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Ulcerative Colitis Disease Activity as Subjectively Assessed by Patient-Completed Questionnaires Following Orthotopic Liver Transplantation for Sclerosing Cholangitis

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To assess whether or not liver transplantation and subsequent immunosuppression with cyclosporine and prednisone affect ulcerative colitis symptomatology, we surveyed by questionnaire all 23 surviving patients with pretransplant colonoscopy-documented ulcerative colitis who were transplanted for primary sclerosing cholangitis between June 1982 and September 1985. At follow-up [89.8 ± 7.6 weeks (mean ± SEM], all six patients who had had asymptomatic colonoscopy-documented ulcerative colitis reported continued ulcerative colitis quiescence. Among the 17 patients who had had symptomatic colonoscopy-documented ulcerative colitis at time of liver transplantation, 88.2% reported improvement in overall ulcerative colitis severity ($P < 0.001$), with significant improvement in the frequency of bowel movements reported by 100%, in crampy abdominal pain by 87.5%, in bowel urgency by 75%, in the occurrence of pus or mucus in stool by 87.5%, in the incidence of ulcerative colitis flares by 81.8%, and in the number of days unable to function normally due to ulcerative colitis symptoms by 78.6% (all at least $P < 0.01$). These data demonstrate that ulcerative colitis symptom severity significantly improves following liver transplantation with immunosuppression with cyclosporine and prednisone.

KEY WORDS: liver transplantation; ulcerative colitis; cyclosporine; sclerosing cholangitis; quality of life.

Primary sclerosing cholangitis is a chronic cholestatic liver disease of unknown etiology that is found in association with inflammatory bowel disease, particularly ulcerative colitis (1–8). Liver transplantation has been used to treat individuals with advanced primary sclerosing cholangitis only recently (9–13).

Whether or not primary sclerosing cholangitis recurs following liver transplantation and what the effect of the persistent presence of inflammatory bowel disease might have upon the clinical course and quality of life of patients receiving a liver transplant for advanced primary sclerosing cholan-

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gitis are unknown. Immunological factors are thought to be important in the pathogenesis of both sclerosing cholangitis and the underlying inflammatory bowel disease (14–19). The present study was performed in a case series to evaluate ulcerative colitis symptomatology as assessed by patient-completed questionnaires following liver transplantation for end-stage liver disease.

MATERIALS AND METHODS

Between June 1982 and September 1985, a total of 35 patients with colonoscopy- and biopsy-documented ulcerative colitis underwent orthotopic liver transplantation (OLTx) at the University of Pittsburgh. The indication for OLTx was primary sclerosing cholangitis in 34 and congenital hepatic fibrosis in one. All patients were evaluated as potential liver recipients using the liver transplant protocol, which includes a full colonoscopy, in use at the institution. All the patients had an intact colon at time of transplant. Of these 35 patients, 12 died within 139 ± 55 days (mean ± SEM) of surgery.

The surviving 23 patients were sent a detailed questionnaire to assess their perception of their ability to function in usual activities, the status and severity of ulcerative colitis symptoms, medication usage, and occurrence of and treatment for ulcerative colitis flares (see Appendix). The response rate was 100%; in addition, follow-up phone calls were made to clarify ambiguous responses and to obtain missing information. Subjects were asked to classify the ulcerative colitis symptoms and severity, during the year prior to transplant and during the three month period prior to the time at which the questionnaire was completed, by indicating which of several categories provided best described a given symptom.

The data were analyzed using the McNemar test of symmetry to evaluate changes in the proportion of patients in ulcerative colitis symptom severity categories, comparing the year prior to OLTx and the follow-up time point, which was at a different postoperative time point for each patient. Because of the relatively small number of patients who had had symptomatic ulcerative colitis prior to transplantation ($N = 17$), frequency categories for crampy abdominal pain, rectal pain, bowel urgency, rectal bleeding, and the presence of pus or mucus in the stool were combined as follows: frequency of symptoms more than or equal to several times a week was classified as high frequency, while the occurrence of symptoms several times a month or less was classified as low frequency. The binomial test was used to examine proportions of patients who either improved or did not improve with respect to symptoms or functional status. Continuous data are reported as the mean ± SEM. Differences at the $P < 0.05$ level were considered to be statistically significant.

