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# Smoking Status Influences Clinical Outcome in Collagenous Colitis

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## Abstract

**Background:** The relationship between clinical and histological parameters in collagenous colitis (CC) is poorly understood. Smoking is a risk factor for CC, whereas its impact on clinical activity and outcome is not well known.

**Methods:** In a *post hoc* analysis of pooled data from two randomized controlled trials we assessed the association between demographic data (gender, age, smoking habits, family history of inflammatory bowel disease), clinical variables (duration of symptoms, mean number of stools/watery stools per day, abdominal pain, clinical remission) and histological data (thickness of the collagen band, inflammation of the lamina propria, total numbers of intraepithelial lymphocytes, degeneration). Moreover, we analysed the predictive value of baseline parameters for clinical outcome in a logistic regression model.

**Results:** Pooled data were available from 202 patients with active CC, of whom 36% were current smokers, 29% former smokers and 35% non-smokers. Smoking status was associated with decreased ability to achieve clinical remission (current smokers vs non-smokers: odds ratio [OR] 0.31, 95% confidence interval [CI] 0.10–0.98, $p = 0.045$; former smokers vs non-smokers: OR 0.19, 95% CI 0.05–0.73, $p = 0.016$). Current smokers had an increased mean number of watery stools at baseline compared with non-smokers ($p = 0.051$) and increased mean number of watery stools *per se* was associated with decreased likelihood of obtaining clinical remission (OR 0.63, 95% CI 0.47–0.86, $p = 0.003$). Patient characteristics and histology at baseline had no association with clinical parameters and no predictive value for clinical outcome.

**Conclusion:** Smoking worsens clinical symptoms in CC and is associated with an increased number of watery stools and decreased likelihood of achieving clinical remission. There is no significant association between histology and clinical data.

**Key Words:** Collagenous colitis; predictive factors; histology; smoking.

## 1. Introduction

Collagenous colitis (CC) is a chronic inflammatory bowel disease (IBD) presenting mainly with non-bloody watery diarrhoea and few or no endoscopic abnormalities. The diagnosis is based on clinical presentation and histopathological findings, typically a characteristic thickening of the subepithelial collagen layer and inflammation of the lamina propria.[1] Recent epidemiological studies have shown that CC is common, with incidence rates comparable to those of other IBDs, e.g. Crohn's disease.[2,3] The pathogenesis of the disease remains unknown but is considered to be multifactorial, involving luminal agents that trigger a mucosal inflammatory reaction.[4] Budesonide, a locally active corticosteroid, is the only evidence-based treatment to have shown clear efficacy in inducing and maintaining clinical remission in CC.[5]

So far, the association between histological findings and clinical presentation has been studied only in small groups of CC patients and no correlation has been found.[6,7]

Smoking seems to be a risk factor for microscopic colitis and smokers develop the disease more than 10 years earlier than non-smokers, which has been shown in 2 independent studies.[8,9] However, the impact of smoking on disease activity and the clinical course has not been described.

The risk of relapse after cessation of successful induction and maintenance therapy with budesonide is high (~60–80%).[10,11] A high stool frequency (>5 per day) and a long duration of diarrhoea (>12 months) are risk factors for symptom relapse after withdrawal of budesonide treatment in collagenous colitis.[12]

The aim of this *post hoc* analysis is to (1) analyse the predictive value of baseline clinical and demographic parameters for clinical outcome after 8 weeks therapy and (2) assess the relationship between histopathological characteristics and clinical severity of collagenous colitis using a logistic regression model. The calculations are based on the data from the clinical studies BUC-60/COC[13] and BUC-63/COC[11]; both trials dealt with the treatment of CC in the context of a double-blind, randomized study design.

