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Budesonide treatment of collagenous colitis

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Budesonide Treatment of Collagenous Colitis

Ph.D thesis

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The present thesis is based on the papers below, which are referred to in the text by Roman numerals and on preliminary studies not yet published. The studies have been carried out in the period from 1996–2007.

I: Collagenous colitis - a long term follow-up study.
O.K. Bonderup, B. Folkersen, P. Gjersøe, P.S. Teglbjærg.
Eur J Gastroentol Hepatol 1999, 11:493-495. ISSN 0954-691X

II: Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis.
O.K. Bonderup, J.B. Hansen, L. Birket-Smith, V. Vestergaard, P.S. Teglbjærg, J.Fallingborg.
Gut 2003; 52: 248-251. doi:10.1136/gut.52.2.248

III. Budesonide treatment and expression of inducible nitric oxide synthase nRNA in colonic mucosa in collagenous colitis.
O.K. Bonderup, J.B. Hansen, P. Madsen, V. Vestergaard, J.Fallingborg, P.S. Teglbjærg.
Eur J Gastroentol Hepatol 2006; 18:1095-1099. doi: 10.1097/01.meg.0000231747.83760.bd

IV. Long-term budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial.
O.K. Bonderup, J.B. Hansen, P.S. Teglbjærg, L.A. Christensen, J.Fallingborg.
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Contents

Abbreviations

5-ASA	5-aminosalicylates
CC	Collagenous colitis
HRQOL	Health-related quality of life
iNOS	Inducible nitric oxide synthase
IBDQ	Inflammatory bowel disease questionnaire
LC	Lymphocytic colitis
MC	Microscopic colitis
mRNA	Messenger RNA
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
RT-PCR	Reverse transcription polymerase chain reaction
[75]SeHCAT	^{75}Se-lablled homocholic acid-taurine

1 Introduction

Gastrointestinal symptoms are a leading cause of morbidity and 25–40% of the population experience gastrointestinal symptoms annually (1). Diarrhoea is a common complaint and the prevalence of chronic diarrhoea is of the order of 4–5%. There is no uniform definition of chronic diarrhoea. According to the guidelines from the British Society of Gastroenterology chronic diarrhoea can be defined as the abnormal passage of loose or liquid stools more than three times daily and/or a stool weight greater than 200 g/day for longer than four weeks (2). Irritable bowel syndrome is the most common cause of chronic diarrhoea; however, further examinations are needed to exclude other causes (2,3).

For patients with chronic diarrhoea, flexible endoscopy is recommended and chronic diarrhoea is one of the most common reasons for referral to a gastroenterology clinic. Many patients are not found to have signs of organic disease, but in such cases biopsies of the colonic mucosa for histological examination are recommended. Biopsies from patients with chronic diarrhoea and normal macroscopic findings at colonoscopy yielded a histological diagnosis in 27–31% of patients without a previous diagnosis (3,4). Microscopic colitis was diagnosed in 7–24% of these cases. In 158 patients with non-bloody diarrhoea 114 had a normal mucosal appearance and biopsies revealed microscopic colitis in 27 patients (24%) (5). Collagenous colitis was found in up to 0.5% of all patients who underwent colonoscopy (6).

The first case of collagenous colitis was described in 1976 by Lindström (7). A remarkable thickened collagen layer was found in rectal biopsies from a 48-year-old woman with chronic watery diarrhoea. During the eighties, several cases of collagenous colitis were published with characteristic histological and clinical findings. Previously the clinical importance of the abnormal collagen layer has been questioned (8), but today collagenous colitis is recognised as a distinct disease entity. In 1980, the term microscopic colitis (MC) was introduced for idiopathic chronic watery diarrhoea, normal endoscopic findings and mucosal inflammation at biopsies (9). In 1989, microscopic colitis was redefined as an umbrella term and specific histopathological appearances are now used, allowing MC to be classified as collagenous colitis (CC) or lymphocytic colitis (LC) (10). Both subtypes are characterised by inflammatory infiltrate in the lamina propria and the epithelium, and are separated only by the presence of the thickened collagen layer in CC. Although MC is different from Crohn´s disease and ulcerative colitis in a clinical setting, it could be classified in a common group of chronic inflammatory bowel diseases without known aetiology (Figure 1).

Figure 1. Classification of inflammatory bowel diseases with unknown aetiology.
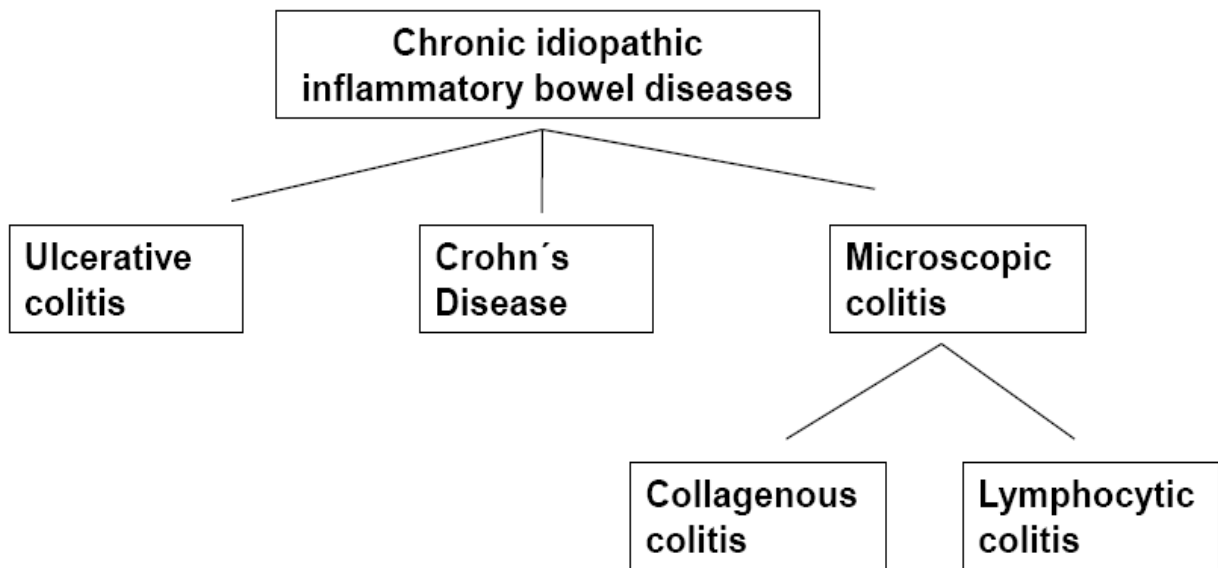
2 Background

2.1 Clinical Presentation

The most prominent symptom in CC is chronic watery diarrhoea with a mean of 6–8 stools per day (Table 1). Up to 20 stools per day has been reported (11). In a recent study, Bonderup et al. (IV) reported the daily stool frequency for 34 patients as an average over three days and in this study a median value of 6 stools per day was found. Bohr et al. (12) reported that 22% of patients had 10 or more stools per day. In a review of the first 14 cases published (13), the stool frequency varied from 3–6 up to 15–20 per day. In all but one patient the diarrhoea was described as "watery". Mucous and blood in the stools are uncommon. Faecal urgency and incontinence are also frequent and often cause socially disabling diarrhoea (Table 1).

Table 1. Bowel habits for patients with collagenous colitis at the time of diagnosis.

	Bohr et al. 1996 N = 163	Fernandez-Banares et al. 2003 N = 37	Chande et al. 2005 N= 66
Stool frequency No/day	6 (1-23)	6.2	-
Nocturnal diarrhoea %	27	-	15
Urgency %	-	65	27
Incontinence %	-	43	17

General health is usually unaffected, and physical examination is normal. Routine laboratory tests are generally normal especially without evidence of inflammation. Bonderup et al. (I) evaluated 24 patients where comprehensive laboratory and malabsorption tests had been done at the time of diagnosis. In one patient, lactose malabsorption was detected but otherwise the examinations were normal. Diarrhoea is often accompanied with other abdominal complains (Table 2). Bohr et al. (12) found weight loss in 42% of patients with a median value of 6 kg. In this population abdominal pain was reported in 41%, fatigue in 14% and meteorism in 8%. This is in accordance with findings in more recent studies (14,15). In most papers the associated gastrointestinal symptoms are mild and transient.

The endoscopic appearance of the colonic mucosa is generally reported as normal. Non-specific changes, such as oedema and hyperaemia have been described, but signs of more severe inflammation are not found. Recently, however, mucosal tears have been reported in several patients with CC and this finding is associated with a high risk of colon perforation (16).

Table 2. Clinical symptoms at presentation for patients with collagenous colitis. All data in %.

	Bohr et al. 1996 N = 163	Baert et al. 1999 N = 96	Chande et al. 2005 N= 66
Weight loss	42	42	38
Abdominal pain	41	52	42
Fatigue	14	-	-
Meteorism/ Bloating	8	21	9

Without effective treatment CC must be considered a chronic disease. The course is often relapsing and remitting and a chronic intermittent or chronic continuous course was reported in 98% of patients (12). Spontaneous resolution of diarrhoea has been reported in 16% (17), but in long-term follow-up studies chronic diarrhoea occurs in 70% of cases (I,18).

2.2 Histology

The primary histological change in CC is a thickened subepithelial collagen layer (Figure 2). In a normal colorectal mucosa the basement membrane is a thin line but a subepithelial band up to 7 µm is considered normal. Bonderup et al. (I) found a subepithelial collagen layer with a thickness of 10–80 µm in biopsies from 24 patients with CC. In a systematic review of 92 colorectal biopsies from 15 patients with CC, it was found that the mean thickness of the subepithelial collagen layer was 14.8 µm (19). In the same study, a mean thickness of the basement membrane in biopsies from

controls was 2.3 μm. A thickness of the subepithelial collagen layer of 10 μm or more is now accepted as a diagnostic criterion for CC.

Figure 2. Histological changes in collagenous colitis: Thickened subepithelial collagen layer, lymphocytic infiltration in lamina propria and epithelial degeneration.
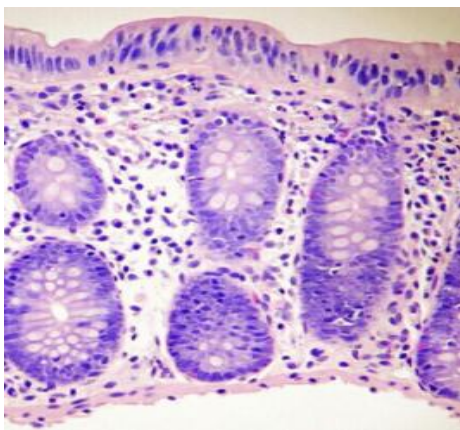
Normal colon mucosa   Collagenous colitis
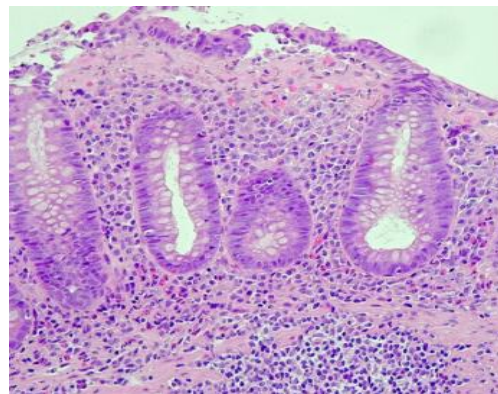
Histological changes also involve infiltration of inflammatory cells into the lamina propria. In the paper from Lindström (7) increased numbers of plasma cells in the mucosa was described. In a systematic evaluation of biopsies from 24 patients with CC (20) the inflammatory infiltrate contained plasma cells in all cases. This is consistent with the findings of Jessurun et al. (19) that demonstrated that the inflammatory infiltrate mainly consisted of plasma cells. In all the fifteen patients a moderate to marked increase in inflammatory cells was present.

In two studies systematic evaluation of the surface epithelium revealed degenerative changes in all biopsies from patients with CC (19,20). Flattening of the epithelial cells and vacuolisation of the cytoplasm was described. Complete or partial detached epithelium was seen in about half of the patients. An increase of the intraepithelial lymphocytes was also present in most patients with CC.

2.3 Nitric oxide

Nitric oxide (NO) is a short-lived free radical gas produced enzymatically from L-arginine. The enzyme NO synthase responsible for the production of NO exists in three forms: a neuronal form,

an endothelial form and an inducible form. In the bowel, the epithelial cell is the most likely cellular source of NO production and immunohistochemical studies have demonstrated expression of inducible nitric oxide synthase (iNOS) in colonic mucosal cells (21). The expression of iNOS is induced by proinflammatory cytokines and by various microorganisms. Increasing evidence suggests that NO participates in the pathophysiology of intestinal inflammation. Increased NO activity has been found in experimental colitis (22) and a pathogenetic role in active ulcerative colitis and Crohn's disease is suggested by enhanced colonic NO generation observed in these patients (23,24). Nitric oxide production is found to be 50 to 100-fold higher in patients with CC than in healthy controls (25,26). At endoscopic examination severe inflammatory changes are not found and the high levels of NO in collagenous colitis is therefore surprising. The cloning and characterisation of the human iNOS gene has made is possible to detect messenger RNA (mRNA) expression by a reverse transcription polymerase chain reaction (RT-PCR). This examination has become an established method of characterising the mucosal production of NO (27)

The exact mechanism causing diarrhoea in CC is not known. The role of the abnormal thickened collagen layer as a barrier of diffusion has been discussed (7). However, we have demonstrated that the symptoms are correlated with the grade of inflammation (II). Nitric oxide is a mediator of intestinal inflammation and the role of NO in inducing diarrhoea in CC is therefore speculated.

2.4 Quality of life

During the last decades the impact of chronic diseases on quality of life has become of more interest. Improvement of health-related quality of life (HRQOL) is an important therapeutic goal in the treatment of chronic diseases. HRQOL is affected in patients with chronic gastrointestinal diseases (28,29). Previous studies have shown that inflammatory bowel diseases lead to considerable reduction of HRQOL (28). A negative effect on physical, psychological and social functions was demonstrated. Chronic diarrhoea especially reduces HRQOL and the subjective reported severity and the numbers of other gastrointestinal symptoms have an influence on the score (29). The more severe the diarrhoea is reported the lower the HRQOL is rated.

Patients with CC mostly have longstanding severe diarrhoea and often additional GI-symptoms (12). Therefore, it is important to quantify the impact of the disease on quality of life for these patients. Several studies indicate severe reduction in HRQOL in active CC (30,31). In a Swedish study a significant reduced HRQOL was found in 123 patients with CC compared with matched

controls (30). Measurement of HRQOL is therefore important in the evaluation of the treatment response.

2.5 Treatment

Treatment of CC was for many years based on empiric data and the experience from treatment of ulcerative colitis. A step-up approach with anti-diarrhoeal agents followed by 5-aminosalicylates (5-ASA) and prednisone was proposed (32). Most treatment algorithms were based on retrospective observations and uncontrolled studies, and no effective standard treatment was established.

In controlled clinical trials budesonide has been shown to be effective in the treatment of Crohn´s disease (33). A study has shown that a daily dose of 9 mg oral budesonide was effective in treating active Crohn´s disease localised in the ileocaecal region. A dose-finding study confirmed that a daily dose of 9 mg was more effective than 3 mg whereas 15 mg gave no additional effect (34).

In two uncontrolled studies, oral budesonide also seemed to be of therapeutic benefit in CC (35,36). In an open-label pilot trial by Tromm et al. (35) budesonide 9 mg daily was given to 7 patients with CC; significant clinical improvement was achieved in all seven patients. In another study by Delarive et al. (36), five patients with longstanding symptoms were treated with budesonide. This therapy resulted in a complete response in 3 patients and a partial response in 2 patients. Budesonide therefore seemed to be a favourable treatment option in CC and controlled studies were desirable.

