

Current trends in inflammatory bowel disease: the natural history

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Abstract: The description of the prognosis of inflammatory bowel disease (IBD) is based on systematic follow-up of population-based cohorts. A steady increase in incidence of IBD has occurred. The distribution of ulcerative colitis (UC) is fairly uniform with a preponderance of left-sided disease. One-third of Crohn's disease (CD) patients present with colonic disease, one-third with ileocolonic disease and one-third with small bowel disease. IBD is associated with extra-intestinal manifestations (EIMs) in up to 36% of patients. Uveitis and episcleritis are the most common. The cumulative probability of a relapsing course in UC is 90% after 25 years. In CD disease behaviour varies substantially with time. At diagnosis behaviour is inflammatory in 70% of patients. At follow-up there is a change to either stricturing or penetrating disease. Most patients with CD will eventually require surgery. Risk factors for CD recurrence after surgery include penetrating/fistulizing disease behaviour, young age, short duration of disease before first surgery and ileocolonic disease. The incidence of colorectal cancer (CRC) in UC seems to be decreasing. The risk of CRC in CD seems to be equivalent to the risk in UC. Patients with small bowel CD are also at increased risk of small bowel adenocarcinoma. CD is associated with a mortality rate 20–70% higher than expected, whereas mortality in UC is equivalent to that of the general population. The improved prognosis of IBD, especially UC, could be due to a chemopreventive effect of the medications used. Further studies are needed to develop the best strategy for the reduction of mortality and cancer risk in IBD.

Keywords: inflammatory bowel disease, epidemiology, prognosis, disease course, mortality, colorectal cancer

Introduction

The natural history of the inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), does not exist since almost no patients with IBD remain untreated during their disease course, but it is possible to gain an impression of the natural course by examining studies published around the middle of the last century. These studies represent a period in which no efficacious treatment existed; that is, prior to the introduction of sulphasalazine and corticosteroids and also safe and efficient surgical procedures in the form of colectomy and Brooke ileostomy for ulcerative colitis.

Before the introduction of these methods the risk of dying from the first severe attack of UC was 33%, and the risk of dying in a later relapse of the disease was 12% [Edwards and Truelove, 1963]. Looking at the long-term prognosis, the same authors in their pioneering work on the prognosis

found a 40% cumulative risk of dying of UC 20 years after diagnosis, with the highest mortality among elderly patients. Furthermore, in a study on the prognosis of children diagnosed with UC a cumulative occurrence of colorectal cancer (CRC) of 40% after 40 years was reported [Devroede *et al.* 1971]. These children had been diagnosed early in the last century long before any efficacious medication existed. A similar finding of a serious prognosis in patients with CD was found by [Weedon *et al.* 1971].

These figures may represent the natural history of untreated IBD. However, in our present time with easy access to medical care with evidence-based medical and surgical treatments available to most patients, the natural history of IBD is historically interesting but hardly relevant for the patients.

The prognosis of the diseases is better described based on systematic follow-up of large

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population-based cohorts of patients treated according to currently accepted efficacious medical and surgical approaches. Such studies have been performed for many years primarily in Scandinavia, but also in Europe and USA.

The systematic approach in unbiased population-based studies provide a solid basis for information on the short- and long-term prognosis in patients treated according to modern and established medical and surgical treatments, and also serve as a reference for evaluating new treatment modalities and the possible effect on the future prognosis of the patients. Hence, this paper is largely based on this type of study.

Occurrence

During the last decades we have seen a steady increase in the incidence of IBD, especially CD and to a lesser extent in UC, pointing to environmental factors as responsible for the rise in incidence, since genetically determined diseases have a stable occurrence. Most incidence studies have been reported from Scandinavia and northern Europe, USA and Israel but, when looked for, IBD is present all over the world. IBD is apparently more common in the northern part of the world and among Caucasians. It appears equally in men and women. A familial occurrence exists. Peak incidences are reported in young adults. In long-term studies results diverge with regard to temporal trends, some report an increase in incidence, others a stable or falling incidence.

