomy specimen.[12] Three pa-

TABLE 2. Indications for Colectomy

Indication	Number of Patients
Emergency	14
Elective, medically refractory or uncontrolled disease	15
Dysplasia	1
Cancer	0
Other	0

tients died of causes unrelated to UC (myocardial infarction, breast cancer, and malignancy of unknown primary). None had *Clostridium difficile* or cytomegalovirus infection on index admission, or during follow-up.

All patients received aminosalicylate maintenance therapy (dose 2–3 g/day). In 17/32 patients azathioprine (AZA 2 mg/kg/day) was added during follow-up for 9/19 CRs and 8/13 IRs. Cyclosporin (4 mg/kg/day) was given as "rescue" therapy to 14/49 patients in the original cohort for a median 4 days (range 1–6). Seven of 14 avoided colectomy on the index admission and oral cyclosporin (5 mg/kg/day) was continued for up to 3 months after discharge, but 3 required colectomy within 3 months. Of the 4 remaining patients given cyclosporin, 3 came to colectomy (2, 4, and 8 years after index admission). One avoided colectomy throughout the follow-up period. In this cohort none received anti-TNFα therapy.

Complete and Incomplete Responders

Disease Duration and Extent Before Index Admission.

Median disease duration and extent before index admission were similar in CR (n = 19) and IR (n = 13) (Table 3).

Relapses

The median number of relapses since index admission and relapse frequency was not significantly different between

TABLE 3. 12–Year Comparison Between Complete Responders and Incomplete Responders on Day 7 of Index Admission for Intensive Treatment of Severe UC and Those Coming to Colectomy on That Admission

		Complete Responders n = 19 (A)	Incomplete Responders n = 13 (B)	Nonresponders (n = 14) (C)	P-value (A: B)	P-value (A : C)	P-value (B : C)
Disease extent before index admission	Proctitis/distal	10	5	3	0.451	0.078	0.358
	Extensive	9	8	11			
Median disease duration before index admission (years)		2 ± 12 (0–42)	10 ± 16 (0–32)	1 ± 10 (0–25)	0.136	0.733	0.085
Median number of relapses since index admission		3 ± 5 (0–16)	5 ± 9 (0–14)		0.880		
Median number of relapses / year of follow up (range)		0.8 ± 1.2 (0–3)	1.1 ± 2.12 (0–5)		0.170		
Maximum interval between relapses (or longest period of remission) (months)		42 ± 48 (0–120)	9 ± 20 (1–35)		0.011		
Median number of steroid courses per patient (range)		2 ± 6 (0–13)	4 ± 6 (0–14)		0.495		
Median number of hospital readmissions for acute severe colitis		0.0 ± 1.0 (0–3)	1.0 ± 1.0 (0–3)		0.633		
Median time from index admission to index surgery for colectomized patients (months)		27.5 ± 47 (6–99)	7.5 ± 32 (3–72)		0.117 0.003[a]		
Median time from index admission to index surgery for the whole group (months)		144 ± 96 (6–144)	10 ± 104 (3–144)		0.006		
Colectomy		6/19	10/13	14/14	0.015		
Median number of operations (range)		1.5 ± 1 (1–2)	3 ±1 (2–3)	2 ± 1 (1–6)	0.001	0.000	0.616
Median number of complications requiring readmission (range)		0.0 ± 0 (0–2)	1.0 ± 2 (0–5)	0.0 ± 2 (0–5)	0.092	0.106	

[a]Moses extreme reaction test (see text).

the 2 groups (Table 3). Numbers are small, but the median rate of relapse in CRs and IRs was not influenced by disease extent. There was a total of 12 and 10 hospital readmissions for CR and IR for acute severe colitis during the follow-up period, which was not statistically different (Table 3).

Remission

The longest period of remission for CRs was 3.5 years, almost 5 times longer than for IRs (median 9, range 1–35 months, $P = 0.011$, Table 3).

Steroid Courses and AZA Therapy

CRs had a median 2 steroid courses each during follow up over 12 years (Table 3). Of the 9/19 who received AZA, all were started on AZA 3–12 months after index admission, and none had received it previously. In 2 patients AZA was discontinued due to intolerance. The median duration of AZA therapy was 12 ± 24 months (95% CI 2–46, range 6–72). In those receiving AZA, the number of relapses after the index admission was about 3 times higher than those who did not (median number of relapses in the AZA group 7 ± 9, range 2–16 versus 2 ± 3, $P = 0.022$).