RESULTS

Quiescent Group. Six (26%) of the 23 patients had quiescent ulcerative colitis prior to liver transplantation and had not required treatment for their ulcerative colitis. Colonoscopy with multiple colonic biopsies documented pancolitis to be present in all. The indication for OLTx in these six patients was primary sclerosing cholangitis. This clinically quiescent ulcerative colitis subgroup of four males and two females was 34.7 ± 6.2 years of age at time of OLTx, and the duration of their follow-up post OLTx was 109.9 ± 5.9 weeks (range: 104–136 weeks). The daily immunosuppressive regimen in this group was 400.0 ± 44.7 mg of cyclosporine and 10.8 ± 0.5 mg of prednisone. At time of follow-up, five patients (83.3%) were working full-time and one was not working but able to care for herself at home. All six patients reported themselves to be free of ulcerative colitis symptoms following transplantation.

Symptomatic Group. Seventeen patients, 11 males and six females, had had symptomatic ulcerative colitis prior to transplantation. Seven of these patients (40%) had mild clinical ulcerative colitis, eight had moderate colitis (47%), and two (13%) had severe clinical colitis. The duration of ulcerative colitis prior to OLTx was 15.4 ± 1.9 years. (The initial onset had been mild in 29.4%, moderate in 47.1%, and severe in 23.5%). The course of the ulcerative colitis had been continuous in 35.3% and intermittent in 64.7%. Among the 11 patients with an intermittent course, the intervening attacks had been severe in two, moderate in seven, and mild in two. Prior to transplant, 66.7% of these patients had been treated for their ulcerative colitis with sulfasalazine, 46.7% with steroid enemas, 40.0% with Lomotil, 26.7% with prednisone, and 18.8% with azathioprine. Colonoscopy performed during evaluation for liver transplantation demonstrated pancolitis to be present in all 17 patients. Histologically, prior to transplantation, 80% of the subjects had minimal disease based upon a histologic examination of multiple colonic biopsies obtained at the time of the preoperative colonoscopy. Ten percent of the subjects had moderate and 10% had severe colitis histologically.

At time of transplant, the mean range was 39.8 ± 1.6 years; the indication for OLTx was primary sclerosing cholangitis in 16 and congenital hepatic fibrosis in one. In this subgroup of 17 patients with symptomatic ulcerative colitis prior to OLTx, the duration of follow-up was 82.7 ± 9.6 weeks. (range: 31–175 weeks). At time of follow-up, the daily immunosuppressive regimen was 383.8 ± 27.2 mg of cyclosporine and 13.8 ± 0.8 mg of prednisone; in

addition, 23.5% were taking sulfasalazine, and 5.9% were using diphenoxylate hydrochloride with atropine sulfate (Lomotil).

In the symptomatic group, in response to the question, "overall, since your liver transplant, are the symptoms of your ulcerative colitis better, worse or the same?", 82.4% indicated improvement, none reported a worsening, and 17.6% indicated no change ($P < 0.001$ compared to pre-OLTx). Of the three patients reporting no change, however, two reported that the overall severity of colitis symptoms continued to be moderate following OLTx and one reported a shift from severe to moderate overall colitis severity.

A separate question was asked about overall symptom severity. During the year prior to transplant, the overall severity of colitis symptoms was rated as having been severe by 35.3%, moderate by 52.9%, and mild by 11.8% of these patients. In contrast, at follow-up, 88.2% patients reported improvement, with 52.9% reporting no colitis symptoms, 29.4% mild symptoms, 17.6% moderate symptoms, and none indicating severe colitis symptoms ($P < 0.001$, pre- versus post-OLTx, mild versus moderate plus severe symptom categories combined).

The frequencies of various ulcerative colitis symptoms before and after transplantation are shown in Table 1. The percentages of patients who indicated improvement in symptom severity or frequency were calculated and tested using the binomial test; the results are summarized in Table 2. In assessing improvement, all stated levels of severity or frequency were used, and a shift from a more severe to a less severe category was considered to be improvement. Further, those patients reporting no abnormality prior to OLTx (eg, 1 to 2) bowel movements per day or a frequency of "never") were not considered to be "at risk" for improvement and thus were not included in the denominator for these calculations. As may be seen in Table 2, compared to the year prior to OLTx, there was significant improvement at time of follow-up in overall colitis symptom severity, and the frequency of occurrence of daily bowel movements, crampy abdominal pain, bowel urgency, the presence of pus or mucus in the stool, and the occurrence of flares. There was no significant improvement in either rectal pain or rectal bleeding. Among the eight patients experiencing a flare, the mean interval between OLTx and the first flare was 37.0 ± 9.1 weeks; the earliest flare reported occurred at 12 weeks, while one patient indicated the first flare to have occurred as late as 85 weeks. Nine patients reported that colonoscopy ($N = 7$) or barium enema ($N = 2$) had been performed during the follow-up period (No patient reported the occurrence of colon surgery following transplantation.) The histological appearance in 16 of the 17 patients with symptomatic colitis

