The Natural Course of Ulcerative Colitis
A European Population-Based Study

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PREFACE

This thesis outlines some aspects of the natural course of Ulcerative Colitis (UC) limited to the first ten years of a disease course of probably at least 40 years on average. To determine what is natural by the course of a disease will never be an easy task. The course may alter over time due to changes in genetic and environmental factors, and to the provision of health care. In this context, the natural course refers to disease outcome in patients diagnosed and treated according to the common standards applied for the last decade. We have focused on disease outcome in terms of mortality, surgery and relapse of symptoms, which we think is important to patients, relatives and physicians. Other disease aspects like hospital admissions, extra-intestinal disease manifestations, the risk of cancer development, working capacity, sick leave and disablement pension, and health related quality of life have been and will probably be addressed by other publications from the European Collaborative study group of Inflammatory Bowel Disease (EC-IBD), The Inflammatory Bowel disease of South-East Norway (IBSEN) study group, and other research groups. The psychological aspects of concerns and worries related to life with a chronic disease of unknown cause may be of great importance to most patients and their family and is therefore a subject of increasing interest in research and patient management. It is our hope that the research work presented here may give a small contribution to the understanding of the nature of UC and thereby to the improvement of patient care.

Abbreviations

ASCA	Anti Saccharomyces Cerevecias Antigen
5-ASA	Sulfasalazine and 5-aminosalicylic acid
CD	Crohn´s Disease
CI	Confidence interval
EC-IBD	European Collaborative study group of Inflammatory Bowel Disease
HR	Hazard Ratio
HR-QOL	Health Related Quality Of Life
IBD	Inflammatory Bowel Disease
IBSEN	Inflammatory Bowel disease of South East Norway
IC	Indeterminate colitis
LTFU	Lost To Follow Up
OCT	Oral contraceptive treatment
p-ANCA	Perinuclear Anti Neutrophil Cytoplasmic Antibody
PpPFU	Patient per Physician Follow Up form
PQ	Patient Questionnaire
SF-36	Short Form 36
SMR	Standardised Mortality Rate
SPSS	Statistical Package of Social Science
UC	Ulcerative Colitis

1 INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease mainly affecting the large intestine, although extra-intestinal manifestations have been reported in 6-25% of the patients (1; 2). Even though immune mechanisms seem to be involved in the pathogenesis (3), and several precipitating factors have been proposed (4), the cause of the disease is still unknown. The disease may start at any point during life, but most commonly affects young adults (5). In Europe there are between 50 000 and 70 000 new cases per year and about 2.2 million people suffer from this disease(6). Due to the young age at onset of disease, the duration of the disease in each patient is substantial. Thus, there is the potential of affecting the general health and well-being of a great number of patient years.

1.1 Incidence studies in UC

A great number of epidemiologic studies have been conducted in the last 50 years. In population-based studies, the incidence of UC varies by time and between different geographic regions throughout the world. High endemic areas are found in North-America and Northern Europe and low endemic areas in Korea, Japan, South-Africa (black population, hospital based) and centres in Latin America . The incidence has been rising with time in the low-endemic areas (7)

1.2 Follow-up studies

Disease outcome of inflammatory bowel disease (IBD) has usually been evaluated by mortality and by various aspects of morbidity. There is, however no general standards of how the disease-outcome should be assessed.

Some population-based cohorts of follow-up are listed in Table 1.

Table 1

Population based cohorts of UC patients who have been subjected to follow-up. References to outcome results are listed.

Country	Area	Design	N of patients	Inclusion period	Years of follow-up	References
Canada	Manitoba	case-control	5128	1984-1995	Mean 7.4	(8-11)
Denmark	Copenhagen	cohort	1161	1962-1987	Median 19	(12-16)
	Copenhagen	cohort	326	2003-2005	Mean 1	(17)
	North-Jutland	cohort	2205	1978-2002	Range 1-26	(18)
Hungary	Veszprem	cohort	619	1977-2001	Range 1-24	(19)
Israel	Tel Aviv	cohort	1035	1970-1980	Mean 11.5	(20)
Italy	Florence	cohort	689	1978-1992	Median 15	(21;22)
Norway	South-East Norway	cohort	496	1990-1994	Median 10	(23-31)
Spain	Asturias	cohort	565	1954-1997	Range 1-43	(32)
Sweden	Stockholm	cohort	1586	1955-1984	Range 6-35	(33-35)
	Uppsala	cohort	2509	1965-1983	Range 3-21	(36;37)
	Malmö	cohort	471	1958-1982	Mean 14.8	(38)
United Kingdom	Nottingham	case-control	16550	1987-2002	Range 1-15	(39)
	Birmingham	cohort	676	1940-1976	Mean 15.8	(40)
	Leicestershire	cohort	1014	1972-1989	Range 1-18	(41)
	Mid-England	cohort	356	1978-1986	Median 8.3	(42)
	North-East Scotland	cohort	537	1967-1976	Range 1-10	(43)
USA	Minnesota	cohort	692	1940-2001	Median 14	(44-46)

According to the references in Table 1, a large number of data of various aspects of disease outcome have been published. The results have been focused on mortality, surgery, relapse and disease activity, cancer, extra intestinal manifestations, hospital admissions and health related quality of life (HR-QOL). The various studies differ in design, inclusion periods, time of follow-up and number of patients. This makes it difficult to compare directly the results and exploring possible geographical differences.

2 RESEARCH ORGANISATIONS OF IBD

2.1 The EC-IBD

The European Collaborative study-group of Inflammatory Bowel Disease was started in The Netherlands in 1988 by Professor M van Blankenstein and Dr. S. Shivananda. This study was conducted from the University of Maastricht by Professor Reinhold Stockbrügger and was financed by a grant from the European Union. Twenty centres across Western and Southern Europe and Israel have been participating. The group has consisted of 50 active members from 20 research centres in 12 European countries and Israel. A prospective population based inception cohort of patients with IBD was formed in close cooperation with the general practitioners in the different regions. The planning of the ten-year follow-up project was started in 1998. The collection of data was performed electronically by the internet and the collected data was processed by the MEMIC Institute for data and information management at the University of Maastricht. Further details of the organisation and performance of this 10-year follow-up study have previously been described (47; 48).

