Ulcerative Colitis and Clinical Course: Results of a 5-Year Population-based Follow-up Study (The IBSEN Study)

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Background: The majority of studies concerning the clinical course and prognosis in ulcerative colitis (UC) are old, retrospective in design, or hospital based. We aimed to identify clinical course and prognosis in a prospective, population-based follow-up study.

Materials and Methods: Patients diagnosed with inflammatory bowel disease (IBD) or possible IBD in southeastern Norway during the period 1990–1994 were followed prospectively for 5 years. The evaluation at 5 years included an interview, clinical examination, laboratory tests, and colonoscopy.

Results: Of 843 patients diagnosed with IBD, 454 patients who had definite UC and for whom there were sufficient data for analysis were alive 5 years after inclusion in the study. The frequency of colectomy in this population was 7.5%. Forty-one percent of the patients were not taking any kind of medication for IBD at 5 years.

Conclusions: The disease course and prognosis of UC appears better than previously described in the literature. The frequency of surgery was low, and only a minority of the patients had symptoms that interfered with their everyday activities 5 years after diagnosis.

Key Words: clinical course, follow-up, prognosis, ulcerative colitis.

Original Article

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MATERIALS AND METHODS

During a 4-year period from January 1, 1990 to December 31, 1993, all new patients diagnosed with inflammatory bowel disease (IBD) or possible IBD were registered in 4 geographically well-defined areas in southeastern Norway (the IBSEN study). On January 1, 1992, the total study population was 966,427. All of the general practitioners in these areas were
invited to participate in the study, and at each hospital, a senior gastroenterologist was made responsible for the diagnostic procedures, registration, and identification of appropriate patients. The organization of the study has previously been described in detail.\textsuperscript{10,11} All of the patients were invited to a follow-up visit at their local hospital 1 year after diagnosis, and the findings have been described elsewhere.\textsuperscript{10}

This cohort was followed up further in the present study. All of the patients were invited to an interview and a new examination at their local hospital 5 years (±1 year) after their inclusion in the study. The purpose of this follow-up was to re-evaluate the diagnosis and to record the clinical course of the disease. Each patient was given a structured interview, which included any family history of IBD, smoking habits, intestinal symptoms, sick leaves, use of medication, the clinical course in the follow-up period, extraintestinal manifestations, and surgical procedures. The examination consisted of a clinical examination, laboratory tests, and colonoscopy. Colonoscopy was not performed if the patient objected. Medical treatment was given according to established clinical practice.

The interview with patients who did not visit the hospital was conducted by telephone and, if necessary, supplemented by information from the hospital records. In some cases, when the patients could not be reached by telephone, our information was based on hospital records alone, provided that they had been recently brought up to date.

Diagnosis and Definitions

Patients were initially classified as having UC, Crohn’s disease (CD), indeterminate colitis (IC), or possible IBD. The diagnosis was based on symptoms consistent with IBD for >4 weeks, excluding infections and other acute or chronic non-IBD conditions. The diagnosis of UC was based on the presence of at least 3 of the following 4 criteria: (1) a history of diarrhea or pus in stools, (2) macroscopic appearance by endoscopy with continuous mucosal inflammation affecting the rectum in continuity with some or all of the colon, (3) microscopic features on biopsy compatible with UC, and (4) no suspicion of CD on small bowel radiograph, ileocolonoscopy, or biopsy. Patients were diagnosed with IC when endoscopy or histopathology was divergent or inconclusive with regard to the diagnosis of UC or CD. If a patient fulfilled the criteria for inclusion in the study, but the quality of the diagnostic examination was not satisfactory or the findings were uncertain or contradictory, then the patient was classified as possible IBD.

At the 1-year visit, the initial classification of subgroups was retained, but at the 5-year visit, an attempt was made to classify these patients into 3 subgroups: UC, CD, and non-IBD. Proctitis was defined as inflammatory changes up to 15 cm from the anus, proctosigmoiditis as disease involving the rectum and sigmoidum. Left-sided colitis was defined as inflammatory changes up to the splenic flexure, and changes beyond the splenic flexure were defined as extensive colitis.

Study Population

In the inclusion period, 843 new cases of IBD or possible IBD were identified. The initial diagnoses in these patients were 518 with UC, 221 with CD, 40 with IC, and 64 with possible IBD. During the 5-year observation period, 56 patients died. Clinical information was available for 739 (94%) patients who were alive after 5 years.

