Patient Preference and Adherence

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ORIGINAL RESEARCH

Low Adherence is Associated with Chronic Active Disease in Ulcerative Colitis: A Retrospective Study from a Single Referral Center

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Purpose: New therapeutic approaches for ulcerative colitis (UC) are now available, but there is still no robust evidence for predictors of poor outcomes. We aimed to evaluate the factors associated with a chronic active UC disease course.

Patients and Methods: Data of all UC outpatients followed for at least 3 years after diagnosis between 2005 and 2018 were retrospectively collected. The primary aim was to identify risk factors for chronic active disease 3 years after diagnosis. Moreover, the following variables were investigated: proximal disease extension or disease regression, proctocolectomy, early use of biologics (BIO) or immunomodulators (IMM), hospitalization, colorectal cancer, and adherence. We defined adherence as both, taking the prescribed therapy and constancy in scheduled follow-up visits.

Results: A total of 345 UC patients followed for a median period of 82 months were included. Patients with extensive colitis at diagnosis had a higher rate of chronic active disease 3 years after diagnosis ($p<0.012$) together with a higher rate of surgery ($p<0.001$) at maximum follow-up. Patients with pancolitis showed significant disease regression over time (51%) without differences in treatment. The only factor associated with chronic active disease was non-adherence ($p < 0.03$; OR 0.49, 95% CI: 0.26–0.95). Adherent patients developed chronic active disease ($p<0.025$) less frequently but did receive more frequent IMM ($p<0.045$) or BIO ($p<0.009$) therapy.

Conclusion: Patients diagnosed with pancolitis were more likely to have chronic active disease and to undergo colectomy. The only predictor for developing chronically active UC regardless of disease extension was the lack of adherence to therapy within the first 3 years after diagnosis, underlining the importance of tight control of UC patients and the need to timely identify potential risk factors for non-adherence.

Keywords: outcome, adherence, surgery, hospitalization, disease course

Introduction

Ulcerative Colitis (UC) is a chronic, potentially progressive and disabling disease that may extend to the entire colon. The clinical course of UC including the risk for surgery is still difficult to predict being characterized by periods of remission and exacerbation which have variable duration. A discrete percentage of patients will develop chronic active disease leading to very poor quality of life (QoL) and a high rate of surgery.[1,2]

Received: 26 September 2022
Accepted: 18 February 2023
Published: 23 March 2023

In a recent paediatric study,[3] the clusters adopted by Henriksen et al[4] were investigated during the first 5 years after diagnosis showing that more than 30% of the patients will develop a chronic active or intermittent disease course despite appropriate treatment.

A timely identification of patients with a more disabling disease course over time would be helpful in order to recognize who to treat with a more aggressive therapy aimed to prevent complications and irreversible tissue damage, while, in those with indolent disease, overtreatment may be avoided, and consequently, potential side effects. However, despite numerous studies having been conducted, we are not yet able to stratify the majority of patients according to the risk for developing a more aggressive disease over time.[5]

Unfortunately, beyond the four items of the risk matrix model proposed by Monstad et al[6] with important negative predictors such as age <40 years at diagnosis, pancolitis, signs of systemic inflammation and the early need for systemic steroids, with a colectomy rate that reaches 40% at 10 years after diagnosis, in the case of the presence of all four predictors, little progress has been made in predicting a more aggressive disease course.

Several years ago, an attempt to define the overall disease severity was carried out by using the Delphi method and various factors were included, from mucosal lesions to impact on daily life, C-reactive protein (CRP), former biologic (BIO) use and recent hospitalizations.[7] The predictive value in the short term of this aforementioned disease severity index (DSI), integrated with other scores concerning the perceived stress, depression, anxiety, and QoL, was demonstrated most recently in a prospective study lasting 12 months.[8]

Social conditions as well as psychological factors such as distress, depression, or anxiety, besides their negative influence on disease activity[9,10] do also impact on adherence to therapy.[11–13] Therapy adherence represents one of the key factors in all chronic diseases determining the achievement of treatment goals, i.e. the induction of remission and the prevention of disease progression and complications.