IRs had similar steroid courses to CRs, consistent with no difference in relapse frequency (Table 3). Of the 8/13 treated with AZA, all patients were started within 12 months of the index admission for a median of 18 ± 26 months (95% CI 5–53, range 2–72). None had previously received AZA and 1 discontinued AZA due to intolerance. The pattern of disease for IRs on AZA compared to those not on AZA was similar to that of CRs, with a 3-fold higher number of relapses in patients on AZA (median 7 ± 9, range 2–16 versus 2 ± 3, range 0–7), but this difference did not reach statistical significance ($P = 0.354$).

Surgery

The cumulative colectomy rate among IRs was 77% (10/13), which was significantly higher than for CRs (6/19 or 32%, $P = 0.015$, Table 3). In CRs, colectomy was necessary in 1/19 within 1 year, 4/19 (22%) within 5 years, and 1/19 within 6–12 years (Fig. 1). Among IRs 7/13 patients (54%) needed colectomy within 1 year and 2 (15%) within 5 years, while 1 patient had a colectomy 6 years after index admission (Fig. 1). Of those IRs who had a colectomy, 7 had extensive and 3 had distal colitis. The median time from index admission to colectomy in the CRs who had a colectomy was 27 ± 47 months (6–99), compared to 7.5 ± 32 (3–72) months in the 10 IRs (Table 3). The median time from index diagnosis to index surgery (ie, total duration of the disease before colectomy) was not significantly different between CRs and IRs. Among CRs who came to colectomy, the median number of operations/patient was lower, but complications requiring readmission were no different from IRs (Table 3). The median number of operations was also significantly lower than in those who had an emergency colectomy because of a higher number of definitive rather than staged procedures. As a measure of the burden of disease for the group of CRs as a whole, the median number of operations was 0.0 ± 1 (0–2) for each patient. Other comparisons with complete responders are shown in Table 3.

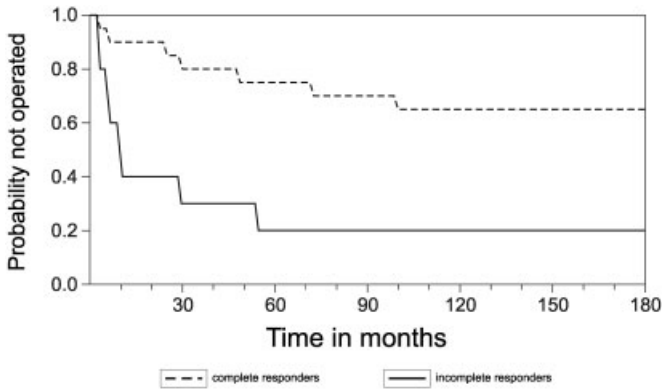

FIGURE 1. Colectomy among patients with a complete and incomplete response. Kaplan–Meier plot of survival without colectomy for complete responders to intensive treatment within 7 days on the index admission ($n = 19$), compared to incomplete responders ($n = 13$); log-rank $P = 0.003$.

Nonresponders

This group included the follow-up of 14 patients (14/46 or 30%) who underwent colectomy on the index admission. Disease duration was no different from the other groups (Table 3). More had extensive colitis (11/14, 79%) than distal colitis (3/14, 21%, $P = 0.0001$), but the numbers were small.

Comparisons Between Groups

IRs had a 3-fold higher risk of colectomy than CRs (relative risk [RR] 3.33; 95% CI 1.1–9.9). IRs also had a significantly higher colectomy rate at 12 months ($P = 0.005$), but not at 1–5 ($P = 1.0$) or 6–15 years ($P = 1.0$). Figure 1 shows the time course to colectomy for complete and incomplete responders in a Kaplan–Meier plot (log-rank $P = 0.003$). The median time from index admission to colectomy was almost 4 times longer for CRs compared to IRs, but the difference did not reach significance, except when the groups were analyzed as a whole (Table 3). The Moses extreme reaction test was therefore used to see if the difference in time to colectomy between the 2 groups was likely to be real, since colectomy was the main outcome of interest. This showed that the expected directions of time to colectomy for the 2 groups were significantly opposed ($P = 0.003$).

