

DRAFT

Working Group 5. Autoimmune Liver Disease

Introduction & Background

Autoimmune liver diseases include autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. All three diseases can be severe, progressive and lead to cirrhosis and death from end-stage liver disease. Because none of the currently available therapies are curative, these diseases remain important causes of liver failure requiring transplantation. Strikingly, these diseases recur in 10 to 30% of patients after liver transplantation.

Autoimmune hepatitis or “AIH” affects ~ 170 persons per million population. AIH occurs most commonly in women particularly during adolescence, but this disease can occur at any age, in both men and women and in persons of any race or ethnicity. AIH often results in severe hepatitis that can rapidly progress to cirrhosis. Diagnosis is based upon clinical features, the presence of autoantibodies, histology and the absence of other causes such as viral hepatitis. Standard immunosuppressive therapy using corticosteroids with or without azathioprine is effective in decreasing mortality, but progression to cirrhosis while on therapy may occur. In most cases, therapy must be continued lifelong, and numerous side effects of therapy are common. If therapy is delayed or ineffective, liver transplantation may be required. Currently, 3% of adult liver transplants performed in the U.S. are for autoimmune hepatitis.

Primary biliary cirrhosis or “PBC” is a progressive cholestatic liver disease that affects ~ 400 adults per million population. The diagnosis is usually made in middle age, and women outnumber men by a ratio of 10:1. The disease is characterized by inflammation and gradual destruction of small intrahepatic bile ducts. Diagnosis is based upon biochemical tests, compatible liver histology and the presence of antimitochondrial antibodies (AMA) or disease-specific antinuclear antibodies. PBC slowly, but almost invariably, progresses to cirrhosis over 10 to 30 years, and the diagnosis is often made late in its natural history. The hydrophilic bile acid ursodiol is effective in decreasing liver injury due to cholestasis and in retarding the progression of disease. Patients who develop decompensated cirrhosis require liver transplantation. Presently, 4% of liver transplants in the U.S. are done for PBC.

Primary sclerosing cholangitis or “PSC” is also a progressive cholestatic liver disease that affects ~ 130 persons per million population. It occurs in children and young adults and is more common in men than women. A majority of patients have associated inflammatory bowel disease, primarily ulcerative colitis. PSC is marked by inflammation and destruction of the intra- and extra-hepatic bile ducts (larger than those affected by PBC). The diagnosis is made based upon typical clinical presentation, biochemical tests, compatible liver histology and strictures of bile ducts as detected by endoscopic retrograde cholangio-pancreatography (ERCP) or imaging. PSC is a progressive disease, which leads to gradual sclerosis of major bile ducts with resulting cholestasis, fibrosis and cirrhosis. Patients with PSC are at high risk of cholangiocarcinoma regardless of the stage of disease. Those with ulcerative colitis also have an increased risk of colon cancer. There are no proven curative therapies for PSC, but high doses of ursodiol may retard progression. At present, 5% of adult liver transplants in the U.S. are done for PSC.

Recent Research Advances

A major focus of research has been on the nature of autoimmunity itself. The causes that trigger autoimmunity (afferent limb) are unknown, and the pathogenesis of injury (efferent limb) is only poorly defined. At issue is why patients develop an aberrant immune response to a self-antigen and how this breakdown of tolerance leads to clinical disease. Theories for the basis of autoimmunity include genetic predisposition, inherited abnormalities of immune regulation, molecular mimicry between an environmental or infectious agent and an autoantigen, and occult infectious disease that triggers an autoimmune process. Recent clues to the etiology of autoimmunity come from studies of inherited diseases of immune regulation in which dysregulation of T cell proliferation is associated with multiple autoimmune conditions. These studies point to immune regulation as central to the etiology of autoimmune diseases.

Ongoing research in autoimmune liver diseases has focused on identifying autoantigens and the association of immune responses (largely CD4 and CD8 T cell responses) to these antigens with disease manifestations. Autoimmune hepatitis has a strong genetic component and has been linked to an extended HLA haplotype (A1-B8-DR3). The autoantigens of classical (type I) autoimmune hepatitis are directed towards multiple nuclear antigens, while those in a subgroup of disease (type II) have been shown to be specific for the hepatic drug-metabolizing enzyme, CYP 2D6. PSC also exhibits strong genetic susceptibility linked to three HLA class II haplotypes. The autoantigens in PSC have not been defined, although many patients have antibodies to neutrophil nuclear antigens that are similar to perinuclear neutrophil cytoplasmic antibodies present in ulcerative colitis. PBC has only weak HLA associations. The autoantigen of PBC, however, has been well-characterized, the typical antimitochondrial antibodies being directed towards the E2 component of the mitochondrial pyruvate dehydrogenase complex. Both B and T cell responses to the E2 autoantigens have been defined, but the genetic or environmental causes that drive these immune responses remain unclear. Interestingly, human AMA cross-reacts with both chemical and bacterial antigens, some of which are broadly present in our environment.