Low adherence in UC is associated with adverse outcomes such as an increased relapse rate at 6 and 12 months.[14] Moreover, more hospitalizations and emergency department admissions[15] were observed in non-adherent patients such as an increased risk of colorectal cancer according to an inconstant use of 5-aminosalicylate.[15] All prospective studies addressing adherence were limited to a 6- to 12-month observation period,[14,16] and none of these considered non-adherence as possible risk factor for chronically active disease.

The aim of our study was to assess predictive factors including non-adherence associated with a more disabling UC course in a cohort of patients followed at our center, from diagnosis over a period of at least 36 months and beyond.

Materials and Methods

Patients

In this single-center retrospective study, patients were included according to the following criteria:

Inclusion Criteria

Patients with a confirmed clinical, endoscopic, and histologic diagnosis of UC diagnosed after the year 2005, ≥18 years of age, attending our center at diagnosis or within 6 months after diagnosis and followed for at least 3 years thereafter. The year 2005 coincides with the introduction of the first BIO agent, infliximab, for UC.

Exclusion Criteria

Patients followed before the year 2005, incomplete uploaded data, patients with discontinuous follow-up, patients followed at our unit for less than 3 years or taken in charge later than 6 months from diagnosis. Patients with IBD-U were also excluded.

Objectives

The primary aim was to identify risk factors for chronic active disease (pattern 3 according to the IBSEN study definition[4] 3 years after diagnosis including the following variables: proximal disease extension or disease regression assessed by endoscopy with respect to onset, proctocolectomy, early use of BIO or IMM, hospitalizations, and adherence. Adherence was defined as taking not only the prescribed medications for UC assessed at each visit but also attending

regular visits in our outpatients' clinic. Since virtually no patient showed a perfect adherence to topical therapies, this parameter was not included in adherence evaluation. Patients were categorized in adherent or not adherent.

Data Collection

Data were extracted from a local database and from clinical charts of patients by the principal (AV) and sub-investigators (G.DM, M.M.). For each patient, the following data were collected at baseline: gender, age at diagnosis, smoking status (never, ex, or active smoker), family history for IBD, and the presence of extraintestinal manifestations (EIMs). Regarding disease extent, patients were classified in accordance with the Montreal classification.[17] Concomitant diseases were assessed for each patient and expressed as the Charlson comorbidity index (CCI) together with concomitant treatments.[18] Anemia at diagnosis, i.e. a hemoglobin level below 13 g/dL for male patients or below 12 g/dL for female patients[19] was recorded. Initial treatment strategies, i.e. use of systemic steroids at diagnosis and early introduction of immunomodulators (IMM) or BIO, were assessed.

All parameters were evaluated at 3 years from diagnosis with the exception of colorectal cancer (CRC), hospitalizations, and proctocolectomy, assessed also at maximum follow-up.

The study was approved by the local Ethics Committee (Comitato Etico Interaziendale-Messina) with protocol n. 137–20. Patient's data were collected and handled anonymously according to the European and national laws on data protection and in compliance with the Declaration of Helsinki. Patient consent was not required due to the retrospective nature of the study.

Statistical Analysis

Statistical analysis was carried out using SSPS version 22.0 software for Windows. Categorical variables were summarized using absolute frequencies and percentages and compared with Chi-square test. Descriptive statistics included the calculation of mean values with standard deviation (SD) or median with their range, for all continuous variables. Risk factors for outcomes were assessed with stepwise logistic regression and multivariate analysis. We estimated the probability of receiving a BIO treatment according to disease extent using Kaplan–Meier curves, comparisons were performed with Log rank test. P-values <0.05 were considered statistically significant.

Results

Patients and Descriptive Data

From all UC patients followed at our center (n=1031), 345 patients met the inclusion criteria. The numbers of patients who met the inclusion/exclusion criteria are summarized in Supplementary Figure 1.

Patient baseline characteristics are given in Table 1. Patient mean age at diagnosis was 37 ± 17 years, 44% were males, 8% were current smokers, and 44 patients (12%) had a family history of IBD. Median follow-up was 82 months (36–108 months). Disease at diagnosis was located mostly at the left colon (42%) followed by pancolitis (41%). EIMs were present at diagnosis in 56 patients (16%), with joint disease the most frequent form at 8%. Anemia was present in 115 patients (34%).

