

Are Patients with Inflammatory Bowel Disease Receiving Optimal Care?

Sarathchandra I. Reddy, M.D., Sonia Friedman, M.D., M.P.H., Jennifer J. Telford, M.D., Lisa Strate, M.D., Rie Ookubo, M.A., and Peter A. Banks, M.D.

Division of Gastroenterology, Crohn's and Colitis Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

- OBJECTIVES:** Guidelines have been published as a framework for therapy of patients with inflammatory bowel disease (IBD). The purpose of this study was to determine whether patients referred for a second opinion were receiving therapy in accordance with practice guidelines.
- METHODS:** Patients with luminal IBD under the care of a gastroenterologist who sought a second opinion at Brigham and Women's Hospital between January 2001 and April 2003 were enrolled in this study. Clinical information was obtained by direct patient interview at the time of initial patient visit and by a review of prior records. Data obtained included the diagnosis, clinical symptoms, prior medical therapy, preventive measures for metabolic bone disease, and colon-cancer screening.
- RESULTS:** The study population consisted of 67 consecutive patients: 21 with ulcerative colitis, 44 with Crohn's disease and 2 in whom the diagnosis of IBD could not be confirmed. Of the 65 patients with confirmed IBD, 56 patients had symptoms of active disease and 9 were asymptomatic. All analyses were carried out on the 56 patients with active disease. Of the 33 patients treated with aminosalicylates, 21 (64%) were not receiving maximal doses. Nine of 12 (75%) patients with distal ulcerative colitis were not receiving rectal aminosalicylate therapy. Within 6 months of their clinic visit, 35 patients had received corticosteroid therapy, and 27 (77%) patients had been treated with corticosteroids for greater than 3 months. In 16 of 27 (59%) there was no attempt to start steroid sparing medications such as 6-mercaptopurine (6MP), azathioprine, or infliximab. Of the 11 patients treated with either 6MP or azathioprine, 9 (82%) were suboptimally dosed without an attempt to increase dosage. Of the 27 patients on prolonged corticosteroid therapy 21 (78%) received inadequate treatment to prevent metabolic bone disease. Three of 9 patients (33%) meeting indications for surveillance colonoscopy for dysplasia had not undergone colonoscopy at the appropriate interval.
- CONCLUSIONS:** Patients with IBD often do not receive optimal medical therapy. In particular, there is suboptimal dosing of 5-ASA and immunomodulatory medications, prolonged use of corticosteroids, failure to use steroid-sparing agents, inadequate measures to prevent metabolic bone disease, and inadequate screening for colorectal cancer.

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INTRODUCTION

Practice guidelines have been developed which provide a framework for the proper diagnosis, optimal medical management, and monitoring of patients with inflammatory bowel disease (IBD) (1, 2). Despite the availability of practice guidelines, it has been suggested that patients often do not receive optimal treatment for IBD (3). To date, there have been no comprehensive studies that have examined the quality of care of IBD. The aim of this study was to assess whether symptomatic patients who were referred to our institution were receiving optimal therapy for IBD in accordance with practice guidelines.

METHODS

Subjects

Consecutive patients under the direct care of gastroenterologists for IBD who presented for a second opinion for management of IBD to Brigham and Women's Hospital, a tertiary care center, between January 2001 and April 2003 were enrolled in the study. Patients who had never consulted a gastroenterologist in the past or who were now under the exclusive care of a nongastroenterologist were excluded. Patients with perianal or fistulizing disease in the absence of luminal disease were also excluded.

Severity Scale for Ulcerative Colitis	
1- mild:	not more than 4 stools/day, small amount of blood may be present, normal ESR, no systemic toxicity
2- moderate:	greater than 4 stools/day, bleeding usually present, minimal toxicity
3- severe:	greater than 6 bloody stools/day, systemic toxicity: fever, elevated ESR
Severity Scale for Crohn's Disease	
1- mild disease:	able to tolerate oral intake; no fever, no abdominal tenderness, no obstruction
2- moderate disease:	fever, weight loss, abdominal pain, nausea, vomiting, anemia, no response to treatment for mild disease
3- severe disease:	persistent symptoms in spite of outpatient steroid therapy, high fever

Figure 1. Severity scales adapted from practice guidelines for ulcerative colitis and Crohn's disease (1, 2).

