Immunosuppression After Liver Transplantation for Primary Sclerosing Cholangitis Influences Activity of Inflammatory Bowel Disease

KRISTIN KAASEN JØRGENSEN,[*,‡,§] LINA LINDSTRÖM,[‖] MILADA CVANCAROVA,[¶] TOM H. KARLSEN,[*,‡,#] MARIA CASTEDAL,[**] STYRBJÖRN FRIMAN,[**] ERIK SCHRUMPF,[*,‡,§] AKSEL FOSS,[§,‡‡] HELENA ISONIEMI,[§§] ARNO NORDIN,[§§] KATHRINE HOLTE,[‖‖] ALLAN RASMUSSEN,[‖‖] ANNIKA BERGQUIST,[‖] MORTEN H. VATN,[*,§,¶¶] and KIRSTEN MURI BOBERG[*,‡]

*Section for Gastroenterology, ‡Norwegian PSC Research Centre, ‡‡Section for Transplantation Surgery, Department of Transplantation Medicine, Division of Cancer, Surgery and Transplantation, Oslo University Hospital, Rikshospitalet, Oslo, Norway; §Institute of Clinical Medicine, ¶Department of Biostatistics, University of Oslo, Norway; ‖Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; #Division of Gastroenterology, Institute of Medicine, University of Bergen, Bergen, Norway; **The Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden; §§Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Helsinki, Finland; ‖‖Department of Surgical Gastroenterology and Liver Transplantation, Rigshospitalet University of Copenhagen, Copenhagen, Denmark; and ¶¶EpiGen Institute, Campus Ahus, Akershus University Hospital, Lorenskog, Norway

BACKGROUND & AIMS: **Previous studies have shown conflicting results regarding the course of inflammatory bowel disease (IBD) after liver transplantation in patients with primary sclerosing cholangitis (PSC). We studied the progression of IBD in patients with PSC who have undergone liver transplantation. We also studied risk factors, including medical therapy, that could influence on IBD disease activity.**

METHODS: **In a longitudinal multicenter study, we analyzed data from the Nordic Liver Transplant Group on 439 patients with PSC who underwent liver transplantation from November 1984 through December 2006; 353 had IBD at the time of transplantation. We compared IBD activity before and after liver transplantation. Two hundred eighteen patients who had an intact colon and had undergone pretransplant and post-transplant colonoscopies were characterized further.**

RESULTS: **Macroscopic colonic inflammation was more frequent after liver transplantation than before liver transplantation (153 vs 124 patients; $P < .001$). The degree of inflammation decreased in 37 patients (17%), was unchanged in 93 patients (43%), and increased in 88 patients (40%) ($P < .001$). The rate of relapse after transplantation was higher than that before transplantation ($P < .001$), and overall clinical IBD activity also increased ($P < .001$). Young age at diagnosis of IBD and dual treatment with tacrolimus and mycophenolate mofetil were significant risk factors for increased IBD activity after transplantation, whereas combination treatment with cyclosporin A and azathioprine had protective effects.**

CONCLUSIONS: **Immunosuppression affects IBD activity after liver transplantation in patients with PSC; a shift from present standard maintenance treatment of tacrolimus and mycophenolate mofetil to cyclosporin A and azathioprine should be considered for these patients.**

Keywords: Crohn's Disease; Colitis; Disease Progression; Therapy.

See editorial on page 524.

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease that eventually leads to cirrhosis and liver failure. PSC is a major cause of liver transplantation (Ltx) in the Nordic countries, constituting approximately 17% of all indications.[1] It is strongly associated with inflammatory bowel disease (IBD), with a prevalence of IBD among PSC patients in Northern Europe in the range of 70% to 84%.[2–4] IBD in PSC seems to differ phenotypically from IBD without concurrent liver disease in several aspects. The frequency of pancolitis, rectal sparing, and backwash ileitis is higher,[5,6] and the clinical course of colitis is milder.[6,7] Nevertheless, the risk of colorectal neoplasia is increased beyond the risk seen in IBD alone,[8,9] with an even further increase after Ltx.[10,11]

Abbreviations used in this paper: CI, confidence interval; CMV, cytomegalovirus; CsA, cyclosporin A; IBD, inflammatory bowel disease; Ltx, liver transplantation; MMF, mycophenolate mofetil; PSC, primary sclerosing cholangitis.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2012.12.027

Because some of the immunosuppressive drugs that are administered after Ltx also are used as treatment for refractory IBD, one might anticipate that the clinical course of pre-existing IBD in PSC should improve after Ltx. Previous studies, however, have shown conflicting results. Some studies have depicted a mainly unchanged or improved course of IBD in PSC after Ltx,[12–14] whereas others have found disease deterioration in a majority of patients.[15–17] We hypothesized that the variable outcome of IBD activity after Ltx might be influenced by the immunosuppressive regimens or by other factors related to the transplantation.[16–18]

In a multicenter study within the Nordic Liver Transplant Group we aimed to describe the natural history of IBD in PSC patients undergoing Ltx by comparing the clinical course of IBD before and after Ltx by a longitudinal follow-up evaluation of the patients. We also aimed to identify potential risk factors associated with altered activity of IBD after Ltx.