2.1.1 Fields of interest to the EC-IBD

1. Study prospectively the incidence of IBD in a multicentre European Study using standard definition of disease classification
2. Investigate the natural course of IBD in a large, inception based, European cohort of patients
3. Investigate the extraintestinal and intestinal complications of IBD in the follow-up
4. Study quality of life in relation to quality of healthcare in IBD
5. Formation of a European collaborating group of experts concerning the clinical epidemiology of IBD
6. Training of clinicians in IBD on a European scale
7. Patient's perspective of information and education

2.2 The IBSEN group

The Inflammatory Bowel disease Study group of South-East Norway was started in 1990 and includes gastroenterologists, pathologists, epidemiologists and statisticians. The group represents nine local, three regional and three university hospitals serving a background population of close to 1 million inhabitants from three counties and Oslo. The IBSEN group has conducted incidence and long-term follow-up studies, which has gained widely international recognition. This strong research group has been an important resource in the participation with the EC-IBD.

3 AIMS OF THE STUDY

The aims of this study was, on the basis of a population based European multicentre inception cohort, firstly to investigate the natural course and disease outcome in terms of mortality, colectomy and relapse, in UC during 10 years of follow-up. Secondly phenotypes and environmental factors, which could possible influence the outcome, were to be studied. Thirdly, we wanted to compare the results from various centres and regions across Europe.

4 MATERIAL AND METHODS

4.1 Patient population

A prospective population based inception cohort of 2201 patients from 20 different centres in Europe and Israel diagnosed with IBD was formed between October 1 1991 and September 30 1993. This cohort served as the basis for incidence studies as well as studies of short time follow up (49-51). The patient's diagnoses at the time of inclusion were UC in 1379, CD in 706 and indeterminate colitis (IC) in 116 patients. The planning of the follow-up project was started in 1998 and all of the centres of the original cohort were invited to participate (52). The collection of data was started at August 1 2002 and was terminated at January 31 2004.

4.2 Diagnosis

For UC the diagnostic criteria of Lennard Jones and Truelove and Witts were applied at all centres (53). A re-evaluation of the diagnosis was performed after one year based on a collection of additional information from clinical development of the disease and subsequent investigations (50). The most updated diagnosis during follow-up was applied as the final diagnosis in patient classification at the end of the follow-up study.

4.3 Follow-up

The patients were followed according to local treatment routines established at each of the centres. In a sub-study, a standard 4-year follow-up form for 796 of the initial 2201 patients was completed by the investigators (51). The 10-year follow-up visit consisted of a consultation by a physician at the local centre where an electronic internet-based Physician per Patient Follow Up form (PpPFU) was completed. The vital status, diagnosis, disease activity, disease location, diagnostics, drug therapy, surgery, extra-intestinal manifestations, colonic dysplasia and cancers were addressed by a multiple questionnaire. Hospital records were used as additional sources of data. Concerning vital status, information was obtained when necessary from relatives and general practitioners. The patients were asked to fill in an

electronic internet based Patient Questionnaire (PQ), if necessary assisted by a study nurse, containing marital status, level of education, cases of inflammatory bowel disease among 1st degree relatives, diet, smoking habits, working capacity, sick leave and disablement pension.(48). In addition, the short form 36 (SF-36) a widely used and evaluated questionnaire for measuring general health was included (54). Response rates of patients completing both the PpPFU and the PQ were calculated for all IBD patients at each centre. A 60% response limit was set for the centre to be included in the final analyses. This was done to ensure the population based nature of the study, as a low response rate could lead to a selection bias of patients often visiting hospitals due to a severe disease course. (48)

4.4 Statistics

We used the Mann Whitney U-test and the Kruskal Wallis test in addition to the Chi square and Fisher's exact tests, when comparing the various groups of patients. To calculate time-dependent events we used the Kaplan-Meier survival curve and the log rank test. Independent variables of statistical significance were identified by the Cox regression and the Poisson regression analysis. The SPSS statistical software packages version 11.5, 12.0, 13.0 and 14.0 (SPSS Inc., Chicago IL) were used in the analyses. For Poisson regression analysis the R software version 2.2.0 by the R Project for Statistical Computing was applied. Mortality data was analysed by calculating standardised mortality rates (SMR's) according to the methods described in article I.

4.5 Ethics

The study protocol was approved by the local and regional ethic committees in all the participating countries. A written informed consent was obtained from all patients who participated.

5 RESULTS

5.1 Patients and centres

The original cohort consisted of 1379 UC patients from 20 centres in Europe and Israel (49). Of these 781 UC patients from nine of the centres, which completed the follow-up study within the response limit, were eligible for analysis. The base line characteristics of sex, age groups at diagnosis and north-south residency of patients from the follow-up centres did not differ statistically from the 11 non-participating centres.

Table 2. The EC-IBD cohort of UC patients – patients and centres participating in the follow-up compared with the incidence study.

