Immunosuppressive Treatment of Primary Sclerosing Cholangitis
Current Status and Recommendations

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Summary

Primary sclerosing cholangitis (PSC) is a disease of unknown aetiology characterised by focal as well as diffuse destruction of bile ducts. The disease frequently, but not always, occurs in association with an inflammatory bowel disease, usually ulcerative colitis and less frequently Crohn’s disease. A small number of cases occur in the absence of a concomitant colonic disease.

In addition to being associated with inflammatory bowel disease, PSC occurs predominantly in individuals who are HLA-B8, Dr3, DW52,53 positive. These same HLA antigens occur at increased rates in individuals with other putative autoimmune diseases.

As a result of these disease and genetic associations, PSC is often conceptualised as an autoimmune disease process. For this reason, immunosuppressive agents have been utilised and currently are the principal agents used in the treatment of patients with PSC. The rationale for the use of these agents, their efficacy, administration schedules and the risks associated with their use are presented. In general, individuals with early stage disease should be treated with immunosuppressive agents that disrupt the pathogenesis of the disease process. In contrast, late stage disease that is effectively irreversible ought to be treated symptomatically with agents that alleviate disease consequence.
Primary sclerosing cholangitis (PSC) is a liver disease of unknown aetiology characterised by acute and chronic inflammation leading to obliterative fibrosis of the intra- and extra-hepatic bile ducts. Prior to the loss of bile ducts, focal strictures and saccular dilatations characterise the disease both radiographically [by endoscopic retrograde cholangio-pancreatography (ERCP)] and histopathologically.

Typically, the course of PSC is one of slow progression, over 5 to 20 or more years, to cirrhosis and, ultimately, liver failure.\textsuperscript{1-3} In a minority of patients (<10%), PSC will degenerate to cholangiocarcinoma. The majority of cases of PSC are recognised and referred for medical treatment only after they have shown evidence of biochemical and clinical overt hepatic disease which is cholangiographically documented.\textsuperscript{12} This is because, in most cases, the diagnosis is established using a combination of clinical, biochemical, histological and radiological criteria. The characteristic findings of ERCP represent the current gold standard for establishing a diagnosis of PSC.\textsuperscript{4,5}

Typically, an individual with PSC is a young adult male, with established, albeit quiescent, inflammatory bowel disease, who is recognised as having PSC as a result of the presence of biochemical finding of cholestasis. The relationship between PSC and inflammatory bowel disease is well established: approximately 75% of PSC patients have ulcerative colitis. Less frequently, PSC is associated with Crohn’s disease.\textsuperscript{6} Moreover, it is well established that human leucocyte (HLA) antigens B8, DR3 and DW 52,53 occur in individuals with PSC and ulcerative colitis at a rate 10 times higher than that present in the general population.\textsuperscript{7} These same HLA antigens are also seen commonly in individuals with a wide variety of putative autoimmune diseases.\textsuperscript{8}

The presence of these inflammatory bowel and other autoimmune diseases, as well as these genetic associations between PSC and certain HLA antigens, suggest and are consistent with a possible, albeit unproven, autoimmune pathogenesis for PSC.\textsuperscript{2,7-14} As a result, it is currently widely held that PSC is a disease process characterised by an autoimmune destruction of the biliary system in genetically predisposed individuals initiated as a result of a prior viral or bacterial infection.\textsuperscript{7}

When thinking about the disease process of PSC, it is important to recognise the fact that bile ductular cells, unlike hepatocytes, do not normally regenerate.\textsuperscript{15} As a direct result, the consequence of any disease process that primarily involves biliary epithelial cells is ultimately characterised by a reduction in the number of functioning bile ducts. With continued disease progression, these become inadequate to sustain normal bile flow. Thus, any therapy, if it is to be effective long term for a disease such as PSC or primary biliary cirrhosis, should begin at an early stage of the disease, at a point in time before bile duct injury has reached a point where inadequate numbers of functioning bile ducts remain to sustain normal hepatobiliary function.

Based on this rationale, the histopathology of PSC is often divided into 4 distinct stages. These are: stage I, bile duct injury; stage II, bile ductular proliferation as a response to injury; stage III, bile duct loss with portal fibrosis; finally, stage IV, a cirrhosis characterised by bile duct loss, ductular proliferation, portal fibrosis and hepatocyte regeneration as nodules. Unfortunately, because the disease process in PSC is usually indolent, the disease is often only recognised late, at a time when signs and symptoms of liver failure are evident. As a result, therapy is often only supportive until the hepatobiliary failure is sufficiently advanced to justify liver transplantation.\textsuperscript{16} When detected early, before irreversible bile duct injury has occurred, medical therapy of PSC may prevent or at least delay the otherwise steady progression of the disease to hepatobiliary failure and the need for orthotopic liver transplantation.

1. Treatment Approaches

At present, there are no established therapies for PSC. Nonetheless, several different medical therapies have been proposed and are being used in an