TABLE 1. FREQUENCY OF ULCERATIVE COLITIS SYMPTOMS IN 17 SYMPTOMATIC PATIENTS BEFORE AND AFTER TRANSPLANTATION

		Percent of patients	
Symptom	*Frequency*	*Before*	*After*
Daily bowel movements ($P < 0.001$)*	low[a]†	11.8	88.2
	high[b]	88.2	11.8
Crampy abdominal pain ($P < 0.01$)	low[c]	23.5	82.4
	high[d]	76.5	17.6
Bowel urgency ($P < 0.01$)	low[c]	5.9	64.7
	high[d]	94.1	35.3
Pus or mucus in stool ($P < 0.002$)	low[c]	47.1	94.1
	high[d]	52.9	5.9
Rectal bleeding	low[c]	70.6	100
	high[d]	29.4	
Rectal pain	low[c]	58.8	94.1
	high[d]	41.2	5.9

*Test of differences in proportions before and after transplantation.

†a = 1–2 bowel movements per day; b = three or more bowel movements per day; c = occurrence several days a month or less; d = occurrence several times a week or more.

TABLE 2. ULCERATIVE COLITIS SYMPTOM IMPROVEMENT IN 17 PATIENTS FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

	Number with symptom	*Number with improvement*	*Significance level** (P)
Overall symptom severity	17	15 (88.2%)	<0.001
Daily bowel movements	15	15 (100.0%)	<0.001
Crampy abdominal pain	16	14 (87.5%)	<0.001
Rectal pain	13	8 (61.5%)	NS
Bowel urgency	16	12 (75.0%)	<0.01
Pus or mucus in stool	14	12 (85.7%)	<0.001
Rectal bleeding	15	10 (66.7%)	NS
Flares requiring treatment	11	9 (81.8%)	<0.006

*Binomial test, one-tailed. NS = not statistically significant.

TABLE 3. NUMBER OF DAYS UNABLE TO FUNCTION NORMALLY IN DAILY ACTIVITIES BECAUSE OF ULCERATIVE COLITIS SYMPTOMS OR COMPLICATIONS—RESPONSES OF 17 SYMPTOMATIC PATIENTS

	Pre-OLTx	*Post-OLTx*
None	3 (17.6%)	8 (47.0%)
1–2 per month	4 (23.5%)	7 (41.2%)
3–4 per month	2 (11.9%)	2 (11.8%)
>6 but <30 per month	4 (23.5%)	0
Nearly every day	4 (23.5%)	0

TABLE 4. OVERALL ABILITY TO FUNCTION FOLLOWING LIVER TRANSPLANTATION—RESPONSES OF 17 SYMPTOMATIC PATIENTS

9 (52.9%)	Working full time
1 (5.9%)	Working part time
3 (17.6%)	Well enough to work but are not working for other reasons
3 (17.6%)	Not able to work but able to care for themselves at home
1 (5.9%)	Requiring intermittent hospitalization unrelated to ulcerative colitis

during the follow-up period revealed mild colitis in six (46%), moderate colitis in six (47%), and severe colitis in three (18%). This distribution in terms of disease severity graded histologically did not differ significantly from that observed prior to transplantation.

Two aspects of quality of life were assessed: the first involved the impact of ulcerative colitis symptoms on the ability to function normally in daily activities, and the second assessed the overall impact of liver transplantation with immunosuppression as estimated by changes in the ability to work or carry out normal activities. As may be seen in Table 3, the impact of ulcerative colitis symptomatology on the ability to function normally was substantially less, but not eliminated, during the follow-up period. Of the 17 with symptomatic disease, 11 patients reported improvement and six reported no change; of these six, three reported that there had been no days during which their ulcerative colitis symptoms had prevented them from functioning normally during the year prior to transplant. Thus, there was overall improvement in 11 of the 14 patients (78.6%) who had been unable to function normally at least once a month pretransplant ($P < 0.006$). None of these patients had been able to function normally, as measured by the ability to work or participate in usual activities, at time of transplantation because of the severity of their liver disease. Thus, the responses to the question "which category best describes your present activity?" primarily reflect the effect of transplantation, which reversed the end-stage liver disease. As may be seen in Table 4, altogether 13 of the 17 patients reported an improvement in their overall ability to pursue normal activities following liver transplantation ($P < 0.006$). This finding suggests that ability to work or feeling well enough to work following transplantation may have reflected factors other than ulcerative colitis disease activity *per se*.

