Biological and Histological Parameters as Predictors of Relapse in Ulcerative Colitis: A Prospective Study
Sheenam Azad, Neena Sood¹, Ajit Sood²

ABSTRACT

Background/Aim: Ulcerative colitis is a chronic inflammatory disease of unknown etiology characterized by periods of remission and relapses. This study has been carried out in a group of North Indian patients, where the disease has shown an increasing prevalence and frequent relapses. Hence, there is a need to predict relapse for better management and to reduce morbidity. To assess the importance of biological and histological parameters in predicting relapse when the disease is in quiescent phase. Materials and Methods: A prospective study of twenty-six patients with quiescent ulcerative colitis was carried out in Dayanand Medical College and Hospital, Punjab. Only patients with clinical and endoscopic remission at the time of screening visit were included. Hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum Interleukin-6 (IL-6) levels were measured. The baseline colonoscopic mucosal biopsies were retrieved and studied. Follow-up was conducted for one year at monthly interval or earlier if relapse occurred. Results: Fifteen out of twenty-six patients (57.69%) had evidence of clinical relapse during the follow-up. Hemoglobin, ESR, CRP and IL-6 levels were not found to be significant predictors of relapse. Increased number of eosinophils and neutrophils in the lamina propria were observed to be associated with significantly higher relapse rate. Conclusion: A higher risk of relapse in patients with quiescent colitis can be predicted by the presence of increased number of eosinophils and neutrophils in the lamina propria.

Key Words: Predictors, remission, relapse, quiescent phase, ulcerative colitis

Received 04.05.2010, Accepted 09.09.2010

How to cite this article: Azad S, Sood N, Sood A. Biological and histological parameters as predictors of relapse in ulcerative colitis: A prospective study. Saudi J Gastroenterol 2011;17:194-8.

Ulcerative colitis is a chronic inflammatory disease of unknown etiology characterized by recurring episodes of inflammation primarily limited to the mucosal layer of the colon. It is a worldwide disorder with significant geographical heterogeneity, the highest prevalence rates having been reported from Northwest Europe and North America.¹ The incidence and prevalence of ulcerative colitis in the Indian subcontinent is rising and the disease frequency is not much less than that reported from Europe and North America.² Clinical course of ulcerative colitis is characterized by periods of remission punctuated by clinical exacerbations. Active disease can be associated with a rise in acute phase reactants like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and decrease in hemoglobin (Hb).³ Cytokines play an important regulatory role in ulcerative colitis; there is an increased production of most of the major proinflammatory cytokines [Interleukin-1, Interleukin-6, Interleukin-8 (IL-1, IL-6, IL-8)] and tumor necrosis factor-α (TNF-α).³ These serum parameters may be useful as markers of disease activity.

Various studies have reported one-year relapse rates ranging from 38 to 89% in patients receiving placebo; with mediation, yearly relapse rates are reduced to 12-50%.⁴ Thus, it is important to identify patients with inactive ulcerative colitis who are likely to relapse subsequently so that an optimal maintenance therapy can be planned. This study has been carried out in a group of patients in North India, where the disease has shown an increasing prevalence, with the aim to assess the importance of biological and histological parameters in predicting relapse when the disease is in quiescent phase.

MATERIALS AND METHODS

This was a prospective study of 26 patients with quiescent ulcerative colitis who presented to Department of Medicine...
Predictors of relapse in ulcerative colitis

Table 1: Baseline clinical parameters in relapsers and non-relapsers

| Parameter                      | Relapsers (n = 15) | Non-relapsers (n = 11) | Significance |
|--------------------------------|--------------------|------------------------|--------------|
| Mean age (years)               | 35.33 ± 13.9       | 40.72 ± 9.07           | t-value 0.82  |
| Age range (years)              | 16 - 65            | 24 - 58                |              |
| Mean duration of disease in years | 5.37 ± 4.75   | 5.90 ± 4.92            | t-value 0.44  |
| Mean number of previous relapses | 2.53 ± 1.73     | 1.40 ± 1.4             | t-value 1.74  |

Table 1: Baseline clinical parameters in relapsers and non-relapsers

| Parameter                      | Relapsers (n = 15) | Non-relapsers (n = 11) | Significance |
|--------------------------------|--------------------|------------------------|--------------|
| Mean age (years)               | 35.33 ± 13.9       | 40.72 ± 9.07           | t-value 0.82  |
| Age range (years)              | 16 - 65            | 24 - 58                |              |
| Mean duration of disease in years | 5.37 ± 4.75   | 5.90 ± 4.92            | t-value 0.44  |
| Mean number of previous relapses | 2.53 ± 1.73     | 1.40 ± 1.4             | t-value 1.74  |

NS* - Not significant
relapsers are shown in Tables 2 and 3. Duration of the disease, increased number of previous relapses, hemoglobin, ESR, CRP and IL-6 levels were not found to be significant predictors of relapse.