## 2. Methods

This *post hoc* multivariate analysis is based on the pooled data of two randomized, controlled trials (BUC-60/COC [EudraCT number 2006-004159-39] and BUC-63/COC [EudraCT number 2007-001315-31]). BUC-60/COC is a double-blind, double-dummy, multicentre, phase III clinical trial in which patients were randomized to receive 9 mg of budesonide once daily (Budenofalk® 3 mg capsules, Dr Falk Pharma GmbH; $n$ = 30), 3 g of mesalamine once daily (Salofalk® 1.5 g granules; $n$ = 25) or placebo ($n$ = 37) to induce clinical remission during an 8-week period. BUC-63/COC is a double-blind, randomized, placebo-controlled, parallel-group, multicentre, 52-week maintenance of remission trial, with an initial 8-week open-label induction phase with budesonide (Budenofalk® 3 mg capsules, Dr Falk Pharma GmbH) at a dose of 9 mg once daily for 4 weeks, then 6 mg once daily for 2 weeks, followed by alternate daily doses of 6 and 3 mg once daily (mean 4.5 mg/day) for the final 2 weeks to achieve clinical remission. Clinical remission was defined as a mean of <3 stools/day, including a mean of <1 watery stool/day during the last week. According to the protocol a full colonoscopy should be performed and 2 biopsies taken from the ascending, transverse, descending and sigmoid colon and rectum. The biopsies were evaluated centrally by Michael Vieth, Bayreuth (BUC-60), and Åke Öst, Stockholm (BUC-63). Collagen was stained with Masson's trichrome in the BUC-63 study and von Gieson stain in the BUG-60 study. The intraepithelial lymphocyte count was based on CD3 staining in the BUC-63 study and on haematoxylin–eosin staining in the BUC-60 study; due to this discrepancy we decided only to show the results of the BUC-63 study. At baseline all patients in both studies had a histologically established diagnosis of CC, defined as thickened subepithelial collagen layer of ≥10 µm on well-orientated sections, and an increased amount of inflammatory cells indicating chronic inflammation in the lamina propria.

The pooled data set consisted of data from patients in the full analysis set in the BUC-60/COC study (92 patients) and patients in the full analysis set in the open-label induction phase of the BUC-63/COC study (110 patients), a total of 202 patients.

The following objectives were the basis of the analyses: (1) Can clinical, histological or demographic parameters at baseline predict clinical remission according to Hjortswang et al.[14] at the final visit (week 8)? (2) Is there, at the time of study entry (baseline), i.e. prior to introduction of therapy, an association between histology and severity of clinical symptoms, such as the numbers of stools and watery stools?

### 2.1. Data collected

The following histological parameters were collected:

- Thickness of the collagen band (µm); inflammation of the lamina propria (semiquantitative score: 0 = none, 1 = mild, 2 = moderate, 3 = severe);
- Total numbers of intraepithelial lymphocytes in the surface epithelium;
- Degeneration of the surface epithelium (1 = present, 0 = absent).

The clinical variables were as follows:

- Duration of symptoms (years), i.e. time between first onset of CC symptoms and baseline;
- Mean number of stools/day registered in a diary in the week prior to baseline;
- Mean number of watery stools/day registered in a diary in the week prior to baseline;
- Clinical remission as defined by Hjortswang, i.e. a mean of <3 stools/day, with a mean of <1 watery stools/day in the week prior to the final visit;
- Number of days with moderate or severe abdominal pain in the week prior to baseline, i.e. number of days with a mean value of at least 1.5 when pain was recorded at every defaecation in the semi-quantitative assessment of pain (0 = none, 1 = mild, 2 = moderate/intermediate, 3 = severe).

The demographic variables were as follows:

- Gender;
- Smoking habit (current/former smoker/never smoked);
- Cigarettes/day;
- Age;
- Family history of IBD.

### 2.2. Statistical analysis

Quantitative data were analysed using the mean and standard deviation or median and quartiles. Qualitative data are provided in terms of absolute and relative frequency distributions. Relative frequencies are based on the number of patients without missing values in the respective variable. Exact Fisher tests were performed to examine bivariate associations in qualitative data.

For all single associations of histology and symptomatology, correlations were calculated using Pearson's correlation coefficient for metrical histological variables and Spearman's rank correlation coefficient for ordinal variables.

A multiple regression model was used to analyse the influence of histological and demographic parameters on clinical symptomatology at baseline. A stratification variable for the study and its interaction with histological parameters were also included in the model.

A logistic regression model for the prediction of clinical remission was calculated. Demographic and clinical baseline variables were included as predictors in addition to stratification variables for study and treatment arm. The inclusion of the treatment arm as an independent variable in the model enables the interpretation of other predictors without confounding by the effect of the treatment, as it is methodologically adjusted for its strong influence on the outcome. By estimating the treatment effect inside the model, the remaining predictors can be interpreted independently of this effect.

