Original Article

Clinical and endoscopic parameters at presentation that predict the need for long-term immunosuppression in ulcerative colitis

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Abstract

Introduction: The clinical course of ulcerative colitis (UC) ranges from a mild course with prolonged periods of remission to severe disease requiring long-term immunosuppression for disease control. There is limited data on the predictors of need for immunosuppression at presentation. **Objective:** The aim was to evaluate clinical, endoscopic and histopathological parameters at presentation in patients with UC that predict the need for long-term immunosuppressive therapy. **Materials and Methods:** We studied 81 patients (males; 40; mean age 38.69 ± 12.90 years) with UC (41 prospectively and 40 retrospectively). The clinical presentation, duration, extra-intestinal features, extent of disease, haematological and biochemical features, histology and outcome (drugs, surgery, and mortality) were recorded and analyzed. Subgroup analysis was done after dividing the patients into two groups depending upon whether they needed long term immunosuppressants or not. **Results:** The presenting symptoms were bloody stools (100%), mucus in stools (98.8%), abdominal pain (35.8%), anorectal pain (14.8%) and extra-intestinal symptoms (4.9%). Of these 81 patients, 7 (8.6%) patients required surgery and 2 (2.4%) patients died. Long term immunosuppressants were used in 19 patients (Azathioprine 16, Mycophenolate mofetil 2 and Tacrolimus 1). The patients who received immunosuppressants had a higher prevalence of pancolitis (47.4% vs. 16.1%, $P = 0.005$). Other clinical, hematological and histological parameters such as inflammatory grade, chronicity grade, cellular infiltrates, submucosal fibrosis, Paneth cell metaplasia, and the presence of neuronal cells were similar in the two groups. **Conclusion:** Of the clinical, biochemical, endoscopic and histological features at presentation only the presence of pancolitis predicts the need for long term immunosuppressants in ulcerative colitis.

Key words

Colonoscopy, immunosuppression, pancolitis, ulcerative colitis

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease of uncertain etiology that is characterized by recurrent episodes of inflammation usually limited to the mucosal layers of the colon. The clinical course of UC ranges from a mild course with prolonged periods of remission to severe disease requiring long term immunosuppression for disease control.[1,2] The severity of disease is influenced by several factors, of which the most important are duration of symptoms, extent of disease and the age of the patient. Patients in extremes of age are more likely to suffer from severe attacks than those in intermediate age groups.

Approximately a quarter of UC patients may remain steroid dependent or refractory.[3] In order to overcome this various dosages, duration, and route of corticosteroid administration

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have been evaluated.[3-5] In such patients, there may be a need to use immunosuppressant agents for the control of disease and then to maintain remission. Various drugs that are helpful to avoid steroid dependency or refractoriness and need for colectomy have become available, including azathioprine, cyclosporine, tacrolimus and infliximab amongst others.[6-9] Colectomy can be delayed by using these drugs.[1]

To the best of our knowledge, there is a paucity of data on the predictors of need for immunosuppression in patients with UC at presentation. Moreover, most of the studies have been done in Western patients. The natural course of UC appears to different in Asian patients and studies from India have shown that the disease has a milder clinical course, lower relapse rate, and lower colectomy rate compared to the western population.[10-12] In this current study, we evaluated the clinical, hematological, biochemical, endoscopic and histopathological parameters at presentation in patients with UC that predict the need for long-term immunosuppressive therapy.

Materials and Methods

The study was conducted from July 2011 to December 2012 at a tertiary care academic institution in North India. The study included patients presenting to hospital with symptoms suggestive of UC present for >4 weeks duration along with endoscopic and histopathological evidence suggestive of UC. In this study, 41 patients of UC were enrolled prospectively and followed-up (prospective group). Also, the data of 40 patients of UC on regular followup from 2008 onwards were retrieved and analyzed (retrospective group). These patients were also prospectively followed up during the study period. Patients who refused consent or were pregnant, <12 years of age, had infectious colitis, granulomatous inflammation, malignancy and comorbid illness requiring modification of therapy were excluded from the study. An informed consent was obtained from all the patients, and the study was approved by the institute's ethic committee.