Among the various histological parameters studied, crypt distortion and increase in chronic inflammatory cells in lamina propria [Figure 1] were noted in all the relapsers and in majority of non-relapsers [Table 3]. Further, increased number of eosinophils and neutrophils in lamina propria [Figures 2 and 3] were seen among relapsers. On the other hand, 90.90% (10/11 cases) of the non-relapsers showed no increase in eosinophils and neutrophils in the lamina propria. This difference was found to be statistically significant (P<0.01). Cryptitis (presence of neutrophils in the crypt epithelium) was noted in 53.33% (8/15) of the relapsers; however, it was absent in all the non-relapsers. Crypt abscess (presence of neutrophils within the lumen leading to crypt destruction) was seen in only one patient who relapsed early at the beginning of the study. Basal lymphoid aggregates were present in 60% (9/15 cases) of the relapsers and 45.46% (5/11 cases) of the non-relapsers which was not statistically significant.

DISCUSSION

Ulcerative colitis is a disease characterized by remissions and relapses. The present study has been conducted prospectively in twenty-six patients having quiescent ulcerative colitis with an aim to identify factors that lead to a higher risk of relapse. It is important to recognize such parameters so that patients with an increased risk of relapse can be put on longer maintenance therapy.

The patients in our study group had a relapse rate of 57.69% (15/26), a finding in accordance with other published reports;[9,10] however, Bitton et al.[6] have reported a lower relapse rate of 36%. The reason for the higher relase rate

| Biological parameters | Relapsers (n = 15) | Non-relapsers (n = 11) | Significance |
|-----------------------|-------------------|------------------------|-------------|
| Hemoglobin (g/dl)     | 13.05 ± 1.54      | 12.35 ± 1.47           | t-value=0.80 NS |
|                       | (10.8 - 15.4)     | (9.8 - 15.0)           |             |
| ESR† (mm/h)           | 10.87 ± 11.51     | 19.18 ± 24.65          | t-value=0.76 NS |
|                       | (5 - 46)          | (4 - 90)               |             |
| CRP (mg/l) (Normal 0-6)| 3.07 ± 3.43      | 2.45 ± 2.33            | t-value=0.56 NS |
|                       | (0 - 13)          | (0 - 6)                |             |
| IL-6 pg/ml (Normal 3-8.5) | 17.78 ± 20.96 | 10.14 ± 3.73           | t-value=0.85 NS |
|                       | (5.5 - 91.8)      | (6.1 - 18.3)           |             |

Figures in parenthesis indicate range of the measured parameter in the study group. *Normal ESR values in different sexes and age groups were calculated on the basis of the table “ESR ranges in health” given by Lewis.[8] NS* - Not significant.
observed in our study group may be either due to differences in the natural course of disease in the Indian subcontinent or poor patient compliance to regular medication. Thus, it is emphasized that due to a higher relapse rate observed in this part of the world, prior identification of various predictors of disease relapse is all the more important.

The patients with quiescent disease who relapsed during the follow up period had a higher frequency of relapses prior to inclusion in this study. Mean number of previous relapses was more among relapers (2.53 ± 1.73) compared to non-relapers (1.40 ± 1.4). However, this finding was not statistically significant probably due to smaller sample size. On the other hand, few studies have reported that previous relapse frequency has a significant association with the risk of relapse.

Biological markers were assessed as predictors of clinical relapse. Hemoglobin, ESR and CRP were not found to be predictive of clinical recurrence, which is in agreement with other published studies. Cytokine IL-6 was studied to assess its role as a marker of disease activity and was found to be increased in 73.33 % (11/15 cases) of the relapsers as well as in 45.45 % (5/11 cases) of the non-relapsers which was not statistically significant. It has been reported that IL-6 might be involved in the pathogenesis of ulcerative colitis and serum levels of these cytokines correlate with disease activity. In our study, difference between the mean value of IL-6 among relapers and non-relapers was not significant (t-value=0.85) and is in concordance with a previous report by Bitton et al.

Most patients with ulcerative colitis run a risk of relapse.