The most recent data from Scandinavia suggest an increase in the incidence of IBD. Earlier studies from Copenhagen reported a stable incidence of UC of approximately $9.2/10^5$ and a steadily increasing incidence of CD of $4.1/10^5$ [Munkholm *et al.* 1992; Langholz *et al.* 1991], while the most recent study for the period 2003–2005 showed a further increase to $8.6/10^5$ for CD and $13.4/10^5$ for UC [Vind *et al.* 2006]. The same trend is seen in Stockholm, Sweden where the incidence of CD nearly doubled from $4.9/10^5$ in the 1980s to $8.3/10^5$ in the period 1990–2001 [Lapidus, 2006].

Studies from southern Europe have previously reported incidence values far lower than the above mentioned [Maté-Jimenez *et al.* 1994; Tsianos *et al.* 1994; Martinez-Salmeron *et al.* 1993; Tragnone *et al.* 1993; Trallori *et al.* 1991; Vucelic *et al.* 1991]. However, these studies were retrospective in design and thereby subject to

different sources of bias. In contrast, a European multicentre study simultaneously employing suitable epidemiological methods, that is, prospective registration and rigorous case ascertainment procedures in 20 areas of 12 European countries, found comparable incidence values between northern and southern Europe [Shivananda *et al.* 1996].

The European incidence rate overall was $10.4/10^5$ for UC (northern centres 11.8 versus 8.7 in southern centres) and $5.6/10^5$ (northern centres 7.0 versus 3.9 in southern centres) showing that the differences in incidence are much less than previously anticipated. In fact it was shown in the study that the best correlation to incidence was not geography but rather the size of the gross national product.

The incidence of IBD is highest among young adults or adolescents with a peak onset of 15–35 years of age. The incidence in children under the age of 10 years is low [Langholz *et al.* 1991].

Regarding gender differences, women in general have a 20–30% higher risk of developing CD, whereas no gender preponderance is found in UC.

Racial and ethnic differences exist. IBD is thought to be more common among Caucasians and Jews.

Clinical appearance

Location of disease

The distribution of disease in UC in population-based studies is fairly uniform. Approximately 30–50% of UC patients have disease confined to the rectosigmoid (proctitis and proctosigmoiditis) at diagnosis, 20–30% have left-sided disease (up to the splenic flexure) and 20–30% have pancolitis (extending beyond the hepatic flexure) [Langholz, 1999].

In CD, the single most affected segment of the gastrointestinal tract is the terminal ileum. The disease is located in more than 90% of cases in the three main sites: large bowel exclusively, isolated small bowel disease, and combined small and large bowel involvement. Approximately one-third of patients present with large bowel disease, one-third with ileocolonic disease and one-third with small bowel disease localization [Munkholm, 1997]. Oesophageal, gastric and duodenal CD lesions occur in 1–4% of patients, most often in association with CD elsewhere in

the gastrointestinal tract. Perianal disease is often seen in connection with concurrent recto-anal CD, but may occur as an initial lesion without apparent disease elsewhere in 2–5% of newly diagnosed patients.

Perianal fistulas

In population-based studies [Schwartz *et al.* 2002; Hellers *et al.* 1980], the occurrence of perianal fistulas varies between 21 and 23%. The cumulative frequency of fistula occurrence was 12% at 1 year, 21% at 10 years and 26% at 20 years.

Presence varies according to disease location. Perianal fistulas have the highest frequency in patients with colonic disease involving the rectum followed by colonic disease with rectal sparing then ileocolonic disease. It appears least frequently in patients with isolated ileal disease [Hellers *et al.* 1980]. Perianal disease often precedes or appears simultaneously with intestinal symptoms [Schwartz *et al.* 2002; Hellers *et al.* 1980].

Extra-intestinal manifestations

IBD is associated with a range of extra-intestinal manifestations (EIMs) that may be the initial presenting symptoms of the IBD. Up to 36% of patients with IBD have at least one EIM [Bernstein *et al.* 2001]. Some are related to active inflammation (i.e. joint, skin, ocular and oral manifestations).