DISCUSSION

In a group of consecutive patients admitted with acute severe UC, our data show that about two-thirds (65%) will come to colectomy within 12 years. The numbers were small, but these are the longest outcome data yet presented and have

clinical credibility. Just 7 days after admission to hospital with acute severe UC, patients can be divided into 3 groups, according to treatment response to intensive medical therapy with intravenous steroids and cyclosporin: CRs who have ≤3 stools/day and no visible blood in the stools, the IRs who have >3 stools/day or visible blood in the stools on day 7, and those heading for colectomy on that admission. At that 7th day it may not be possible to discriminate precisely between IRs and those who will have a colectomy on that admission, but this discrimination still has practical value even when applied retrospectively. This is because the symptoms on the 7th day have a bearing on the long-term outcome, which informs both patients and physicians when deciding on future therapy. The questions that matter to patients are the likelihood of colectomy, the likelihood of relapse or a further severe attack needing hospital admission, and the expectation of an extended period of remission.

The 5-, 10-, and 25-year cumulative colectomy rates in the largest population-based study of 1586 patients with UC was 20% (95% CI 18%–22%), 28% (95% CI 26%–30%), and 45% (95% CI 41%–49%), respectively.[12] Other population-based studies of UC have reported similar figures (24% after 10 years and 31% after 18 years),[13,14] although colectomy rates may be decreasing in the Copenhagen population in recent years.[15] These studies do not discriminate between degrees of severity and reported colectomy rates, for severe UC remain unchanged over 30 years[4] in spite of the introduction of cyclosporin as rescue therapy 20 years ago. It is too early to determine the impact of infliximab, but unpublished data from the Swedish-Danish study[9] suggest that only a third come to colectomy even after 3 years. Kohn et al[16] showed that among 83 patients with severe UC treated with infliximab, 15% underwent colectomy within 2 months and about 60% (of which most were on immunosuppressive therapy) avoided colectomy during a median 23 months' follow-up. On the other hand, Jakobovits et al[17] reported that 16/30 (53%) patients treated with infliximab for refractory UC came to colectomy after a median 140 days from their first infusion. Only 17% (5/30) achieved steroid-free remission after a median follow-up of 13 months and there is no doubt from the patient profiles that these had more treatment-refractory disease than the Kohn et al study.[16] Biologics have the potential to change disease activity and colectomy-free or steroid-free remission in severe UC, but the magnitude of that impact in the long term remains to be tested.

Those with the highest risk of colectomy in the current study (77%) were the IRs (RR 3.3, 95% CI 1.1–9.9; $P = 0.016$). It is remarkable that it may be possible to indicate the likely need for colectomy over the succeeding decade just 7 days after admission with severe UC. Those with an IR to intensive therapy had a more rapid progression to colectomy than CRs. Within a year of the index admission, 54% of IRs underwent colectomy, while only 5% of those with a CR came to colectomy ($P = 0.005$). The median time to colectomy among CRs who came to colectomy was over 2 years, compared to 7 months for IRs. Even though this difference did not reach significance when only patients who had a colectomy were analyzed, 2 further analyses suggest that the difference is real. There was a highly significant difference when the groups as a whole were analyzed for the whole follow-up period ($P = 0.006$; Table 3) and a test to analyze the expected direction of travel of the 2 groups (the Moses extreme reaction test) also showed a highly significant difference ($P = 0.003$). Factors influencing this disease behavior remain to be established. Extensive disease was associated with the need for colectomy on the index admission, but not during follow-up. The numbers, however, were small, even if the point is made that distal colitis can be just as refractory to medical treatment as more extensive disease. It is notable that the need for surgery in UC appears to be highest within the first few years of diagnosis.[18] In contrast, 13 of the 30 patients who came to colectomy (43%) in our cohort had been diagnosed with UC 10 or more years before entering the study. This suggests that short disease duration may not be a predictive factor for colectomy in the context of severe UC. This is consistent with the finding that there was no difference between CRs and IRs in disease duration measured by time from index diagnosis to index surgery.

