Karolinska Institutet

Institutionen för Medicin, Huddinge

Inflammatory Bowel Disease, Colorectal Neoplasia and Treatment with Ursodeoxycholic Acid in Primary Sclerosing Cholangitis

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ABSTRACT

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease closely associated with inflammatory bowel disease. PSC is progressive and ultimately leads to death or need for liver transplantation. Patients are also at high risk of developing colorectal neoplasia (CRN).

Aims: The main aim of this thesis was to study IBD in patients with PSC. We aimed to describe the phenotype of Crohn's disease (CD) in patients with PSC and to determine the risks of CRN and IBD activity before and after liver transplantation. The secondary aim was to study the drug ursodeoxycholic acid (UDCA) in patients with PSC and UDCAs effect on the development of CRN and survival in PSC.

Results: In Paper I we investigated CD in 28 patients with PSC and compared them with a matched control group of 46 patients with CD without PSC. We found that smoking, perianal fistulas, bowel strictures and small bowel involvement were rare in PSC patients. We also found a significantly increased risk for development of CRN in PSC patients (P=0.001, log rank).

Papers II and III are multicentre studies of IBD in PSC patients undergoing liver transplantation (OLT), and include all liver-transplanted Nordic PSC patients (n=439). The IBD activity was increased after transplantation and the choice of immunosuppression influenced the activity. A univariate analysis identified age <20 years at diagnosis of IBD, use of tacrolimus, and dual therapy with tacrolimus and mycophenolate mofetil as significant risk factors for worsening of IBD, whereas dual treatment with cyclosporine A and azathioprine showed a significant protective effect. The cumulative risk of any type of neoplasia in the group of patients still at risk after OLT (n=244, 36 cases of neoplasia) was higher than the corresponding number before OLT (353, 52 cases) (HR: 1.9: 95% CI 1.3-2.9, P = 0.002).

In Papers IV and V the effect of UDCA at a dose of 17-23 mg/kg in patients with PSC was evaluated using an extended follow-up of a previous randomised controlled trial. In paper IV all patients with concomitant IBD at risk for CRN were included (n=98). There was no detectable difference in dysplasia- and cancer-free survival when the groups were compared using the Kaplan-Meier method (p = 0.73 log-rank test). Paper V evaluated the effect of UDCA on long-term survival without liver transplantation. No difference in endpoint-free survival was detected between UDCA treated and untreated patients. However we found that a reduction in alkaline phosphatase (ALP) by 40% or more was associated to significantly better long-term survival in patients with PSC (P = 0.0001, log rank).

Conclusions: Our studies show that patients with IBD and PSC have a high risk of developing CRN regardless of IBD phenotype, and that the risk of CRN and IBD activity increases after OLT and appears correlated to the type of immunosuppression given. In patients undergoing OLT a shift from the present standard maintenance treatment with tacrolimus and mycophenolate mofetil to cyclosporine A and azathioprine should be considered. The evidence that UDCA improves survival in PSC or that it should be used as a chemopreventive agent in PSC-IBD is weak. ALP is a marker for disease progression in PSC and should be used in future clinical trials.

Keywords: Inflammatory bowel disease, colorectal neoplasia, ursodeoxycholic acid, immunosuppression, liver transplantation

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