The reported incidence of arthropathies is 4–23% [Orchard *et al.* 1998]. It can either be axial in the form of sacroiliitis or ankylosing spondylitis or in the form of two types of peripheral arthropathy. Type I is a large joint pauci-articular arthropathy, which occurs at times of IBD activity, affects weight-bearing joints, affects fewer than five joints, is usually acute, self-limiting, resolves within weeks as disease activity decreases, and leaves no permanent joint damage, while type II is a poly-articular small joint symmetrical arthropathy, whose activity is independent of IBD activity and usually persists for months or years.

Uveitis and episcleritis are probably the most common EIMs of IBD. These complications are commonly associated with joint symptoms. The reported incidence is 4–12% in both UC and CD, although uveitis and iritis are more common among patients with UC and episcleritis in CD patients [Orchard, 2003; Bernstein *et al.* 2001; Orchard *et al.* 1998].

The incidence of various cutaneous symptoms is 2–34%. Erythema nodosum is characterized by raised, tender, red or violet subcutaneous nodules 1–5 cm in diameter and commonly affects the extensor surfaces of the extremities, and usually occurs at times of colitis activity. Treatment is based on that of the underlying disease. Pyoderma gangrenosum can occur anywhere on the body, including the genitalia, but the commonest sites are the shins and adjacent to stomas.

The incidence of hepatobiliary disorders in patients with IBD is 5–15% [Orchard, 2003; Bernstein *et al.* 2001]. Primary sclerosing cholangitis (PSC) constitutes the most important condition and has been reported in up to 10% [Orchard, 2003; Bernstein *et al.* 2001]. In 70–90% of patients with PSC, especially young males, the disorder is associated with UC. PSC may precede symptoms of IBD by several years. Although there is a strong association of UC with PSC, there is no relation to the onset, duration, extent or activity of colitis. It is often seen in pancolitis that is symptomatically mild and characterized by prolonged remission. Colectomy does not alter the clinical course of PSC, and liver disease may develop several years after a total colectomy has been performed. PSC substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma.

Disease course and clinical activity in ulcerative colitis

The course of disease in UC is often described in terms of disease activity, risk of progression of the inflammation, number of relapses, need for surgery, and ultimately, mortality. In UC the distribution of disease activity in a cohort of 1161 patients was fairly constant each year with half of the patients in remission every year, although the cumulative probability of a relapsing course with intermittently occurring activity was 90% after 25 years. The clinical course varied from remission to relapse without significant predictors except for disease activity in the preceding period (year). In the first 3–7 years after diagnosis 25% of patients were in remission, 18% experienced disease activity every year, whereas 57% had intermittently occurring relapses. After 10 years the cumulative probability of colectomy was 24%. More than half of the patients with initial proctosigmoiditis eventually progressed proximally during 25 years, whereas patients with more extensive disease at diagnosis regressed in 75% of cases [Langholz *et al.* 1996; 1994].

In a short-term study on the disease course and prognosis from Norway (IBSEN) in a cohort of 454 patients followed for 5 years, it was found that the frequency of surgery was low, 7.5% after 5 years, a relapse-free course was observed in 22% of patients and among patients initially diagnosed as proctitis 28% had progressed to more extensive colitis during the observation period (10% to extensive colitis) [Henriksen *et al.* 2006].

In a European study (ECIBD) on 781 patients with UC followed for 10 years after the initial disease attack, the cumulative relapse rate after 10 years was 67%. Patients who experienced a relapse within 1 year of the initial diagnosis had a greater total number of relapses compared with patients who experienced a relapse later in the disease course. The relapse rate was higher for women than for men and higher for those who stopped smoking during follow-up compared with those who had never smoked [Höie *et al.* 2007a].

Disease course and clinical activity in Crohn's disease

Although the anatomical distribution of CD is fairly stable over time the behaviour of the disease varies substantially with time passing. In a French study on the course of CD the phenotypes of CD was evaluated by the Vienna Classification. Disease behaviour was described as nonstricturing or nonpenetrating in 70% of patients, stricturing in 17% and penetrating in 13%. Disease extent was the terminal ileum in 47%, colon in 28%, the ileocolon in 21% and upper gastrointestinal tract in 3%.

At follow-up there was a change from nonstricturing to either stricturing in 27% or penetrating disease in 28% [Louis *et al.* 2001].