Retrospective analysis
Forty patients with a diagnosis of UC on regular follow up under Gastroenterology and surgery services since 2008 were enrolled, and their data was retrieved. Presenting clinical features were recorded and severity at presentation and exacerbations was classified using the Truelove and Witt's criteria. Ileocolonoscopic findings including grade of colitis, extent of disease and ileal involvement were retrieved and recorded [Figures 1 and 2]. The histopathological examination slides were retrieved and re-examined by an expert histopathologist who was blinded to clinical details regarding severity and clinical course of the patient. These were looked for inflammation, inflammatory infiltrate, and grade of chronicity by studying architectural distortion. Other histopathological features studied were presence of abnormal vessels, Paneth cells and neuronal cells. The data

Figure 1: Photograph showing loss of vascular pattern and multiple superficial ulcers

of these patients was studied, and patients needing long-term immunosuppressive drugs were identified.

Prospective analysis
A total of 41 patients of idiopathic ulcerative colitis who satisfied the inclusion criteria were prospectively followed up for at least 1 year. Patients' clinical features and investigations were recorded as described above in the retrospective analysis. Colonoscopy and Ileoscopy were performed as per standard method. After obtaining informed consent, patient was administered 4 L of polyethylene glycol solution over a period of 3 h and endoscopic pinch biopsies were obtained and properly oriented specimen were mounted separately on a filter paper and transported in a formalin vial to the histopathology department for serial sections. Biopsies were examined by a histopathologist under light microscopy after staining with hematoxylin and eosin. The specimens were also subjected to certain special stains if needed to identify superadded complications. The details of histopathology findings were recorded.

Statistical analysis
The clinical, histopathological and endoscopic parameters of patients who had their disease controlled with 5-amino salicyclic acid derivatives alone without long term immunosuppressants and surgery were compared with patients who required immunosuppressants. The quantitative variables were estimated using measures of the central location, that is, mean, median, measures of dispersion and standard deviation. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi-square or Fisher's exact test whichever was applicable for two groups as well as for within groups. For normally distributed data means of two groups were compared using student *t*-test. For skewed data Mann–Whitney test was applied. All statistical tests were two-sided and were performed at a significance level of $P \leq 0.05$.

Results

Of the total 81 patients studied, 40 patients were in the retrospective group and 41 patients were in the prospective group. Most of the patients belonged to the north Indian state of Punjab (56.8%), followed by Haryana (27.2%). The mean age of the study group was 38.69 ± 12.9 years with a range of 14-76 years (males: 40). In the prospective group 2 patients died one due to acute severe colitis with perforation and another due to a cerebrovascular accident.
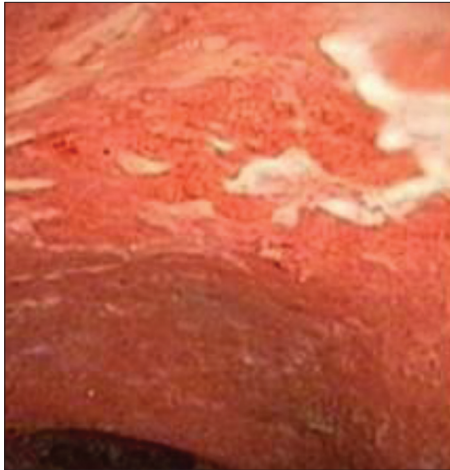
Figure 2: Photograph showing loss of vascular pattern with multiple large ulcers

Bloody diarrhea was the most common symptom observed (100%). Other symptoms observed were mucus in stools

Table 1: Comparison of clinical and biochemical parameters between immunosuppressant and nonimmunosuppressant group