Concerning comorbidities, 171 patients (50%) had at least one comorbidity at diagnosis. We observed cardiovascular diseases in 56 (16%) patients, renal disease in 20 (6%) patients, respiratory tract disorders in 12 (4%) patients, liver disease in 14 (4%) patients, metabolic disorders in 37 (11%) patients and neurologic/psychiatric disorders in 18 (5%) patients. Seventy-three patients had comorbidities classified as "others". Regarding concomitant treatments, 172 (50%) patients were treated with non-IBD drugs at baseline and more specifically were antihypertensives in 56 (16%) patients, anticoagulants or antiplatelet agents in 30 (9%) patients, antidiabetics in 15 (4%) patients, proton pump inhibitors (PPIs) in 64 (19%) patients, drugs for thyroid diseases in 17 (5%) patients, drugs for metabolic diseases in 24 (7%) patients, drugs for neurological/psychiatric diseases in 32 (9%) patients.

Treatment strategies at diagnosis included systemic corticosteroids in 65% of the patients, and almost all patients were also treated with mesalazine (5-ASA) (98%).

Table 1 Baseline Patient's Characteristics

Baseline Characteristics	Overall N= 345
Age at diagnosis; years; mean (SD)	37 (17)
Gender-male; n (%)	153 (44)
Family history; n (%)	44 (12)
Median follow-up; months (range)	82 (36–108)
Disease extent*; n (%)	
E1	60 (17)
E2	143 (42)
E3	142 (41)
Smokers; n (%)	
Yes	29 (8)
No	314 (91)
Former	71 (21)
	missing data: 2
Anemia at diagnosis; n (%)	115 (34)
EIMs; n (%)	
Joints;	29 (8)
Skin;	20 (6)
Eyes;	7 (2)
CCI; n (%)	
0	240 (69)
1	42 (12)
2	23 (7)
3+	40 (12)
Treatment strategy at diagnosis; n (%)	
Systemic Steroids;	226 (65)
5-ASA at diagnosis;	337 (98)

Note: *Disease extension according to Montreal Classification.[17]
Abbreviations: EIMs, extra intestinal manifestations; CCI, Charlson Comorbidity Index; 5-ASA, mesalazine.

Outcomes at 36 Months

Outcomes at 3 years are shown in Table 2A. Patients were divided into two groups according to disease extent at diagnosis: Group 1 (E1+E2) and Group 2 (E3). Thirteen patients (4%) with proctitis and 10 (3%) with left-sided colitis at diagnosis had a proximal disease extension after 3 years for a total of 23 patients (11%) in Group 1. The same group had 81 patients (40%) with endoscopic regression 3 years after diagnosis compared to Group 2 (E3) with 73 patients (51%) that showed a reduction of disease extension compared to diagnosis (p=0.034). Overall, in 168 patients (48%) endoscopic disease extension remained the same.

Chronic active disease was observed in 24% of the patients in Group 1 and in 37% in patients in Group 2 (p=0.009). In the first 3 years from diagnosis, 9 patients (3%) underwent colectomy; there was no statistical difference between the two groups (3 patients of Group 1 and 6 patients of Group 2; p=0.12).

Concerning treatment, 88 patients (25%) received BIO and 107 (31%) IMM within 3 years from diagnosis; no differences were found between the two groups (see Table 2). We assessed the probability to receive BIO or IMM treatment within 3 years from diagnosis between Group 1 and Group 2: no statistically significant differences in the Kaplan–Meier curve were observed (log rank 0.43 and 0.75, respectively) (data not shown). We repeated the same analysis to assess the probability to receive BIO or IMM at 10 years with similar results (data not shown).