Two population-based studies have looked at the long-term prognosis: a study from Olmsted County, Minnesota, USA on 225 patients followed from 1940 to 1993 and one from Copenhagen County, Denmark following 373 patients from 1962 to 1987. Regarding disease activity, it was found that 10–30% of CD patients have a relapse or exacerbation of disease after the first year of diagnosis, 15–25% experience low disease activity, whereas 50–65% are in remission. Long-term follow-up (more than 10–15 years) showed that 10–13% of patients remain in remission for several years, 67–73% experience a chronic intermittent course and 13–20% have a

chronic course with continuous activity [Loftus *et al.* 2002; Munkholm *et al.* 1995]. Most patients with CD require surgery with time. After 20 years most patients with CD have been operated on at least once [Cosnes *et al.* 2002]. Approximately 30% are operated on during the first year after diagnosis. Subsequently the surgery rate is about 5% per year. The cumulative risk for surgery is 50–80% and the half of these will experience re-operation during the disease course [Munkholm *et al.* 1995]. The risk is highest for patients with ileocaecal disease and the risk for a hemicolectomy in CD patients is approximately 35% after 10 years. Extensive or radical surgery with disease free margins is not effective in preventing disease recurrence. On the contrary, nonradical or less extensive surgery seems to cause fewer and later recurrences [Ewe *et al.* 1989]. At present there is no known treatment which is completely effective in preventing disease recurrence. Different medical treatments, azathioprine/6-mercaptopurine, methotrexate and biologicals (infliximab and adalimumab), may be able to reduce this risk by up to 50% [Feagan, 2003].

Risk factors for recurrence

Risk factors for CD recurrence after surgery include penetrating/fistulizing disease behaviour, young age, short duration of disease before first surgery and ileocolonic disease [Avidan *et al.* 2005; Greenstein *et al.* 1988; Lautenbach *et al.* 1998; Caprilli *et al.* 1996].

Cigarette smoking has been studied extensively and is found to be associated consistently with endoscopic, clinical and surgical CD recurrence. The risk for re-operation 5 and 10 years after the first surgery for CD is significantly higher in smokers compared with nonsmokers (36% *versus* 20% at 5 years and 70% *versus* 41% at 10 years) [Cosnes *et al.* 1996; Sutherland *et al.* 1990].

The major goal of medical therapy in CD is to modify or alter the clinical course by reducing the need for surgery, reducing disease progression and avoiding the need for potentially harmful medications. So far none of the traditional anti-inflammatory drugs have consistently been found to alter the clinical course of CD, but it emerges from the literature that the new biological treatment modalities might have this potential. It was recently reported in a small study however, that infliximab after intestinal resective surgery was effective at preventing

endoscopic and histological recurrence of CD [Regueiro *et al.* 2009].

This was further substantiated by a study from Belgium on infliximab and mucosal healing among 214 patients in long-term treatment with infliximab. Among patients who achieved mucosal healing, the need for abdominal surgery was significantly reduced compared with patients without mucosal healing (14.1% *versus* 38.4%, $P < 0.0001$) [Schnitzler *et al.* 2009].

The concept of mucosal healing, irrespective of ways to achieve it, had previously been shown in a Norwegian population-based cohort where the authors found that mucosal healing reduced the subsequent disease activity course in CD and predicted a lower need for colectomy in UC [Frøslie *et al.* 2007]. Since infliximab at present seems to be the most potent inducer of healing we might see a change in the prognosis of CD in the future with the increasing use of biologics earlier in the disease course.

Colorectal cancer occurrence

The increased risk of CRC in UC has been long recognized; however the present risk is much lower than previously anticipated. Patients with long-standing IBD have an increased risk of developing CRC, the risk increases with longer duration of colitis, greater anatomic extent of colitis, the presence of PSC, a family history of CRC and the degree of inflammation of the bowel.