3 Aims

The aims of the studies were:

1. To investigate the clinical effects of budesonide in the treatment of CC.
2. To investigate the histological effects of budesonide in the treatment of CC.
3. To investigate the effect of budesonide treatment on the level of iNOS in the colonic mucosa in CC.
4. To investigate the effect on HRQOL of budesonide treatment of CC.
5. To investigate the long-term effect of budesonide treatment of CC.

4 Results

Paper I:

A retrospective follow-up of 24 patients (22 females, 2 males) with CC diagnosed in the period 1979–1990 was done. The diagnosis was made on biopsies from the rectal mucosa and nine patients also had biopsies from the whole colon done by colonoscopy. The follow-up was done more than five years after the diagnosis. The mean duration of follow-up was 11 years (range 5–16). At the time of diagnosis additional comprehensive examinations were done to exclude other causes of diarrhoea. At follow-up none of the patients had evolved signs of other diseases that could explain the diarrhoea. Ten of fourteen patients suffered from continuous or intermittent diarrhoea (Table 3).

Table 3. The course for 24 patients with collagenous colitis evaluated more than 5 years after the diagnosis. Mean follow-up time 11 yrs. (range 5–16). CC: Collagenous colitis

24 patients with dignosed CC	4 patients. No data available.	
	6 patients Dead at follow-up	
	14 patients Follow-up 5 -16 years	10 patients + diarrhoea
		4 patients - diarrhoea

The conclusions of the study were that CC is a benign disease but runs a chronic course.

Paper II

Twenty patients with CC were randomised in a double blind placebo-controlled trial. Ten patients were randomised to eight weeks of once daily budesonide treatment (9mg for four weeks, 6 mg for 2 weeks, 3 mg for 2 weeks) and ten patients to eight weeks of placebo. All ten patients in the budesonide group had a clinical response, compared with two patients in the placebo group. In the budesonide group, there was a significant reduction in stool weight and stool frequency (Figure 3).

In the sigmoid mucosa, the grade of inflammation and the thickness of the collagen layer were significantly reduced. After discontinuation of treatment, eight of ten patients relapsed.

The conclusions of the study were that budesonide was a highly effective and well-tolerated treatment option for CC. There was a high risk of relapse after stopping treatment.

Figure 3. Stool weight (A) and stool frequency (B) before and after 8 weeks therapy with budesonide or placebo.
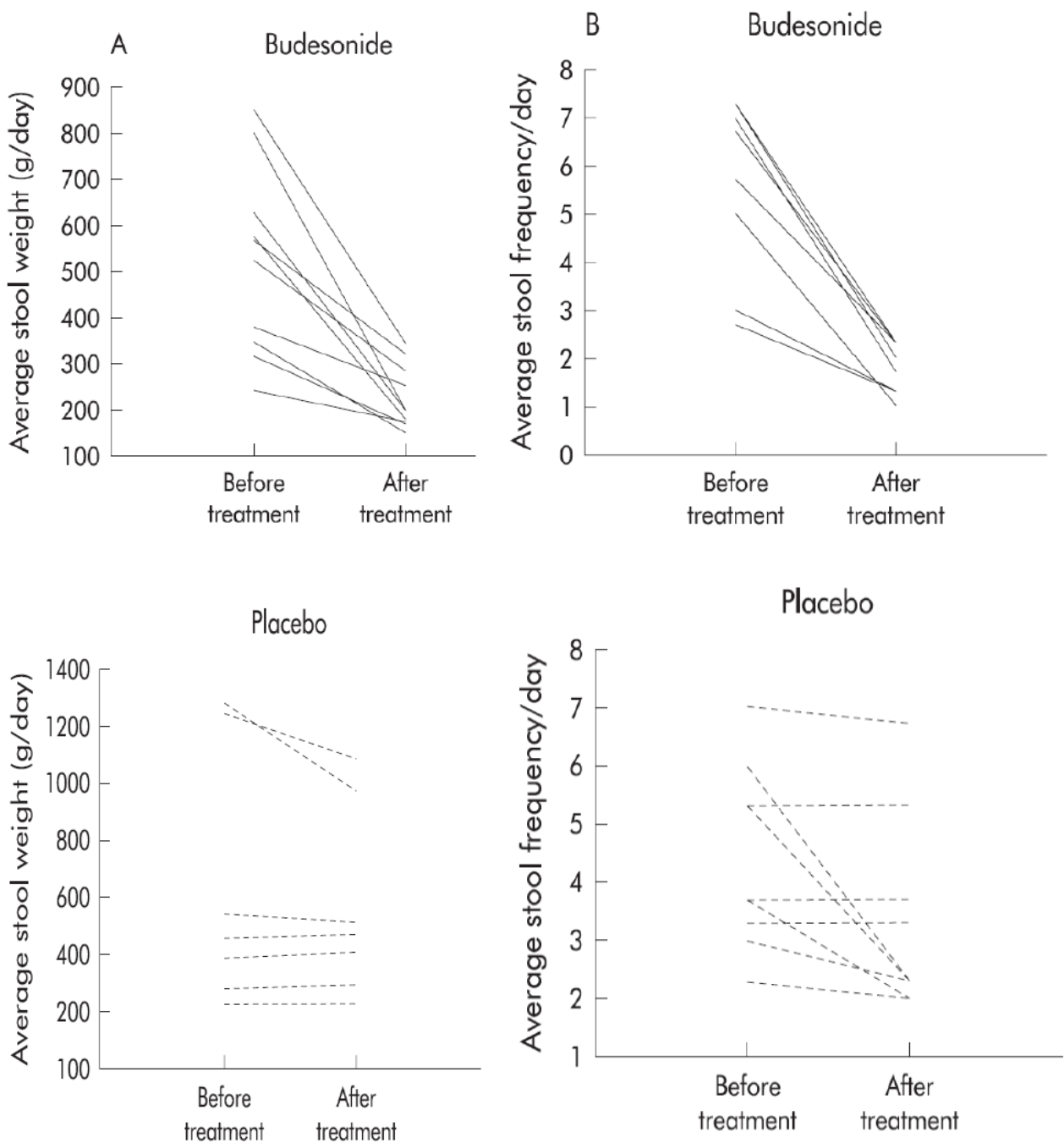
Paper III

Determination of iNOS mRNA was performed in biopsies from the sigmoid colon of 16 patients with active CC. Eight patients treated with budesonide for 8 weeks and seven patients given placebo for 8 weeks had new determination done after treatment. In the budesonide group, a significant reduction of iNOS mRNA was found whereas no difference was found in the placebo group (Figure 4).

A correlation between iNOS mRNA and stool frequency and between iNOS mRNA and stool weight was found. A correlation between iNOS mRNA and grade of inflammation was found but no correlation between iNOS mRNA and the thickness of the collagen layer was observed.

Figure 4. Inducible nitric oxide synthase (iNOS) activity before and after 8 weeks of therapy with budesonide or placebo. NO: nitric oxide
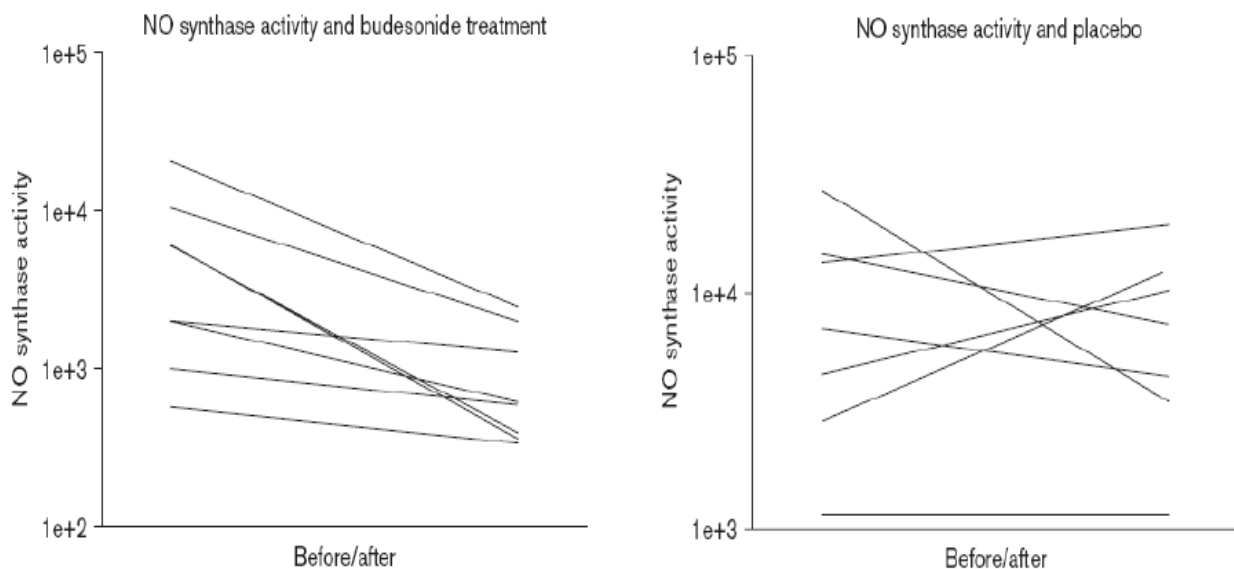
The conclusion of the study was that the findings suggest that NO is involved in the pathogenesis of CC.

Paper IV

Thirty-four patients in remission after open-label treatment with budesonide 9 mg daily for 6 weeks were randomised to 24 weeks of maintenance treatment with budesonide 6 mg daily (n=17) or placebo (n=17) (Figure 5). Health related quality of life was assessed by inflammatory bowel disease questionnaire before and after open-labelled treatment.

Figure 5. Long-term budesonide treatment of collagenous colitis. Study design of the 54 week randomised, double-blind, placebo-controlled trial.
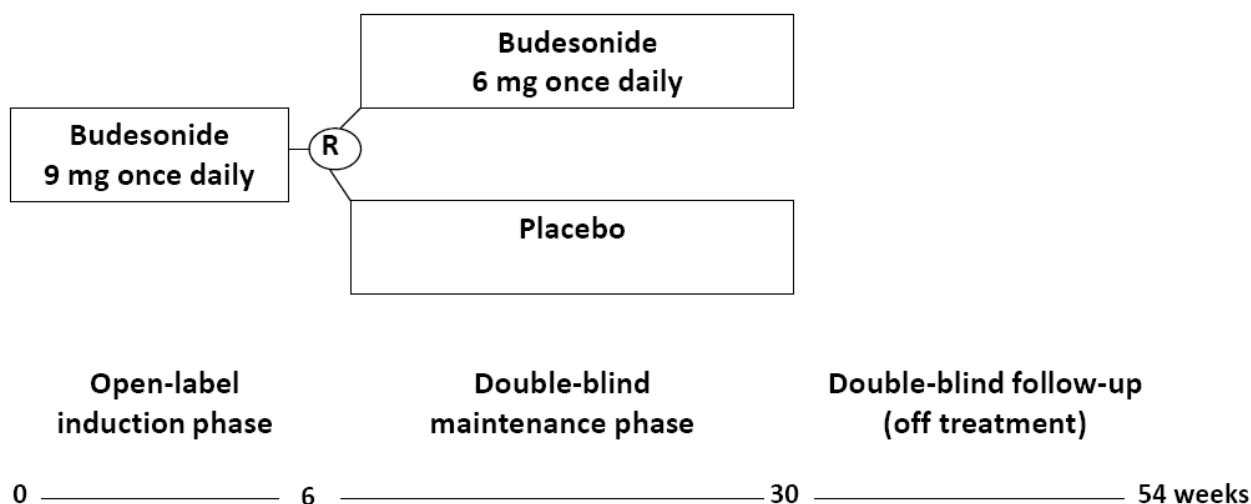
The patients were controlled until relapse up to 24 weeks after stopping maintenance treatment. The numbers of patients in remission at week 30 were 13 of 17 (76.5%) in the budesonide group and 2 of 17 (12%) in the placebo group (p<0.001) (figure 6). At week 54, 2 of 17 (12%) placebo recipients and 4 of 17 (23.5%) in the budesonide group were in remission (NS). The median time to relapse after stopping 6 weeks open-label treatment was 199 days in the budesonide group vs. 38 days in the placebo group (p<0.02). The median times to relapse after stopping active treatment (6+24 weeks in the budesonide group; 6 weeks in the placebo group) were 39 and 38 days respectively.

Figure 6. Long-term budesonide treatment of collagenous colitis. Remission rates at week 30 and week 54.

	Double-blind maintenance phase		Double-blind follow-up (off treatment)	
6		30		54 weeks
Budesonide 6 mg once daily	13/17 (76.5%)		4/17 (23.5%)	
Placebo	2/17 (12%)		2/17 (12%)	

The conclusions of the study were that budesonide 6 mg daily was effective as maintenance treatment for CC. However, the risk of relapse was not reduced after 30 weeks of treatment.

5 Discussion

5.1 Epidemiology

Incidence and prevalence

Collagenous colitis occurs worldwide. Most reported cases of CC are from Europe, North America and, to some extent, from Australia. Recently, cases from Asia and Africa have also been published. Primarily CC was regarded to be exceptionally rare (Figure 7). The early reported incidence rates have ranged from 0.6 to 0.8 per 10^5 per year (37,38); however, incidence rates seem to be increasing. In an epidemiological study from Sweden a mean annual incidence of $1.8/10^5$ was calculated for the period 1984–1993 (38). From the same area incidences for the period 1993-1995 and 1996–1998 were $3.7/10^5$ and $6.1/10^5$ per year respectively (39). In a study from Iceland the mean annual incidence for CC in the period 1995–1999 was found to be $5.2/10^5$ (40). In a Spanish study the incidence of CC during a 5-year study period from 1993 to 1997 was reported to be $1.1/10^5$ per year (6).

A recent study from US also suggests that the incidence of CC is higher than previously considered. Epidemiological data from 1985 to 2001 from Olmsted County, Minnesota revealed a mean annual incidence of $3.1/10^5$ for CC (41). There was a temporal trend with significantly increasing incidence over time (Figure 7). The rising incidence is without doubt to some extent explained by increased awareness and increased diagnostic activity. Whether there is a true rise in the incidence is not settled.

Figure 7. Incidence rates of collagenous colitis related to time periods in two populations (Örebro, Sweden and Olmsted County, USA).
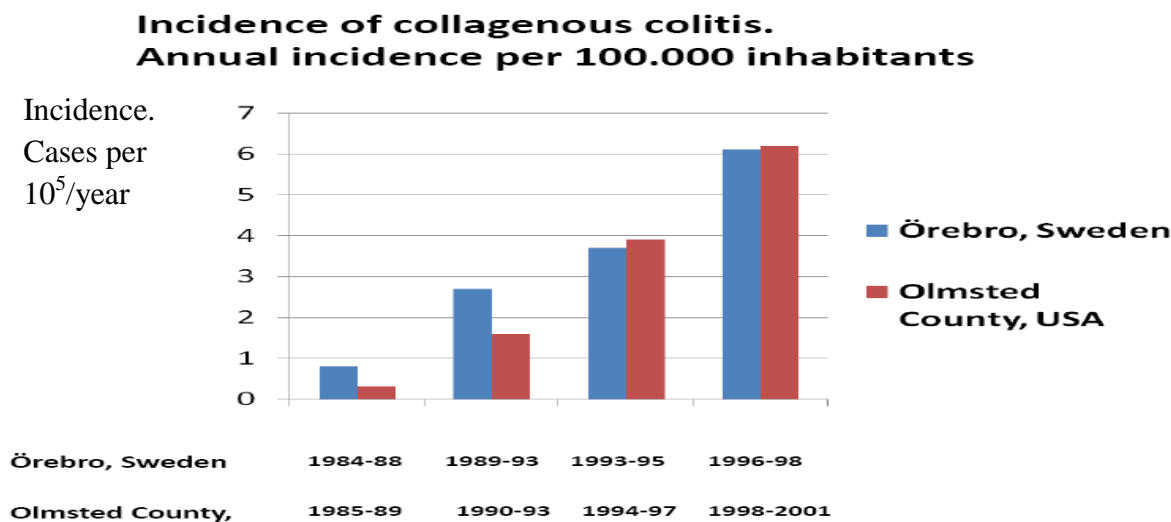
Gender and age.