Patients and Methods

Patients

The Nordic Liver Transplant Registry[1] was used to identify a total of 461 PSC patients who underwent Ltx from November 1984 through December 2006. Twenty-two patients (5%) were excluded because the diagnosis of PSC could not be confirmed by histology or they were lost to follow-up evaluation. Among the remaining 439 patients, 122 (28%) underwent Ltx in Gothenburg, Sweden; 95 (22%) underwent Ltx in Oslo, Norway; 93 (21%) underwent Ltx in Stockholm/Uppsala, Sweden; 83 (19%) underwent Ltx in Helsinki, Finland; and 46 (10%) underwent Ltx in Copenhagen, Denmark. PSC was diagnosed according to accepted criteria, with typical findings of bile duct irregularities on cholangiography.[19] The diagnosis of IBD was based on conventional clinical, endoscopic, and histopathologic criteria.[3] All patients were followed up regularly at the transplant centers. The medical records were reviewed by experienced physicians at each transplant center. Data regarding the activity of IBD before and after transplantation were retrieved according to a common protocol. When necessary, the patients' medical charts were obtained from the referring hospitals.

Macroscopic Findings at Endoscopy

The macroscopic inflammatory findings at colonoscopy were recorded at the last colonoscopy before Ltx, the first after Ltx, and at the examination closest in time to the last clinical follow-up evaluation. The colonoscopies both before and after Ltx were performed as part of the general follow-up evaluation of PSC-IBD patients, independently of the time of transplantation. The inflammation was graded as normal, mild, moderate, or severe.[20] Of the 2 endoscopies after Ltx, the one with the most severe inflammation was selected for comparison with the pre-Ltx investigation. The diagnosis of de novo IBD was based on macroscopic and microscopic findings at endoscopy after Ltx and required normal macroscopic and microscopic findings before Ltx.

Inflammatory Bowel Disease Relapses

The frequency of IBD relapses during the last 3 years before and the first 3 years after Ltx were recorded. Patients with a history of IBD less than 2 years before Ltx and/or less than 2 years of follow-up evaluation after Ltx were excluded for this purpose. The definition of relapse was based on a modification of the relapse criteria in 2 previous studies.[21,22] A relapse was considered present if one or more of the following events were recorded: (1) an increase in IBD-related symptoms leading to a consultation by a specialist, (2) initiation or increase in dose of anti-inflammatory medication for IBD, (3) increase in stool frequency related to IBD, (4) macroscopic fecal blood related to IBD, (5) verified IBD-related inflammatory findings at endoscopy, and (6) colectomy owing to high IBD disease activity.

Inflammatory Bowel Disease Activity Curves

Based on the investigators' general impression of all factors related to IBD activity, the total course of IBD in each patient was recorded from diagnosis of IBD until Ltx and from Ltx to the last clinical follow-up or colectomy, according to 5 disparate predefined IBD activity curves, based on a modification of previously reported disease course patterns (Figure 1).[23]

Medication

We obtained detailed records of the medical therapy for PSC and IBD and of the immunosuppressive therapy after Ltx. Because a majority of the transplanted patients used drugs that have a potential effect on IBD activity, we wanted to study the effect of such medication on the IBD activity after Ltx. The use of a specific drug was defined as a minimum of 3 months' medication during the first 6 months after transplantation. Acute cellular rejections treated with steroids, antithymocyte globulin, or muromonab-CD3, and treated cytomegalovirus (CMV) infections during the first 6 months after Ltx were recorded. We also recorded the recipients' HLA status.

The study was approved by the ethical committees in the respective countries.

Statistical Analyses

Data were described with proportions for categoric variables and median with range for continuous variables. Crude associations between categoric variables were assessed with the chi-square test or the Fisher exact test, when appropriate. For comparison of dependent observations such as the frequency of colonic inflammation before and after Ltx, the McNemar test was used. Cumulative risk of de novo IBD-free survival and patient survival after Ltx were calculated using the Kaplan–Meier method, and survival times were compared with the log-rank test. The different outcomes in IBD activity after Ltx were presented as percentages with 95% confidence intervals (CI) where CIs were constructed using a normal distribution approximation. The severity of IBD activity before and after Ltx in each patient and the rate of relapse before and after Ltx were compared using the Wilcoxon signed-rank test for paired data. The cumulative risks of colectomy caused by refractory IBD before and after Ltx were estimated using competing risk regression analysis,[24,25] where colectomy for refractory IBD defined the main event of interest and colectomy owing to other reasons and death were the competing events. The effect of medication and other factors on the course of IBD after Ltx was studied using Cox proportional hazards models stratified by the different transplant centers. P values of .05 or less were considered statistically significant. All statistical analyses were performed with SPSS version 18 (IBM Corp,