Of the 518 patients initially classified as UC, 14 turned out to have CD, 32 were diagnosed with non-IBD, 36 died during the 5-year period, and 25 were excluded from the study because of insufficient data. Forty-three patients classified as UC at 5 years were initially classified as CD (7 patients), IC (17 patients), or possible IBD (19 patients). Patients who were included and excluded from the initial cohort of UC patients are shown in Figure 1. At 5 years, 454 patients who had definite UC and for whom there were sufficient data for analysis were alive. When first diagnosed, the initial extent of the disease was proctitis in 146 (32%) patients, proctosigmoiditis in 90 (20%) patients, left-sided colitis in 68 (15%) patients, and extensive colitis in 150 (33%) patients.
Colonoscopy at Follow-up

Colonoscopy was performed in 208 (46%) patients at 5 years. In addition, 380 patients had undergone colonoscopy at 1 year, and 94 patients had had an unscheduled colonoscopy during the period between 1 and 5 years. Only 38 patients had not had an additional colonoscopy after diagnosis; 8 of these had undergone surgery during the observation period.

Ethical Requirements

The study was approved by the regional ethics committee. Permission was also obtained from the Norwegian Data Registry.

Statistics

Descriptive statistics are expressed as mean and range or as frequency counts or percentages. Data were analyzed by Pearson’s chi-square test. All of the statistical analyses were performed with SPSS Version 12.0.1 (SPSS, Inc, Chicago, Ill) for Windows.

RESULTS

The cohort in the present study consisted of 219 females and 235 males, with a median age at diagnosis of 37.0 (range 4–87) years. A total of 417 (92%) patients made the 5-year visit to the hospital. The mean time interval from diagnosis to the 5-year visit was 5.4 years. Clinical data were based on telephone interviews and hospital records in 15 (3%) patients and on hospital records alone in 22 (5%) patients.

Of the 36 patients initially classified as UC who died during the 5-year follow-up period, 2 died of causes related to IBD. One 65-year-old patient died from cholangiocarcinoma related to primary sclerosing cholangitis, and 1 patient age 48 died of colon perforation and septic shock. Patients who died during follow-up were significantly older compared with patients who survived the first 5 years (mean age 72.6 vs 40.1 years, \( P < 0.001 \)). No difference in rate of surgery (\( P = 0.67 \)), frequency of extensive colitis (\( P = 0.29 \)), or use of systemic glucocorticosteroids in treating the first flare (\( P = 0.10 \)) was observed between those who died and those who survived the first 5 years after diagnosis. The majority of deaths in this population were caused by cardiovascular and malignant diseases.

Surgery

During the 5 years, 34 (7.5%) of the patients underwent colectomy, the majority (71%) during the first 2 years after diagnosis. Two patients had left-sided colitis and 32 had extensive colitis at the time of surgery.

Medication

The medication being taken at 5 years by patients who did not receive surgery is shown in Table 1. At 5 years, 210 of 420 (50%) patients who did not receive surgery were taking sulfasalazine or 5-aminosalicylic acid (5-ASA). The number of patients taking these medications varied according to the extent of disease (Table 1). Twenty-nine (7%) patients were taking systemic glucocorticosteroids, and 4 (1%) patients were taking azathioprine. Forty-one percent of the patients were not taking any medication for IBD 5 years after the diagnosis. A total of 84 (19%) patients had not taken systemic sulfasalazine or 5-ASA at any time during follow-up. A total of 195 (43%) patients had taken systemic glucocorticosteroids at some time during follow-up. The maximal extent of disease in these patients was extensive colitis in the majority (62%) and proctitis in a minority (5%).

Extent of Disease

Further extension was observed in 78 (17%) patients during follow-up. Of 146 patients with initial proctitis, the colitis had progressed during the observation period in 41 (28%; 20 patients to proctosigmoiditis, 7 patients to left-sided colitis, and 14 patients to extensive colitis). In patients with proctosigmoiditis and left-sided colitis, further progression to extensive colitis was observed in 16 (18%) and 9 (13%) patients, respectively. The observed increases in the extent of disease during follow-up are shown in Figure 2.