In all reported populations of patients with CC there is a female predominance. In a long-term follow-up study by Bonderup et al. (I), 22 women (92%) and 2 men were identified and this ratio is in accordance with what is found in most populations. In an early paper from Johns Hopkins Hospital from 1987 (19), 93% of patients were females, and in a study presented by Fausa et al. (42) 91% patients were females. In more recent studies it seems that more males are identified (Table 4). The female ratio in a Spanish manuscript from 1999 was 82% (6), and in a Swedish study 87% were females (12).

Most often women in their fifties and sixties are affected but children in the age of 2–15 years have been reported with CC. We found a median age of 54 years (range, 40–80) (I) and 61 years (range, 33–82) (II). In a recent Spanish population (6) the mean age at onset of symptoms was 53.4 years (range, 29–82) for CC. Bohr et al. (12) reported a median age at the time of diagnosis of 55 years (range, 18–87). There is a wide range of age distribution and 25% of patients were reported younger than 45 years at the time of the diagnosis (12).

Table 4. The reported age, duration of symptoms and female frequency in different populations of collagenous colitis.

	Bohr et al. 1996 N = 163	Fernandez-Banares 1999 N = 23	Bonderup et al. 2003 N = 20	Chande et al. 2005 N = 66
Age (years)	55 (18 – 87)	58 (34 -83)	54 (40 - 80)	65 (31- 88)
Duration of symptoms (months)	47 (1 – 421)	25 (4 – 78)	96 (12 – 300)	-
Female Frequency %	87	82	80	84

Course

There are only limited data describing the long-term course of CC. In previous studies the symptoms most often had been present for an extended period at the time of diagnosis (Table 4) (11,12). In a study population of 20 patients, we (II) found that the median duration of symptoms was 8 years (range 1–25). In a comprehensive review of 163 patients (12), it was found that the median duration of symptoms before diagnosis was about 4 years, and in a recent study (15), a mean duration of 5.4 years was found. Fausa et al. (42) reviewed the clinical data of 11 patients with CC and median symptom duration of 7 years was reported. One patient had profuse diarrhoea for more than 20 years. Palmer et al. (43) described four cases of CC in women with long-standing diarrhoea and one of the cases had 40 years` history of fluctuating diarrhoea. These data indicate that CC runs a chronic course and this is in accordance with the findings in most follow-up studies.

In a long-term follow up study of 24 patients, we (I) found that CC runs a chronic but benign course. Ten of 14 (71%) patients suffered from chronic or intermittent diarrhoea in a follow-up period of 5–16 years. In five symptomatic patients, colonoscopies were performed more than five years after the diagnosis and the thickened collagen layer was unchanged. This is in accordance with findings in most other reports. In a case report from 1986 the course of CC for six patients was reported (11). They have had symptoms of 4–33 years and were regularly followed-up for between 2 and 13 years after the diagnosis. Despite treatment with conventional anti-inflammatory drugs they were still symptomatic. In a Danish report (18), 67% had unchanged symptoms at the follow-up after 0.5–12 years. In conclusion, these data show that, without effective treatment, about 70% of patients with CC will have persisting symptoms for years.

Prognosis

CC runs a benign course and there is no evidence of increased mortality. In a follow-up study (I), we found that none of the patients died from CC. The patients were clinically unremarkable in respect of physical appearance and laboratory tests. Bohr et al. (12) also found that no patients died from CC and no development of severe colitis was observed. Laboratory tests were essentially normal and no malignant potential was observed. The risk of colorectal cancer has been especially studied in 117 patients with CC from the Johns Hopkins Registry (44). No cases were found in CC patients during a mean follow-up period of 7.0 years (range 2–12 years) after the diagnosis.

5.2 Histology

Reliability of histological findings

In a previous study, it was found that blinded re-evaluation of the biopsies from patients with MC resulted in changing the diagnosis in 19% (45). However, in only 3% was there disagreement between normal histology and CC. In the studies by Bonderup et al. (II, IV), the histopathological evaluations were performed in specimens stained with haematoxylin and eosin and Masson´s trichrome. Systematic measurements of the thickness of the subepithelial collagen layers were done. At every biopsy level, 10 randomly chosen measurement points were found and the median thickness of the collagen layer was 15.5 µm in 20 patients (II) and 25µm in 34 patients. (IV).This is in accordance with the findings in other study populations, where the median thickness was 14.8–19.5 µm (46,19). The inflammation in the lamina propria was measured semiquatitatively on a scale from 0–3 (Figure 8).

Figure 8. The graduation of inflammation in biopsies from the sigmoid colon. 0 = no inflammation; 1 = mild inflammation –inflammatory infiltrate confined to the luminal part of the mucosa; 2 = moderate inflammation – inflammatory infiltrate extends beyond the base of the crypts; 3 = severe inflammation – inflammatory infiltrate occupies the entire lamina propria and infiltrates the lamina muscularis.
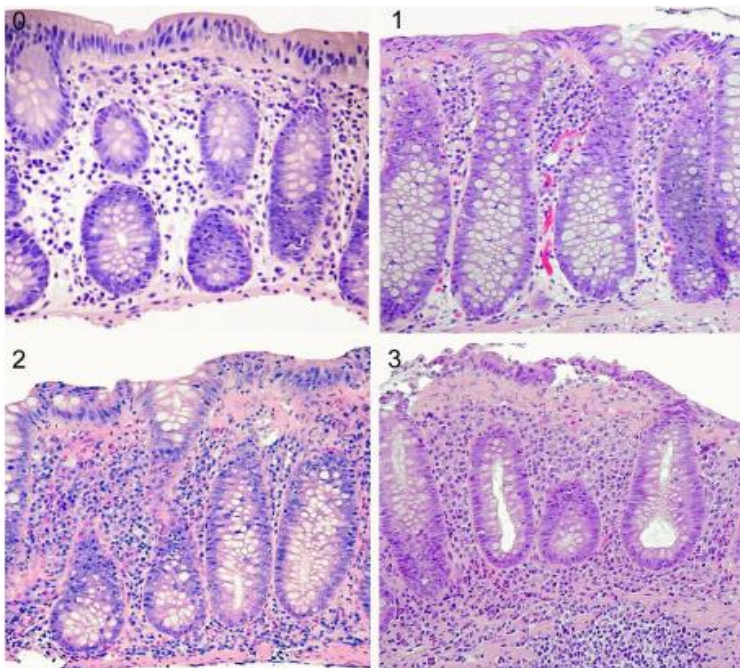
Reproducibility of the morphometric methods was estimated by double measurements by two pathologists of both the thickness of the collagen layer and the grade of inflammation. No systematic difference was observed and good concordance rate between two pathologists was found (II). In conclusion the evaluation of morphology in CC seems reliable in clinical trials. Evaluation of biopsies by a computer-assisted method to measure the thickness of the collagen layer and a quantative morphometric analysis to assess inflammation have previously been described (47). These methods allow an unbiased evaluation of the morphological findings but are regarded as time-consuming. Therefore, extensive histological evaluation is not convenient for daily clinical practice, but needed for research purposes only.

Prognostic value of histological findings.

Goff et al. (48) found no histological parameters at the time of diagnosis to be predictive of the subsequent clinical course. The thickness of the collagen layer and the grade of inflammation were not different in patients with continuous symptoms compared with patients with resolution of symptoms. This is in contrast to the findings by Abdo et al. (49) that demonstrated that mild inflammation in the lamina propria increased the chance of spontaneous remission. Most studies have found that the diarrhoea is related to the grade of inflammation. We (II) found significant correlation between the grade of inflammation in the sigmoid colon and the stool weight (Figure 9).

Figure 9. Correlation between grade of inflammation in colonic mucosa and stool weight.
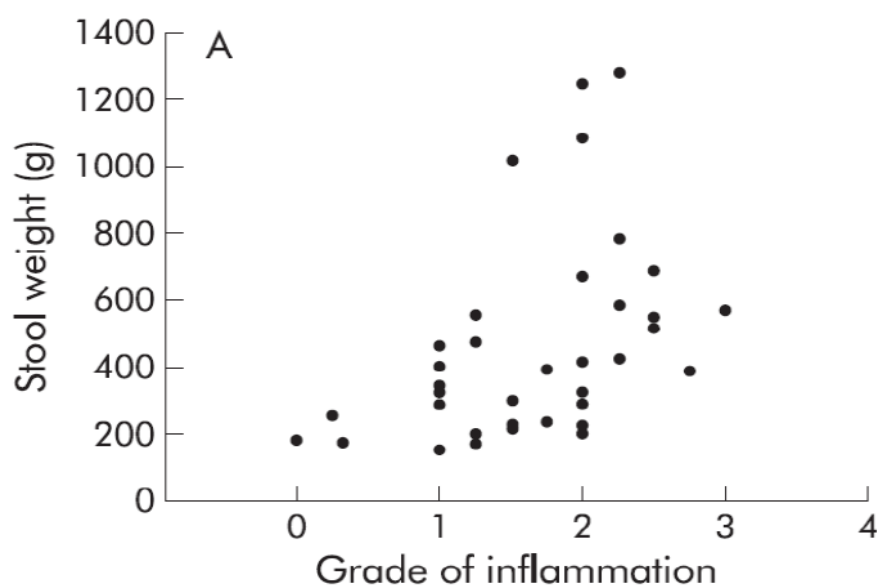
This is in accordance with the study of Lee et al. (47) that revealed the same correlation in a mixed population of CC and LC. In this study the thickness of the collagen layer was independent of the age of the patient and the duration of the symptoms. No correlation between the thickness of the collagen layer and the stool weight was found. In a review of 17 patients with CC, a similar result was found (50). There were no correlations between the thickness of the collagen layer and the stool frequency or the stool weight. In our study, only a weak correlation between collagen layer and stool weight was shown (Figure 10). These findings suggest that the diarrhoea is more closely related to inflammation than to the subepithelial collagen deposition.

Figure 10. Correlation between thickness of collagen layer in colonic mucosa and stool weight.
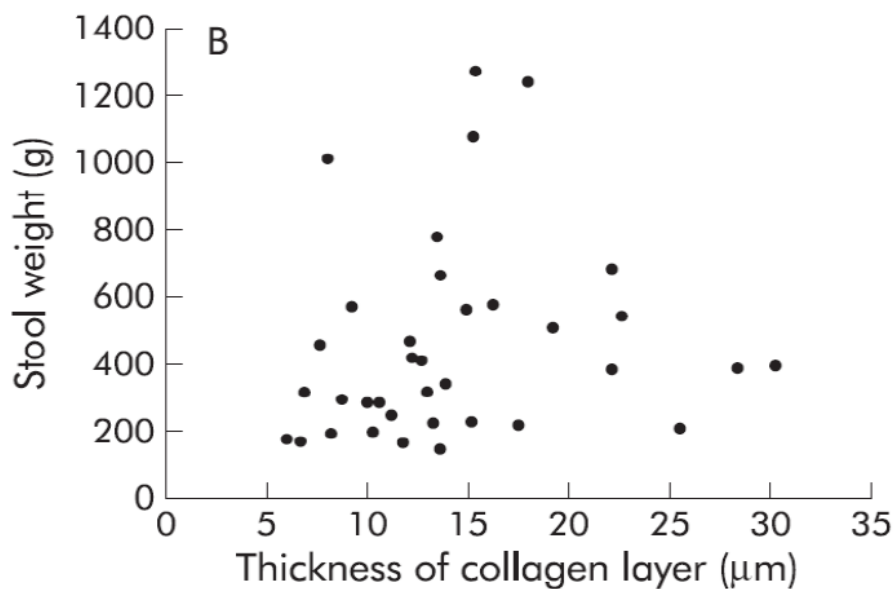
Distribution of histological findings

In previous studies, it was found that that the thickened collagen layer could not be detected in rectal biopsies in 10–43 % of cases of CC (6,19,48). We (II) found that the histological changes were less pronounced in the rectum than in the sigmoid colon. The median collagen layer was thinner in the rectum (9.7) µm compared with (15.6 µm) in the sigmoid colon. In 11 of 20 patients, the collagen layer in the rectum was less than 10 µm. In a study of 12 patients (19), biopsies were available from the proximal colon as well as the distal colon. The thickened collagen layer was found to be more pronounced in biopsies from the right side of the colon (16.8 µm) than in the recto-sigmoid colon (12.8 µm) and the rectum (10.0 µm). In three patients (25%) the diagnosis of

CC could not be established on the basis of distal biopsies alone. However, in a study from 1992 (51), multiple colon biopsies were available from 19 patients. In this study it was found that biopsies from the recto-sigmoid colon were sufficient to diagnose CC in more than 90% of the cases. Fernandez-Banares et al. (6) evaluated biopsies of 23 cases of CC. In 43% of cases, normal histology was found in the rectum whereas the sigmoid colon showed diagnostic changes in all but one patient. A review of biopsies from 27 patients (48) showed that the histological changes were equivalent in both sides of the colon in all but five patients. The diagnosis of CC could be established of the basis of left-sided biopsies alone in 24 patients (89%). In conclusion, the histological changes of CC can be absent in the rectum in 10 to 50% of cases. Therefore, multiple biopsies proximal to the recto-sigmoid colon are recommended to rule out CC.

Differential diagnosis

The histological diagnosis of CC can normally be done easily by the conventional haematoxylin and eosin staining. The collagen layer is best visualized using special collagen staining, such as Masson´s trichrome. The histological features of CC are to some extend similar to those found in LC and the relationship between the two diseases is still debated (10,20). The infiltration of lymphocytes in the epithelium and the lamina propria is almost identical (10). The distinct histological difference is the absence of a thickened collagen layer in LC. In a follow-up of six patients with LC for 4–7 years, no transformation from LC to CC was seen (20) Repeated biopsies did not reveal development of a thickened collagen layer. In this study a subgroup of patients with a thickened collagen layer but no increase in the numbers of intraepithelial lymphocytes were described. The clinical implication for these findings was uncertain. In most patients the histology reveals normal crypt architecture, and cryptitis or crypt abscesses are not seen. However, mild and focal crypt distortion has been described (19). More specific histological changes such as severe mononuclear inflammation in the lamina propria as seen in ulcerative colitis, is not described. Epithelioid granulomas, as seen in Crohn´s disease, were likewise not found in MC. In conclusion, the morphological findings in CC are distinct and the histological diagnosis should be reliable in daily clinical practice. However, the diagnosis is still connected with problems and pitfalls to the interpretations of findings. The measurement of the collagen layer must be done perpendicularly to the surface epithelium in well-oriented biopsies. In tangential sections, the normal basement membrane can erroneously be interpreted as thickened.

5.3 Aetiology

The aetiology of CC is unknown and the pathogenesis of this disease remains unclear. There is some evidence to propose that one or more luminal stimuli in predisposed individuals initiate the disease. In a Swedish paper (52), it was found that faecal stream diversion induced clinical and histological remission in CC. A temporary ileostomy was performed in 8 patients with CC and all had normal ileostomy output. In biopsies from colonic mucosa obtained at colonoscopy 4–36 months postoperatively, the thickness of the collagen layer was significantly reduced. In 3 patients a closure of the ileostomy was later performed and the clinical symptoms and histological changes hereafter recurred. In one patient, a sigmoidostomy was done and the collagen layer in the excluded sigmoid colon and rectum normalised. In the proximal colon, however, a persisting collagen layer was found. The nature of this luminal stimulus has not been identified; however, various substances have been suspected (Figure 11).