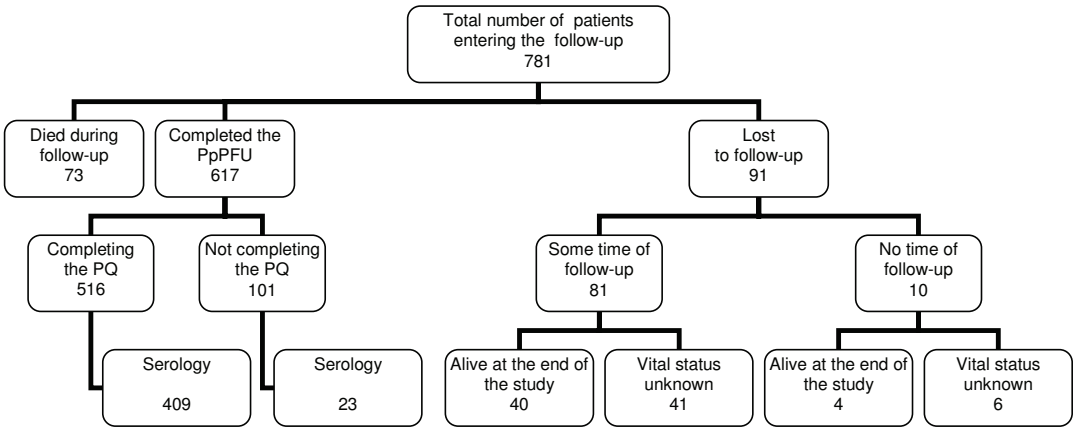
Original incidence cohort		Follow-up cohort				
Centre	**N of patients****	**N of patients**	**PpPFU completion***	**PQ completion**	**LTFU***	**Dead**
Northern						
Reykjavik (Iceland)	95					
Oslo (Norway)	251	269	203	157	29	37
Copenhagen (Denmark)	92	89	70	62	4	15
Dublin (Ireland)	137					
Leicester (United Kingdom)	45					
South Limburg (The Netherlands)	140	140	123	96	10	7
Essen (Germany)	60					
Amiens (NW France)	49					
Southern						
Milan-Varese (Italy)	34					
Cremona (Italy)	39	41	30	28	7	4
Reggio-Emilia (Italy)	56	50	38	37	9	3
Florence (Italy)	87					
Vigo (NW Spain)	58	63	50	45	11	2
Sabadell (NW Spain)	52					
Braga (N Portugal)	22					
Ioannina (NW Greece)	35	37	33	32	3	1
Almada (S Portugal)	8					
Palermo, Sicily (Italy)	19					
Heraklion, Crete (Greece)	60	53	38	31	13	2
Beer Sheva (Israel)	40	39	32	28	5	2
Total	**1379**	**781**	**617**	**516**	**91**	**73**

Lost: Patients who had their last visit at the centre before the time when the 10 year data collection was started. For some of the centres the number of patients in follow-up may be higher than the number in the original incidence cohort due to changes in diagnosis between UC, CD and IC during the follow-up. * See appendix B: data modification. **Data according to Shivananda et al. (49)

The status of the 781 UC patients from the nine centres during follow-up has been shown in the flow chart of Figure 1.

Figure 1

Flow chart demonstrating the distribution of patients in accordance with their different status in the follow-up analyses.



Of the 617 patients who had their last visit to the centre after start of 10 year data collection, 516 (84%) completed the PQ. At the end of the 10 years of follow-up serologic samples were collected from 432 patients of whom 409 did complete the PQ. The 73 patients who had died and 81 of the 91 patients who were lost to follow-up (LTFU) were included in the analysis in accordance with the time they had been followed. Ten of the 91 patients LTFU had no time of observation, and were therefore not entered into analysis. A total of 771 patients were then available for follow-up analyses.

Concerning the vital status 44 of the 91 patients LTFU was known to be alive by the start of the data collection at August 1 2002. This includes four of the ten patients with no time of follow-up. Thus, a number of 775 patients were included in the cumulative mortality rate analysis.

5.2 Summaries of articles

I

Høie O, Schouten LJ, Wolters FL, Solberg IC, Riis L, Mouzas IA, Politi P, Odes S, Langholz E, Vatn M, Stockbrügger RW, Moum B. Ulcerative colitis: No rise in mortality in a European-wide population-based cohort 10 years after diagnosis. Gut 2007; 56(4):497-503

Aims

To assess overall mortality in a European cohort of UC patients 10 years after diagnosis and to investigate national UC-related mortality across Europe.

Methods

Population based multicentre European inception cohort study of UC patients formed between 1991 and 1993. The causes of mortality observed in a 10 year period after diagnosis was recorded. The expected mortality calculated from the sex-, age- and country-specific mortality in the WHO Mortality Database for 1995-1998 was used for the calculation of standardised mortality ratios (SMR´s).

Results

At follow-up 661 of 775 patients were alive. Seventy-three patients had died versus an expected number of 67. The overall mortality risk was no higher: SMR 1.09 (CI: 0.86-1.37). Mortality by sex was: SMR 0.92 (CI 0.65-1.26) for males, and: SMR 1.39 (CI 0.97-1.93) for females. There was a slightly higher risk in older age groups. For disease-specific mortality a higher SMR was only found for pulmonary disease. Mortality by European region was: SMR 1.19 (CI 0.91-1.53) for the north and SMR 0.82 (CI 0.45-1.37) for the south.

Conclusions

Higher overall mortality was not found in UC patients 10 years after disease onset. However, a significant rise in SMR for pulmonary disease, and a trend towards an age-related rise in SMR, was observed.

II

Høie O, Wolters FL, Riis L, Bernklev T, Aamodt G, Clofent J, Tsianos EV, Beltrami M, Odes S, Munkholm P, Vatn M, Stockbrügger RW, Moum B. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. Gastroenterology 2007; 132 (2):507-15.

Aims

To determine the colectomy risk in ulcerative colitis in the first decade after diagnosis and to identify factors that may influence the choice of surgical treatment.

Methods

Population based multicentre European inception cohort study of UC patients formed between 1991 and 1993. Information of surgery were obtained from patient interviews and from the medical records.

Results

The 10-year cumulative risk of colectomy was 8.7%: 10.4% in the northern and 3.9% in the southern European centres ($p < 0.001$). Colectomy was more likely in extensive colitis than in proctitis, with an adjusted hazard ratio (HR) of 4.1 (2.0-8.4). Compared to the southern centres, the adjusted HR was 2.7 (1.3-5.6) for the Netherlands and Norway together, and 8.2 (3.6-18.6) for Denmark. Age at diagnosis, sex and smoking status at diagnosis had no statistically significant influence on colectomy rates.