### Table 3: Summary of histological findings in relapers and non-relapers

| Histological parameters | Grade and subgrade | Relapers (n = 15) | Non relapers (n = 15) | Significance |
|-------------------------|--------------------|-------------------|----------------------|--------------|
| Structural change       | Grade 0            | 15 (100)          | 9 (61.23)            | Not significant |
| (crypt distortion)      | No abnormality     | 0.0               | 2                    |              |
|                         | Mild abnormality   | 0.1               | 7                    |              |
|                         | Mild or moderate diffuse or multifocal abnormalities | 0.2 | 4 | 2 |
|                         | Severe diffuse or multifocal abnormalities | 0.3 | 1 | 0 |
| Chronic inflammatory cells | Grade 1           | 15 (100)          | 8 (72.73)            | Not significant |
|                         | No increase        | 1.0               | 3                    |              |
|                         | Mild but unequivocal increase | 1.1 | 11 | 8 |
|                         | Moderate increase  | 1.2               | 0                    |              |
|                         | Marked increase    | 1.3               | 0                    |              |
| Eosinophils in lamina propria | Grade 2A         | 11 (73.34)        | 1 (6.67)             | P<0.01 significant |
|                         | No increase        | 2A0               | 4                    | 10           |
|                         | Mild but unequivocal increase | 2A1 | 9 | 1 |
|                         | Moderate increase  | 2A2               | 1                    | 0            |
|                         | Marked increase    | 2A3               | 1                    | 0            |
| Neutrophils in lamina propria | Grade 2B         | 10 (66.67)        | 1 (6.67)             | P<0.01 significant |
|                         | None               | 2B0               | 5                    | 10           |
|                         | Mild but unequivocal increase | 2B1 | 5 | 1 |
|                         | Moderate increase  | 2B2               | 5                    | 0            |
|                         | Marked increase    | 2B3               | 0                    | 0            |
| Neutrophils in epithelium (cryptitis) | Grade 3 | 8 (53.33)        | 0                    | Cannot be determined |
|                         | None               | 3.0               | 0                    | 11           |
|                         | < 5 % crypts involved | 3.1 | 8 | 0 |
|                         | ≤ 50% crypts involved | 3.2 | 0 | 0 |
|                         | > 50% crypts involved | 3.3 | 0 | 0 |
| Crypt destruction (crypt abscess) | Grade 4 | 1 (6.67)        | 0                    | Cannot be determined |
|                         | None               | 4.0               | 14                   | 11           |
|                         | Probable local excess of neutrophils in part of crypt | 4.1 | 0 | 0 |
|                         | Probable marked attenuation | 4.2 | 1 | 0 |
|                         | Unequivocal crypt destruction | 4.3 | 0 | 0 |
| Basal lymphoid aggregates | Present           | 9 (60)            | 5 (45.46)            | Not significant |
|                         | Absent             | 6                  | 6                    |              |

Figures in parenthesis indicate percentage
In the present study, cryptitis was seen only among relapsers. Hence, these predictors of relapse in the present study. In addition, in the lamina propria were found to be the most significant studied, presence of increased eosinophils and neutrophils Among all the biological and histological parameters

CONCLUSION

reported by Bitton predictive value for disease relapse, a finding similar to that might be a feature of ulcerative colitis but were not of inflammatory bowel disease. Gastroenterology 1994;107:755-63.

ACKNOWLEDGMENT

We thank Dr. Sandip Kadesia, Professor and Head, and Dr. Sanjiv Kishore, Professor, Department of Pathology, Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun for their guidance in preparation of this research article.

REFERENCES

1. Whelan G. Epidemiology of inflammatory bowel disease. Med Clin North Am 1990;74:1-12.
2. Sood A, Midha V, Sood N, Bhatia NS, Avathgi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut 2003;52:1587-90.
3. Buckell NA, Lennard-Jones JE, Hernandez MA, Kohn J, Riches PG, Wadsworth J. Measurement of serum proteins during attacks of UC as a guide to patient management. Gut 1979;20:22-7.
4. Kishimoto T. The biology of interleukin-6. Blood 1989;74:1-10.
5. Tracey KJ, Vlassara H, Cerami A. Cachectin/tumour necrosis factor. Lancet 1989;1:1122-6.
6. Bitton A, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, et al. Clinical, biological and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001;120:13-20.
7. Geboes K, Riddell R, Ost A, Jensen B, Persson T, Lofberg. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47:404-9.
8. Lewis SM. Miscellaneous tests. In: Lewis SM, Bain BJ, Bates I, editors. Practical Haematology, 9th ed. London: Churchill Livingstone, 2001. p. 528-9.
9. Moum B, Ekbom A, Vatn MH, Aadland E, Sauraj J, Lygren I, et al. Clinical course during 1st year after diagnosis in ulcerative colitis and Crohn’s disease. Scand J Gastroenterol 1997;32:1005-12.
10. Schumacher G, Sandstedt B, Kollberg B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis. Clinical findings and early diagnosis. Scand J Gastroenterol 1994;29:265-74.
11. Riley SA, Mani V, Goodman MJ, Lucas S. Why do patients with ulcerative colitis relapse? Gut 1990;31:179-83.
12. Leo S, Leandro G, Di Matteo G, Caruso ML, Lorusso D. Ulcerative colitis in remission: it is possible to predict the risk of relapse? Digestion 1989;44:217-21.
13. Holtkamp W, Stollberg T, Reis HE. Serum interleukin-6 is related to disease activity but not disease specificity in inflammatory bowel disease. J Clin Gastroenterol 1995;20:123-6.
14. Niederau C, Backmerhoff F, Schumacher B, Niederau C. Inflammatory mediators and acute phase proteins in patients with Crohn’s disease. Hepato-Gastroenterol 1997;44:90-107.
15. Fochios SE, Korelitz BI. The role of sigmoidoscopy and rectal biopsy in diagnosis and management of inflammatory bowel disease: personal experience. Am J Gastroenterol 1988;83:114-9.
16. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis 1966;11:847-57.
17. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? Gut 1991;32:174-8.
18. Surawicz CM, Belic L. Rectal biopsy helps to distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. Gastroenterology 1984;86:104-13.
19. Surawicz CM, Haggitt RC, Hussemann M, McFarland LV. Mucosal biopsy diagnosis of colitis-Acute self limited colitis and idiopathic inflammatory bowel disease. Gastroenterology 1994;107:755-63.

Source of Support: Nil. Conflict of Interest: None declared.