Figure 11. Possible intraluminal noxious factors.
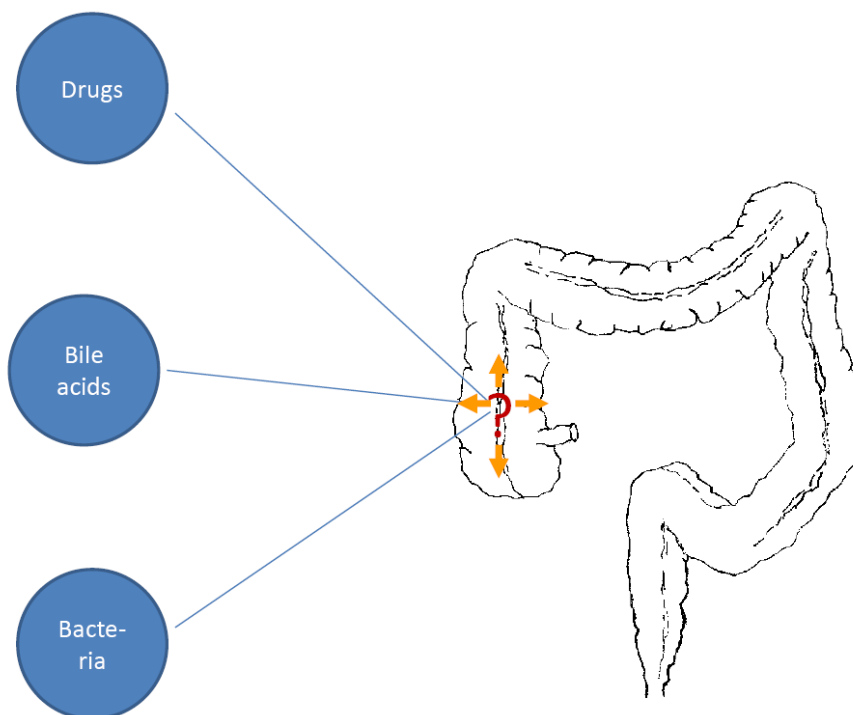
Bacteria

Enteric bacterial flora has been proposed to be involved in the pathogenesis of CC. Especially infections with *Clostridium difficile* and *Yersinia enterocolitica* have been connected with the

development of CC (53,54). However, there are no indications of ongoing infection at the time of diagnosis. In a retrospective analysis of 24 patients by Bonderup et al. (I), stool culture at the time of diagnosis did not reveal intestinal pathogens. Stool cultures were performed in two studies before budesonide treatment and no detection of pathogens were done (II, IV). This is in accordance with most studies that consistently show negative faecal bacteriological examinations (11,13,55). In nine patients stool cultures for *C. difficile* were all negative and no cytotoxic activity in faeces could be detected. In a comprehensive examination of 20 patients with newly diagnosed CC, breath tests for bacterial overgrowth were also performed (55). The test was found to be abnormal in only one patient with a strong predisposing factor in the form of a previous gastric resection. In a case report (56) faeces from a patient with CC showed a cytotoxic effect on McCoy cells lines. A bacterial cytotoxin was suspected as responsible for development of CC but no microorganism could be identified. Previously gastrointestinal infection cannot be excluded as the initiator of the pathogenic mechanism. In a retrospective analysis of six patients with CC, three of the patients had signs of a *Y. enterocolitica* infection preceding the diagnosis of collagenous colitis. (53). Bohr et al. (57) found that *Yersinia* antibodies were more common in patients with CC than in controls. Antibodies were found in 9 of 32 patients (28%) with CC compared with 1 of 17 healthy controls (6%), and it was speculated that *Yersinia* infections might have been the triggering event in the development of CC.

Altered permeability of the colonic mucosa and increased bacterial invasion has been proposed as the initiating factor. In previous electron microscopic examination of mucosal biopsies the presence of bacterial invasion in the intraepithelial space was found. However, no deeper invasion was seen (20,42,). In vitro studies of the transmucosal transmission of a non-pathogenic *Escherichia coli* revealed increased mucosal bacterial uptake in CC (58). Bacterial uptake was increased in biopsies from 8 patients with CC in remission and from 11 patients with active CC compared with biopsies from 8 controls. After 6 weeks of budesonide treatment, new biopsies were done and the bacterial uptake was still found to be increased.

This could be an indication of bacterial invasion as a trigger for a local inflammatory response. However, there is not sufficient evidence to consider a specific bacterium to be an aetiological factor. An altered permeability in the colonic mucosa can cause superficial bacterial invasion but it is not clarified that this is involved in the pathogenesis of CC.

Drugs

Drugs produce a wide spectrum of lesions throughout the gastrointestinal tract and have also been implicated in inflammation of the colon. Non-steroidal anti-inflammatory drugs (NSAIDs) have been related to different forms of colitis (59). The compound inhibits the production of prostaglandin and thereby reduces mucosal protection. This may leave the mucosa susceptible to other stimuli that can initiate an inflammatory response.

Collagenous colitis has been associated with the use of NSAIDs with reported frequencies of 30–70% (12,15,48). Therefore, it has been suggested that NSAIDs are involved in the causation of the disease. Long-term use of NSAIDs in patients with CC has been described in many case reports (60). Among 27 patients, Goff et al. (48) found that 71% were taking NSAIDs at the time of diagnosis, whereas Bohr et al. (12) showed use of NSAIDs (regularly or for limited intervals) among 33% of patients. In a more recent paper, the use of NSAIDs was reported in 39% of CC and 29% of LC (15). In a case-control study the use of NSAIDs for more than six months was found in 19 of 31 cases (61%) compared to 4 of 31 controls (13%) (61). The use of the drug preceded the symptoms by 0.5–15 years. In a case-control study from Spain (62) drug consumption for 39 patients with CC was compared with controls. Intakes of NSAIDs were found in 46% of cases compared with 23% of controls. In a Swedish study however, no association with CC was found among 30 patients with MC (20). Five patients (17%) had a history of intake of NSAIDs including three patients taking low dose salicylic acid. The high frequency of NSAID intake in patients with CC makes a pathogenic role likely but a causal relation has not been established. The possible role of NSAIDs could be to initiate the inflammatory reaction; however, the drug could also change the permeability of the mucosa or aggravate existing diarrhoea.

Many other drugs have been suspected to be implicated in the pathogenesis of CC (62,63). Proton pump inhibitors and antidepressants have been associated with a high likelihood of inducing CC. The use of proton pump inhibitors has been associated with development of CC in case reports (64, 65). Two cases of collagenous colitis associated with lansoprazole were reported. Both patients had rapid clinical improvement after discontinuation of the drug and histological normalisation on follow-up biopsies was reported. In another study (62), it was found that 14% of patients with CC were taking omeprazole at the time of diagnosis. Selective serotonin reuptake inhibitors have been reported to be associated with CC, and it was found that 18% of 39 patients were taking these compared with 1% of controls (62). However, this frequency has to be compared with an occurrence of 15% in a group of patients with chronic watery diarrhoea of functional

characteristics. Drug consumption might be the trigger factor of CC in predisposed hosts. However, CC occurs frequently in patients without any drug consumption and the role of drugs is not settled.

Bile acid

Bile acid normally undergoes enterohepatic circulation by reabsorption in the distal ileum. When this circulation is interrupted, bile acids enter the colon resulting in diarrhoea. Resection of the distal ileum may lead to bile acid malabsorption and idiopathic bile acid malabsorption has also been described. The ^{75}Se-lablled homocholic acid-taurine (^{75}SeHCAT) test is used to detect bile acid malabsorption. After oral ingestion of ^{75}SeHCAT the retention of bile acid could be measured after 7 days. Previous studies have shown that bile acid malabsorption may be common in patients with chronic diarrhoea (66).

The involvement of bile acid as part of the pathophysiology in CC has been suggested but the role of bile acid malabsorption is not clear. Bile acid malabsorption has been described more frequently in patients with CC compared with healthy controls. We (I) found that 27% of patients with CC had identified bile acid malabsorption at the time of diagnosis. This is in accordance with the findings in other studies where frequencies of 24–44% were reported (55,67,68). However, this has to been compared with the presence of bile acid malabsorption in 58–75% in the populations of patients with chronic diarrhoea without an established cause (66, 67). Fernandez-Banares found bile acid malabsorption in 31% of patients with CC (17). This frequency was lower than the frequency found in a population of patients with LC (60%) and in patients with unexplained chronic diarrhoea (75%). In two prospective studies (55, 68), systematically performed ^{75}SeHCAT tests revealed abnormal findings in 24–44% patients. Bile acid malabsorption is frequently found in patients with chronic diarrhoea but can be explained by the diarrhoea *per se*. The combination of CC and bile acid malabsorption is common but does not always explain the diarrhoea.

Celiac disease

An association of CC and celiac disease has been found in many studies (12,51) with reported frequencies of 7–17%. In a study population from Sweden, 8% were reported to have celiac disease (12). In an Australian study from 1992, 11% were diagnosed on basis of duodenal biopsies (51). However, in a retrospective analysis, the criteria for the diagnosis of celiac disease are not clearly stated, and the risk for misinterpretation of bowel biopsies must be accounted for. In more recent papers, the relationship between celiac disease and CC has been questioned. In a population of 66

CC patients, none had celiac disease (15). The presence of genetic and serologic markers of celiac disease in 34 patients with CC was not different to the findings in 70 controls (69). In this study, duodenal biopsies were done in 23 patients and none had villous atrophy. In a study by Bonderup et al. (I), 14 of 24 patients had duodenal biopsies done, and no cases of celiac disease were diagnosed.

The possible association of CC and celiac disease has raised the speculation that gluten in the diet could be the noxious factor that initiates CC. However gluten withdrawal did not induce clinical remission in four patients with concomitant CC and celiac disease (51). Despite reversal of small bowel pathology there was persistent diarrhoea. In a population of 28 patients with newly diagnosed CC, three had known celiac disease (55). All three patients were still symptomatic despite a gluten-free diet. Duodenal biopsies revealed normal histology in two patients. The immune mechanisms underlying celiac disease is different from what is involved in CC. There is insufficient evidence to suspect gluten as the initiating factor in CC.

Auto-immune diseases

Several studies have suggested a possible auto-immune mechanism for the development of CC (12, 15). This is supported by the predominance of females and the possible association with other auto-immune diseases. An association between CC and a wide spectrum of rheumatologic and known auto-immune diseases has been described. Possible associations include auto-immune thyroid disease, recurrent idiopathic uveitis, polymyalgia rheumatica/giant cell arteritis, myasthenia gravis, vitiligo, scleroderma, Sjögren's syndrome/sicca syndrome, idiopathic pulmonary fibrosis, discoid lupus, systemic lupus erythematosus, sarcoidosis, mixed connective tissue disease, and rheumatoid arthritis. Lindström suggested that an immunological process with antigen-antibody reaction was involved (7). However, subsequent immunohistochemical studies did not demonstrate deposits of immunoglobin and the numbers of immunoglobulin-producing cells in the lamina propria were normal (42,70). The frequency of the auto-immune associated HLA antigens was not found to be increased in patients with CC (71,72) and no excess of auto-antibodies were found. Despite the association with auto-immune diseases there is no evidence of auto-immune reaction in CC.

5.4 Pathophysiology

The mechanism of diarrhoea in CC is not fully explained. Lindström originally hypothesised that the abnormal thickened collagen layer was a barrier of diffusion (7). Impairment of colonic absorption of fluid and electrolytes was believed to be the cause of the diarrhoea. A correlation

between collagen layer thickness and clinical symptoms could support this mechanism. In previous studies no correlation between collagen layer thickness and stool weight was found (47,50). However, recent data concerning the consequence of the thickness of the collagen layer are conflicting and the pathophysiology of the diarrhoea in CC is still unsettled.

Osmotic or secretory diarrhoea

A previous study has indicated that the diarrhoea was of secretory nature (73). One female patient had persistent diarrhoea during a fasting period and no osmotic gap was found in faeces. Usually the results of fasting will distinguish between secretory or osmotic diarrhoea, and the findings in this case indicate a secretory nature of the diarrhoea. This was supported by the findings at colon perfusion where passive sodium transport and active chloride secretion in the colon could be demonstrated (73).

Subsequent studies however, did not confirm this finding and it has not been possible to clarify which form of diarrhoea is dominant in CC. A Swedish study (74) of nine patients with symptomatic CC indicated multifactorial causes of diarrhoea. Compared with normal diet, fasting resulted in significant reductions in stool weight and 7 patients were able to normalise stool weight during a 48-hour fasting period. This indicates osmotic diarrhoea; however examination of the faecal osmotic gap was not unequivocal. It was concluded that both secretory as well as osmotic factors seem to be involved. This is, in some respect, in accordance with the findings in a study by Bürgel et al. (75). Comprehensive *in vitro* examinations of colonic mucosal specimens from 8 patients and 7 controls were done. Analyses of electrolyte and water diffusion were done along with impedance measurements. Western blot analysis to determine tight junction protein expression was performed. Combinations of three important factors were found to cause the diarrhoea.

1. A marked decrease in absorptive net fluxes of sodium and chloride.
2. An activated chloride secretion from colonic mucosa.
3. An impaired epithelial barrier in colonic mucosa leading to a passive leak of electrolytes and water.

The predominant mechanism of diarrhoea in CC in this study seemed to be the reduced sodium and chloride absorption in the colon.

Mucosal permeability

Altered permeability in the colonic mucosa of a noxious stimulus has been proposed as the basic defect in patients with CC (76). In a case report (76), the mucosal permeability was found increased in a female patient with resistant CC. The patient was treated with a temporary loop ileostomy and repeated biopsies from the sigmoid colon were taken before and after surgery. The paracellular and transcellular permeability was examined in the colonic mucosa in an Ussing chamber and compared with the findings in healthy controls. An increased mucosal permeability was present at the period of active inflammation before ileostomy was done. In biopsies taken four months after ileostomy, normal colon histology and normal permeability was found. Seven months after closure of the ileostomy, new biopsies revealed recurrence of the increased permeability. Altered permeability of the colonic mucosa and increased bacterial invasion has been proposed as the initiating factor. *In vitro* studies of the transmucosal transmission of a non-pathogenic *E. coli* revealed increased mucosal bacterial uptake in CC (58). In this study the increased permeability was not restored after budesonide treatment.

Figure 12. Proposed pathogenetic mechanism for collagenous colitis.
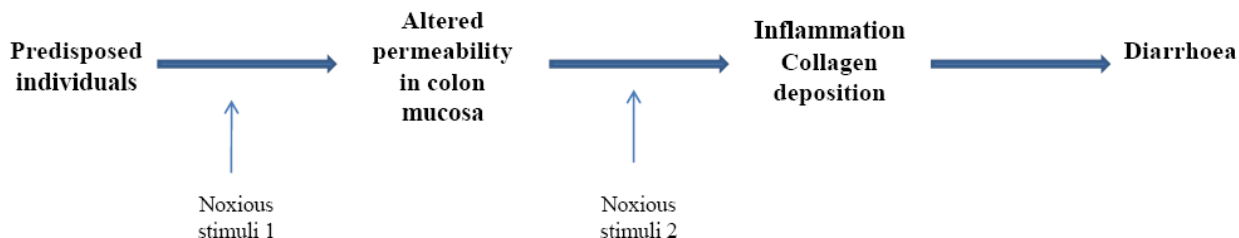
Nitric oxide

Experimental studies in animals and studies in human have shown that NO is involved in intestinal inflammation and may play a role in the pathogenesis of inflammatory bowel diseases (22,23). The increased production of NO in the colon of patients with CC has been demonstrated in previous studies (25, 26). We found that the level of iNOS mRNA correlated to the grade of inflammation and also to the stool frequency and the stool weight (III) (Figure 13). The NO-production in colonic tissue can be assessed by various direct and indirect methods. With the use of immunostaining, a

good correlation between the level of colonic NO and iNOS activity was found (21,). In this study a more intense staining in the apical part of the epithelial cells was found. The apical expression of iNOS in the colonic mucosa of patients with CC is likely to be a response to a luminal factor. These findings support the role of NO for inducing the inflammatory process and the diarrhoea in patients with CC.