Of 147 patients with initial proctitis, 81 (55%) patients had initially been treated with topical medication, 54 (37%) TABLE 1. Medication Being Taken at 5-Year Visit in Patients Who Did Not Receive Surgery According to Extent of Disease and for Group of Patients Who Did Not Receive Surgery as a Whole

<table>
<thead>
<tr>
<th>Extent of Disease</th>
<th>Proctitis, n = 114 (%)</th>
<th>Proctosigmoiditis, n = 86 (%)</th>
<th>Left-sided Colitis, n = 73 (%)</th>
<th>Extensive Colitis, n = 147 (%)</th>
<th>All Patients, n = 420 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>13 (11)</td>
<td>21 (24)</td>
<td>17 (23)</td>
<td>54 (37)</td>
<td>105 (25)</td>
</tr>
<tr>
<td>5-ASA</td>
<td>11 (10)</td>
<td>22 (26)</td>
<td>27 (37)</td>
<td>45 (31)</td>
<td>105 (25)</td>
</tr>
<tr>
<td>Glucocorticosteroids</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>8 (11)</td>
<td>17 (12)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Local treatment</td>
<td>25 (22)</td>
<td>14 (16)</td>
<td>10 (14)</td>
<td>8 (5)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>No treatment</td>
<td>74 (65)</td>
<td>36 (42)</td>
<td>25 (34)</td>
<td>38 (26)</td>
<td>173 (41)</td>
</tr>
</tbody>
</table>

5-ASA indicates 5-aminosalicylic acid.
Symptoms at 5 years were more frequent in patients with
125 patients and normal appearance of the mucosa in 70.
was given for 195. Macroscopic inflammation was observed in
classification into mild, moderate, and severe inflammation
Of the patients undergoing a colonoscopy, a detailed descrip-
tion of the macroscopic appearance of the mucosa and
Symptoms were reported more frequently by the
patients who underwent colonoscopy at 5 years (P < 0.001).
Of the patients undergoing a colonoscopy, a detailed description of the macroscopic appearance of the mucosa and classification into mild, moderate, and severe inflammation was given for 195. Macroscopic inflammation was observed in 125 patients and normal appearance of the mucosa in 70. Symptoms at 5 years were more frequent in patients with

with oral sulfasalazine or 5-ASA (with or without topical
treatment), and 11 (8%) received no medical treatment in connection with the initial diagnosis. The progression of the disease was not affected by initial use of oral sulfasalazine or 5-ASA (P = 0.14).

Symptoms
The patients were asked about their IBD symptoms
during the 2 weeks before the 5-year visit. Mild symptoms
were defined as symptoms that did not interfere with
everyday activities, moderate symptoms as those that did interfere with everyday activities, and severe symptoms as those that prevented the patient from carrying out everyday activities or that had resulted in sick leave or hospitalization.

This question was answered by 410 of 420 (98%)
patients who did not receive surgery. The majority of these patients, 235 of 410 (57%), had no symptoms at 5 years and 148 (36%) had mild symptoms. Moderate symptoms were reported by 27 (7%) patients and only 1 patient had severe symptoms; this patient underwent colectomy shortly afterward. There was no relationship between the extent of the disease and the number of patients reporting symptoms (P = 0.57) or between the extent of the disease and the severity of the reported symptoms (P = 0.79).

Symptoms were reported more frequently by the
patients who underwent colonoscopy at 5 years (P < 0.001).

Relapse
A relapse was defined as an aggravation of the symptoms resulting in the need for more intensive medical therapy or surgery. Relapses after 1 and 5 years of follow-up and relapse in the course of the last year of follow-up were recorded.

During the 5-year observation period, a total of 354 (78%) patients had at least 1 relapse. Relapse was recorded in 79% of the patients with proctitis, in 81% of the patients with proctosigmoiditis, and in 77% of the patients with left-sided and extensive colitis. However, relapse during the 5-year period was not influenced by the extent of disease (P = 0.88). Relapse was more frequent in females (83.5% vs 73.5%, P = 0.01). Patients having relapse were younger than those who did not have relapse (mean age 38.5 vs 46.0 years, P < 0.001). However, smoking at diagnosis did not influence the risk of relapse (P = 0.37).

