Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland☆

Pia Manninen a,b,⁎, Anna-Liisa Karvonen a,b, Heini Huhtala c, Martin Rasmussen d, Maarit Salo e, Leena Mustaniemi f, Ismo Pirttiniemi g, Pekka Collina a,b

a Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland
b School of Medicine, University of Tampere, Tampere, Finland
c School of Health Sciences, University of Tampere, Tampere, Finland
d Tampere Health Centre, Tampere, Finland
e Valkeakoski Regional Hospital, Valkeakoski, Finland
f Vammala Regional Hospital, Vammala, Finland
g Mänttä Hospital, Mänttä-Vilppula, Finland

Received 13 August 2011; received in revised form 21 October 2011; accepted 22 October 2011

Abstract

Background: An increased mortality has been reported in patients with Crohn's disease (CD), while figures have remained similar or decreased in patients with ulcerative colitis (UC) compared to the population in general. We evaluated the long-term mortality risk of patients with inflammatory bowel diseases (IBD) in a well-defined population.

Methods: The data were based on a prospective IBD register in our catchment area; follow-up covered 1986–2007. The population based cohort comprised 1915 adult patients, 1254 with UC, 550 with CD, and 111 with inflammatory bowel disease unclassified (IBDU). The mortality rate and causes of death were obtained from Statistics Finland.

Results: We recorded 223 deaths among the 1915 patients with IBD within a follow-up of 29,644 person-years. The standardised mortality rate (SMR) was 1.14 in CD and 0.90 in UC. In cause-specific mortality; the risk of death in diseases of the digestive system was significantly increased in CD (SMR 5.38). The mortality in colorectal cancer was non-significantly increased in both UC and CD (SMR 1.80 and 1.88, respectively). Compared to the background population, there were significantly fewer deaths due to mental and behavioural disorders due to use of alcohol (0 observed, 10.2 expected in IBD).

☆ Preliminary results from this study were presented as poster at XLI Nordic meeting of gastroenterology 2010 in Copenhagen (abstract published in Scand J Gastro 2010; 45, Suppl 247: 48–49).

⁎ Corresponding author at: Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Teiskontie 35, FIN-35211 Tampere, Finland. Tel.: +358 33116 6961; fax: +358 33116 5969.
E-mail address: pia.manninen@uta.fi (P. Manninen).
1. Introduction

It is important to take account of the mortality rate in inflammatory bowel disease (IBD) when planning surveillance strategies. In studies undertaken in this field, there has been a similar or slightly reduced mortality rate in ulcerative colitis (UC),\textsuperscript{1–6} while in Crohn’s disease (CD) the overall mortality rate has been increased compared to that in the general population.\textsuperscript{3–5,7–11} This increase among CD patients has been attributed to an excess mortality in gastrointestinal, respiratory and genitourinary diseases.\textsuperscript{8–9,11}

Patients in referral centres usually represent the most severe diseases and mortality rates may therefore be overestimated. In multicentre studies detection rates and diagnostic methods may vary, and data collection may be imprecise. Prospective population-based epidemiological surveys are thus to be preferred in estimating the risk of overall and cause-specific mortality.

We have from 1986 maintained a prospective IBD register in our catchment area. An increase in the incidence of IBD was observed during the follow-up period, and prevalence figures have been relatively high: 291 per 100,000 for UC, 124 for CD and 27 for inflammatory bowel disease unclassified (IBDU).\textsuperscript{12} The aim of this study was to assess the overall and cause-specific mortality among our IBD patients, who had in general been under regular surveillance.

2. Material and methods

2.1. Data collection

A prospective register for all adult patients with IBD was set up in 1986 in the catchment area of Tampere University Hospital, and cases detected before 1986 were collected retrospectively. The data on mortality and causes of death were obtained from Statistics Finland. Retrospective and prospective cases were both included, as the data were as accurate in both series.

The area covers both urban and rural locations, and now comprises 485,000 inhabitants, of whom 405,000 are 15 years of age or older. The diagnosis and management of IBD were carried out mainly in one university hospital, in four local hospitals, and in one large health centre where open access colonoscopy was available for general physicians (City of Tampere). Small centres and general physicians were contacted regularly to obtain all new cases for the register. The results were combined, because smaller centres managed milder and the university hospital more severe cases. Patients receiving care in Pirkanmaa, but living outside the catchment area were excluded.

The diagnosis of UC was based on the following criteria: a history of diarrhoea or blood in stools, and clinical, endoscopic and histopathological findings consistent with ulcerative colitis.\textsuperscript{13,14} The criteria for CD included a history of abdominal pain, weight loss or diarrhoea, together with characteristic clinical endoscopic and histopathological or radiological findings compatible with CD.\textsuperscript{13,15} Intestinal involvement with chronic colitis but no characteristic histological signs of CD or UC was regarded as IBDU, until some more specific diagnosis might emerge.\textsuperscript{16}

Symptoms and the endoscopic and histopathological extent of the diseases were recorded and scrutinised to ensure that the diagnostic criteria were fulfilled. Extent in UC was classified as extensive, left-sided and proctitis; in CD upper gastrointestinal, ileal, ileocolonic and colonic involvement were assessed. One specialist physician in each centre was responsible for data collection; all data were saved at the Department of Gastroenterology and Alimentary Tract Surgery in Tampere University Hospital. The endpoint for the follow-up was set at the end of 2007.