Study Design

A retrospective review of patient records was conducted by a single investigator (SIR). Clinical information that was obtained from patient records included documentation of prior clinical, radiologic, and pathologic records as well as a review of radiologic images and pathology if indicated. Data were recorded on a standardized data collection form including basic patient demographic information, information about initial diagnosis, duration of disease, and assessment of severity as outlined in the ACG practice guidelines (Fig. 1). Data regarding medical therapy included use of oral and topical 5-ASA agents at the time of the clinic visit, corticosteroid agents within the previous 6 months, and use of steroid sparing agents including 6-mercaptopurine (6MP), azathioprine, and infliximab. Preventive measures for metabolic bone disease including pharmacologic therapy and bone mineral density scan were also recorded. In addition, colorectal cancer surveillance was assessed.

Statistical Analysis

Data were analyzed to assess for proportions of patients receiving particular therapies, dosing of medications, and duration of corticosteroid therapies. Proportions were expressed as percents. Variables including age, sex, underlying disease, location, and disease duration were evaluated to determine whether they predicted certain modes of treatment. Chi-square test or Fisher's exact test were used for the analysis depending on sample size. All analysis was conducted at 5% two-sided level of significance.

RESULTS

Patient Characteristics

A total of 67 consecutive patients referred for evaluation of IBD were enrolled. The referral base consisted of 64 gastroenterologists in practice settings including both private and academic practices. The diagnosis of UC could be confirmed

Table 1. Distribution of Disease

Disease	Number of Patients
Ulcerative colitis (21)	
Proctitis	5
Left-sided colitis	7
Extensive colitis	6
Missing information	3
Crohn's disease (44)	
Small bowel involvement only	23
Colonic involvement only	12
Small bowel and colonic disease	9

in 21 and Crohn's disease in 44 patients. The median age was 35 yr (range 19–74). A total of 21 (31%) patients were male and 46 (69%) were female. Two patients in whom a diagnosis of IBD could not be confirmed were excluded. In both of these patients, neither the endoscopic nor pathologic findings supported the diagnosis of IBD.

Of the 65 patients with confirmed IBD, 56 (86%) were symptomatic at the time of their clinical assessment. Severity of symptoms was classified as mild, moderate, or severe according to criteria delineated in ACG practice guidelines (1, 2) (Fig. 1). Based on these criteria, 32 of 56 (57%) of the patient group had mild disease, 23 of 56 (41%) had moderate disease, and 1 of 56 (2%) had severe disease. Information regarding location of disease was present in 18 of 21 patients with ulcerative colitis and all 44 patients with Crohn's disease (Table 1).

Medical Therapy

A detailed analysis of medical therapy was conducted among the 56 symptomatic patients in the patient cohort.

The use of oral and topical 5-ASA agents was assessed. Overall, 33 of 56 (59%) patients were receiving oral 5-ASA therapy. A list of oral 5-ASA agents and proportion of patients receiving optimal dosing of these agents is detailed in Table 2. Twenty-one of 33 (64%) of these patients had not received optimal doses of these medications. There was no significant difference in proportion of symptomatic patients with UC *versus* CD receiving suboptimal dosing of oral 5-ASA agents (data not shown). Additional analysis revealed that use of optimal 5-ASA dosing was not associated with other variables such as sex, age, location of disease, and severity of disease. Of the 23 symptomatic patients who were not receiving oral 5-ASA agents, 7 patients (30%) had not

Table 2. 5-ASA Agents and Dosing

5-ASA agent	Optimal Dose	Patients	Number (%) Suboptimally Dosed
Asacol	4.8 g/day	14	11 (79)
Pentasa	4.0 g/day	14	8 (57)
Azulfidine	4.0 g/day	2	1 (50)
Balsalazide	6.75 g/day	3	1 (33)
Total		33	21 (64)

Table 3. Prolonged Corticosteroid Therapy and Disease Severity among Symptomatic Patients

Disease Severity	Patients Receiving Steroid Therapy	Patients Receiving Prolonged Steroid Therapy (%)
Mild	17	13 (76)
Moderate	18	14 (78)
Severe	0	0 (0)
Total	35	27 (77)

This table illustrates the proportion of patients within disease severity groups who were receiving prolonged steroid therapy (continuous steroid therapy for greater than 3-month duration). There was no association between disease severity and likelihood of having received corticosteroids for greater than 3 months. $p = 1.0$ by Fisher's exact test.

tolerated 5-ASA agents. Medical therapies used by the 23 symptomatic patients not receiving 5-ASA agents included topical and oral corticosteroids, antibiotics, immunomodulatory agents, infliximab, and topical 5-ASA agents.