Figure 13. Correlation between inducible nitric oxide (iNO) synthase and (a) grade of inflammation; (b) collagen layer thickness; (c) stool weight and (d) stool frequency.
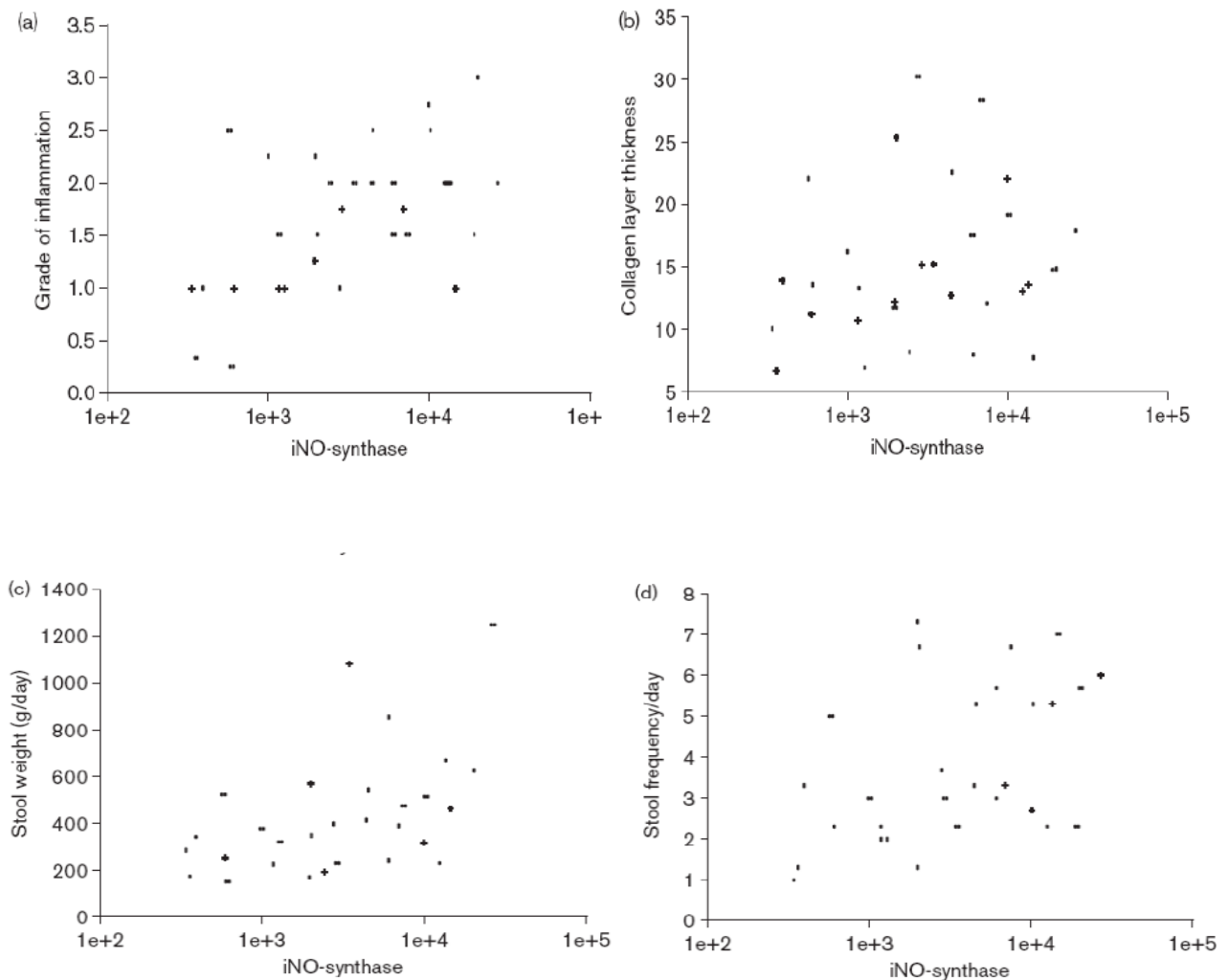
6 Treatment

The prognosis of CC is good concerning mortality and general health. Nevertheless patients experience continuous symptoms for years with a great impact on quality of life. The goal of the treatment is therefore, to normalise bowel habits and to improve quality of life.

Anti-diarrhoeal agents (*e.g.*, loperamide), sulphasalazine/5-aminosalicyclic acid (5-ASA) compounds, antibiotics and cholestyramine have been reported as treatment options for CC (12,77) (Table 5). These medical therapeutic options have primarily been evaluated in retrospective analyses. Treatment with budesonide (II,IV, 78, 79) prednisolone (80) and bismuth subsalicylate (81) has been evaluated in placebo-controlled trials. Recently also probiotics (82) and *Boswellia serrata* extract (83) have been tested in placebo-controlled trials.

Table 5. Drugs with reported effect in treatment of collagenous colitis

Anti-diarrhoeal agents	Loperamide Diphenoxylate Psyllium
Aminosalicylates	Sulfasalazine Mesalamine Olsalazine
Bile acid binders	Cholestyramine
Antibiotics	Metronidazole Erythromycin Penicillin G Mepacrine
Immunosuppression	Azathioprine 6-mercaptopurine Methotrexate
Glucocorticoid	Prednisolone Budesonide
Probiotics	E. Coli strain Nissle 1917 Lactobacillus acidophilus/Bifidobacterium animalis
Other	Boswellia serrata extract Bismuth subsalicylate

Drug withdrawal

Drug consumption may play a role in the initialisation of the inflammatory process in CC. Before beginning medical treatment of CC; withdrawal of a suspected drug is worth trying. In a retrospective analysis of 27 patients, Goff et al. (48) found spontaneous or treatment-related resolution in 17 patients. The majority of these patients were taking NSAIDs at the time of diagnosis, and the discontinuation of the drug could explain the high resolution rate. Resolution of the symptoms of CC after withdrawal of NSAIDs has been reported in several small series (61, 84). In three patients with CC (61), clinical symptoms improved after withdrawing NSAIDs. Rechallenge in one patient was followed by a recurrence of diarrhoea. Therefore patients who are treated with NSAIDs should be advised to stop treatment and the effect of this action should be awaited.

Anti-diarrhoeal agents

The effectiveness of anti-diarrhoeal agents such as loperamide in the treatment of chronic diarrhoea has been confirmed in previous studies (85, 86). A combination of ispaghula and calcium is also widely used for treatment of idiopathic chronic diarrhoea (87). The effect of anti-diarrhoeal medications in CC is reported in several retrospective analyses; however, these treatment options have not been tested in controlled trials. Bohr et al. (12) reported the effect of loperamide in 71% of 69 patients. No serious side effects were reported but the drug often had to be given in a relatively high dose of 4 g three times daily. Among 19 patients with CC (88), 17 patients were initially treated with diphenoxylate 20 mg daily with poor response. One patient reported a partial response and one patient a complete response, while 15 patients did not improve on this treatment. In consideration of the low risk of adverse events, treatment with anti-diarrhoeal agents is worth trying. However there is no proven effect of this treatment in CC.

Sulphasalazine/5-aminosalicyclic acid (5-ASA) compounds

Sulphasalazine is an azo-compound of 5-ASA and sulphapyridine that is dependent on bacterial cleavage in the colon to deliver the active compound. Sulphasalazine has been the mainstay for the treatment of ulcerative colitis for many years; however, the use of this drug has declined because of increasing awareness of the side effects. Therefore different types of controlled released formulations with lower risk of adverse effects are now widely used. 5-ASA has antiprostaglandin

effects and the anti-inflammatory effect of these drugs may relate to inhibition of prostaglandin synthesis.

In previous reports sulphasalazine has been widely used in the treatment of CC (12, 88, 89). However, no placebo-controlled trials of efficacy in CC have been performed. Case reports and retrospective analyses are contradictory with respect to the relevance of these drugs in the treatment of CC. In a retrospective evaluation of the treatment of 163 cases of CC (12), 108 patients had been treated with sulphasalazine and 31 patients with 5-ASA. Treatment response was reported in 34% and 38% respectively. Adverse reactions to sulphasalazine were relative common and occurred in 42%. In another retrospective analysis, Fiedler et al. (32) reported the treatment response of 26 patients with CC diagnosed in the period 1991 to 1994. Twenty patients were primarily treated with sulphasalazine and/or 5-ASA and 9 patients had a complete response with normalisation of bowel habits. In a follow-up, five patients relapsed when treatment was withdrawn and subsequently needed treatment with prednisolone. Pimentel et al. (88) reported treatment response in 19 patients with CC. Eight patients that had not responded to anti-diarrhoeal agents were subsequently treated with sulphasalazine. There was an insufficient treatment response at a dose of 2–3 g daily. Six patients did not respond to treatment and complete response was observed in only two.

In a recent prospective randomised study (90), 23 patients were randomised to treatment with mesalazine 2.4 g daily or mesalazine 2.4 g daily plus cholestyramine 4 g daily for 6 months. Response to treatment was found in 73% and 100% of patients in the two groups, respectively. Marked histological improvement was found in biopsies after 6 months` treatment and in 18 patients complete normalisation of the histological changes was found. At a follow-up after 24 months, three patients with CC relapsed: two patients in the mesalazine group and one in mesalazine/cholestyramine group. In conclusion, treatment with sulphasalazine must be regarded as obsolete because of the reported risk of side effects. Treatment with mesalazine has been found effective in one prospective study, but this result has not been tested in a placebo-controlled study.

Cholestyramine

Patients with marked idiopathic bile acid malabsorption respond well to treatment with cholestyramine (66, 67). The effect of cholestyramine in this setting is related to the bile acid binding property of the drug. Cholestyramine has the ability to bind different substances and besides bile acid it also binds bacterial toxins. This capacity to bind noxious substances could be the

basis for a therapeutic effect in CC. However, the clinical effect of cholestyramine in CC has not been tested in placebo-controlled clinical trials.

In a case report Andersen et al. (56) describes the clinical and histological response of seven months` continuous treatment with cholestyramine. The symptoms and the histological changes reappeared after cholestyramine was discontinued and treatment was restarted. The effect of cholestyramine has been reported in two retrospective analyses and is found in 30–60% of patients (77, 12). In a prospective uncontrolled study, Ung et al. reported an effect in 78% of symptomatic patients treated with a bile acid binder (55). The response to a bile acid binder was dependent on the presence or absence of bile acid malabsorption. Eleven of twelve patients (92%) with CC and demonstrated bile acid malabsorption responded whereas only eleven of fifteen (67%) without bile acid malabsorption responded. This is in accordance with the findings in a study by Fernandez-Banares et al. (67). Cholestyramine induced clinical remission in 7 patients with CC and bile acid malabsorption, whereas none of eight patients without bile acid malabsorption responded. Patients were treated with median doses of cholestyramine 8–10 g daily (range 2–24 g). The treatment was generally well tolerated and only few side effects were reported. However, cholestyramine did not have a sustained long-term effect (91). In a follow-up after more than three years, the clinical course was evaluated in 25 patients primarily treated with cholestyramine. It was found that four patients had recovered, seven patients had an intermittent course and 14 had continuous diarrhoea. There was no improvement in histology.

The combination of cholestyramine with mesalazine has been found to be very efficient (90), but this treatment option was not studied in a placebo-controlled trial.

In conclusion there is no substantial evidence for using cholestyramine as the first-line treatment of CC. However, cholestyramine can be a treatment option in patients with concomitant CC and bile acid malabsorption. The effectiveness of the combination of cholestyramine with other drugs has to be studied.

Prednisone/Prednisolone

Glucocorticoids play an established role in the management of Crohn´s disease and ulcerative colitis (92). Glucocorticoids have a wide variety of anti-inflammatory effects and also induce changes in the immune system. They decrease capillary permeability, reduce migration of leucocytes into the inflamed tissue and inhibit cell-mediated immunity. The clinical effect of glucocorticoids in treating inflammatory bowel diseases is most likely related to the anti-

inflammatory effect. However, glucocorticoids seem to have an additional direct effect on intestinal mineral and water transport (93, 94). Experimental studies have shown that methylprednisolone treatment increased the sodium and water absorption in the small intestine as well as in the colon (93). Human studies indicated that the clinical effect of prednisolone could be due to a combination of the anti-inflammatory effect and the direct effect on sodium and water transport (94). Based on the experiences from the treatment of other inflammatory bowel diseases, an effect of glucocoticoids on CC could be expected.

The effect of prednisolone has been reported in several retrospective reports and case reports. In a retrospective analysis (88) the response to prednisone was significantly higher than to other forms of treatment. Nine of 10 prednisolone-treated patients responded to a dose of 20 mg for three months. During treatment, complete responses with normalisation of stool frequency were reported. Two of the patients relapsed after discontinuation of the treatment. Histological data after treatment were not available. Bohr et al. (12) performed a retrospective evaluation of treatment in 163 patients. Thirty nine patients had been treated with prednisolone and an effect was reported in 32 patients (82%). Relapse often occurred early after withdrawal, and a high dose of prednisolone was required to maintain remission. In a retrospective analysis (32) eight patients who had failed 5-ASA treatment were treated with prednisone at doses of 20–60 mg. All patients responded to treatment however, only one patient had a sustained complete response after steroid withdrawal.

In an uncontrolled prospective trial Sloth et al. (95) treated 6 patients with prednisolone for three months. The starting dose was 50 mg daily for a week, with the dose subsequently tapered during the following weeks. Treatment was associated with a decrease in stool frequency. However, the effect was temporary and diarrhoea recurred when treatment was discontinued. After the treatment, biopsies from the sigmoid colon showed that the thickness of the collagen layer was unchanged, but diminished inflammation in the lamina propria was observed.

In a recent Swedish report, a marked effect of prednisolone treatment was observed (96). The trial was designed to study inflammatory markers in colon perfusates. A part of the trial was treatment with prednisolone 40 mg daily. After one weeks` treatment a marked reduction of stool frequency was found. All the 12 patients who were treated responded within one week and the number of daily stools was reduced from a median of 5 to 0–1 per day. The daily dose of prednisolone was successively reduced by 5 mg per week. After 4 weeks` treatment clinical remission was still achieved in all patients. Long-term clinical follow-up in these patients were not reported.

In a prospective double-blind trial, Munck et al. (80) randomised 9 patients to prednisolone treatment and 3 patients to placebo. Prednisolone was given in a dose of 50 mg daily for two weeks and thereafter the dose was tapered. The effect of treatment was evaluated after a relatively short period of 2 weeks` treatment and no long-term follow-up were done. Reduced stool frequency and reduced stool weight were found in both treatment groups but no difference in remission rate was found. Two of 9 patients in the prednisolone group were in remission compared with none in the placebo group. No histological follow-up was done. The low number of enrolled patients only allows limited conclusions; however in this study incomplete remission was obtained by short-term prednisolone treatment.

In conclusion, systemic prednisolone is effective in CC, but has not become an established treatment option. This is mainly because of a relative high dose needed for remission and a high risk of relapse after discontinuation.

Bismuth subsalicylate

Bismuth subsalicylate is widely used for the treatment of gastrointestinal disorders. Several studies have documented the efficacy of bismuth subsalicylate for the treatment of traveller's diarrhoea. The compound is able to bind bacteria and to exert a bactericidal effect. It is proposed that these effects contribute to the efficacy for the prophylaxis and treatment of bacterial diarrhoea. Moreover bismuth subsalicylate possesses unspecific anti-diarrhoeal and anti-inflammatory effects that could be of benefit in CC.