When patients who had undergone colectomy during the first 4 years of the follow-up period were excluded, relapse during the fifth year was recorded in 53% of the patients with proctitis, in 46% of the patients with proctosigmoiditis, and in 51% and 43% of patients with left-sided and extensive colitis, respectively. Relapse during the fifth year of the follow-up period was not related to the extent of disease (P = 0.40). In the first year of the observation period, 50% of the patients experienced relapse, whereas the corresponding figure for the last year of the period was 48%.

Course of the Disease
The clinical course was predefined and illustrated by 4
different curves (Figure 3), which were designed to reflect the
nature of symptoms during the 5-year period. The patients
were asked to choose the curve that best described the course of their disease during this period.
Of 420 nonoperated patients, 248 (59%) experienced a decline in the severity of intestinal symptoms during the follow-up period (curve 1). Only 4 (1%) patients experienced an increase in severity (curve 2). Chronic continuous symptoms (curve 3) and chronic relapsing symptoms (curve 4) were experienced by 36 (9%) and 129 (31%) patients, respectively. Data were missing for 3 patients.

Although curve 1 was less frequently found in patients with left-sided colitis and curve 3 more frequently found in the same patients, the difference in the course of disease in relationship to the maximal extent of disease was not statistically significant ($P = 0.15$). The different courses in relationship to the maximal extent of disease are shown in Table 2.

## DISCUSSION

The present population-based study in which UC patients were followed up for 5 years has resulted in several important findings. First, only 7.5% of the patients underwent colectomy. Second, as many as 41% of the patients were not taking medication for IBD 5 years after the diagnosis. Third, in 26% of patients with restricted extent of disease at diagnosis, a progression was observed during follow-up. Fourth, the majority of the patients did not have intestinal symptoms at 5 years. Fifth, 22% of the patients did not have a relapse during follow-up. Sixth, a decrease in symptoms over time was the most common course of the disease.

The course of disease in UC is often described in terms of the degree of progression of the inflammatory process, the number of relapses, the need for surgery, and the mortality. These parameters are objective, but they give us little information about the patients’ experience of the disease and how it affects their daily lives. Quality of life interviews and the various clinical activity indexes introduced during the last few decades are often too comprehensive to be used in clinical follow-up. Because no single parameter provides exact information about the clinical course of UC, we used a combination of subjective and objective parameters.

### TABLE 2. Different Courses of Disease According to Extent of Colonic Disease

<table>
<thead>
<tr>
<th>Extent of Disease (%)</th>
<th>Proctitis</th>
<th>Proctosigmoiditis</th>
<th>Left-sided</th>
<th>Extensive</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curve 1</td>
<td>72 (63)</td>
<td>54 (64)</td>
<td>38 (52)</td>
<td>84 (58)</td>
<td>248 (59)</td>
</tr>
<tr>
<td>Curve 2</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Curve 3</td>
<td>5 (4)</td>
<td>7 (8)</td>
<td>13 (18)</td>
<td>11 (7)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>Curve 4</td>
<td>35 (31)</td>
<td>23 (27)</td>
<td>22 (30)</td>
<td>49 (34)</td>
<td>129 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>114 (100)</td>
<td>85 (100)</td>
<td>73 (100)</td>
<td>145 (100)</td>
<td>417 (100)</td>
</tr>
</tbody>
</table>

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Only 2 patients initially diagnosed with UC died from IBD-related causes during the observation period. The patients who died were significantly older at diagnosis, but did not appear to have a more serious disease than those who survived the 5-year period.

A population-based prospective study is an ideal way to arrive at a general understanding of the clinical course in patients with UC. In the present study, which had a high follow-up rate, only 7.5% of the patients had been colectomized during the 5-year follow-up period. This figure is much lower than those previously reported in other Scandinavian countries. In a population-based study from Stockholm, the cumulative colectomy risk was 20% (95% confidence interval 18%–22%) after 5 years.\textsuperscript{12} Langholz et al\textsuperscript{13} also found a cumulative risk after 5 years of 20% in Copenhagen. The proportion of patients with proctitis and proctosigmoiditis was no higher in our study than it was in the material from Copenhagen, which excludes the extent of disease as an explanation for the lower frequency of surgery. When comparing our findings with those of studies performed before 1990, however, the possibility that the extent of disease was underestimated cannot be ruled out because only radiology was used before the colonoscopic era.