Attempts to develop animal models of autoimmune liver disease have been only partially successful. As a consequence, advances in therapy of autoimmune liver diseases have relied on human studies. Studies from the late 1960s and early 1970s helped define the current regimen of therapy of AIH, which is the combination of corticosteroids and azathioprine. There has been little improvement on therapy since then, despite the recent development of a broad armamentarium of immunosuppressive medications. The current therapy for PBC is the long-term use of ursodiol, a safe and well-tolerated hydrophilic bile acid, which appears to act by replacing naturally produced hydrophobic and hepatotoxic bile acids. Combined analysis of four large multicenter trials of ursodiol have shown that therapy improves survival, but does not result in reversal or cure of disease. Clearly, therapy of PBC warrants further investigation, particularly with the availability of more potent and specific immune-modulatory and anti-inflammatory agents. Finally, current therapy for PSC is problematic and unsatisfactory. Large-scale trials of high-dose ursodiol therapy are currently under way, but there is little evidence that ursodiol has any action beyond slowing the progression of disease. Thus, therapies for autoimmune liver disease are limited to medications that blunt the effector or efferent limb of the response. None are directed at the still elusive fundamental causes of these diseases.

Research Goals

The major goals for research in autoimmune liver diseases are to understand the etiology and pathogenesis of these three diseases and develop effective means of treatment and prevention.

Pathogenesis & Animal Models of Autoimmune Liver Disease: Progress in research on autoimmune liver disease is hampered by the lack of accurate animal models of these diseases. Current mouse models such as the concanavalin A-treated or Met-K^b transgenic mice focus on a narrow component of immune hepatic injury and do not reflect the complexities of the human diseases. Most mouse models reflect acute hepatocellular injury only, and rely upon one or a few pathways of cell injury or destruction. Fully realized models should reflect the chronic nature of these disorders and exhibit chronic necroinflammation and fibrosis. In other disciplines, such as diabetes, rheumatology and gastroenterology, murine models of human diseases have been helpful in elucidating pathogenesis (e.g., insulinitis in type 1 diabetes), as well as providing insights into targets for therapy (e.g., anti-TNF for rheumatoid arthritis and Crohn's disease). Several pathways might be taken to develop animal models of autoimmune liver diseases. These might include: (1) mouse mutagenesis studies combined with a practical screen for both liver disease and autoimmunity (such as serum ALT levels and T cell activation markers); (2) innovative means of expressing neoantigens in liver and bile ducts in adult animals while avoiding thymic tolerance (e.g., by conditional liver-specific expression of transgenes); (3) ablation of normal mechanisms of hepatic immune tolerance (e.g., by increasing pro-inflammatory or decreasing anti-inflammatory cytokine expression in liver in transgenic animals); or (4) development of models of non-specific, bystander injury to the liver (e.g., by the homing of cytotoxic T cells to the liver and the disposition of these T cells during extrahepatic viral infection). The effort to develop animal models for autoimmune liver diseases would be helped by interactions with other disciplines with experience in this area and could be significantly facilitated through a research workshop on the topic of animal models (Matrix Cell A1). Once murine models of disease are developed (Matrix Cell B3), they would provide means of defining the mechanisms of immune injury to the liver and might well provide clues to pathogenesis and insights into targets for therapy (Matrix Cells A3 and C3).