It seems from the literature that the risk has been declining over time. In fact, a population-based study from Denmark on 1160 patients involving 22,290 person-years of follow-up from 1962 to 1997 found no increased risk of CRC among UC patients with a 30-year cumulative risk of 2.1% [Winther *et al.* 2004]. The same was found in a population-based study from Olmsted County in the USA, where 378 patients were followed for 5567 person-years in the period 1940–2001. The cumulative probability of CRC development after 30 years was 2%, not significantly different from the risk of the background population [Jess *et al.* 2006]. Slightly higher risk estimates were found in a study from Hungary with the cumulative risk of CRC was 0.6% after 10 years, 5.4% after 20 years and 7.5% after 30 years of UC [Lakatos *et al.* 2006]. In a referral-based study from UK, the cumulative incidence of CRC was 2.5% after 20 years,

7.6% after 30 years and 10.8% after 40 years [Rutter *et al.* 2006]. The slightly higher figures in the latter study may be explained by referral bias and a different study design.

It is obvious that the incidence of CRC in UC seems to be decreasing and this may be the result of the medical and surgical treatment strategies with a chemoprotective effect of the maintenance treatments and more aggressive surgical intervention strategies. The results may indicate that a comprehensive approach to control of inflammation with maintenance treatment and regular clinical controls are highly effective tools and should be continued in this potentially high-risk population.

The risk of CRC in CD seems to be equivalent to the risk in UC in a meta-analysis of both hospital-based and population-based studies. An overall relative risk of CRC in patients of 2.5 (95% confidence interval (CI) 1.3–4.7) was revealed. This was the case for patients with colonic involvement, whereas the risk in patients without colonic involvement was similar to that of the background population [Canavan *et al.* 2007]. When restricting the analysis to population-based studies lower estimates were found by Jess *et al.* [2005]. Six studies were included and reported varying estimates of the cumulative risk of CRC ranging from 0.9 to 2.2 with a pooled estimate of 1.8 (95% CI 1.4–2.5).

Patients with small intestinal CD disease are at increased risk of small bowel adenocarcinoma. All studies on small bowel cancer (SBC) and CD report an increased risk from that of the background population in the range from a relative risk of 3–100. In the largest population-based studies from Scandinavia [Jess *et al.* 2004; Mellekjaer *et al.* 2000; Persson *et al.* 1994], the relative risk was between 16 and 60 and in a meta-analysis of eight studies the pooled relative risk was 31.2 compared with the general population [Canavan *et al.* 2006]. This difference is highly statistically significant; however the real risk is low since SBC is a rare cancer form and accounts for less than 5% of all gastrointestinal cancers. From the different studies it is apparent that the cancers develop in the inflamed areas of the small bowel and are difficult to diagnose at an early stage, thus making the prognosis severe since they are often diagnosed at a late stage of disease.

Mortality in Crohn's disease

CD is associated with a small but increased risk of death. Population-based studies from Denmark, Sweden, UK, Italy, USA and Europe indicate an increased mortality rate among CD patients in the range of 20 to 70% higher than expected (Table 1). A recent meta-analysis [Canavan *et al.* 2007] reported a pooled standardized mortality ratio (SMR) of 1.5 showing that the risk of dying for patients with CD is 50% higher than would be expected for someone in the general population of same age and gender. A meta-regression analysis was also performed pointing to a slightly decreased SMR over time, but the decrease was not statistically significant.

When looking at cause-specific mortality approximately 25–40% of deaths can be attributed to CD. In some studies patients are more likely to die from intestinal cancer and lung cancer and also from nonmalignant-gastrointestinal diseases [Masala *et al.* 2004; Card *et al.* 2003; Jess *et al.* 2006, 2002; Persson *et al.* 1996; Ekbohm *et al.* 1992].

The majority of the studies are limited by the fact that they were identified and assessed

retrospectively, but were also diagnosed before the introduction of effective medications for CD. In the most recent study from the ECIBD group however, the excess mortality is still present pointing to the fact that the prognosis of CD has not really changed in terms of mortality over the past 40 years despite the introduction of more efficient medications (i.e. immunomodulatory treatments) [Wolters *et al.* 2006]. With the introduction of biologics in the treatment of CD it will be interesting to see if future data on the mortality of CD show a decrease or even an increase in the mortality risk related to immunosuppression.

Mortality in ulcerative colitis

Population-based studies of UC mortality from Denmark, UK, Italy and USA [Jess *et al.* 2006; Masala *et al.* 2004; Winther *et al.* 2003; Farrokhyar, 2001] have shown an equivalent or even improved survival in UC compared with the general population, whereas some studies from Sweden have shown a slightly increased mortality among patients [Persson *et al.* 1996; Ekbohm *et al.* 1992] (see Table 2).