2.2. Statistical analysis

Mortality figures are updated annually and are based on the death certificates. Frequencies and medians (with ranges) were used to describe the patients and their follow-up time. Person years at risk were calculated at 5-year age and calendar intervals using the R environment (version 2.10.1, R Foundation for Statistical Computing, Vienna, Austria). Expected numbers of deaths were calculated using age, gender and calendar-year-specific mortality in the Finnish population, separately for CD and UC. Standardised mortality ratios (SMR) were calculated by dividing observed numbers of deaths by expected numbers. SMRs were accompanied by 95% confidence intervals assuming that the observed number of cases followed a Poisson distribution. They were calculated using CIA (Confidence Interval Analysis, version 2.1.2, University of Southampton, UK).

3. Results

3.1. Overall mortality

The study involved 1915 adult patients, 1254 with UC, 550 with CD, and 111 with IBDU. Forty-seven percent were female, median age was 33 years at diagnosis of IBD and median follow-up time was 13.5 years (Table 1). Altogether 501 (26%) patients were enrolled from the retrospective series. The overall follow-up period was 29,644 person-years. Of the patients with UC, 621 (49%) had extensive and 433 (35%) left-sided disease and 199 (16%) proctitis. In CD, ileocolonic disease was found in 232 (42%), ileal in 98 (18%), colonic in 208 (38%) and upper gastrointestinal involvement in 13 (2%). The prospective section comprised 1415 cases (74% of all).
We observed 223 deaths among 1915 patients with IBD during the follow-up time: 151 with UC, 52 with CD and 20 with IBDU. The overall mortality in CD was increased (SMR 1.14, 95% CI (0.84–1.49)) while the overall mortality in UC was decreased (SMR 0.90, 95% CI .77–1.06) (Table 2.). The number of deaths among patients with IBDU was too small for meaningful statistical analysis.

3.2. Cause-specific mortality

Nine had died of colorectal cancer, 7 with UC and 2 with CD (SMR 1.8 and 1.88, respectively); the total number of colorectal cancer patients was 22. Nine patients had died of malignancies of the trachea or lung and four of malignancies of the liver or biliary tract (one cholangiocarcinoma).

In analysis of disorders of the digestive system (ICD-codes K00–K93, n=20), the death rate was significantly increased in CD (SMR 5.8; primary cause of death in 4), and not significantly in ulcerative colitis (SMR 2.1; 2). Of the remaining 14 patients (Table 2) six had alcoholic liver disease, three had died of acute vascular disorder of the intestine, one of gastric ulcer, one of ulcer in the oesophagus, one of Mallory–Weiss syndrome, one of volvulus and one of unspecified pancreatitis.

Compared to the background population, there were significantly fewer deaths due to disorders classified as mental and behavioural disorders due to use of alcohol (ICD-code F10) (Table 2).

4. Discussion

Compared to the population in general, we found in Crohn’s disease an increased and in UC a decreased mortality rate, though the results did not reach statistical significance. Comparable results have been obtained in several other studies,1–6 but also contrary results have been reported: Probert et al. reported that in Europeans the overall mortality was not increased.17 In cause-specific mortality, an increased SMR for diseases of the digestive system was observed in our patients with CD. However, deaths due to colorectal cancer were not significantly increased in UC or CD. As a whole, the SMR for IBD in general and colorectal cancer in particular were both close to 1. Close follow-up and effective surveillance may explain this favourable result. In accordance, Solberg et al.18 stated that the prognosis for CD seems better than previously reported, although they did not give any risk ratios for mortality.

A recent Finnish study reported that coronary heart disease was more common in IBD patients than in controls.19 In the present series, the SMR for circulatory diseases did not differ significantly between patients with UC and CD; although those