With regard to topical therapy among 12 symptomatic patients with distal ulcerative colitis (defined as either proctitis or left-sided colitis extending to the splenic flexure), topical aminosalicylates were not used in 9 (75%) patients.

Oral corticosteroid use within the prior 6 months was assessed. Thirty-five of 56 (63%) patients had been treated with corticosteroids within 6 months of their clinic visit. Twenty-seven of 35 (77%) had received prolonged steroid therapy defined as continuous steroid therapy for greater than a 3-month duration. There was no association between likelihood of receiving prolonged corticosteroid therapy and severity of disease (Table 3). The median dose of prednisone at the time of clinical assessment was similar among patients with mild disease and those with moderate or severe disease (mild disease: median dose 20 mg/day, range 10–60 mg/day; moderate to severe disease: median dose 20 mg/day, range 2.5–40 mg/day). Among the 27 patients who had received prolonged steroid therapy, in 16 (59%) there was no attempt to start steroid sparing medications such as 6MP, azathioprine, or infliximab.

There were 11 patients receiving treatment with 6-MP or azathioprine at the time of their clinic visit. Suboptimal dosing was defined as a dose of 6-MP less than 1.0 mg/kg or azathioprine less than 2.0 mg/kg in the absence of leukopenia (1, 2, 4). Using these criteria 9 of 11 (82%) received suboptimal doses of these medications without an attempt to increase dosage (6/8 with CD, 3/3 with UC). In all nine patients receiving suboptimal doses of these medications, there was no prior history of leukopenia or other intolerance to either 6-MP or azathioprine. Furthermore, in none of the 11 patients treated with 6-MP or azathioprine were TPMT enzyme activity or metabolite levels utilized to guide dosing of these agents. A total of five symptomatic patients, all of whom had Crohn's disease, received treatment with infliximab. Of the five symptomatic patients who had received infliximab, four were on concomitant therapy with 6MP or azathioprine, and one patient was receiving infliximab as

Table 4. Suboptimal Care in Inflammatory Bowel Disease

Clinical parameter	Proportion (%)
Suboptimal dosing of 5-ASA agents	21/33 (64)
Failure to use topical 5-ASA therapy	9/12 (75)
Treatment with corticosteroids >3 months	27/35 (77)
Failure to utilize steroid sparing medications*	16/27 (59)
Suboptimal dosing of immunomodulatory agents	9/11 (82)
Inadequate preventive measures for metabolic bone disease*	21/27 (78)
Inadequate surveillance for colorectal cancer	3/9 (33)

*Among patients receiving steroid therapy for greater than 3 months.

monotherapy. No patients in this cohort had been treated with methotrexate.

Metabolic Bone Disease

Among the 27 patients receiving steroid therapy for greater than 3 months, 21 (78%) patients had not received pharmacologic therapy for prevention of metabolic bone disease. Preventive measures for patients on prolonged corticosteroid therapy included calcium and vitamin D supplements, bisphosphonates, or hormone replacement therapy. Twenty of 27 (78%) had not undergone bone mineral density scanning.

Colorectal Cancer Screening

A total of 10 patients with ulcerative colitis or Crohn's colitis had either left-sided or extensive colonic disease with duration of disease for 8 yr or greater. Information regarding colonoscopic surveillance was available in nine patients. Three of nine (33%) patients meeting indications for biannual colonoscopy had not undergone colonoscopy within the appropriate interval. There were no differences between patients with Crohn's disease and those with ulcerative colitis with regard to the likelihood that they had undergone screening colonoscopy at appropriate intervals.

A summary of the major findings which illustrate suboptimal care of patients with IBD is presented in Table 4.

DISCUSSION

Guidelines for management of mild-to-moderate Crohn's disease and ulcerative colitis have been available for many years and have not changed significantly (1, 2, 4–6). Thus far, no studies have assessed whether patients with IBD receive care in accordance with practice guidelines. We found that the management of IBD is often suboptimal as evidenced by underdosing of maintenance medications, prolonged use of steroids, underutilization of steroid-sparing agents, and inadequate attention to metabolic bone disease and screening for colorectal cancer.

Multiple studies and reviews on medical therapy for IBD suggest that the therapeutic benefits of 5-ASA agents are

dose related and are rarely achieved at lower doses (7–11). Although the data for use of these medications as first line agents is more convincing for ulcerative colitis than for Crohn's disease, higher doses of pentasa may be required to achieve remission in patients with Crohn's disease (12). In our study, greater than 60% of symptomatic patients were not receiving the optimal dose of aminosalicylates although these patients were tolerating lower doses of these medications.