Two studies by Fine et al. (81, 97) have shown an effect of bismuth subsalicylate in CC. In an open-label study, a mixed population of 13 patients (6 with LC and 7 CC) were treated with 8 tablets of bismuth subsalicylate for 8 weeks (97). Eleven patients responded to treatment with resolution of the diarrhoea and histological improvement. Nine patients had a sustained effect of the treatment and no relapses in a follow-up period of 7–28 months. This study was followed by a controlled study of fourteen patients with MC of whom nine had CC (81). Four patients on active treatment had clinical and histological improvement while no improvement was seen in the placebo group. The treatment was well tolerated and no side effects were observed. However, the evidence of bismuth subsalicylate treatment is not sufficiently documented. The concern of long-term toxicity with the drug limits its use and the drug is not available in many countries.

Immunosuppression

Methotrexate, azathioprine and 6-mercaptopurine are widely used in the treatment of inflammatory bowel diseases. However no controlled studies of immunosuppressive treatment of CC have been performed. Limited data are available from retrospective analyses and open-label studies, and the role of this therapeutic option in CC is still unclear.

In a retrospective review of 43 cases of CC, 19 patients had been treated with methotrexate (98). The median dose was 7.5–10 mg per week (range 5–25 mg). Good or partial responses were reported in 16 patients. Histological evaluation was done after treatment in ten patients and revealed normal histology in five, improvement in two and unchanged histology in three patients. No serious side effects were observed but three patients discontinued methotrexate.

Two patients with steroid-dependent CC have been treated with azathioprine (99). Both had been treated with prednisone, with good responses but symptoms recurred after a reduction of the dose. One patient on azathioprine 75 mg daily was stable without symptoms and able to discontinue prednisolone. There was no histological data given for the patient. The other patient did not tolerate the treatment.

Immunosuppressive treatment has to be studied further before it can be generally recommended. At the moment, immunosuppression should be restricted to patients who do not respond to or have intolerable side effects on other treatments.

Probiotics

The intestinal microflora may play an important role in the development of inflammatory bowel disease. Therefore, modification of the intestinal flora has become a focus in treating inflammation in the colon. Probiotics are defined as living microorganisms with a beneficial effect on the host by improving intestinal microbial balance. Probiotics have been studied in several gastrointestinal disorders. A Cochrane review concluded, however, that there is insufficient evidence that probiotics provide benefits in ulcerative colitis or Crohn´s disease (100, 101).

Two studies have been performed in CC with different types of probiotics (82, 102). In an open-label uncontrolled study, 14 patients were treated with capsules containing the probiotic *E. coli* strain Nissle 1917 (102). The dose varied between 1–6 capsules daily. Two patients discontinued the treatment after 3 and 10 days because of worsened diarrhoea. The rest of the patients were treated for 4–20 weeks. Marked reductions in stool frequency were achieved in 9 patients (64%) and the mean stool frequency was reduced from 7.6 to 3.7 per day. However, in five patients,

increased or unchanged high stool frequency was observed. No histological data after treatment were reported.

In a placebo-controlled study, Wildt et al. (82) investigated the effect of the combination of *Lactobacillus acidophilus* and *Bifidobacterium animalis* in treating patients with active CC. In total 29 patients were enrolled in the study and 21 patients were randomised to active treatment and 8 patients to placebo. The intended duration of treatment was 12 weeks. Compared with placebo, no effect was demonstrated on stool frequency, stool weight or stool consistency. Histological data after treatment were available for 11 patients and no improvements of histopathological changes were found. In conclusion, there is no indication for probiotics at the moment. The treatment option has to be studied further before it can be recommended for CC.

Boswellia serrata extracts

Extracts from the plant species *Boswellia* are commonly used in some countries for complementary or alternative medicine in inflammatory bowel diseases (103). The anti-inflammatory activity is supposed to be related to the content of boswellic acids. In a German trial (83), 31 patients with CC were enrolled in a double-blind, randomised, placebo-controlled study of the efficacy of *Boswellia serrata* extracts. Sixteen patients were randomised to active treatment and 15 patients to placebo. After six weeks' treatment, patients were evaluated for clinical remission, quality of life and histology. Regarding clinical effect, no difference between active treatment and placebo was found in an intention-to-treat analysis. Response was observed in 7 of 16 patients (44%) in the *Boswellia serrata* extracts group and in 4 of 15 (27%) in the placebo group. The treatment had no effect on histology. The thickness of the collagen layer and the grade of inflammation were unchanged compared with baseline and no difference was found compared with placebo. No improvement in quality of life was found. In conclusion, there is no evidence for the use of *Boswellia serrata* extract in CC.

Surgery

Temporary ileostomy and colectomy have been described as a treatment option (52, 76). However, surgery is seldom necessary and should currently be reserved for severe, disabling diarrhoea that is refractory to drug treatment.

7 Budesonide treatment

Budesonide is a topical acting glucocorticoid (104). The effect of budesonide is similar to other glucocorticoids and is mediated by binding to the intracytoplamatic receptors. A high affinity of budesonide for the glucocorticoid receptors results in a potent anti-inflammatory response. The drug undergoes a high first-pass metabolism in the liver and therefore, the systemic bioavailability is low. The pharmacokinetic characteristics of budesonide favour the balance between clinical effect and the risk of corticosteroid-related side effects. After oral administration, budesonide is rapidly and completely absorbed. Therefore, targeted delivery systems to optimise the effect of budesonide were developed. In the form of Entocort® CIR capsules, budesonide is released in the distal small intestine and ascending colon. An acid-resistant enteric coating prevents release of budesonide in the stomach. The coating dissolves at pH above 5.5 and slow-release properties control the release in the small bowel. Budenofalk® capsules have a pH-dependent release that results in release of budesonide 2–4 h after ingestion.

Clinical effect

Two uncontrolled studies have reported a therapeutic effect of oral budesonide treatment of CC. In an open label study, Tromm et al. (35) treated 7 patients with a tapering dose of budesonide. A significant reduction of stool frequency was achieved in all patients within ten days and the effect was sustained during a ten-week treatment period. The number of stools was reduced from 10.4 per day to 1.9 per day after ten weeks treatment. Delarive et al. (36) treated 5 patients with budesonide 9 mg per day for 3–24 months and a clinical response was observed in all 5 patients. A complete response with normalised stool frequency was found in 3 patients. In 2 patients, a partial response with more than 50% reduction of stool frequency was observed.

At present there are three prospective, randomised placebo-controlled studies of oral budesonide treatment of CC. (Table 6).

Table 6. Clinical effect of budesonide treatment in three randomised placebo controlled studies.

	Study design	Clinical improvement	
		Budesonide	Placebo
Baert et al. 2002	Budesonide 9 mg once daily. 8 weeks	8/14	3/14
Miehlke et al. 2002	Budesonide 9 mg once daily. 6 weeks	20/26	3/25
Bonderup et al. 2003	Budesonide 9 mg o.d 4 weeks; 6mg o.d. 2 weeks; 3 mg o.d. 2 weeks	10/10	2/10

We (II) found that ten patients randomised to eight weeks' treatment with budesonide all responded compared to two of ten patients in the placebo group. Patients with more than 4 stools per day and/or stool weight more than 200 g per day were included in the study. Clinical remission was defined as a reduction in stool frequency or stool weight by more than 50%. Budesonide was given for eight weeks in a tapering dose: 9 mg once daily for four weeks; 6 mg once daily for two weeks; 3 mg once daily for two weeks. The median stool frequency was reduced from 6.2 per day to 1.9 per day, and stool weight from 574 g per day to 200 g per day.

Baert et al. (78) found that treatment with budesonide 9 mg once daily for 8 weeks was significantly better than placebo. Patients with at least 3 stools per day for at least 8 weeks were included in the study. Clinical response was defined as a reduction of more than 50% in the numbers of stools. In an intention-to-treat analysis, 57% in the budesonide group responded compared with 21% in the placebo group.

In a study by Miehlke et al. (79), 26 patients were randomised to 6 weeks' treatment with budesonide 9 mg once daily and 25 patients to placebo. It was found that treatment with budesonide

resulted in clinical remission in 77%. This was significantly higher than the 12% in the placebo group. The median stool frequency in the budesonide group was reduced from 6 per day to 2 per day compared with an unchanged 5 per day in the placebo group. In this study, the stool consistency was also evaluated by the patients. A total of 87% of the patients in the budesonide group experienced improvement compared with 14% in the placebo group.

In a Cochrane review (105), analyses of 94 patients enrolled in these three studies was performed. A response rate of 81% for budesonide treated and 17% for placebo recipients was found. The number needed to treat was calculated as two patients. In a meta-analysis the odds ratio for improvement of clinical symptoms with budesonide treatment was determined to be 20.1 (106). In conclusion, these studies have consistently shown that budesonide is highly effective in inducing clinical remission in patients with CC

Patients with prednisone-refractory CC have been treated with budesonide. Three female patients were treated with prednisone 50 mg/day with a tapering dose, but clinical remission could not be achieved. After the administration of 9 mg/day of budesonide, the symptoms resolved. Two of the patients needed continuous treatment to remain symptom-free. The high affinity of budesonide for glucocorticoid receptors can be an advantage in the treatment of CC compared with conventional steroids.

The time to clinical effect

The time to clinical effect after starting budesonide treatment is reported in several studies (36, 35, 78, 79). In an open-label study (35), the effect was achieved in all 7 patients within 10 days after the start of treatment and the effect was sustained during the following 10 weeks' treatment. This is in accordance with the findings in other studies, where the clinical effect was observed within 2–4 weeks. In a controlled study by Miehlke et al. (79) the median time to clinical remission among patients in the budesonide group was 13 days (range, 2–30 days). The remission was achieved in 75% of responding patients within two weeks of treatment. In conclusion, most studies found that the clinical effect of budesonide treatment occurs within a few weeks.

The risk of relapse

The risk of relapse after withdrawal of short-term budesonide treatment has been reported in several studies (II, 35, 36). Delarive et al. (36) treated five patients with budesonide and only one patient was in stable remission without treatment for six months. Four of five patients needed continuous

treatment because of relapse of clinical symptoms at withdrawal. In another study (35) 3 of 7 patients had a sustained effect and no recurrences of clinical symptoms were observed 7, 12 and 15 months after discontinuation of treatment. In a retrospective analysis Bonderup et al. evaluated the long-term treatment response of 99 patients with CC (107) (Figure 13). The mean follow-up time from diagnosis to the last in-clinic visit was 84 weeks (range 4–240). The total accumulated duration of treatment was 42 weeks (4–180 weeks). A total of 32% of the patients needed treatment for more than 24 weeks, 18 % for more than 52 weeks.

Figure 13. The accumulated duration of budesonide treatment in 99 patients with collagenous colitis.

No of patient — Accumulated duration of treatment. Weeks
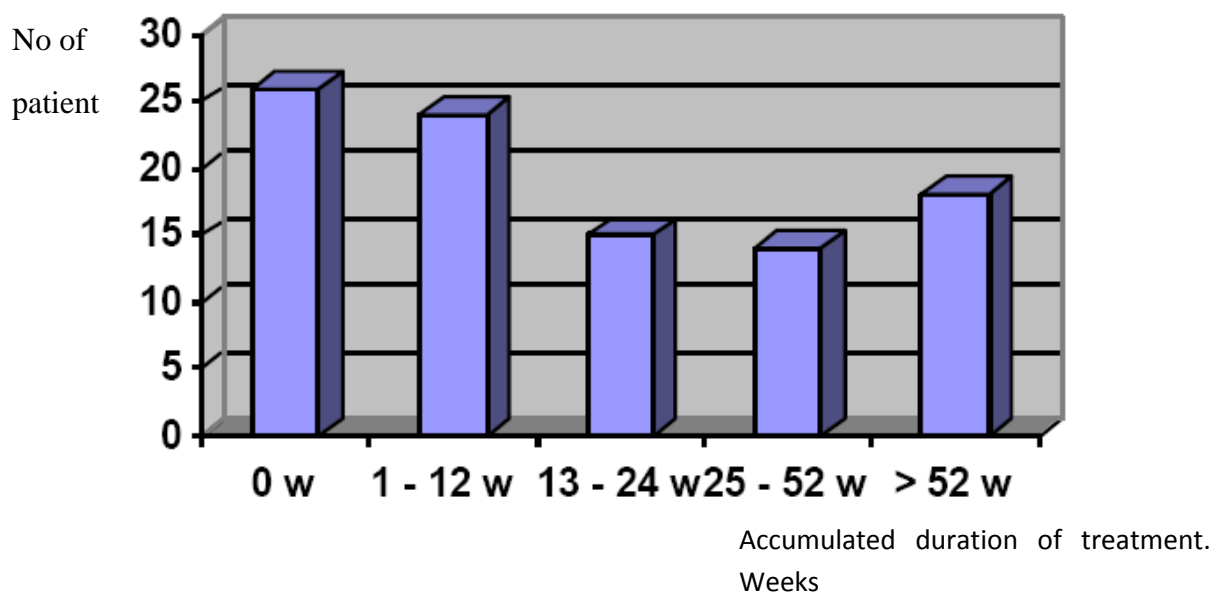
These observations indicate that there could be a high risk of relapse after stopping budesonide treatment. This is confirmed in follow-up data from patients in controlled trials (II,78,108).

Ten patients in clinical remission after 8 weeks of budesonide treatment were followed in a study by Bonderup et al. (II). After discontinuation of treatment, relapse of symptoms occurred in 8 of 10 patients (80%) in a follow-up period of eight weeks (Figure 14).

Figure 14. Kaplan-Meier curve of the risk of relapse after 8 weeks budesonide treatment
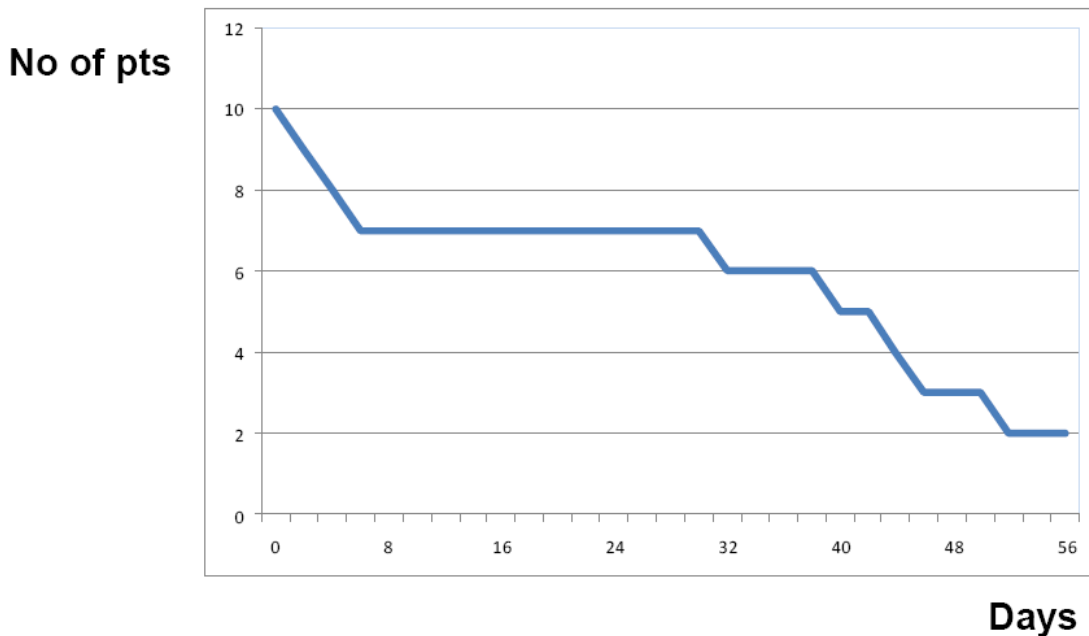
Baert et al. (78) found that 12 of 19 (67%) patients needed further treatment because of clinical relapse after discontinuation of 8 weeks of budesonide treatment. A follow-up of 33 patients in remission after treatment with budesonide 9 mg once daily for 6 weeks was done by Miehlke et al. (108). The median follow-up time was 16 months. Twelve patients (39%) were in stable remission at least 12 months after discontinuation of budesonide treatment .Twenty patients relapsed which gave a cumulative relapse rate of 61%. The median time to relapse was 2 weeks and 88% of relapses occurred within the first 3 months. In conclusion, the risk of relapse is 60–80% within the first 8–12 weeks after discontinuation of short-term budesonide treatment.