	Immunosuppressant group (*n*=19)	Nonimmunosuppressant group (*n*=62)	*P*
Age	38.6±10.6 years	38.6±13.6	1.000
Sex:Male (*n*)	9	31	0.847
Abdominal pain (%)	42.1	33.9	0.347
Mucus in stools (%)	92.7	100	0.235
Blood in stools (%)	100	100	
Anorectal pain (%)	21.1	12.9	0.462
Fever (%)	10.5	4.8	0.344
Extra-intestinal symptoms (%)	10.5	3.2	0.233
Hemoglobin g/dl	9.7±2.61	10.9±2.4	0.102
TLC/mm^3	7726±2761	9360±5266	0.251
Platelets/mm^3	323153±131144	291037±98377	0.328
ESR	31±19	32±16	0.769
Total protein g/dl	7.05±1.38	7.03±1.88	0.951
Albumin g/dl	3.14±1.57	3.6±1.14	0.389

TLC=Total leukocyte count, ESR=Erythrocyte sedimentation rate at end of first hour

Table 2: Comparison between immunosuppressant and nonimmunosuppresant group vis-à-vis endoscopic and histological parameters

	Immunosuppressant group (*n*=19)	Nonimmunosuppressant group (*n*=62)	*P*
Proctosigmoiditis (%)	10.5	17.7	0.453
Left sided colitis (%)	42.1	66.1	0.061
Pan colitis (%)	47.4	16.1	0.005
Inflammatory grade (%)			
0	0	4.9	0.324
1	26.3	14.8	0.247
2	47.4	50.8	0.793
3	26.3	29.5	0.788
Chronicity grade (%)			
0	5.3	19.7	0.137
1	5.3	13.1	0.344
2	52.6	32.8	0.119
3	36.8	29.5	0.547
4	0	4.9	0.324
Lamina propria (%)			
None	57.9	78.3	0.079
Fibrosis	26.3	20.0	0.559
TMA	10.5	1.7	0.078
Fibrosis+TMA	5.3	0	0.074
Sub mucosal (%)			
None	52.6	44.1	
Present (fibrosis+TMA+IEL)	47.4	55.9	0.515
MMD	57.9	57.4	0.722
Presence of abnormal features*	21.1	27.9	0.570

*Presence of Paneth cells, neuronal cells, or both. TMA=Thrombotic microangiopathy, IEL=Increased intra epithelial lymphocytes, MMD=Muscularis mucosae disarray

(98.8%), abdominal pain (35.8%), anorectal pain (14.8%) and extra-intestinal symptoms (4.9%). Majority of patients had left sided colitis (60.5%). Pancolitis was seen in (23.5%) patients and proctosigmoiditis were seen in 16% patients.

19 patients (*n* = 81; 9 males) required immunosuppressants during the course of illness. Their mean age was 38.68 ± 10.6 years. All patients (*n* = 19) presented with bloody stools (100%) and mucus in stool (94.7%) with no statistically significant difference compared with the nonimmunosuppressant group (*P* = 0.334 and *P* = 0.235). The frequency of other clinical features like pain abdomen, anorectal pain, duration of illness and extra-intestinal manifestations were similar between the two groups [Table 1]. Four patients (*n* = 81) had extra-intestinal manifestations, two of them were from the group using immunosuppressants constituting (10.5%). Involvement of other organ systems such as hepatobiliary, renal, and musculoskeletal did not have any statistical significance among the two groups (*P* = 0.466). The baseline investigations including haematological and biochemical parameters did not show significant statistical difference among both the groups [Table 1].

Among the immunosuppressant group, 9 patients had pancolitis constituting (47.4%), whereas 10 patients from nonimmunosuppressant group had pancolitis constituting (16.1%) and this difference was statistically significant (*P* = 0.005). Patients with left sided colitis in the immunosuppressant group were 8 (*n* = 19) and those from nonimmunosuppressant group were 41 (*n* = 62) and this was not significantly different (*P* = 0.061). None of the features like inflammatory grade, chronicity, cellular infiltrates, submucosal fibrosis or infiltrates and abnormal features like Paneth cell metaplasia, and the presence of neuronal cells were statistically significant in the two groups [Table 2].