One would expect populations from Scandinavia to be very much alike, so we were surprised by these differences and have no immediate explanation. Most of our colectomized patients were operated on during the first 2 years after diagnosis, and this is in accordance with the observations of others.\textsuperscript{5,12–14}

In our study, few patients were treated with immunosuppressive medication. However, some of our data were collected before azathioprine and 6-mercaptopurine were suppressive medication. However, some of our data were collected before the possible cancer-preventive effect of these drugs was known.\textsuperscript{16,17} Systemic glucocorticosteroids were only being taken by a minority of the patients 5 years after diagnosis. As many as 41% of the patients were not taking any kind of medication for UC 5 years after diagnosis.

The initial extent of the disease in the present study was similar to that found in other studies.\textsuperscript{5,18–20} Further extension in the colon was most frequently observed in patients with proctosigmoiditis (31%), and progression to extensive colitis was also most frequently observed in this group (18%). In patients with proctitis, further extension was observed in 28% of the patients and progression to extensive colitis in 10%. In other studies, considerable variations in the numbers of patients (5%–53%) with further extension have been observed.\textsuperscript{1–3,5,7,14,21–25} However, the study design and duration of follow-up vary a great deal in these studies.

The majority of the patients in our study (57%) did not have any intestinal symptoms 5 years after diagnosis. The majority of the symptomatic patients had only mild symptoms, which did not interfere with everyday activities. Only a minority of the patients (7%) had symptoms that interfered with everyday activities. There was no relationship between the number of patients reporting symptoms or the severity of these symptoms and the extent of disease.

To our knowledge, no other prospective study has recorded symptoms at a fixed time after the diagnosis and registered the impact of such symptoms on everyday activities. In a Danish population, \approx 50% of the patients with UC were without symptoms at any particular time during a follow-up period.\textsuperscript{26} In a recent prospective multicenter study in Europe, a similar figure was found after an observation period of 4 years.\textsuperscript{27} In a retrospective study, Farmer et al\textsuperscript{5} reported an even higher proportion of patients (67.2%) without symptoms at the time of the last control in a study of 1116 cases of UC. It is important to note that the intestinal symptoms experienced by patients with UC do not necessarily reflect the activity of the underlying disease. Studies have shown that irritable bowel–like symptoms are common in IBD in remission, even more common than in the background population.\textsuperscript{28–30} The reason for this is not known. A possible explanation is that the inflammation may result in a “hypersensitive gut” even after the inflammatory infiltrate has regressed. However, this theory does not explain why only some of the patients have irritable bowel–like symptoms. The role of psychologic factors is not known.

In our study, 38% of the patients with macroscopic inflammation at colonoscopy did not have intestinal symptoms. It is possible that these patients were not receiving optimal medical treatment and that they may in the long run have an increased risk of cancer.

The number of patients who experience a relapse-free course varies in the literature. This could be caused by study design, selection bias, poorly defined patient groups, historic data, or variations in follow-up period. In addition, the term “relapse” is not always accurately defined. In our study, 22% of patients experienced no relapse during 5 years of follow-up. However, it is difficult or even impossible to rule out minor fluctuations in disease course that a patient fails to remember and for which he or she did not seek help. The threshold for symptoms is probably also an important factor. Furthermore, it is difficult to distinguish between a patient in a long-term remission after a single initial attack and a patient with real self-limiting colitis. Langholz et al\textsuperscript{20} found that the cumulative probability of a completely relapse-free course was 18.4% after 5 years and 10.6% after 25 years. In an older study, 12.6% of the patients were found to have had no relapse after 5 years, but some of these data were obtained before the introduction of steroids and sulfasalazine.\textsuperscript{6} From these studies it appears that the number of patients experiencing a relapse-free course has increased during the last several decades. If this is true, then it could be caused...
CONCLUSIONS

In this prospective population-based study, the clinical course and prognosis for UC was found to be better than that described in other studies. The extent of the colonic disease influenced the risk of colectomy but not the risk of relapses, the course of the disease described by curves in the 5-year follow-up period, or the risk of being symptomatic at the 5-year visit.

The favorable disease course of UC and the relatively low frequency of surgery during the first 5 years after diagnosis may be partly explained by the population-based design of the study. Other factors such as improved medical treatment may have contributed to a better prognosis with an improved level of functioning 5 years after diagnosis.

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