Conclusion

The colectomy rate was found to be lower than that in previous publications, but there was a difference between northern and southern Europe. Colectomy was associated with extensive colitis, but the geographic variations could not be explained.

III

Høie O, Wolters FL, Riis L, Aamodt G, Solberg IC, Bernklev T, Odes S, Mouzas IA, Beltrami M, Langholz E, Stockbrügger RW, Vatn M, Moum B. Ulcerative colitis: Patient characteristics may predict 10-year disease recurrence in a European-wide population-based cohort . Am J Gastroeterol 2007;102:1692-1701

Aims

To determine the relapse rate in UC in a European population-based cohort 10 years after diagnosis and to identify factors that may influence the risk of relapse.

Methods

Population based multicentre European inception cohort study of 781 UC patients formed between 1991 and 1993. A relapse was defined as an increase in UC-related symptoms leading to changes in medical treatment or surgery. The cumulative relapse rate, time to first relapse and number of relapses in the follow-up period were recorded and possible causative factors were investigated.

Results

The cumulative relapse rate of patients with at least one relapse was 0.67 (95% CI 0.63-0.71). The time to first relapse showed a greater hazard ratio (HR) (1.2, CI 1.0-1.5) for women and for patients with a high level of education (1.4, CI 1.1-1.8). The number of relapses decreased with age, and current smokers had a lower relapse rate (0.8, CI 0.6-0.9) than non-smokers. The relapse rate in women was 1.2 (CI 1.1-1.3) times higher than in men. An inverse relation was found between the time to the first relapse and the total number of relapses.

Conclusion

In 67% of patients there was at least one relapse. Sex, smoking status and level of education were found to influence the risk of relapse.

IV

Høie O, Aamodt G, Bernklev T, Odes S, Wolters FL, Riis L, Politi P, Tsianos EV, Clofent J, Stockbrügger RW, Munkholm P, Vatn M, Moum B. Serologic markers may predict disease course in ulcerative colitis. A study in an unselected population based cohort followed for 10 years. Journal of Crohn´s and Colitis (JCC) accepted for publication Oct 2007.

Aims

To investigate the predictive value of perinuclear anti neutrophil cytoplasmic antibody (p-ANCA) and anti saccharomyces cerevecias antibody (ASCA) in a 10 year disease outcome in terms of colectomy and relapse in a population based European inception cohort of ulcerative colitis (UC) patients.

Methods

Population based multicentre European inception cohort study of 781 UC patients formed between 1991 and 1993. Blood samples were obtained at the end of the follow-up period. The results of serology were compared with colectomy, relapsing disease and the total number of relapses in 10 years of follow-up. Multiple regression analyses adjusting for age, sex, residency, disease extent at diagnosis smoking, familial IBD and drug treatment were performed.

Results

Between the tested and not tested patients, except for age, there were no differences in sex, residency or disease extent at diagnosis. Positive p-ANCA was noted in 105 (24%) and ASCA in 28 (6%) of the patients. The relapse rate was higher, 82% (95% confidence interval [CI] 75-89%) in the p-ANCA positive patients compared with negative patients 67% (CI 62-72%, p=0.011). The risk for having a relapsing disease course was increased by a factor of 1.4 (CI 1.1-1.8, p=0.009) for p-ANCA positive patients compared with the negative patients, and the corresponding relative risk (RR) for the total number of relapses was 1.9 (CI 1.7-2.1, p<0.001). In ASCA positive patients RR for the total number of relapses was 1.8 (CI 1.5-2.1, p<0.001). No significant influence on colectomy rate was found for p-ANCA or ASCA.

Conclusion

In terms of relapse in UC, patients with a positive test for p-ANCA and possibly also for ASCA may have a more unfavourable long term disease outcome in terms of relapse compared with patients without these markers.

6 GENERAL DISCUSSION

6.1 Methodological considerations

6.1.1 Study design

This incidence cohort was formed on a population basis representing well-defined geographic areas. Using the general practitioners as important co-workers all new cases of UC from the study areas were included from the time of inception. In addition, the short inclusion period of two years represents an advantage to reduce biases from alterations in populations and in environmental exposure. This design represents a strong methodological advantage when addressing disease outcome in ordinary UC patients.

6.1.2 Case ascertainment

The patients were classified according to the widely accepted diagnostic criteria and endoscopy with biopsy or operation specimen was available in almost every patient at inception. The one-year clinical re-evaluation of diagnosis did not reveal any trends of diagnostic alterations (50). Also in the 4-year sub-study, the original diagnosis remained unchanged for the majority of patients (51). However, these re-evaluations did not systematically include endoscopy as in the IBSEN cohort (30; 55). To reduce the probability of misclassification, the diagnosis, which last appeared in the 10-year follow-up, was applied as the final diagnosis. We therefore think that a bias of importance concerning diagnostic errors probably did not occur.

6.1.3 Follow-up

The patients were followed according to local routines at each centre without using any pre-scheduled appointments or pre-defined investigations at regular time points in disease course before the 10-year follow-up visit. The results from the four-year sub study did not reveal any major difference between centres regarding the methods of follow-up (51). However, in the Copenhagen patients, not included in this four-year evaluation, the follow-up was carried out in a gastroenterology clinic with regular appointments once a year (13). Despite the prospective nature of the study, data on drug use and smoking behaviour, which was obtained from the medical records or at the ten-year interview could be regarded as retrospective. This could have created biases, which have to be taken into consideration when evaluating the results.

6.1.4 Generalisation of results

The original cohort included 1379 UC patients recruited from 20 centres across Europe and Israel from a background population of about 6.3 million people. Even if the routines of follow-up may have shown some differences, the definition of disease, the clinical presentation and therapeutic management in the first year of follow-up after diagnosis was shown to be similar between centres (50). Thus patients from different centres are most likely comparable to each other with respect to the various parameters, and the results from the statistical analyses may be regarded as valid.