DISCUSSION

The results of this study using a survey questionnaire suggest that ulcerative colitis disease activity as subjectively characterized by each patient significantly improves in the short run (31–175 weeks) following liver transplantation for end-stage liver disease. This improvement following transplantation could be ascribed to the transplant, the use of cyclosporine and prednisone, the changes in lifestyle or emotional support, or the mandatory period of rest. With respect to the possible role of immunosuppression, it is to be noted that short-term cyclosporine administration to small groups (N = 1–6 patients) with ulcerative colitis or Crohn's disease has been reported to improve symptoms in the majority of such patients (20–22). Similarly, corticosteroids also have been used successfully to treat ulcerative colitis. Thus it should be noted that in the current study, the steroid portion of the immunosuppression regimen was 10.8 ± 0.5 mg/day of prednisone among the six asymptomatic patients and 13.8 ± 0.8 mg/day among the 17 patients who had been symptomatic prior to transplantation. In addition, psychological factors also may play a role in perceived improvement. The reversal of end-stage liver disease, resulting in a lessened inward focus on status of physical being and an increased interest in or more hopeful attitude toward outward activities that have come within reach as a result of the liver disease having been "cured," may be a reason for the observed improvement (23–25).

The findings of this study also raise questions about the perception of ulcerative colitis symptoms and their severity. Specifically, prior to transplantation, the study group could be divided into two groups: those with and those without ulcerative colitis symptoms. The first unanswered question arises from the fact that both of these groups were comprised of individuals with comparable colonoscopy-documented pancolitis. The second unanswered question

arises from the information provided by the 17 patients who had had symptomatically active ulcerative colitis prior to transplant: Why is it that during the follow-up period, 17.6% of these patients reported no change in response to the question "are the symptoms of your ulcerative colitis better, worse, or the same," when at the same time they indicated the overall severity of their colitis to have decreased at the time of follow-up? Such discrepancies emphasize the problem of deciphering the interrelationships of perceived improvement, recall of symptomatology, and relative changes either in actual disease activity or symptom severity. Specific answers to the questions and issues raised are beyond the scope of the current study. Future studies, which may include such objective measures as colonoscopy findings or adsorption/absorption assessment of topical versus humoral delivery of cyclosporine or new immunosuppressive drugs such as FK506, may provide useful information. Neuropsychological assessments might also increase our understanding. Finally, however, it will be interesting to determine how long the currently reported survey questionnaire findings of ulcerative colitis symptom severity improvement will continue.

APPENDIX: QUESTIONNAIRE USED TO OBTAIN INFORMATION FROM PATIENTS CONCERNING ULCERATIVE COLITIS SYMPTOMS

1. Overall, since your liver transplant, are the symptoms of your colitis better, worse, or about the same? (circle one)
2. Compare the severity of your colitis symptoms during the year before you had your liver transplant and now (during the last three months). Use the code shown below.
   The year before transplant____ Now____
   0 = no colitis symptoms
   1 = mild colitis symptoms
   2 = moderate colitis symptoms
   3 = severe colitis symptoms
3. On the average, how many bowel movements were/are you having per day? Use the code shown below.
   The year before transplant____ Now____
   A = 1–2 per day
   B = 3–5 per day
   C = 6 or more per day
4. On average, how often do/did you experience crampy abdominal pain in the time periods specified? Use the code shown below.
   The year before transplant____ Now____
   0 = never
   1 = several times per month
   2 = several times per week
   3 = just about every day
5. On average, how often do/did you have rectal pain in the time periods specified? Use the code shown below.
   The year before transplant____ Now____
   0 = never
   1 = several times per month
   2 = several times per week
   3 = just about every day
6. On average, how often do/did you have a sense of bowel urgency during the time periods indicated? Use the code shown below.
   The year before transplant____ Now____
   0 = never
   1 = several times per month
   2 = several times per week
   3 = just about every day
7. On average, how often do/did you experience pus or mucous in your stool during the time periods specified? Use the code shown below.
   The year before transplant____ Now____
   0 = never
   1 = several times per month
   2 = several times per week
   3 = just about every day
8. On average, how often do/did you have bleeding from your rectum during the time periods specified? Use the code shown below.
   The year before transplant____ Now____
   0 = never
   1 = several times per month
   2 = several times per week
   3 = just about every day
9. On average, how many flares of your colitis *requiring treatment in the hospital* did you have during the year before your transplant and during the entire time since your transplant and now. (Put the number of flares on the corresponding line).
   The year before transplant____
   The time after transplant____
10. On average, how many flares of your colitis did you have that *required you to see your doctor as an outpatient* during the year before your transplant and during the entire time since your transplant and now. (Put the number of flares on the corresponding line).