The pattern of disease as determined by the number of relapses, median number of relapses per patient, number of courses of steroids, and median number of hospital readmissions for acute severe colitis did not show differences between CRs and IRs. However, the observation period for CRs was much longer, because of the high colectomy rate among IRs. The impact of immunomodulation is difficult to evaluate. The median number of relapses for CRs and IRs on AZA was almost identical. This could mean that AZA corrects for the impact of IR, potentially changing the natural course of disease. It could also mean that AZA is not that effective in UC. The most likely explanation, however, is that treatment with AZA identifies the most refractory group of patients and that small numbers should not be overinterpreted.

The maximum interval between relapses was different for CRs and IRs. The longest period of steroid-free remission was 3.5 years for CRs, but less than a year (median 9 months, $P = 0.011$) for IRs. This is useful information when advising patients who are recovering from a severe attack of UC, since a patient with an IR on that admission can expect to relapse sooner than CRs.

The key weakness of this study is the small sample size and retrospective nature that limit the applicability of these results, but patients admitted with severe UC are relatively uncommon in individual practice. The key strength is the long follow-up period and the fact that the study comes from a single center with a special interest in the management of severe UC. The outcomes in Oxford most closely match the

median colectomy rate of all published series over a period of 30 years.[4]

The poor long-term outcome of IRs to intensive treatment should be recognized. Two-thirds of a series of consecutive patients admitted to the hospital with severe UC came to colectomy within the next decade. Just 7 days after admission it may be possible to predict the likelihood of colectomy among responders in whom a severe attack was treated with corticosteroids and/or cyclosporin, but not infliximab. IRs to medical treatment seem to be at particular risk. This includes anyone who has >3 stools/day or visible bleeding on day 7, but who avoids colectomy on that admission. These patients had a 70% chance of colectomy within the next 5 years. In contrast, the maximum duration of remission in CRs was almost 5 times longer than for IRs. These are material facts that help inform clinicians' decision-making and are relevant to patient care, albeit from the prebiologic era. The long-term effect of biologics as rescue and maintenance therapy in acute severe UC remains to be tested.

ACKNOWLEDGMENT

We thank Helen Small and Rosemary Kershaw for clerical and administrative help.

REFERENCES

1. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. *Gut.* 1963; 4:300–308.
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J.* 1955;ii:1041–1048.
3. Jakobovits S, Travis SPL. The management of acute severe ulcerative colitis. *Br Med Bull.* 2006;75–76:131–144.
4. Turner D, Walsh C, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and meta-regression. *Clin Gastro Hepatol.* 2007;5:103–110.
5. Gupta S, Kesharvazian A, Hodgson HJF. Cyclosporin in ulcerative colitis. *Lancet.* 1984;2:1277–1278.
6. Campbell S, Travis SPL, Jewell DP. Ciclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol.* 2005;17: 79–84.
7. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastro Hepatol.* 2006;4:760–765.
8. Fellerman K, Tanko Z, Herrlinger KR, et al. Response of refractory colitis to intravenous or oral tacrolimus (FK506). *Inflamm Bowel Dis.* 2002;8:478–479.
9. Järnerot G, Hertevig E, Ingalill FL, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology.* 2005;128:1805–1811.
10. Travis SPL, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut.* 1996;38:905–910.
11. Satsangi J, Silverberg MS, Vermeire S, et al. The Montréal classification of inflammatory bowel disease: controversies, consensus and implications. *Gut.* 2006;55:745–753.
12. Leijonmarck CE, Persson PG, Hellers G. Factors affecting colectomy rate in ulcerative colitis: an epidemiologic study. *Gut.* 1990;31:329–333.
13. Hendriksen C, Kreiner S, Binder V. Long term prognosis in ulcerative colitis based on results from a regional patient group from the county of Copenhagen. *Gut.* 1985;26:158–163.
14. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history and progression of ulcerative colitis. A long term follow-up of 1116 patients. *Dig Dis Sci.* 1993;38:1137–1146.
15. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol.* 2006;101:1274–1282.
16. Kohn A, Daperno M, Armuzzi A, et al. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther.* 2007;26:747–756.
17. Jakobovits SL, Jewell DP, Travis SPL. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. *Aliment Pharmacol Ther.* 2007;25:1055–1060.
18. Langholz E, Munkholm P, Davidsen M, et al. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology.* 1994;107:3–11.