A meta-analysis of 10 population-based cohorts [Jess *et al.* 2007] found varying SMRs

Table 1. Crohn's disease-related mortality from selected population-based cohorts.

Author	Site	Study period	Number	Follow-up Years	SMR (95% CI)
Jess	Olmsted, USA	1940–2001	314	13	1.2 [0.9–1.6]
Persson	Stockholm, Sweden	1955–1984	1251	–	1.5 [1.3–1.7]
Jess	Copenhagen, Denmark	1962–1997	374	17	1.3 [1.0–1.6]
Ekbohm	Uppsala, Sweden	1965–1983	1655	–	1.6 [1.4–1.9]
Masala	Florence, Italy	1978–1992	231	15	1.5 [1.1–2.1]
Card	GPRD, UK	1987–?	5960	3.6	1.7 [1.5–2.0]
Wolters	Europe	1991–93	371	10	1.9 [1.3–2.5]

GPRD, General Practice Research Database; SMR, standardized mortality ratio.

Table 2. Ulcerative colitis-related mortality from selected population-based cohorts.

Author	Site	Study period	No	Follow up Years	SMR (95% CI)
Jess	Olmsted, USA	1940–2004	378	14	0.8 [0.6–1.0]
Persson	Stockholm, Sweden	1955–1984	1573	–	1.4 [1.2–1.5]
Winther	Copenhagen, Denmark	1962–1997	1160	17	1.1 [0.9–1.2]
Ekbohm	Uppsala, Sweden	1965–1983	2509	–	1.4 [1.2–1.5]
Masala	Florence, Italy	1978–1992	689	15	0.7 [0.56–0.88]
Farrokhyar	Leeds, UK	1978–1986	356	–	1.03 [0.79–1.40]
Hoie	Europe	1991–1993	775	10	1.09 [0.86–1.37]

SMR, standardized mortality ratio.

from 0.7 to 1.4, with an overall pooled estimate of SMR of 1.1 (95% CI 0.9–1.2), showing that the overall mortality did not differ from the background population, although subgroups of patients were at a greater risk of dying. By subgroup analysis it was shown that mortality was increased during the first few years after diagnosis and in patients with extensive colitis, whereas mortality was significantly reduced in patients who had never received immunosuppressive treatment, probably reflecting that this kind of treatment is given to patients with more severe disease. UC-associated mortality accounted for 17% of all deaths and cause-specific analyses revealed increased mortality from respiratory diseases, liver diseases and pulmonary embolisms, whereas mortality from pulmonary cancer was reduced contrary to the findings in CD [Jess *et al.* 2007]. This divergent pattern could possibly reflect the different patterns of smoking in the two diseases.

In the most recent publication on prognosis in UC in Europe by ECIBD, mortality was equal to that of the reference population [Höie *et al.* 2007b]. The improved prognosis of IBD, especially UC could be due to the chemopreventive effect of the medications used in the treatment of active inflammation. Chemoprevention is an area that shows promise in the reduction of morbidity and mortality associated with IBD. Further studies, including prospective trials need to be performed to develop the best strategy for the reduction of cancer risk in patients with IBD.

Conclusion

The prognosis of UC in terms of mortality and CRC occurrence is not different from that of the general population in epidemiological studies in contrast to the prognosis of CD where an increased mortality exists together with an increased risk of SBC. Patients with CD also have a high risk of undergoing surgical resection during the disease course.

With the increasing use of biologics in the treatment of CD it will be interesting to see if future data on mortality show a decrease or even an increase in the mortality risk related to immunosuppression. Since biologics at present seem to be able to induce mucosal healing, we might see a change in the prognosis of CD regarding surgery in the future, with the

increasing use of biologics earlier in the disease course.

The improved prognosis of IBD, especially UC, could be due to the chemopreventive effect of the medications used in the treatment of active inflammation. Further studies, including prospective trials, need to be performed to develop the best strategy for the reduction of surgery, mortality and cancer risk in patients with IBD.

Conflict of interest statement

The author states that there is no conflict of interest.

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