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients with inflammatory bowel disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1254</td>
</tr>
<tr>
<td>Female (%)</td>
<td>566 (45)</td>
</tr>
<tr>
<td>Age at diagnosis years, median (range)</td>
<td>34 (1–89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The standardised mortality rates (SMR) for inflammatory bowel diseases; O = observed, E = expected, 95%CI=95% confidence intervals a.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Group (n)</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis, (n=1254)</td>
<td></td>
</tr>
<tr>
<td>All deaths (ICD code)</td>
<td>52/57</td>
</tr>
<tr>
<td>Diseases of the circulatory system (I00–I99)</td>
<td>17/13</td>
</tr>
<tr>
<td>Diseases of the digestive system (K00–K93)</td>
<td>2/2</td>
</tr>
<tr>
<td>Malignant neoplasm of colon and rectum (C18–C20)</td>
<td>3/1.6</td>
</tr>
<tr>
<td>Mental and behavioural disorders due to use of alcohol (F10)</td>
<td>0/0.4</td>
</tr>
<tr>
<td>Crohn’s disease, (n=550)</td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>22/19</td>
</tr>
<tr>
<td>Diseases of the circulatory system (I00–I99)</td>
<td>5/4</td>
</tr>
<tr>
<td>Diseases of the digestive system (K00–K93)</td>
<td>3/0.6</td>
</tr>
<tr>
<td>Malignant neoplasm of colon and rectum (C18–C20)</td>
<td>1/0.5</td>
</tr>
<tr>
<td>Mental and behavioural disorders due to use of alcohol (F10)</td>
<td>0/0.4</td>
</tr>
</tbody>
</table>

a Cases with inflammatory bowel disease unclassified n=20, 10 deaths of diseases of the circulatory system, 4 of diseases of the digestive system, 2 malignant neoplasms, 1 neurological disorder and 1 accidental death.
with UC are typically non-smokers, the SMR was marginally below 1 only in men with UC. The number of cases was probably too small to show any possible differences here.

An interesting finding was the significantly decreased mortality in disorders classified as mental and behavioural disorders due to use of alcohol, as we observed no such cases in our series. This category embraces acute drunkenness in alcoholism, harmful effects of alcohol and withdrawal state with delirium. We consider that this finding is valid, since same trend was seen in both UC and CD (Table 2), and when combining both disorders, the 95% confidence intervals for SMR become 0–0.36. The majority of our patients had been under regular surveillance, which may explain the good social behaviour. However, since our follow-up mortality rates also comprised the few cases lost to follow-up, the selection bias in surveillance does not explain this finding. High alcohol intake has been associated with an increased risk of relapse. This might be the case especially in countries where drinking habits involve high amounts of alcohol once in a while as is the case in Finland. The alcohol-related mortality in Finland is higher than in e.g. France, Sweden, United Kingdom, but lower than in Russia. Patients with IBD possibly avoid heavy drinking if they have noticed an activation of the disease in such circumstances. Whether the alcohol consumption is lower in IBD than in the population in general is a subject for further studies, but on the other hand, our cases were not free of deaths due to alcohol liver disease.

Our data were based on a local register designed to catch all IBD patients in the area. We made meticulous efforts to enrol cases fulfilling the diagnostic criteria for IBD. The participating hospitals and health centres were contacted regularly to ensure registration of new patients. Diagnostic facilities including open access endoscopy were easily available throughout the study.

The IBD prevalence up to 1986 may be an underestimate as it was based on retrospectively scrutinised hospital records. Nevertheless, even prior to 1986, almost all symptomatic patients with IBD were treated in the same centres which participated in the prospective survey. For these reasons, it is evident that the series represented IBD in general, not only cases managed in tertiary centres. Even in the retrospective series, the date of diagnosis and possible death was as accurate as in the prospective series. Some patients with mild proctitis or distal IBD may have remained unregistered as having been treated exclusively in private care. The smaller endoscopy units in this study were in fact primary centres for detecting IBD. Thus, probably only a few cases could not be traced, which does not make any significant selection bias. In other words, we consider that this is population-based incident cohort.

Statistics Finland covers all the mortality causes in our country. The case records were scrutinised to ensure that there is no discrepancy between the records and death certificates. In some cases, the disease history before the death was not available. This may obviously make some bias, but it is also the case in the controls, that is in the general population.

To conclude, the overall mortality in IBD was not different from that in the population. In cause-specific mortality diseases of the digestive system were significantly increased in CD, though the number of cases remained relatively low. Deaths related to mental and behavioural disorders due to alcohol use were significantly less common in IBD than in the population. The risk of colorectal cancer was only non-significantly increased. As to the surveillance policy in IBD, we consider that patients with CD have a minor increased risk of mortality, especially in diseases of the digestive system, while patients with CU are not at increased risk of mortality when they are subject to regular follow-up.

Conflict of interests

The authors have no conflict of interests to declare. The authors alone are responsible for the content and writing of the manuscript.

Acknowledgements

All authors have made significant contributions to the research described in this manuscript. ALK founded and maintained IBD-register. PM carried out the study, collected and analysed the data and drafted the manuscript. HH carried out the statistical analysis. PC and ALK took part in the planning and designing of the study and revised the draft of the manuscript. MR, MS, LM and IP carried out the enrolment of patients and the collection of data. All authors read and approved the final manuscript. We acknowledge Robert McGilleon M.A., for revising the English language to the manuscript.

This study was financially supported by the Competitive Research Funding of the Pirkanmaa Hospital District, Finland (9M005 and 9H166). The sponsor did not have any involvement in study design, collection, analysis, interpretation, writing or submitting the manuscript.

References