Discussion

Ulcerative colitis is a chronic idiopathic inflammatory bowel disease in which patients require long-term treatment. Various studies have shown that the standard medical therapy with amino salicylates and steroids do not alter the long-term outcome or the rate of surgery in patients with UC.[3,6,9] The most relevant events in the course of UC are remission, relapse, quality of life, extension of disease over time, surgery, cancer and mortality. Identifying the factors that predict the course of the disease, may help in offering effective maintenance therapy with immunosuppressants, biologicals and early surgery that may benefit the outcome. Most of the studies done in this regard are on the western population. Only few studies have been done in the Indian sub-continent until date. In the present study, we evaluated 81 patients of UC and tried to identify the predictors of immunosuppressant usage. The mean age of the study population was 38.69 ± 12.9 years (*n* = 81) ranging from 14 to 76 years and most of the patients were between 35

and 46 years. The mean age of the patients who required immunosuppression was 38.8 years. In our study age did not show any role in predicting the course. Sinclair *et al*. in their study showed that the risk of relapse was twice as great in the younger age group (80% at 5 years) than in the older age group (40% at 5 years).[13] Similar study done on Indian population by Azad *et al*. also showed that age had no significance impact on the outcome or the course of the disease.[14] There was no statistically significant difference between the gender distributions in patients who required immunosuppressant vis-à-vis those who didn't require it. Previous studies done on short or long-term course, and prognosis in UC have also not described any role of gender on the course of the disease.[15,16]

The clinical features among the study population did not show much variation. The most common symptoms being bloody stools seen in 100% of cases (*n* = 81) and mucus in stools seen in 98.8% of cases (*n* = 81) associated with increased frequency of stools at presentation. Langholz *et al*. in their study found that the clinical features like bloody stools that was present in 93.4% (*n* = 228) and mucus in stools that was seen in 68.4% (*n* = 228) were common symptoms at presentation, but did not show any significance with increasing extent of inflammation.[17] Diarrhoea, abdominal pain, weight loss and fever were recorded significantly more frequently with increasing extent of inflammation. Analysis of the parameters like haemoglobin, albumin and erythrocyte sedimentation rate, did not show any significance in either group of patients. Bitton *et al*. correlated the serum markers with histological markers in their study, no serum marker showed a significant association with histological findings.[18] Similar study done by Bessissow *et al*. also did not show any correlation with serum markers in predicting the relapses.[19]

Among the study population, proctosigmoiditis was seen in 16% (*n* = 13), left sided colitis in 60.5% (*n* = 49) and pancolitis in 23.5% of cases (*n* = 19). In our study, the patients who had a greater extent of disease at presentation were in need of long term immune suppressants during the course of illness. Thus, the results of our study showed that the anatomic extent of UC at diagnosis is an important factor in the long-term prognosis with regard requirement of immunosuppressants in the course of the disease, and similar results have been shown by earlier studies also.[20-22]

In two studies conducted by Bitton *et al*. and Bessissow *et al*. basal plasmacytosis was an important independent predictor of relapses.[18,19] In a study conducted by Azad *et al*. among all the histological parameters, presence of eosinophils and neutrophils in the lamina propria were found to be significant predictors of relapse.[14] Riley *et al*. in his study confirmed the high prevalence of histological abnormalities in patients with clinically and sigmoidoscopically quiescent colitis.[15] Thus, the role of histology in predicting the need of immunosuppression

or course of the disease remains debatable. In the present report, the histological parameters could not help predict the need for immunosuppression.

Conclusion

Of the clinical, biochemical, endoscopic and histological features at presentation, only the presence of pancolitis predicts the need for long-term immunosuppressants in UC.

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