Clinical Studies of Autoimmune Liver Disease: Pathogenesis, Etiology and Therapy: Another major roadblock to progress in research on autoimmune liver diseases is that they are relatively uncommon. New cases of autoimmune hepatitis, PBC and PSC are rare and, therefore, the numbers of patients available to be studied at the onset of disease and before treatment with immunosuppressive or other medications are few. For these reasons, patient-based research on autoimmune liver diseases would be greatly facilitated by a multicenter, nationwide network of clinical centers interested in these conditions. A multicenter clinical research network of investigators to study the natural history, clinical course, pathogenesis, etiology and therapy of autoimmune hepatitis, PBC and PSC would greatly facilitate clinical and translational research (Matrix Cell A2). A well-characterized cohort of patients followed in a standardized fashion both in a cross-sectional manner (retrospective protocol) and from the disease onset forward (prospective protocol) would facilitate studies on the etiology of these diseases and the pathogenesis of injury. These studies might include: (1) clinical and epidemiological studies assessing risk factors and possible triggering events and comparing these diseases in different age- and racial/ethnic-groups for clues to etiology; (2) proteomic analyses for serum biomarkers

of disease activity and stage (Matrix Cell B2); (3) screens for antibodies including use of protein arrays, at different stages of disease; (4) correlations of T cell responses to autoantigens to disease activity measured during flares of illness and during quiescence (Matrix Cell A3); (5) search for viral pathogens in liver and biliary tissue to discover therapeutic targets closer to the root causes of the diseases (Matrix Cell C3); and (6) analyses of genetic linkages including use of family and sibling studies (Matrix Cell B3). The network could initiate pilot studies of new approaches to therapy of autoimmune hepatitis and PBC and serve as planning groups to launch full-scale, randomized controlled trials of therapy (Matrix Cell C1). Finally, the network could interact with currently conducted trials in PBC and PSC to facilitate ancillary studies of diagnosis, screening, pathogenesis and therapy (Matrix Cells B1, C2 and C3).

Steps to Achieve Research Goals

A research workshop on animal models for autoimmune liver disease would be both practical and useful in promoting progress in studies of the pathogenesis of autoimmune liver diseases. This workshop should include discussion of animal models of other autoimmune diseases, as well as models for viral-induced liver disease. Investigator-initiated research project grants focusing on the development of animal models should be encouraged as an area of high priority.

A single or several interlocking clinical research networks on autoimmune liver diseases would provide a strong stimulus to both clinical and laboratory research on these conditions. The network would ensure nationwide and broad representation of these diseases including patients in all age, socioeconomic, racial and ethnic groups, reflecting the diversity of the U.S. population. The network could serve to develop practical but reliable diagnostic criteria and uniform definitions of endpoints for successful therapy. The network might interact with other NIH funded networks (e.g., inflammatory bowel disease or type 1 diabetes networks) with joint or collaborative projects. The network could also serve to help investigators share resources and apply newer techniques to issues in autoimmune liver diseases. Examples of new techniques that might be investigated or facilitated by a clinical research network include imaging modalities aimed at *in vivo* identification of inflammation and neoplasia in bile ducts; molecular fine-definition of B and T cell reactivities present in liver biopsy tissue; application of proteomics, gene expression arrays and haplotyping to serum, DNA and tissue samples acquired by the network; and direct translation of findings from animal model research to human disease.

Matrix of Research Goals in Autoimmune Liver Disease

	Short-term Goals (0-3 years)	Intermediate-term Goals (4-6 years)	Long-term Goals (7-10 years)
High Risk	A3. Define the roles of CD4+ and CD8+ T cells, other effector immunocytes, dendritic cells & the innate immune system in liver injury in humans (& animal models) with autoimmune liver disease.	B3. Identify genetic linkages in PBC and refine the HLA-associations in autoimmune hepatitis and PSC. Develop animal models for each of the autoimmune liver diseases.	C3. Identify modifiable environmental (\pm genetic) triggers for induction of autoimmune hepatitis (from human studies or murine models).
Intermediate Risk	A2. Develop multicenter network of investigators to study natural history, pathogenesis, etiology & therapy of autoimmune liver diseases.	B2. Develop sensitive & specific biomarkers for disease activity and stage in PBC and PSC. Develop diagnostic criteria and standard definitions for endpoints of therapy.	C2. Develop sensitive serum markers for early detection of cholangiocarcinoma in PSC.
Low Risk	A1. Organize & convene an international, interdisciplinary research workshop on development of animal models of autoimmune liver diseases.	B1. Demonstrate whether high dose ursodiol therapy is effective in retarding the progression of PSC & identify risk factors for progression and for response to treatment.	C1. Develop alternatives to prednisone/azathioprine as maintenance therapy of autoimmune hepatitis & define markers for when & how therapy can be safely stopped.