All statistical analyses were carried out by means of the SAS® package (version 9.2).

## 3. Results

Pooled data from 202 (170 female) patients with active CC at baseline were available. One hundred and forty patients had been treated with budesonide, 25 with mesalazine and 37 with placebo in the original trials. After 8 weeks of treatment, 139/202 (69%) patients were in clinical remission according to the Hjortswang criteria. The baseline characteristics are given in Table 1.

### 3.1. Association between demographic parameters, histopathology and clinical symptoms at baseline

Current smokers had an increased number of watery stools at baseline compared with non-smokers ($p = 0.051$). However, this was not the case in former smokers ($p = 0.809$). There was no association between the quantity of smoking (cigarettes/day) at baseline and the number of watery stools ($r = -0.02$, $p = 0.859$). Data on the duration of smoking had not been collected. Gender, age, duration of symptoms and family history were not associated with the number or consistency of stools.

No histological variables were associated with clinical symptoms in the correlation analyses (Table 2). There was no association between duration of symptoms and the thickness of the subepithelial collagen layer (Pearson's correlation coefficient $r = -0.221$)

Despite slight differences in the two protocols, the results concerning the association of histology and clinical parameters were concordant.

### 3.2. Prognostic factors at baseline for clinical remission after 8 weeks of treatment

The likelihood of obtaining clinical remission was significantly reduced in patients with higher mean numbers of watery stools per day (odds ratio [OR] 0.63, 95% confidence interval [CI] 0.47–0.86, $p = 0.003$). An association was found between smoking status (current smokers vs non-smokers: OR 0.31, 95% CI 0.10–0.98, $p = 0.045$; former smokers vs non-smokers: OR 0.19, 95% CI 0.05–0.73, $p = 0.016$) and decreased likelihood of obtaining clinical remission in the logistic regression model. There was no association between the quantity of smoking at baseline and the likelihood of achieving remission (data not shown).

Histopathology had no predictive value for clinical remission at week 8. Furthermore, age, gender, duration of symptoms, number of stools/day and abdominal pain in the week prior to baseline had no predictive value for clinical outcome (Table 3).

Considering the bivariate association of current smoking and clinical remission after 8 weeks in the different treatment arms, there was a significant difference between current smokers and non-smokers in the placebo group (Table 4).

## 4. Discussion

By pooling the data of two randomized controlled trials, this *post hoc* analysis represents the largest study to date to find predictive factors for clinical outcome in CC and to assess the association between histological and clinical data. We found that both former and current smokers have a decreased likelihood of achieving clinical remission in CC. The findings in ex-smokers may represent a carry-over effect of smoking that may disappear in time. We have, however, no data on the length of time since ex-smokers stopped smoking that may support such an interpretation. Furthermore, current smokers seemed to have increased watery stools with active disease, which *per se* is also associated with a significantly poorer

**Table 1**. Patient characteristics at baseline ($n = 202$).

| | Number (%) | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| Age (years) | | 58.6 | 12.1 | 59.0 | 50–67 |
| Female sex | 170 (84) | | | | |
| Current smokers | 73 (36) | | | | |
| Former smoker | 58 (29) | | | | |
| Non-smoker | 71 (35) | | | | |
| Time since first symptoms (y) | | 5.4 | 7.1 | 2.1 | 0.7–8.1 |
| Mean number of stools/d* | | 5.7 | 2.3 | 5.1 | 4–6.7 |
| Mean number of watery stools/d* | | 4.4 | 2.6 | 4.0 | 2.3–5.9 |
| Numbers of days with moderate to severe pain* | | 1.9 | 2.5 | 0 | 0–3 |
| Family history of inflammatory bowel disease | | | | | |
| Yes | 14 (7) | | | | |
| No | 95 (47) | | | | |
| Missing data | 93 (46) | | | | |

IQR, interquartile range.
*Recorded during the week prior to baseline.