The year before transplant____
The time after transplant____

11. On average, how many days per month were you unable to function completely normally in your daily activities because of ulcerative colitis or its complications during the year before your transplant and during the last 3 months? Use the code shown below.
The year before transplant____ Now____
A = 1–2 days per month
B = 3–4 days per month
C = 4–6 days per month
D = more than 6 but not every day
E = nearly every day
12. Which description best describes your present activity? (Circle the correct answer)
1. working full-time
2. working less than 20 hours per week
3. not able to work but caring for self at home
4. requiring hospitalization intermittently
5. requiring hospitalization constantly
6. feel well enough to work but not working for other reasons
13. If your colitis became active after your liver transplant, what was the length of time between your transplant and the onset of your colitis activity? (Please record the answer in weeks)
14. For each time period below, what was your dose (number of tablets per day) of Azulfidine (sulfasalazine)?
The year before transplant____ Now____
15. For each time period below, what was your dose (in milligrams per day) of prednisone?
The year before transplant____ Now____
16. For each time period below, what was your dose (number of tablets per day) of Lomotil or Imodium?
The year before transplant____ Now____
17. For each time period below, what was your dose (number of tablets per day) of Imuran (azathioprine)?
The year before transplant____ Now____
18. For each of the time periods below, put a check mark if you used steroid enemas at any time (for example, Proctofoam, Cortenema).
The year before transplant____ Now (the last three months)____
19. *List all of the medications you are currently taking.* You should also include in the list, all over-the-counter medications such as aspirin, tylenol, metamucil, vitamins, etc. (please print).
For each medication provide:
Name_____
Tablet strength_____
No. of tablets/dose_____
No. of doses/day_____
20. Have you had any surgery on your colon since your transplant?
Yes No I don't know (circle one)
20a. If yes, what was/were the reasons?
____ cancer in my colon
____ abnormal colon biopsies but not cancer (dysplasia)
____ severe colon symptoms that could not be cured by medications
____ large, distended colon with abdominal pain (toxic megacolon)
____ severe hemorrhage
____ perforation (hole) in the colon
____ stricture of the colon
____ for treatment of complications of ulcerative colitis not directly related to the colon (extraintestinal complications)
____ I don't know
____ other reasons (explain)_____
20b. If yes, what were the approximate dates of surgery?
_____
_____
21. Have you developed:
21a. Cancer of the colon?
Yes No I don't know (circle one)
21b. Dysplasia of the colon?
Yes No I don't know (circle one)
22. Have you had a colonoscopy since your transplant? Yes No
If yes, what was the approximate date?
What was the reason?
What were the results (if known)?
23. Have you had a barium enema since your transplant? Yes No
If yes, what were the dates?____
What was the reason?
What were the results (if known)?
24. When you were originally diagnosed as having ulcerative colitis how much of your colon was involved?
____ my entire colon
____ just the left colon
____ rectum and sigmoid colon
____ just the rectum
____ don't know

25. Which description best characterized the initial onset of your colitis? (Check one)
    ___ 1. *Mild*—less than four bowel movements a day; no fever, weight loss or anemia.
    ___ 2. *Moderate*—4–5 bowel movements a day; loose usually with *blood*, sometimes with *crampy abdominal pain* relieved by passing the bowels; occasionally *fatigue* or lowered appetite and *weight loss* and sometimes the presence of *fever*
    ___ 3. *Severe*—more than six stools per day; usually large amounts of constant liquid stool, with loss of weight, low blood count (anemia), considerable bleeding from the colon, fever, extreme fatigue, weakness and prostration

    25a. If the course of your colitis, since it first started, has been one consisting of periods of worsening alternating with periods of quiescence (minimal or no symptoms), were most of your attacks mild, moderate, or severe?
26. Which description best describes the course of your colitis since initial onset? (Check one)
    ___ 1. Intermittent attack of symptoms with complete resolution between attacks
    ___ 2. No further attacks since initial attack
    ___ 3. Mostly continuous symptoms without remission
27. When did you learn you had ulcerative colitis?
    Years:____ or Age:____
28. Since your transplant, has your doctor detected blood in your stool? (circle one)
    Yes No I don't know
29. What new medical problems, if any, have arisen since your transplant?

Thank you very much for completing the questionnaire. The space below is for you to give any additional information that you think would be helpful and for further explanation of any of your answers above.

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