A possible selection bias in this study could have happened. Firstly by the selection of centres participating in the follow-up, and secondly by the patients lost to follow-up at each centre. Only nine of the 20 centres representing 57% of the patients in the original EC-IBD cohort participated in the follow-up study. The reason for this was entirely technical or logistical and not a lack of interest in IBD research. Concerning the problem of selection bias, a follow-up rate of 60% for each centre was arbitrarily set as a limit to be included in the final analyses. This was done in order to maintain the population based nature of the cohort. However, there were no statistical calculations to assure that this 60% limit did completely protect the cohort from turning from an unselected population based into a selected referral based cohort. The patient baseline characteristics in terms of age groups, sex and north-south distribution did not differ significantly between centres, which met this 60% limit from the centres, which did not complete the follow-up. We do therefore believe that patients from the participating centres were representative for the original cohort and thereby representing the background population. However, the results cannot be applied to each country without reservations.

6.1.5 The importance of outcome measures

Mortality, surgery and relapse of symptoms have been chosen because they were considered to be important end points in this study. The absence of a definite cause of disease may lead to a feeling of uncertainty for patients concerning the possible consequences of their disease in daily life. In a review article by Casati, the main categories of concern for IBD patients have been listed (56). In a study of 121 patients with UC, the concerns, regardless of gender, age and level of education were related to body image, interpersonal relations, general physical impact and stigmata of the disease (57). Several of these items could be related to outcome variables like surgery and relapse of disease in our study, which would therefore be relevant not only to doctors, but also to patient concerns. The results in our study of UC being a non-lethal disease, with a lower risk of surgery and of major relapses should encourage the patients to live a normal life and also to guide the physicians when deciding between the available treatment options. However, the importance

of the various aspects of disease may differ between patients and physicians (58). In a study by Robinson et al., UC patients who were put on a self-medication program were more satisfied with the treatment during follow-up than patients followed by physicians at regular appointments (59). No differences in treatment outcome were found. Thus, the feeling of being in control of the disease by self-medication might be important to patients.

Other variables could also have been relevant. Extra-intestinal manifestations in IBD is a topic of great interest, however our data on this subject were insufficient for proper analysis. Data on 10-year cancer development will in the near future be presented by other investigators in the EC-IBD. In addition, a 10-year follow-up period may be too short to demonstrate a possible increase in cancer risk. Health related quality of life has gained considerable interest in the later years. Data on HR-QOL has- and will be further addressed by other members of the research group.

6.1.6 The selection of independent variables

The selection of these variables have been made from demographic, phenotypic and environmental factors, which in former studies have been shown to be of importance to the incidence or the course of the disease. The nature of our cohort gives a unique possibility to explore the importance of these variables during long-term follow up and also to perform geographic comparisons between variables related to the outcome of disease. Smoking has been recognised as the strongest environmental factor influencing the incidence and prognosis of IBD (6). Our results concerning the relation between smoking habits and the risk of relapse in long-term follow-up supports this current knowledge in a population based setting. From a clinical point of view, both the selection of variables and the results obtained from the analysis should be relevant to patient care.

6.1.7 Statistical analysis

Most of our data was not normally distributed. In addition, there were frequently needs for creating smaller groups of patients to be analysed. Therefore, non-parametric methods were used when comparing the various groups of patients (60). Because such tests are less sensitive than parametric methods, existing differences might not have been detected. Kaplan-Meier survival curve and the log rank test (61) were applied for time-dependent analyses in order to adjust for patients lost to follow-up. When analysing data of relapses, which were very asymmetrical and most likely Poisson-distributed we used the Poisson regression analysis. (62) These methods of analysis require the effect of the independent variables to be constant over time. Even if this stability of variable influence cannot be stated by certainty, we judge our variables to have met this requirement at least for the 10 years follow-up period. In summary the results found by the statistical analyses seems clinically

meaningful and are considered reliable results suitable for generalisation. However, it is the outcome for the average UC patient, which is described in this statistics. On could argue that when addressing the cause of the disease it would have been of more interest to focus on the results from the "outliers" with respect to further analysis of phenotypes and environmental exposure of possible importance.

6.2 Main results of disease outcome

This study confirms UC as a non-lethal disease (15; 22; 41; 42; 63) which is important knowledge to patients. For the physicians this fact has always to be born in mind in the treatment decision process. A high level of patient safety must be demanded, in particular when new therapies are introduced (64; 65). In our study, the cause of mortality from UC was closely related to surgical complications. Therefore, before elective surgery is decided, the individual risk of complications including mortality must be carefully balanced against disease severity. In patients who are poor candidates for surgery, the use of cyclosporine in acute disease (66) might at least temporarily postpone surgery while improving the patient's preoperative status.

The risk of colectomy showed a low rate of 8.7% in the first ten disease years. Regardless of centres, about two thirds of the procedures were carried out within the first two years of disease. An increased risk of colectomy early during the disease course has also been found by others (12; 67; 68). In extensive colitis at presentation, the ten-year colectomy rate was 18% and for patients with progressive disease from distal to extensive colitis, the rate was 39%. The cumulative colectomy rate for patients with distal colitis was not more than 2%. This is important knowledge in assessing the risk of colectomy. Thus, patients with extensive or progressive disease might benefit from intensive treatment and follow-up at specialist centres from the time of diagnosis.

In our study, the rate of complications was 32%, the majority being infections. This is in line with previous results from the period when colectomy was more frequently performed (69-71). Results from later series have shown improved results (72-74). The complication rate of 36% in early surgery compared with 26% in late surgery was not statistically significant. Thus, the risk of complication seems to be independent of the duration of the disease. The type of surgical procedure did not show any statistically significant impact on the risk of complications. However, patients suffering from complications had a median age at surgery of 52 years compared with 32 years for patients without complication. This significant difference could be due to increased co-morbidity with age. Thus, complications to surgery seemed to be age related.