Maintenance treatment.

Two controlled long-term studies with budesonide maintenance treatment have been published (IV, 109). In a study by Bonderup et al. (IV) patients with a histologically confirmed diagnosis of collagenous colitis and diarrhoea were treated with oral budesonide 9 mg/day. After induction treatment for 6 weeks, 34 patients in remission were subsequently randomised to 24 weeks of maintenance treatment with budesonide 6 mg/day (N=17) or placebo (N=17) (Figure 5). The patients were controlled until relapse or up to 24 weeks after stopping maintenance treatment. The

numbers of patients without relapse after 30 weeks were 13 of 17 (76.5%) in the budesonide group and 2 of 17 (12%) in the placebo group (p<0.001). At 54 weeks however, no significant difference was observed. Four of 17 (23.5%) in the budesonide group had no relapse compared with 2 of 17 (12%) in the placebo group (NS). The median time to relapse after stopping 6 weeks open-label treatment was 199 days in the budesonide group vs. 38 days in the placebo group (p<0.02). The median time to relapse after stopping active treatment (6+24 weeks in the budesonide group/6 weeks in the placebo group) was 39 vs. 38 days respectively (NS).

Figure 15. Kaplan-Meier curves of relapse-free survival during maintenance and follow-up.
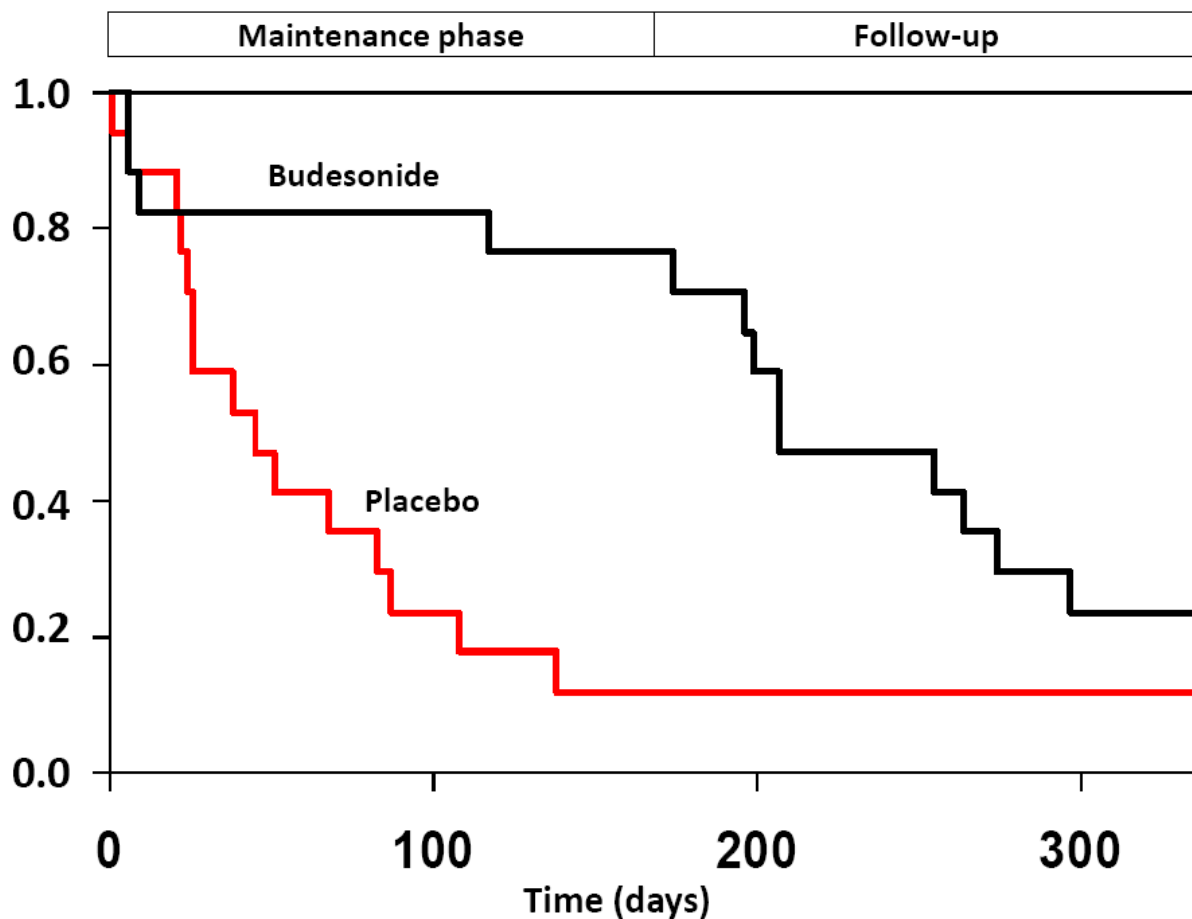
In a similar study by Miehlke et al. (109), 46 patients in clinical remission after 6 weeks of 9 mg budesonide treatment were randomised. Twenty-three patients were randomised to budesonide 6 mg/day and 23 to placebo. Within a 6-month observational period the numbers without relapse were significantly higher in the budesonide group 20/23 (87%) compared with the placebo group 9/23

(39%). In conclusion budesonide is effective for the maintenance treatment of CC. However, the risk of relapse is not reduced after an additional 24 weeks' treatment with budesonide 6 mg daily.

Histological improvement

In an open-label pilot trial (35), biopsies from 3 patients before treatment showed a thickened collagen layer. After budesonide treatment had induced sustained remission, biopsies were repeated. A marked reduction of the collagen layer was found; a mean thickness of 12.8–21.1 μm before treatment compared with 5.0–9.2 μm after treatment.

We (II) found a significant reduction of the grade of inflammation and the thickness of collagen layer in the sigmoid colon after 8 weeks budesonide treatment compared with placebo (Figure 16).

Figure 16. Regression of histological changes in sigmoid mucosa after 8 weeks treatment with budesonide. a) before treatment; b) after treatment
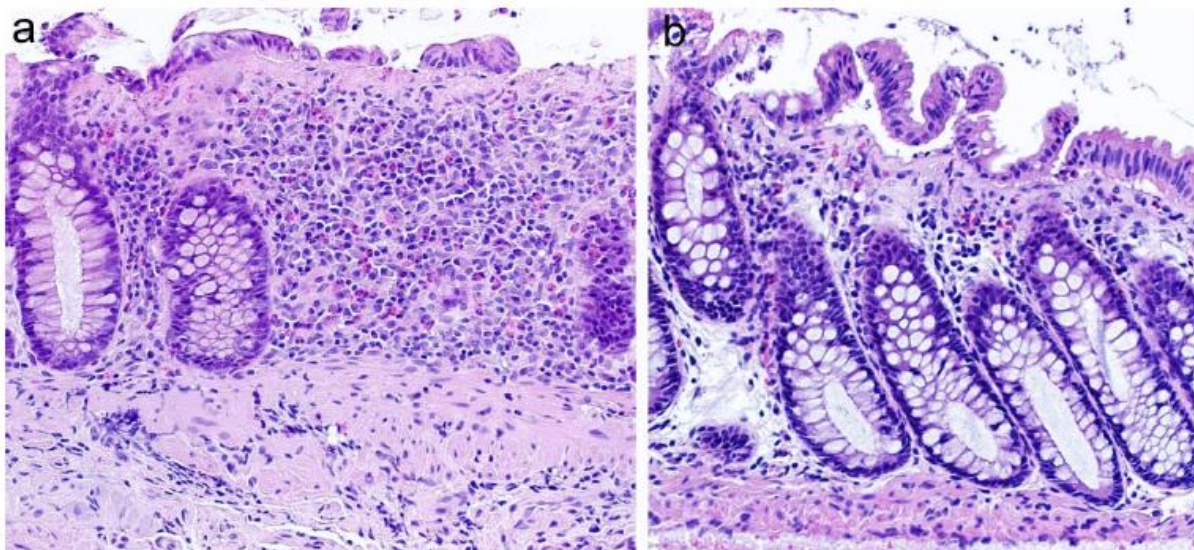
In the sigmoid colon, the inflammation was reduced from 2.3 to 1.0 (p<0.001) in the budesonide group compared with a non-significant reduction in the placebo group from 1.9 to 1.5. The thickness of the collagen layer was systematically measured at 10 points. The median collagen layer in the sigmoid colon was significantly reduced after budesonide treatment from 15.6 μm to 10.2 μm (p<0.02) but no reduction in the placebo group (15.3 μm to 12.7 μm). Biopsies were measured blindly by two pathologists and a good concordance rate was found. The variation coefficient was

0.19 concerning measurement of the thickness of the collagen layer and 0.17 for the determination of the grade of inflammation.

Baert et al. (78) performed blinded histological evaluation of biopsies from the left side of the colon at baseline and after 8 weeks of budesonide treatment. All patients in the budesonide group had a significant reduction of the inflammatory infiltrate in the lamina propria. Nine of 13 patients had complete normalisation of the inflammation and 4 had a partial response. A reduction in the thickness of the collagen layer was also found, but this reduction was not significant compared with the placebo group. Miehlke et al. (79) observed histological improvement in 14 of 23 patients in the budesonide group and in 1 of 22 patients in the placebo group. The grade of inflammation of the lamina propria was estimated by a semiquantitave score and a marked reduction of the inflammation in the budesonide group was found. The thickness of the collagen layer was measured in the entire colon before and after treatment. Reduction of the thickness occurred in both groups however, Bonderup et al. (IV) did not find that the morphological changes on the initial biopsies were predictive for the result of budesonide treatment. Morphology after 30 weeks of budesonide treatment was normalised with respect to inflammation and the thickness of the collagen layer. Despite this there was a high risk of relapse after discontinuation of treatment. The histology at termination of treatment did not predict the risk of relapse. Endoscopy and biopsies for follow-up histological examination after treatment are still important in clinical trials. In daily clinical practice histological examination after treatment has no value and there is no indication for routine follow-up endoscopy.

Quality of life

Patients with active CC have significantly reduced quality of life compared with patients in remission (30). HRQOL is, therefore, an important measure of the medical treatment efficacy in CC. In patients with inflammatory bowel disease the inflammatory bowel disease questionnaire (IBDQ) is widely used for assessment of quality of life. It was developed as a measure of subjective health status in clinical trials for patients with inflammatory bowel disease (110). We assessed quality of life before and after treatment with oral budesonide 9 mg daily for 6 weeks with the IBDQ (111) (Figure 17). Thirty-nine patients (9 males and 30 females), with a median age of 62 years (range 33–81 years) participated in the study. All patients reported an increase in HRQOL after budesonide treatment. The median IBDQ values increased from 135 before treatment to 190 at

the end of the study (46%, p<5 x10^{-9}). The IBDQ scores did not correlate to frequency or stool weight however, a correlation between increment of IBDQ score and reduction of stool was found.

Figure 17. Quality of life (QoL) assessed by inflammatory bowel disease questionnaire (IBDQ) before and after 6 weeks treatment with budesonide.
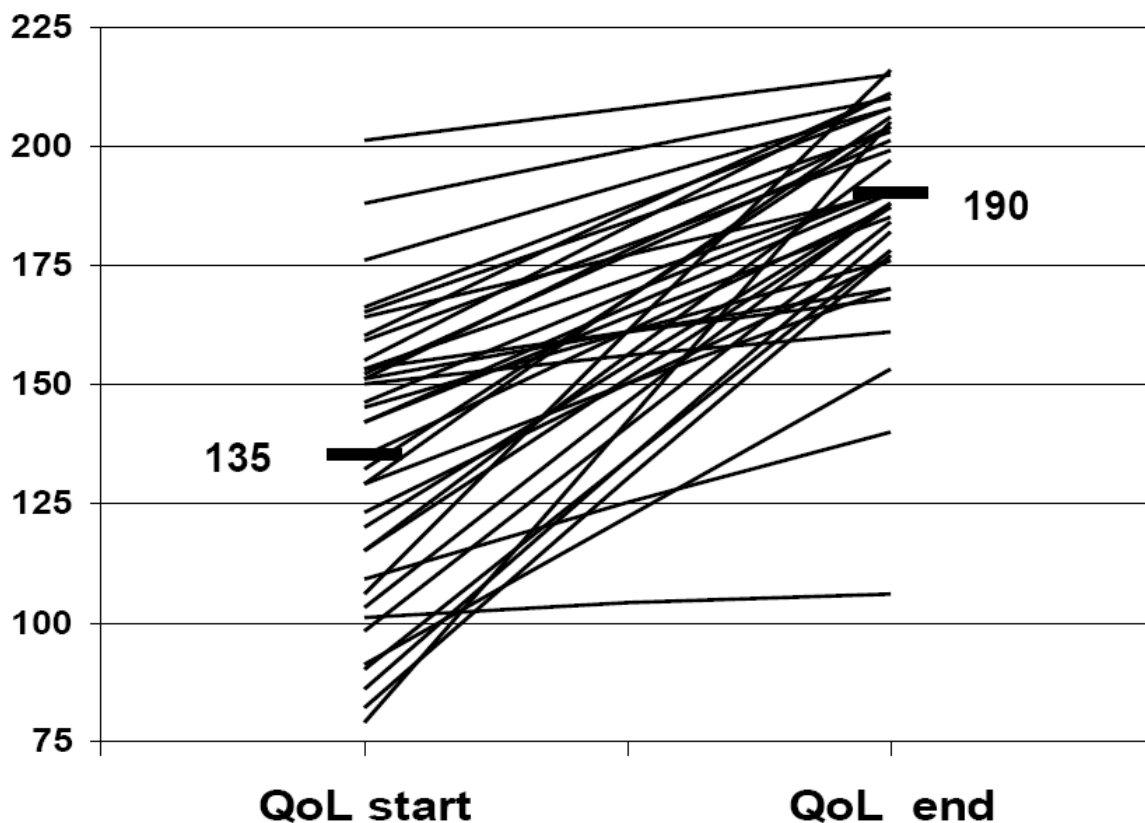
In a similar study Madish et al. (31) assessed HRQOL in patients with active CC using the Gastrointestinal Quality of Life Index. The quality of life scores were low compared with scores in healthy controls. In a placebo-controlled trial the patients were randomised to oral budesonide 9 mg daily or placebo treatment and repeated assessment was possible for 29 patients (budesonide 17; placebo 12). After 6 weeks treatment, the mean value increased significantly in the budesonide group but remained unchanged in the placebo group. Both studies have shown that short-term budesonide treatment improves quality of life in patients with active CC.

Side effects

Budesonide is mainly metabolised in the liver and the high first-pass elimination reduces the systemic bioavailability. The cytochrome P450 enzyme system is involved in the metabolism and

impaired effect of this enzyme system increases the systemic effect of budesonide. The anti-fungal drug itraconazole is a potent inhibitor of cytochome P450 and concomitant treatment with budesonide may result in unwanted corticosteroid-related side effect.