Studies have also demonstrated that topical therapy in combination with oral agents is an effective means of inducing and maintaining remission in distal ulcerative colitis (13, 14). We found that 75% of symptomatic patients with distal disease were not receiving topical 5-ASA agents.

Perhaps the most striking finding in this study pertains to the use of corticosteroids. While studies have shown that steroid therapy may be effective in the induction of remission in both Crohn's disease and ulcerative colitis, controlled trials have shown that steroids are ineffective as maintenance therapy for Crohn's disease and ulcerative colitis (7, 15–17). We found that prolonged corticosteroid therapy was common among our patient cohort. In the preceding 6 months, more than 75% of the patients who been treated with steroids had received prolonged steroid therapy. Nearly one-half of the patients receiving prolonged steroid therapy had mild disease, and the median dose of prednisone did not differ between patients with mild *versus* moderate to severe disease. While there may be many reasons for the continuation of steroid therapy, these findings suggest that corticosteroids were often used for excessive duration even in patients with mild disease without a clear "exit" strategy utilizing alternative agents for induction of remission.

Immunomodulatory therapies with 6MP, azathioprine, and biologics such as infliximab provide one possible exit strategy for patients who are unable to taper off of steroid therapy. Immunomodulatory therapy with 6MP or azathioprine is effective in both ulcerative colitis and Crohn's disease for the induction and maintenance of remission (18, 19). Among patients who had received prolonged steroid therapy, we found that approximately 60% had not been started on therapy with azathioprine or 6-MP as steroid-sparing agents.

Furthermore, immunomodulatory agents, when used, were underdosed in greater than 80% of patients. While dosing of these agents could be limited by leukopenia or liver function test abnormalities, none of the patients in this study who were treated with 6-MP or azathioprine had a history of leukopenia or abnormal liver function tests either in the past or at the time of their clinical assessment. Furthermore, assessment of TPMT enzyme activity and metabolite levels was not utilized in determining the optimal dose of 6-MP and azathioprine.

Multiple studies have established that patients with IBD receiving prolonged corticosteroid therapy or those with longstanding disease are at greater risk of metabolic bone disease (20, 21). Bone loss is most rapid in the first few weeks to months of steroid therapy (21). While our study did not examine the full range of detrimental corticosteroid induced side effects, we did examine whether adequate pharmaco-

logic measures had been undertaken for the prevention of metabolic bone disease. We determined that 78% of patients who had received steroid therapy for greater than 3 months had not received any medical therapies to prevent metabolic bone disease and had not undergone bone mineral density scanning.

Numerous studies have established that the risk of colorectal cancer is significantly increased in patients with longstanding ulcerative colitis and Crohn's colitis and have established screening guidelines for patients with ulcerative colitis and Crohn's colitis (1, 22). In our patient group, one-third of the patient cohort with left-sided or extensive colitis and duration of disease for at least 8 yr had not undergone colonoscopy within 2 yr of their clinical assessment.

There are several potential limitations of this study, which preclude broad generalizations concerning the quality of care of patients with IBD. Our study involved ambulatory patients referred to a single tertiary care center. As such, our data may reflect the specific practice patterns of our referral base and may not be representative of the practice patterns of most gastroenterologists caring for patients with IBD. Furthermore, as it was focused on ambulatory patients who had predominantly mild or moderate disease, our study did not examine the quality of care of patients with severe disease who may have been admitted directly to a hospital.

In addition, this study did not address the important issue of patient compliance, which encompasses multiple behaviors that can impact on medical care. Patient compliance includes adherence to the treatment plan as outlined by the gastroenterologist. Our study did not examine possible discrepancies between the doses of medications, which were prescribed by gastroenterologists and those actually being taken by patients. In the only study on this subject, Kane *et al.* found a high rate of nonadherence with mesalamine among patients with quiescent ulcerative colitis (23). Patient compliance also includes adherence to scheduled appointments. Missed appointments may represent a lost opportunity for the gastroenterologist to modify the treatment plan. Patient compliance with medical therapy and appropriate clinical follow-up are important variables that impact on the quality of care of patients with IBD.