UC has been regarded as a chronic relapsing disease in most patients. In addition, population-based studies have shown high relapse rates (13; 75-77). However, in our study,

after the initial attack, as many as 1/3 of patients did not suffer from relapses of clinical importance. This finding could be explained by the fact that our population-based cohort had included a high number of patients with a mild disease course. An additional explanation could be the exclusion of minor relapses, which did not imply any changes in therapy. Medical therapy could most likely have influenced the risk of relapse. However, for reasons outlined below (6.3.5) it is not possible from our data to analyse the impact of drug treatment on the risk of relapse. We found a high relapse rate in patients who had their first relapse early in the disease course. Also, a decline in relapse risk has previously been documented (13; 31; 78). This finding could be of importance to patient management. Based on the analyses of the risks of relapse and of colectomy being time dependent, the initial therapeutic strategy could be to intensify early medical treatment in order to improve long-term disease course and reduce the risk of colectomy. Treatment with biologic agents like infliximab has been shown to induce mucosal healing in UC (64). Mucosal healing has shown to be related to maintenance of remission, less complications, hospitalizations and surgery (79; 80). Infliximab, as a first-line therapy, has been used in clinical practice because of its superior efficacy (81). First-line therapy using biologic agents might reduce the risk of early relapse and thereby reduce the risk of later relapses. In order to prove a beneficial effect of such a therapeutic approach on the long-term disease course, results from controlled clinical trials are needed (82). Regardless of strategies for drug treatment, referrals for surgery in severe UC patients not responding to medical treatment (83-85) must not be unnecessarily delayed.

The method used in the analysis of p-ANCA in our cohort of patients has previously shown a prevalence of 49.7% in a referral cohort of patients diagnosed with UC (86). In our UC patients, the prevalence of p-ANCA was lower, compared with most previous findings (87). This could partly be due to the population-based nature of the cohort (88). Due to the low prevalence of both p-ANCA and ASCA, the use of these tests as markers of disease course in UC is of limited value even if we found a significant increase in the risk of relapse in patients with positive serologic tests as a possible predictor of a more severe disease course (76; 89; 90). However, in selected patients a positive p-ANCA and/or ASCA could be used as guidance in the decision of long-term treatment and follow-up strategies. The stability of these markers, which are probably independent of changes in disease activity, indicates a limited clinical use in monitoring disease activity and the effect of therapy (91-93).

6.3 Risk factors influencing disease outcome

6.3.1 Age and sex

In studies from Copenhagen and Mid-England increased SMR early in disease course in patients of older age at diagnosis have been reported (15; 42). In a study from Stockholm,

increased mortality for males was found (33). These results cannot be supported by our data, which showed no significant increase in SMR according to sex and age groups, even if a trend of a high SMR was noted in the elderly and could be attributed to co-morbidity. Our data are therefore in line with results from more recent studies showing no increase in SMR for UC patients (22) possibly as a result of improvements made in disease management over time. However, in females of 80 years or more at diagnosis, a significant rise in the overall SMR was noted. No similar effect on SMR was noted for older males. There is no obvious biological explanation to this finding. The disease was inactive on conventional treatment at the time of death in these seven older females. Due to the small number and the short life expectancy in this group of patients, this result must be interpreted with great caution. The shorter life expectancy from the time of diagnosis in the five patients with a UC related cause of death could largely be related to surgery, which was performed in four of these patients. The operations were carried out within 1 month prior to death, which occurred at a median age of 75 years.

For the risk of colectomy, no differences between age groups or sex were found. However, the risk of complications was increased by higher age at the time of surgery. This finding is probably not as much related to UC as to age itself possibly in combination with the well-known risk of infections in abdominal surgery (94). No difference in complication rates were found between women and men.

We noted a significantly increased risk for the total number of relapses among women, and for age below 30 at diagnosis. Results of increased risk of relapse (25; 43; 95; 96) and disease severity (97) in patients at lower age at diagnosis has been found by others. However, no explanation of this possible relation between age and disease activity has been established. Disturbances in the development of oral immune tolerance have been proposed in the pathogenesis of UC (98). Impaired oral tolerance could lead to an increase in disease activity seen at young age. However, the underlying mechanisms of these processes are complex, and have so far been insufficiently explained (99). In patients aged 80 and above, we found an increased risk of relapse. Even if this was not statistically significant in the multivariate regression, together with the increased SMR shown in older females, these findings could be consistent with a more unfavourable disease course of UC in patients diagnosed at older age.

We could not find any biological explanation for the increased risk of relapse in females. This gender difference in relapse risk was adjusted for colectomy and for medical treatment. The use of OCT could influence the vasculature, which has been shown to be of importance in IBD (100) and thereby increase the disease activity. Even if a meta analysis showed a statistical relationship between the risk of developing UC and the use of oral contraceptive treatment (OCT) (101), in our data a significant increase in relapses for OCT

users was only found in univariate and not in the multivariate analysis. The increased risk of relapse in women could also be a result of selection bias due to sex differences in health care seeking behaviour (102). Also the HR-QOL in women has been reported as lower than in men (23). However, an increased risk of relapse in females with CD should then be expected, but this could not be demonstrated (103). In the third trimester, pregnant women compared with early post-partum period changes in the level of pro-inflammatory cytokines (like Tnf-α), cortisol, norepinephrine and active vitamin D3 in favour of reducing autoimmune disease activity, have been found (104). Possible sex differences in the secretion of pro and anti-inflammatory substances could also be proposed in explaining differences in relapse risks between women and men.

For p-ANCA and ASCA no significant differences between sex and age were found, which could have explained the increased risk of relapse found in women or for aged groups less than 30 years. This could be due to the low prevalence of these markers even if the specificity for UC was high in p-ANCA positive patients (86; 105; 106). In addition, it has been debatable whether these serologic markers could predict disease course in UC (107-109).