**Table 2**. Association between histology and clinical symptoms at baseline.

| | Total number of stools | | Number of watery stools | |
|---|---|---|---|---|
| | Correlation | *p*-value | Correlation | *p*-value |
| Thickness of subepithelial collagen layer | 0.01 | 0.893 | 0.09 | 0.236 |
| Total number of intraepithelial lymphocytes (only in the BUC-63 study) | 0.09 | 0.384 | 0.06 | 0.544 |
| Inflammation of lamina propria | –0.10 | 0.147 | 0.03 | 0.686 |
| Degeneration of surface epithelium | 0.05 | 0.529 | 0.11 | 0.112 |

**Table 3**. Prediction of clinical remission at 8 weeks by baseline clinical and histological data (estimates from logistic regression analysis).

| | Odds ratio (adjusted) | 95% confidence interval | *p*-value |
|---|---|---|---|
| Study protocol BUC-60 vs BUC-63 | 0.73 | 0.15–3.60 | 0.701 |
| Treatment: | | | |
| **Budesonide vs placebo** | **10.77** | **2.58–44.98** | **0.001** |
| Mesalazine vs placebo | 0.36 | 0.08–1.54 | 0.167 |
| Gender: female vs male | 0.81 | 0.23–2.90 | 0.750 |
| Smoking: | | | |
| **Current smoker vs never smoker** | **0.31** | **0.10–0.98** | **0.045** |
| **Former smoker vs never smoker** | **0.19** | **0.05–0.73** | **0.016** |
| Age | 1.01 | 0.97–1.05 | 0.548 |
| Duration of symptoms | 1.00 | 0.94–1.07 | 0.960 |
| Number of stools/day | 1.24 | 0.89–1.75 | 0.209 |
| **Number of watery stools/day** | **0.63** | **0.47–0.86** | **0.003** |
| Number of days with at least moderate pain | 0.99 | 0.83–1.18 | 0.898 |
| Thickness of subepithelial collagen layer | 1.03 | 0.99–1.07 | 0.216 |
| Surface epithelium: degeneration vs no degeneration | 0.35 | 0.06–2.18 | 0.262 |
| Lamina propria: inflammation vs no inflammation | 2.27 | 0.74–7.01 | 0.154 |

Bold type represent significant findings

**Table 4**. Prediction of clinical remission by smoking habits at baseline.

| | | | **Remission** | | | |
|---|---|---|---|---|---|---|
| | | | **Yes** | | **No** | |
| | | | **n** | **%** | **n** | **%** |
| **Study** | **Treatment** | **Smoking status** | | | | |
| BUC-60 | Budesonide | Current smoker | 5 | 20.8 | 3 | 50.0 |
| | | Former smoker | 5 | 20.8 | 2 | 33.3 |
| | | Never smoked | 14 | 58.3 | 1 | 16.7 |
| | | Total | 24 | 100.0 | 6 | 100.0 |
| | Mesalazine | Smoking status | | | | |
| | | Current smoker | 3 | 37.5 | 8 | 47.1 |
| | | Former smoker | 1 | 12.5 | 3 | 17.6 |
| | | Never smoked | 4 | 50.0 | 6 | 35.3 |
| | | Total | 8 | 100.0 | 17 | 100.0 |
| | Placebo | Smoking status | | | | |
| | | Current smoker | 2 | 14.3 | 10 | 43.5 |
| | | Former smoker | 3 | 21.4 | 7 | 30.4 |
| | | Never smoked | 9 | 64.3 | 6 | 26.1 |
| | | Total | 14 | 100.0 | 23 | 100.0 |
| BUC-63 | Budesonide | Smoking status | | | | |
| | | Current smoker | 37 | 39.8 | 4 | 28.6 |
| | | Former smoker | 29 | 31.2 | 8 | 57.1 |
| | | Never smoked | 27 | 29.0 | 2 | 14.3 |
| | | Total | 93 | 100.0 | 14 | 100.0 |

Current + former smokers vs non-smokers in the placebo group: odds ratio (OR) 0.21, 95% confidence interval (CI) 0.04–1.00, $p = 0.04$.
Current smokers vs non-smokers in the placebo group: OR 0.14, 95% CI 0.01–1.04, $p = 0.05$.

clinical outcome. However, a dose–response association between numbers of cigarettes per day and watery stools or clinical outcome does not seem to be present.

On the other hand, the histological findings with active CC at baseline were not associated with symptoms and cannot predict the clinical course.