Table 2 (A) Outcomes at 36 Months After Diagnosis According to Disease Extension at Diagnosis. (B) Outcomes at Maximum Follow-Up According to Disease Extension at Diagnosis

A				
n (%)	**E1-E2 n = 203**	**E3 n=142**	**p**	**Whole UC Population n=345**
Proximal disease extension	23 (11)	-	-	23 (11)
Disease regression	81 (40)	73 (51)	0.034	154 (45)
Chronically active disease	49 (24)	52 (37)	0.009	101 (29)
Proctocolectomy	3 (1.4)	6 (4)	0.126	9 (3)
Use of BIO	61 (30)	33 (23)	0.150	88 (25)
Use of IMM	60 (30)	47(33)	0.554	107 (31)
Adherence (n=316) Missing data: 29	121/183 (66) missing data: 20	79/133 (59) missing data:9	0.22	200/316 (63)
B				
n (%)	**E1-E2 n = 203**	**E3 n=142**	**p**	**Whole UC Population n=345**
Proctocolectomy	4 (2)	21 (15)	<0.001	25 (7)
Hospitalization	35 (17)	34 (24)	0.109	69 (20)
CRC (at any time-point in F-U)	2 (1)	5 (4)	0.064	7 (2)

Abbreviations: BIO, biologics; IMM, immunomodulators; CRC, colorectal cancer.

Adherence was evaluated after 3 years; 121 patients (66%) and 79 patients (59%), respectively, in Groups 1 and 2, were adherent to the prescribed treatment and to follow-up (not statistically significant).

Outcomes in Further Follow-Up

At maximum follow-up, 25 patients (7%) underwent proctocolectomy (Table 2B). As mentioned above, 9 of these patients underwent colectomy within 3 years from diagnosis and the other 16 at a later timepoint. According to the group stratification, patients of Group 2 had a higher rate of colectomy at maximum follow-up ($p<0.001$).

Sixty-nine (20%) patients were hospitalized due to IBD and 16 (6%) patients had a diagnosis of cancer (7 of them were diagnosed with CRC). No statistically significant differences were observed between the two groups for either outcome.

Risk Factors for Chronic Active Disease

Factors potentially associated with chronically active disease included in the multivariate analysis were the following: gender, age at diagnosis, family history, smoking, proctitis, anemia at diagnosis, steroids at diagnosis, early use of IMM, early use of BIO, and adherence. At stepwise logistic regression, the only risk factor associated with chronic active disease was non-adherence ($p < 0.03$; OR 0.49, 95% CI: 0.26–0.95) (Table 3). Finally, we did not identify any risk factors for disease extension in follow-up, proctocolectomy, and early use of BIO or IMM.

Outcomes According to Adherence

We performed the same analysis shown in Table 2, regarding the status of "adherent" or "non-adherent" exploring the same outcomes. As reported in Table 4A, adherent patients developed chronic active disease (p=0.025) less

Table 3 Factors Associated with Chronically Active Disease

Factors	p	OR (95% CI)
Sex	0.79	1.09 (0.57–2.08)
Age at diagnosis	0.97	1.00 (0.98–1.02)
Family history	0.09	2.06 (0.84–4.89)
Smoking status	0.14	1.62 (0.84–3.12)
Proctitis	0.39	0.69 (0.29–1.62)
Anemia at diagnosis	0.27	0.68 (0.34–1.34)
Systemic steroid at diagnosis	0.35	1.38 (0.68–2.75)
Early use of IMM	0.68	1.15 (0.59–2.16)
Early use of BIO	0.89	0.94 (0.40–2.19)
Adherence	0.03	0.49 (0.26–0.95)

Abbreviations: IMM, immunomodulators; BIO, biologics.

frequently and were more frequently treated with BIO therapies and IMMs in the first 3 years from diagnosis (p = 0.018 and p = 0.040, respectively). No differences were found for the other variables. At maximum follow-up (Table 4B), no difference was found between adherent and non-adherent patients for surgery, hospitalizations, and diagnosis of CRC.