6.3.2 Residency across Europe

The SMR for UC patients in our cohort was not increased in any of the seven participating countries. No significant difference in SMR between Northern and Southern centres were found. In former studies of mortality in UC, no distinct geographic patterns have been reported. Of five studies showing increased SMR all were from Northern Europe (33; 35; 37; 39; 40). Of six studies showing no increase in SMR, two were from Southern Europe (22; 63) and four from Northern Europe (15; 18; 41; 42). In a large population based study from Minnesota, the mortality in UC was similar to the background population (44). Because the studies showing increased SMR are older, our study results confirm that UC should now be considered as a non-lethal disease regardless of latitude of residency. This is probably a result of improvement of disease management by time, as seen in easy access to specialist care, more intensive medical treatment and improvement of surgical procedures (74).

Even though the cumulative colectomy rate was substantially lower than what has been reported in most previous studies (12; 67; 68; 110; 111) considerable geographic differences were found. The colectomy rate of 25% found in Copenhagen could most likely be regarded as a result of the treatment policy at this centre having a low threshold for surgery in failure of corticosteroid therapy (13). However, a significant difference in North-South colectomy rate was found even if the Copenhagen data was left out of the analysis. This could be explained by a milder disease course parallel to the lower incidence of UC, which have been found in this European region (112). However, in a study from Athens with

disease of limited extent and severity the 6 years colectomy rate was 14% (113). The introduction of a more "westernised" life style may be of greater importance to disease course thereby influencing colectomy rate, than latitude or genes (114). This is in line with the finding of a decline in geographical difference in incidence over time (49)

In contrast to surgery, the risk of relapses from UC did not show a North-South pattern. The variations, which were found between the centres, were not related to latitude. Because of the low number of colectomies, the geographic difference in surgical rates could not explain this lack of difference of relapse rates. In Copenhagen, a high risk of colectomy together with a high long-term relapse rate was found. Different attitudes of patients in seeking medical care and of physicians in the evaluation and treatment of symptoms, may explain the differences in relapse found in Heraklion and Copenhagen. Except for patients from these two centres, the risk of relapse seems to be independent from European residency.

Even though regional differences in the prevalence of p-ANCA in UC have been reported (115), there has been no previous description of a distinct geographic pattern. In our study, the prevalence for p-ANCA was significantly higher in the Northern compared with the Southern centres. However, this did not seem to implicate a higher risk of relapse in the Northern centres as one could expect from our findings. This could be due to the overall low prevalence of p-ANCA in the cohort implying a low contribution of p-ANCA to the risk of relapse in sub group analyses.

The results of dietary studies in IBD have been difficult to interpret (6) even if IBD have been negatively associated with a high intake of fibre, fruit, and vegetables and negatively with the intake of animal fat (116). Differences in the diet could be an explanation to the differences in the prevalence of p-ANCA between Northern and Southern centres. This antibody has been shown to express an antigen linked to bacteria in the colonic mucosa (117) which could be modified by diet (118). However, the genetic predisposition for p-ANCA (119) could differ between geographic regions, thus explaining the results.

6.3.3 Extent of disease

In the Copenhagen study, an increase in mortality risk was found in patients with extensive disease (15). This was confirmed in a large population based study from North Jutland (18). Also in the Stockholm study by Broström et al, excess mortality was seen in extensive disease. In that study, 26 of 41 deaths from UC were related to surgery. Since surgery mostly, as in our study, is performed in patients with extensive disease, the increased mortality was probably not related to the extent per se but to surgery. However, in a few cases extensive colitis may develop into fulminant disease, which carries an increased risk of mortality (120). Of the five UC related deaths in our cohort, three were related to

complications to surgery. Two patients had distal disease at diagnosis, and the SMR for extensive colitis was not increased. We therefore conclude that, based on our data, extensive colitis does not seem to be an independent risk factor of mortality in UC.

The total colectomy rate in our cohort was low, however the rate in patients initially diagnosed with extensive colitis was nine times higher than for distal disease. Extensive colitis was an independent risk factor for surgery, and was found in 89% of the patients at the time of colectomy. High colectomy rates in extensive disease have also been found by others (12; 68; 110). Factors responsible for the development into extensive colitis and also for disease severity leading to surgery could be proposed. However, our study was not designed to investigate changes in extent of disease over time.

Studies by Bresci and Hiwatachi demonstrated a relationship between extensive disease and relapse rate (43; 96). In a cohort from Scotland, Sinclair et al. found a relationship between extensive disease in each patient year, number of attack-years and the severity of the attacks (43). In a large Copenhagen study, and in the IBSEN cohort extent was not a risk factor of relapse (13;31) In our cohort there was even a reduction of the risk of relapse both in distal and in extensive disease compared with proctitis, but this finding was not statistically significant in the multivariate analysis. Relapses could be related to the intensity of the inflammatory process more than to the extent of inflamed mucosa. This could explain the inconclusive results concerning relapse risk and extent of disease.

In UC, no definite relation between p-ANCA and extent of disease has been found (121; 122). In our study, the prevalence of p-ANCA did not differ significantly according to extent of disease at diagnosis. This is consistent with the findings of extent of disease but not p-ANCA as risk factor for colectomy.

6.3.4 Smoking

The risk of developing UC was significantly higher in non-smokers than in current smokers (6; 123-125) and UC is being regarded largely as a disease of non-smokers or former smokers. Cigarette smoking may even improve the course of the disease. However, no single mechanism explaining the effect of smoking on IBD has so far been established (126).

The Florence IBD study showed a reduction of SMR for smoking related conditions like cardiovascular disease and lung cancer (21; 22). However, studies from Sweden (35; 38) and also from Denmark (15) showed an increase in SMR for pulmonary diseases including asthma, emphysema, bronchitis, pneumonia and pulmonary embolism. The significant increase in SMR for pulmonary disease in our cohort is attributed to the centres in Denmark and Norway responsible for 10 of 11 cases. Eight of these patients died from pneumonia, possibly influenced by high co morbidity not necessarily related to smoking. Only three patients died from chronic obstructive pulmonary disease, which most likely could be caused

by smoking. An increased risk of Nordic UC patients dying from respiratory infections could then be proposed. The reason could be an increased susceptibility to infections due to an unfavourable environment combined with the chronic disease (127). In a Norwegian study, the incidence of UC was increased in the winter, possibly associated with respiratory tract infections (128).