Finally, this study did not focus on factors relating to the expertise of physicians, such as number of years in practice, general experience in IBD, or impact of continuing medical education in IBD. In this regard, the introduction of practice guidelines for IBD in a tertiary care center has been shown in one report to reduce practice variation and result in an improved quality of care for patients (24).

In summary, our study found that symptomatic patients in our cohort were often being treated with suboptimal doses of maintenance medications including 5-ASA and immunomodulatory agents. Furthermore, patients were often treated with corticosteroids for prolonged periods without an attempt to employ steroid sparing agents. Finally, there were inadequate measures to prevent metabolic bone disease and colorectal cancer. Patient compliance, management decisions

by gastroenterologists, and patient tolerance of various therapies are all factors that influence the care of patients with IBD. Larger prospective studies will help to elucidate the most important factors that influence the quality of care of patients with IBD.

Reprint requests and correspondence: Sarathchandra I. Reddy, M.D., M.P.H., Division of Gastroenterology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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REFERENCES

1. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. *Am J Gastroenterol* 1997;92(2):204–11.
2. Hanauer SB, Meyers S. Management of Crohn's disease in adults. *Am J Gastroenterol* 1997;92(4):559–66.
3. Sachar DB. Ten common errors in the management of inflammatory bowel disease. *Inflamm Bowel Dis* 2003;9(3):205–9.
4. Kornbluth A, Sachar DR. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004;1371–85.
5. Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001;96:635–43.
6. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53(Suppl V):V1–16.
7. Hanauer SB. Inflammatory bowel disease. *N Engl J Med* 1996;334(13):841–8.
8. Sutherland LR, May GR, Shaffer EA. Sufasalazine revisited: A meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993;88:540–9.
9. Singleton J, Gitnick G, Hanauer S, et al. Response of Crohn's disease to oral Pentasa (controlled release mesalamine) as a function of disease location and prior therapy: Results of a multicenter study. *Gastroenterology* 1993;104:1293–300.
10. Sachar DB. Maintenance therapy in ulcerative colitis and Crohn's disease. *J Clin Gastroenterol* 1995;20:117–22.
11. Hanauer S, Schwartz J, Robinson M, et al. Mesalamine capsules for the treatment of active ulcerative colitis: Results of a controlled trial. *Am J Gastroenterol* 1993;88:1188–97.
12. Singleton JW, Janauer SB, Gitnick L, et al and the Pentasa Crohn's disease study group. Mesalamine capsules for the treatment of active Crohn's disease: Results of a 16 week trial. *Gastroenterology* 1993;104:1293–301.
13. Safdi M, de Micco M, Sninsky C, et al. A double blind comparison of oral versus rectal mesalamine vs combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867–71.
14. D'Abasio G, Pacini F, Cawam E, et al. Combined therapy with 5-aminosalicylic acid tablet and enemas for maintaining remission in ulcerative colitis: A randomized double-blind study. *Am J Gastroenterol* 1997;92:1143–7.
15. Summers RW, Switz DM, Sessions JT, et al. National cooperative Crohn's disease study: Results of drug treatment. *Gastroenterology* 1979;77:847.
16. Malchow H, Ewe K, Brandes JW, et al. European cooperative Crohn's disease study (ECCDS): Results of drug treatment. *Gastroenterology* 1984;86:249.
17. Baron JH, Connell Am, Kanaghinis TG, et al. Outpatient treatment of ulcerative colitis, comparison between three doses of oral prednisone. *BMJ* 1962;2:441–3.
18. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. *Am J Gastroenterol* 1996;91:423–33.
19. Stein RB, Hanauer SB. Medical therapy for inflammatory bowel disease. *Gastroenterol Clin North Am* 1999;28(1):297–321.
20. Stoffel EM, Wolf JL. Osteoporosis in inflammatory bowel disease. *Semin Inflamm Bowel Dis* 2002;Suppl 1(4):1–7.
21. Valentine JF, Sninsky AC. Prevention and treatment of osteoporosis in patients with inflammatory bowel disease. *Am J Gastroenterol* 1999;94(4):878–82.
22. Friedman S, Rubin PH, Bodian C, et al. Screening and surveillance colonoscopy in chronic Crohn's colitis. *Gastroenterology* 2001;120(4):820–6.
23. Kane SV, Cohen RD, Aikens JE, et al. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol* 2001;96(10):2929–33.
24. Tremaine WJ, Sandborn WJ, Loftus EV, et al. A prospective cohort study of practice guidelines in inflammatory bowel disease. *Am J Gastroenterol* 2001;96(2):2401–6.