Table 4 (A) Outcomes at 36 Months After Diagnosis According to Adherence. (B) Outcomes at Maximal Follow-Up According to Adherence

A			
n (%) Missing Data: 29	**Adherent n= 200**	**Non-Adherent n= 116**	**p**
Proximal disease extension	10 (5)	12 (10)	0.090
Disease regression	94 (47)	44 (38)	0.120
Chronically active disease	52 (26)	44 (38)	0.025
Proctocolectomy	4 (2)	4 (3.4)	0.444
Use of BIO	61 (30)	21 (18)	0.018
Use of IMM	68 (34)	27 (23)	0.040
B			
n (%) Missing Data: 29	**Adherent n= 200**	**Non-Adherent n= 116**	**p**
Proctocolectomy	9 (4.5)	7 (6)	0.557
Hospitalization	45 (23)	20 (17)	0.206
CRC (at any time-point in F-U)	4 (2)	3 (3)	0.573

Abbreviations: BIO, biologics; IMM, immunomodulators; CRC, colorectal cancer; F-U, follow-up.

Discussion

Adherence

Our study aimed to assess risk factors for chronic active disease 36 months after diagnosis in an adult cohort of patients with UC. Our main findings were that adherent patients developed less frequently chronic active disease and that non-adherence to therapy and follow-up visits was the only variable significantly associated with this more aggressive disease pattern. Adherence represents a major problem in every chronic disease needing continuous therapy. Most studies on adherence in UC focus on 5-ASA maintenance treatment, but non-adherence was reported also with IMM and even BIO therapies.[20–24] In the present study, overall adherence according to regular drug utilization and follow-up visits reached 58%, a figure in line with former, dedicated studies.[25,26] The strength of our analysis is the length of follow-up, while almost all studies investigating prospectively non-adherence were limited to shorter periods not exceeding 6 to 12 months[14,16,20] or were cross-sectional.[25]

Investigating adherence, most studies adopted the Morisky adherence scale[27] or calculated adherence from prescriptions[16] or measured 5-ASA metabolites in urines,[25] whilst in the present setting we used a wider term for adherence, i.e. we evaluated the willingness to comply with scheduled visits combined with a regular interview on medication adherence. Interestingly, our study demonstrated a higher use of IMM and BIO in adherent patients, which may be an expression of early identification of patients that needed therapy escalation and, thus, may be compared to a form of "tight control" as proposed in the CALM study in Crohn's disease.[28] There was no difference between the two groups for other variables usually associated with worse outcomes such as proximal disease extension, hospitalization, or surgery.

Non-adherence may result from factors related to therapies such as safety concerns or a high pill load, to disease such as being in remission or having a recent diagnosis, to the patient itself,[29] or the relationship between patient and its physician.[13] Other factors which negatively impact adherence but also QoL of patients with UC are represented by coexisting psychological/psychiatric disorders.[10] A systematic review showed that in young IBD patients the presence of psychological morbidity decreased treatment adherence by 12%.[30] Anxiety, depression, stress, stigmatization leading to isolation,[31–33] are all problems investigated in UC patients. Addressing mental health problems in patients with IBD can improve their adherence to treatment and the somatic disease course and, consequently, reduce morbidity.[34]

In the present study, non-adherence was identified as being associated with a worse disease course in UC, but an investigation on the causes for non-adherence unfortunately was not included. In our cohort, the rate of psychological morbidity was low (about 5%), but these data were probably underestimated due to the retrospective nature of the study and to the fact that comorbidities and concomitant treatments were registered only at diagnosis for patients with an established psychiatric diagnosis.

Disease Regression

Another important result of our study was disease regression found in 45% of the whole study population, statistically more important in patients with pancolitis at diagnosis. Although numerically higher, in adherent patients, the difference failed to achieve statistical significance. While most studies focus on progression of disease extension,[35] less data are available on disease regression over time. Predictors of disease regression were not assessed, and apparently subgroup analysis between E1/E2 and E3 did not reveal a higher use of more aggressive therapy. A statistically significant difference for treatments was found when analyzing adherent versus non-adherent patients. This result is in line with the finding that early introduction of thiopurines may reduce the risk of surgery and proximal disease extension,[36] whereas the use of anti-TNF agents in preventing surgery is still matter of debate.[37]

Proximal Disease Extension

Concerning disease progression, in our cohort 11% progressed to a more extensive form within 3 years. Using the Montreal classification, E3 includes subtotal colitis which may potentially progress to pancolitis and this may have led to an underestimation of the rate of proximal disease extension. Proximal disease extension is deemed to be present in 15%

of the patients at 5 years reaching 30% at 10 years and 50% at 30 years.[35] In the present study, adherence was associated with halving of disease progression to 5% although this figure failed to reach statistical significance.