We found no evidence of smoking to protect against colectomy, but this could be due to the low number of colectomies as well as the number of current cigarette smokers during follow-up. Therefore, a protective effect of smoking against surgery could still be present, as have been proposed in a study of 556 UC patients from Paris (129). However, this study was retrospective and hospital based. In Denver, Colorado, an increased risk of colectomy was found in heavy smokers who stopped before disease onset (130). In an Italian study of patients with ulcerative proctitis who ceased smoking, the risk of developing extensive disease was increased (131) and could subsequently lead to a greater risk of colectomy. However, in an other study from Paris no difference of colectomy rate was found between non smokers, smokers and ex smokers in follow-up even if a more aggressive disease course of UC was noted in ex-smokers after they stopped smoking (132).

According to former studies, the number of relapses during follow-up was reduced among current smokers, and increased among patients who stopped smoking during follow-up, compared with non-smokers (133-135). This is in line with our data, which also supports a possible rebound effect on relapse risk for patients who quit smoking during the course of disease.

A lower prevalence of p-ANCA was found in smokers compared with non-smokers at the time of inclusion. A possible relationship between p-ANCA, smoking status before diagnosis and the risk of relapse during the course of disease could therefore exist. Most likely p-ANCA is merely a marker of underlying factors of importance to disease activity, which could then be influenced by smoking.

6.3.5 Medical treatment

Various drugs have been used in the treatment of UC (136-138) and adverse effects could be of importance to mortality. In the UK Ransford and Langman analysed 2.8 million prescriptions of 5-ASA and 2.9 million for Sulfasalazine given for IBD (139). A low number of serious adverse events and no deaths from medication were reported. However, the results were based on spontaneous reports to the Committee on Safety of Medicine. Also, the use of corticosteroids and azathioprine has been regarded as tolerable and quite safe (140-142). When evaluating each single cause of death we found only one case where drugs used for UC could possibly be causally related to mortality. Of the 68 deaths that we judged to be not related to UC, only seven had been using steroids and/or azathioprine related to the time

they died. Even if we cannot totally exclude that these drugs could have contributed to mortality in some of the patients, adverse effect of drugs in UC does not seem to have any major impact on mortality. Due to the inability to perform regression analyses because of the strong influence of high age on mortality, further information on the importance of drugs for mortality cannot be extracted from our data.

No study has shown that medical treatment could reduce the risk of colectomy over time. Because sulfasalazine, 5-aminosalicylic acid (5-ASA) (143) and corticosteroids (144) were frequently used to treat relapses, including those often preceding colectomy, the data on these drugs could not be regarded as independent of the risk of relapse or colectomy. Also in our study, the introduction and dose adjustments of drugs were included in the definition of relapse. In addition, our data did not give information on whether the drugs were used for induction or maintenance of remission, or in steroid refractory disease. Due to the slow onset of action, azathioprine was regarded as used for maintenance or refractory disease only (145). This drug was therefore included in the regression analyses of relapse and colectomy showing no significant influence on risk. The analysis of colectomy rate did also include steroids, which could not demonstrate any risk reduction. Because the wide use of 5-ASA especially for maintenance (146), these drugs were left out of the regression models. In summary, for reasons stated above, our study was not suitable for showing any beneficial effect of drug treatment on disease outcome.

6.3.6 Other risk factors

Incidence studies have showed that the risk of developing UC could be reduces after appendectomy (6;123;147;148). The risk has also shown to be increased in persons with a high level of education (149;150) and in persons with 1st degree relatives with IBD (151). In regression analysis of relapse, risk both factors turned out negative, even if a significant effect in familial IBD was found in the univariate regression model. For patients with higher education the increase in risk of having a relapsing disease may at least partly be attributed to the lack of physical activity and sun exposure during work, which has been proposed as risk factors in this group of patients (149;150). A possible easy access to specialist care in the highly educated patients could have biased the result.

7 SUMMARY

7.1 Conclusions

The results of the present study can be summarised as follows

- The 10-year cumulative mortality rate in UC was similar to the background population
- The 10-year cumulative colectomy rate of 8.7% for the total cohort was substantially lower than what has previously been reported.
- The risk of colectomy during a 10-year course of disease was significantly higher in patients from Northern compared with Southern European centres.
- About one third of the patients were free from relapse during a 10 years course of disease.
- The risk of a relapse seems to be higher in women than in men.
- Patients who were never-smokers or ex smokers at diagnosis, or ceased smoking during the follow-up period, had an increased risk of relapses during follow up compared with current smokers.
- A positive test for p-ANCA may predict an active disease course in terms of relapses during the first 10 years.
- Except for colectomy rate, no significant difference in disease outcome between the North and the South of Europe was found.

7.2 Further research

This large epidemiologic study of long-term disease outcome in UC has yielded important information both to the average patient in their concern and attitude to the disease, and to the physician regarding decision of treatment and assessment of prognosis. For further epidemiologic research, attention has already been more focused on the causes and underlying mechanisms of disease. For these kinds of studies, one should probably have a greater focus on the patients with increased risk. Studying patients with either high exposure to possible independent risk factors, or patients showing extreme results on the outcome parameters could possibly reveal more information of great interest to causality. The conventional statistical methods with their goal of “average and normality in distribution” make it easy to generalise the results, but at the same time could conceal important information highly needed for future improvement of treatment and prognosis. Furthermore, one could study genetic, phenotypic and environmental factors in relation to new subgroups of UC patients according to high disease activity at presentation or early relapsing disease. Treatment strategies, which induce mucosal healing, should be studied with regard to improvement in long-term disease outcome.

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