Current smoking has been described to be a risk factor for the development of microscopic colitis,[15,16] and two independent studies have shown that smokers develop CC 10 years earlier than non-smokers.[8,9] However, the association of smoking with clinical activity and outcome has not been investigated previously. When considering our findings together with prior results on smoking in CC, it becomes apparent that smoking has a negative impact on CC. Consequently, physicians should recommend that CC patients should stop smoking. These results are interesting even though smoking seems to have contradictory effects in patients with Crohn's disease compared with ulcerative colitis.[17,18] In Crohn's disease smoking has detrimental effects on disease activity and treatment outcome, whereas in ulcerative colitis cigarette smoking ameliorates symptoms and decreases relapse. At present this contradiction is not understood in detail but highlights that different pathomechanisms underlie intestinal inflammation in IBD. Recent evidence suggests that smoking induces alterations in both the innate and the acquired immune system as well as changes in the intestinal microbiota.[19] Furthermore, it has been hypothesized that smoking alters epigenetic events like methylation and histone modification of the genome, which might indicate why even former smokers are involved.[20]

Miehlke et al.[12] have shown that high stool frequency at baseline and a long duration of diarrhoea are risk factors for symptom relapse in CC after withdrawal of budesonide. Similarly, risk factors for relapse during the maintenance phase (budesonide 4.5 mg or placebo) of the BUC-63/COC trial were decreased age, higher mean number of stools per day at randomization and higher mean number of watery stools per day at baseline.[11]

The fact that the consistency rather than the frequency of the stools is associated with decreased likelihood of achieving clinical remission in this analysis is an important observation. The special characteristic of CC is that stool consistency is watery in >80% of cases, resembling type 7 on the Bristol stool scale. A quality of life study in CC demonstrated that stool consistency was the main determinant of impaired quality of life.[21] Watery stools lead to urgency, and in approximately 40% of patients may cause faecal incontinence,[22] which is of great concern for patients. This observation should alert the physician to focus rather on the consistency than the frequency of the stools when treating patients with chronic diarrhoea. According to the Hjortswang criteria for clinical activity in CC, treating patients with a mean of ≥1 watery stools/day can be justified.[14]

The finding that classical histological findings in CC are not associated with the degree of symptoms has been demonstrated in small studies previously.[6,7] The hypothesis that a long duration of symptoms may be associated with more distinct histological findings, e.g. increased thickening of the collagenous band, is not confirmed by this study. This indicates that histology, although essential for establishing the diagnosis of microscopic colitis, cannot help in the understanding of the symptomatology or predict the clinical outcome. More advanced analyses are required to understand mucosal inflammation, mucosal barrier function and ion transport in CC to gain more insight into the pathophysiology of diarrhoea.

By pooling the data of two randomized controlled trials, our study represents one of the largest cohorts of well characterized CC patients, allowing us to perform multiple regression analyses.

Despite the fact that the two protocols were slightly different in some points (e.g. collagenous staining, intraepithelial lymphocyte counts), the results of the studies were concordant. That two different pathologists assessed the biopsies can be seen as a limitation as inter-observer variability cannot be excluded.

In summary, this analysis and prior studies underline the importance of smoking on the development and manifestation of CC. Smoking worsens disease activity and reduces the likelihood of achieving remission or increases the risk of relapse.

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## Conflict of Interest

Andreas Münch received speaker's honoraria from Dr Falk Pharma and MEDA. Stephan Miehlke received speaker's honoraria from Dr Falk Pharma. Curt Tysk received speaker's honoraria from Dr Falk Pharma, Tillotts Pharma, Ferring, MSD and AstraZeneca. Ralf Mohrbacher, Ralph Mueller and Roland Greinwald are employees of Dr Falk Pharma. All other authors have no conflict of interest.

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## Author Contributions

The study was initiated and designed by members (all authors) of the European Microscopic Colitis Group (EMCG) in collaboration with the sponsor of the two randomized controlled trials, Dr Falk Pharma. Analysis and interpretation of data: AM, MS, CT, RMO and the statistician MO. JB, OKB, SM have recruited patients in both studies and help with study design. Drafting of the manuscript: AM, CT, MS. Critical revision of the manuscript for important intellectual content: AM, MS, CT, RG, RMO. All authors approved the final version of the manuscript to be submitted. No writing assistance was received.

This manuscript (including all tables) has not been published previously and is not being considered for publication elsewhere.

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