A recent retrospective Asian paper in 518 UC patients showed that a disease extension during follow-up occurred with a cumulative rate of 19.6% at 3 years after diagnosis, which is a higher percentage compared to ours (11%). Their only risk factor for disease progression was the disease extent at diagnosis (odds ratio (OR), 1.74, 95% confidence interval (CI) 1.18–2.57, p = 0.01).[38]

Chronic Active Disease

Chronic active disease represents a subtype of UC leading to extremely poor QoL, functional deficits of the colon, and, in up to 27%, to proctocolectomy at 3 years.[2] In the present study, this pattern was present in 37% of the patients with pancolitis and in 24% of the patients with more limited forms. In the present study, we showed that chronic active disease was significantly more frequent 3 years after diagnosis in non-adherent patients.

Colectomy

Our study confirmed that extensive colitis per se at diagnosis had a higher rate of colectomy within the first 3 years from diagnosis. Our rate of colectomy at maximum follow-up reached 15% in patients with extensive colitis, whereas only 2% of the patients with less extensive forms were operated on. The overall surgery rate was 7% in the present study. Our data are comparable to the rate of the largest prospective study on UC long-term prognosis, the IBSEN study, including patients with 20 years of follow-up.[6] Although the cumulative colectomy rate for the total cohort [n = 519] was 13.0% [95% CI (11.4–14.6)] at 20 years, almost half of the colectomies were performed within the first 2 years from diagnosis (about 5%) quite similar to our 3% in 36 months of our whole cohort. However, the IBSEN cohort was established between 1990 and 1993, long before the introduction of BIO therapies and was composed of patients mainly on mesalazine and steroids. A quite higher surgery rate was reported in chronic active disease with a colectomy rate at 3 years of 27%.[2]

Colorectal Cancer

In our population, the rate of CRC was 2% during a median follow-up of 7 years. Our rate was similar or slightly higher compared to other larger studies. In a large two-nation cohort study, CRC was diagnosed in 1.2% of UC patients from Denmark and 1.5% of the patients from Sweden while the IBSEN study showed a cumulative incidence of developing CRC of 1.6% in UC patients after 20 years of follow-up from diagnosis.[39,40] In our cohort, patients with extensive colitis had a higher rate of cancer diagnosis compared to Group 1, but this difference was not statistically significant. Analysis on adherence showed no significant differences in cancer development in non-adherent versus adherent patients.

The main strengths of our study are the elevated number of patients (all of them from the era of BIO drugs) and the prolonged observation period. Moreover, we evaluated cumulative adherence after 3 years of follow-up and not only in the short term. Nonetheless, there are several limitations. The retrospective nature of the study that affected data collection including the lack of biochemical markers at diagnosis (ie, CRP) and of numerically scoring of clinical and endoscopic activity during follow-up. Moreover, data on psychiatric comorbidities and data on concomitant treatments were assessed only at baseline and, thus, may be incomplete and underreported. Although the study was conducted at a referral center, the potential bias of following more "severe" patients was overcome by including all patients meeting the inclusion criteria at diagnosis or shortly thereafter.

Conclusion

Our study is a picture of almost 10 years of the course of ulcerative colitis in the era of biologic treatments. Adherence to therapy and follow-up visits led to less chronic active disease and was the only protective factor at multivariate analysis for a lower risk of developing chronic active UC.

Despite the introduction of new of treatments, we confirmed the finding that patients diagnosed with pancolitis were more likely to undergo colectomy or to develop a chronic active disease, but the present study adds a piece to the whole picture underlining the importance of adherence that may permit a timely intervention with more powerful treatments.

Psychologic/psychiatric problems interfering potentially with adherence are frequently not investigated during visits but should be addressed, if possible, together with trained psychologist/psychiatrist during follow-up visits.

All clinical information is easy to obtain in daily practice, but the path to identifying other predictors related to poor outcomes is still long and ongoing.

Acknowledgments

The study was supported by an unconditional grant from Ferring S.p.A., Italy.

Disclosure

The authors report no conflicts of interest in this work.

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