Conventional oral corticosteroids have a well-known risk profile. The risk of side effects depends on the dose and the duration of treatment. Long term, high doses of corticosteroids usually produce predictable and potentially serious side effects. Side effects include moon face, headache insomnia, weight gain as well as thinning and easy bruising of the skin. More serious side effects can be seen such as Cushing syndrome, glaucoma, osteoporosis and psychic disturbances.

The pharmacokinetic characteristics of budesonide minimise the risk of corticosteroid-related side effects. The high topical affinity and a low bioavailability favour the balance between clinical effects and side effects. The possibility that long-term treatment with budesonide may cause side effects similar to traditional corticosteroids however cannot be excluded. The safety profile of budesonide has previously been evaluated mainly in patients treated for Crohn's disease (34). In an 8-week trial, treatment with oral budesonide in doses of 3, 9 and 15 mg daily resulted in a dose-related suppression of the adrenal gland function. This was however, not associated with clinically important symptoms. The proportion of patients with corticosteroid-related side effects in the group treated with budesonide 9 mg daily was not significantly different from the placebo group. Several long-term studies of budesonide treatment of Crohn's disease have been performed (112, 113). In all studies it was found that maintenance treatment with budesonide is well tolerated and only has limited effect on the adrenal gland function. A dose-dependent suppression of adrenal function was found, but the treatment was not associated with clinically important corticosteroid-related side effects. In these studies, it was found that corticosteroid-related side effects were not different from placebo.

The risk of side effects related to budesonide treatment of CC is described in several controlled studies (II, 79,78). In three short-term studies, budesonide was given for 6–8 weeks in doses of 3–9 mg daily. In these studies, the risk of side effects was not different from placebo and no serious adverse events related to study medication were reported. In a long-term study by Bonderup et al. (IV), the risk of side effect in the budesonide group (29%) of was not different from that in the placebo group. One patient in each group stopped medication because of a serious adverse event not deemed to be related to treatment. The other side effects were mild and transient. The same results were found in a maintenance study by Miehlke et al. (79). Twenty-three patients with CC were treated with budesonide 9 mg for 6 weeks followed by 6 mg for 24 weeks. Budesonide therapy was

generally well tolerated and the risk of side effects was not higher in the budesonide group compared with placebo. The side effects were mild, and premature discontinuation because of side effects occurred in 3 patients in the budesonide group and in 1 patient in the placebo group. In this study, 82% of patients on maintenance treatment rated the tolerability of the treatment as 'good' or 'very good'. In conclusion, patients with CC can be safely treated with budesonide for up to 30 weeks without subjective side effects.

Glucocorticoid-induced osteoporosis is a significant problem. Corticosteroids accelerate the bone loss, and the risk of osteoporosis has to be considered in patients with the need for long-term treatment (112). The risk of osteoporosis under long-term budesonide treatment has mainly been studied in patients with liver diseases (114). The reduction in bone mass density in liver disease patients seems to be different from what is seen in inflammatory bowel diseases. The underlying liver disease to some extent explains the higher risk and the relative high dose of budesonide has also to be taken in consideration. The risk of bone mass reduction in patients with CC has not been examined. Osteoporosis has to be taken into consideration in CC patients who need maintenance treatment with budesonide.

Mechanism of action

Although the effect of budesonide on clinical symptoms and histology is well documented the mechanism of action is unknown. We have shown that budesonide significantly reduces the inflammatory infiltrate in the colonic mucosa and reduces the expression of NO production (II, III). Therefore, the most likely mechanism of action is a direct anti-inflammatory effect on the colonic mucosa, and this is in accordance with the effects of conventional steroids. However, there is a high risk of relapse after discontinuing budesonide treatment. This could indicate a more basic defect in the colonic epithelium that is not restored by budesonide treatment. This is in accordance with the proposed pathogenesis in Figure 12. Therefore, budesonide could have an effect on inflammation but does not affect the noxious stimuli that alter the permeability in the epithelium.

Budesonide is released in the distal ileum and exerts the major effect here and also in the ascending colon. The effect of budesonide in the more distal part of the colon therefore is surprising. However, active budesonide is also transported to the descending part of colon (115) and this could be the explanation of an anti-inflammatory effect throughout the colon. A primary effect of budesonide on the morphology and function of the small bowel has been speculated. Budesonide has some effect on the regulation of transport proteins in the terminal ileum (116) and also increases

bile acid absorption in CC (79). Various morphologic abnormalities have been described in biopsies from the terminal ileum in patients with CC (117). However there is no consistent finding that explains the pathogenesis of CC. Therefore, the effect of budesonide in CC is not fully explained and the pathogenesis of CC is not elucidated by the effect of budesonide.

8 Conclusions

The incidence of CC has increased during recent years and is now reported to be about 4–6/10^5 per year. The rising incidence observed can be explained by increased diagnostic activity and increased awareness of the disease. The natural history of CC has not been studied in a long-term prospective way but the disease runs a benign course and no reports of increased mortality or increased risk for malignancy is found. However, we found that without treatment, CC results in continuous symptoms for years.

Patients with chronic watery diarrhoea should be examined by endoscopy and biopsies should be taken even in the event of normal macroscopic appearance. We found that the histological changes diagnostic for CC can be absent in the rectum. In most cases biopsies from the left side of the colon will be sufficient; however, full colonoscopy should be done if there is persistent clinical suspicion of MC and no diagnosis is established.

Oral budesonide treatment is the best documented treatment option for CC. The efficacy of the treatment has been proven in controlled prospective randomised trials. We found that oral budesonide treatment of CC for 8 weeks was effective for:

1. Inducing clinical remission and normalisation of stool habits.
2. Reducing histological changes in colonic mucosa.
3. Reduction of iNOS expression in colonic mucosa
4. Improving HRQOL

There is a high risk of relapse after discontinuing treatment after 8 weeks. We found that maintenance treatment for 30 weeks was effective in keeping patients in remission. However, the risk of relapse is not reduced after 30 weeks` treatment.

Oral budesonide 9 mg daily for 4–6 weeks is recommended as the first-line medical treatment for severe CC. Long-term maintenance treatment with budesonide is often necessary and treatment for up to 30 weeks is regarded as effective and safe. With a budesonide dose of 3–6 mg only few and mild side effects are seen.

9 Perspectives

In this thesis we focused on the treatment of collagenous colitis. We found that budesonide treatment is effective in inducing remission; however, the optimal dose and the optimal duration of treatment are not fully established. Based on the previous dose-finding studies of budesonide treatment in Crohn´s disease, the starting dose in the treatment of collagenous colitis was estimated to be 9 mg once daily. This dose, given for 4 – 6 weeks is effective for inducing clinical and histological remission and most patients will remain in remission after a tapering of the dose. Based on clinical experience, 3 mg once daily will be sufficient to keep most patients with collagenous colitis without symptoms and this dose should be tested in clinical trials.

Few patients do not respond to budesonide treatment; therefore, other treatment options have to be examined especially the effect of 5-ASA. The clinical effect of 5-ASA should be studied in placebo-controlled trials and should also be compared with budesonide treatment. The effect of cholestyramine is not clear; specifically the effect of this drug in subgroups of collagenous colitis patients with bile acid malabsorption needs to be clarified. Combination therapy with two or more drugs can be a treatment option. The combination of mesalazine + cholestyramine seems to be a possible choice for the treatment of collagenous colitis, but likewise further studies are warranted. Probiotics can be useful in some settings, but more clinical trials are needed to establish the relevance of this therapy in collagenous colitis. The most convenient probiotic is not defined and the duration and the dosing of treatment are not established.

Because of the high risk of relapse the efficacy of treatment should include long-term follow-up. In most studies, relapses occur early after discontinuation of treatment, but relapses after several months have been observed. Therefore, a follow-up period of 6–12 months seems reasonable.
The health related quality of life is affected in patients with collagenous colitis. This parameter is important in the evaluation of treatment options and therefore standardised questionnaires should be used in controlled trials. The short form of the IBDQ seems to be an appropriate tool for this.

There is a high risk of relapse after stopping short-term budesonide treatment and the risk is not reduced after 30 weeks treatment. Whether this risk can be reduced by further prolongation of the initial treatment is not settled. However, based on clinical experience there is a persistent risk of relapse even after long-term treatment and different options for maintenance treatment should be tested. Induction treatment for 4–6 weeks with budesonide followed by 5-ASA should be compared with continuous treatment with budesonide.

The risk of side effects of budesonide is minimal in short-term treatment; however, the risk of maintenance treatment has to be taken into account. Especially awareness of the effect of bone mineral density is important. The typical collagenous colitis patient is female in her fifties or sixties, and this population are at increased risk for bone loss. The risk of osteoporosis in long-term treatment with budesonide in this specific population should be included in future studies.

10 Summary

Collagenous colitis was first described by the Swedish pathologist Lindström in 1976. A thickened collagen layer was detected in biopsies from colonic mucosa from a patient with chronic watery diarrhoea. Collagenous colitis is now recognised as a distinct disease entity. An increased awareness and increased diagnostic activity among clinicians and pathologist has resulted in a rise in the number of diagnosed patients. The incidence is now estimated to be $4-6/10^5$ per year. Mostly females in the fifties and sixties are affected, but the disease affects a broad age spectrum.

The cause of the collagenous colitis is unknown. An autoimmune mechanism has been proposed, however the usual associations to auto-antibodies are lacking. From faecal diversion studies it is recognised that a luminal factor initiates the clinical and histological changes. The nature of this noxious stimulus is not settled but several endogenous and exogenous substances have been suspected. Different drugs primarily NSAIDs have been associated with an increased risk of collagenous colitis but the relation to drugs is unclear. The relation to other luminal substances such as bacteria and bile acids is likewise unsettled.

Clinically, collagenous colitis is characterised by watery diarrhoea often combined with urgency and sometimes faecal incontinence. Other abdominal symptoms such as weight loss and abdominal pain are often recognised; however these symptoms are mild and transient. Severe systematic symptoms are not seen and the disease runs a benign course. In a follow-up study we confirmed that the disease has a chronic course, with relapsing and remitting symptoms for years. Without effective treatment, continuous symptoms and severe reduction in quality of life must be expected.

Collagenous colitis should be suspected in patients with chronic watery diarrhoea and normal mucosal appearance at endoscopy. Therefore, multiple biopsies are recommended in these cases. We found that the histological changes were absent in the rectum in about 50% of the patients with collagenous colitis and biopsies proximal to the sigmoid colon are recommended. The characteristic histological finding is a thickened subepithelial layer in the colonic mucosa, but inflammatory infiltrate in the lamina propria and epithelial degeneration are also recognised as diagnostic findings.

Previously the treatment of collagenous colitis was based on the experience from other inflammatory bowel diseases and the results of retrospective analyses. We performed two randomised, double-blind placebo-controlled studies of the effect of oral budesonide treatment on the clinical symptoms and histological changes of collagenous colitis. The first study showed that budesonide was effective in inducing clinical remission of the disease in short-term treatment. The

treatment was given for 8 weeks in a tapering dose with a starting daily dose of 9 mg. However, there was a high risk of relapse after discontinuing treatment and maintenance treatment was often necessary. The second study showed that budesonide 6 mg daily was effective in maintaining remission as a long-term treatment. However, the risk of relapse was unchanged after discontinuing long-term treatment. The two studies also demonstrated that budesonide treatment was able to normalise the morphological changes seen in collagenous colitis. There was an improvement of the inflammation and a marked reduction in iNOS expression observed in patients treated with budesonide. We also found that budesonide treatment significantly improved quality of life in patients with collagenous colitis.

These results are confirmed in comparable studies and budesonide can now be recommended as a first line treatment of severe collagenous colitis.

11 Danish summary

Kollagen colitis blev første gang beskrevet af den svenske patolog Lindström i 1976. Et fortykket subepithelialt kollagen bånd blev påvist i rectum-biopsier fra en patient med kronisk vandig diaré. Kollagen colitis betragtes nu som en selvstændig sygdomsenhed. En øget opmærksomhed omkring sygdommen og øget diagnostisk aktivitet blandt klinikere og patologer har medført en stigning i antallet af diagnosticerede patienter. Incidencen anslås nu til at være 4-6 pr. 100.000 indbyggere pr. år. Kollagen colitis optræder hyppigst hos kvinder i halvtredsårs og tresårs alderen, men sygdommen påvises i et bredt aldersspektrum.

Årsagen til kollagen colitis er ukendt. En autoimmun sygdomsmekanisme har været foreslået, men den sædvanlige associationer med auto-antistoffer har imidlertid ikke kunne påvises. Undersøgelser af patienter med kollagen colitis med ileo- og sigmoideostomi har sandsynliggjort at en luminal påvirkning af colon slimhinden er årsag til de histologiske forandringer og de kliniske symptomer. Det er ikke afklaret hvilken form for påvirkning det drejer sig om, men flere endogene og eksogene stoffer har været mistænkt. Flere medikamenter, primært NSAID-præparater, har været forbundet med en øget risiko for at udvikle kollagen colitis, men relationen til medicinforbrug er fortsat uafklaret. En sammenhæng med andre undersøgte luminale påvirkninger så som bakterier og galdesalte er ligeledes uafklaret.

Klinisk er sygdommen karakteriseret ved vandig diaré ofte i kombination med imperiøs afføringstrang ligesom afførings inkontinens kan forekomme. Yderligere abdominale symptomer som vægttab og mavesmerter optræder ofte, men disse symptomer er sædvanligvis milde og forbigående. Alvorlige almene symptomer forekommer ikke og sygdommen har et godartet forløb. I et follow-up studie fandt vi at sygdommen havde et kronisk forløb med langvarige svingende symptomer i flere år. Uden et effektivt behandlingstilbud må patienter med kollagen colitis forvente vedvarende symptomer og reduceret livskvalitet.

Kollagen colitis må mistænkes ved patienter med kronisk vandig diaré og normalt udseende colonslimhinde ved endoskopisk undersøgelse. Derfor anbefales omfattende bioptering i disse tilfælde. Vi påviste at de histologiske forandringer kan være fraværende i rectum hos omkring 50 % af patienterne med kollagen colitis, og det anbefales at der tages biopsier proksimalt for sigmoideum. Det karakteristiske histologiske fund er et fortykket subepithelialt kollagent bånd in colon mucosa, men inflammatorisk infiltration i lamina propria og epithelial degeneration betragtes også som diagnostiske fund.

Tidligere har behandlingen af kollagen colitis været baseret på erfaringerne fra behandling af andre inflammatorisk tarmsygdomme samt resultaterne af retrospektive analyser. Vi har gennemført to randomiserede, dobbelt-blindede placebo-kontrollerede studier af effekten af oral budesonid på de kliniske symptomer og de histologiske forandringer ved kollagen colitis. Ved det første studie blev det vist at budesonid behandling af kollagen colitis effektivt medførte klinisk symptomfrihed ved korttids-behandling. Budesonid behandlingen blev givet i alt 8 uger startende med 9 mg dagligt efterfulgt af planlagt dosis aftrapning. I behandlingsperioden forblev patienterne symptomfri, men der var imidlertid en stor risiko for symptomrecidiv efter ophør med behandlingen. Vedligeholdelses behandling er derfor ofte nødvendig. Ved det andet studie blev det påvist at budesonid 6 mg dagligt var effektivt til at vedligeholde symptomfrihed ved langtids-behandling. Risikoen for symptomrecidiv er imidlertid ikke reduceret efter ophør af langtids-behandling. De to studier påviste herudover, at budesonid behandling normaliserede de morfologiske forandringer ved kollagen colitis. Der blev fundet reduktion af inflammationen og en betydelig reduktion af iNOS ekspressionen in colon mucosa efter behandling med budesonide. Vi påviste tillige at budesonid behandling signifikant forbedrede livskvaliteten.

Disse resultater er bekræftet ved andre sammenlignelige undersøgelser og budesonid kan nu anbefales som førstevalgs behandling af svær kollagen colitis.

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