Primary Biliary Cirrhosis: Report of a Focus Study Group

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To provide a forum for discussion in specific areas of liver disease, the Clinical Research Committee of the American Association for the Study of Liver Disease (AASLD) conceived the Focus Study Group. The first Focus Study Group was organized by Nora V. Bergasa and Howard H. Worman. It was dedicated to primary biliary cirrhosis (PBC) and met on October 25th, 2003, during the AASLD annual meeting. The purpose of this symposium was to identify areas of research and to establish national and international collaborations to study PBC and its complications. The program was prepared from topics provided by investigators in the field, in response to questions posed by the organizers, and it was divided in three sections: pathogenesis, the study of fatigue, and treatment of PBC.

An overview on the pathogenesis of PBC was presented by Dr. Eric M. Gershwin (University of California at Davis, CA)1 and was followed by the presentations of invited speakers, all of whom are investigators in the field. In this report, abstracted presentations provided by the speakers and the salient points that evolved from the discussion sections are provided.

Primary Biliary Cirrhosis and the Human
(Andrew Mason)

Working on the hypothesis that infectious/environmental agents trigger autoimmunity in genetically susceptible individuals, we have identified a retrovirus infection in patients with PBC.2,3 This agent is referred to as the human betaretrovirus (HBRV) because of the genetic, morphological and antigenic relatedness to the mouse mammary tumor virus (MMTV). In fact, HBRV also shares some of the biological properties of MMTV. During MMTV infection in mice and HBRV infection in humans, the viral burden is greatest in lymphoid tissue and less so in liver and breast (where HBRV has been detected in humans with and without breast cancer).4 In PBC, immunochemistry and reverse transcription polymerase chain reaction studies of perihepatic lymph nodes suggest that 75% of patients have evidence of tissue infection, whereas HBRV infection is only found in a third of patients in the liver by reverse transcription polymerase chain reaction.2

Knowledge of the natural biology of MMTV may also provide clues to understanding specific clinical features of PBC. For example, MMTV can be detected in salivary tissue of mice, providing a possible link with xerostomia in PBC patients; assuming that HBRV can be identified in the same tissue compartment in humans. Also, the marked preponderance of PBC in women may be linked with HBRV infection. Like MMTV, HBRV has female steroid-responsive elements in the long terminal repeats that serve as functional promoters for viral replication.3,5 Accordingly, pregnancy and the monthly cycle of female hormone production provide an impetus to stimulate viral replication. If HBRV infection does impact on the development of PBC, the lack of female hormone production prior to puberty may account for the absence of PBC in children and the gender bias observed in PBC patients in adulthood.

The characterization of HBRV infection in patients with PBC, however, does not provide evidence for a causal association. We have taken 2 approaches to interrogating whether the HBRV plays a central role in the pathogenesis of PBC. In the first instance, we have conducted open-label pilot studies that have shown biochemical and histological improvement with reversal of ductopenia in PBC patients treated with Combivir (lamivudine and zidovudine) combination antiviral therapy.6 We have also developed a cell culture model of PBC to test Koch’s postulates in vitro.7 In vivo, we found HBRV proteins in the same cells that demonstrated aberrant expression of an antimitochondrial antibody (AMA) reactive protein, a known phenotypic marker of PBC. We also
linked virus to the aberrant AMA-reactive antigen presentation in vitro, by coculturing lymph node homogenates from PBC patients with normal biliary epithelial cells. The transmissible agent was found to be γ-radiation sensitive, to promote the PBC phenotype in serial passage, and to have the morphological, enzymatic, hydrodynamic, and genomic characteristics of a betaretrovirus. The demonstration that pure isolates of mouse derived MMTV can infect BEC and also promote the PBC phenotype with increased AMA reactivity in normal BEC also argues for an infectious disease process with PBC. Additional laboratory and clinical studies, however, will be required to reproduce these findings and to link betaretrovirus infection with autoimmune liver disease.

**Immunogenetics of PBC (Annarosa Floreani)**

Current theories on the etiopathogenesis of PBC favor the hypothesis that the disease develops as a result of an inappropriate (genetically controlled) immune response following stimulation by an environmental or infectious agent. All the published data on genetic predisposition to PBC have been obtained from association studies, based on comparison of the frequency of an allele in unrelated affected and unaffected individuals from a population. The primary susceptibility allele is DRB1*0801 in Northern European white patients and DRB1*0803 in Japanese patients. In the Japanese population another genotype, DRB1*0501, is strongly associated with PBC. A recent study reported that resistance to PBC is associated with DRB1*11 in the Italian population. All of these studies confirm that different PBC populations may have a peculiar genetic background. HLA polymorphisms, however, do not seem to be a major determinant of susceptibility and clinical expression of PBC.

A number of candidate genes encoding T-cell response, immunoglobulins, adhesion molecules, cytokines, and growth factors have been explored. The cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene (located on chromosome 2q33) is a T-cell surface molecule that interacts in competition with the costimulatory molecule CD28, with the ligand B7-1 and B7-2 on antigen presenting cells to influence the induction, maintenance, and particularly termination of peripheral T cell responses. The exon 1 polymorphism of the CTLA-4 gene was significantly associated with susceptibility to PBC in patients from Newcastle, but not in Italian patients. This difference between Southern and Northern European patients with PBC may be due to different patterns of linkage in the two populations.

Another interesting allele, CCR5-Δ32, which has been shown to be associated with protection from rheumatoid arthritis and with lower rate of recurrence in multiple sclerosis, failed to demonstrate any association in both British and Italian patients with PBC. Currently, there are many cytokines to investigate, but preliminary data do not seem to show a strong association with disease susceptibility.

The multidrug resistance 3 (MDR3) mutations have been described in association with different cholestatic liver disease, including intrahepatic cholestasis of pregnancy, juvenile cholelithiasis, PFIC3, and biliary cirrhosis. MDR3 sequencing gene technique is under investigation in PBC (personal data); preliminary data seem to exclude an involvement of MDR3 mutation in this disease.

Some genetic polymorphisms of candidate genes for osteoporosis have been studied in PBC populations, including vitamin D receptor (VDR), bone matrix proteins, and sex hormones and their receptors. Restriction fragment polymorphisms at VDR gene locus, i.e., for TaqI, BsmI, and FokI have been associated with osteoporosis. Conflicting results, however, have been reported in other studies. No exhaustive results have been obtained with association studies assessing both estrogen α and β in PBC populations (personal data).

The future in studies of the immunogenetics of PBC includes studies involving bile salt transporters. It is now becoming clear that impaired or downregulated transporter function may be involved in the resistance to ursodeoxycholic acid (UDCA) therapy and in some pathogenic mechanisms of acquired cholestatic syndromes. Presently, new functional genomic approaches are changing research strategies in a more systematic fashion. These advances will identify genetic variations influencing multifactorial disease and response to treatment.

**Predicting Disease Progression in PBC (Jenny Heathcote)**

As the majority of individuals given a diagnosis of PBC in the 21st century have asymptomatic disease, it is essential that we develop methods by which we can predict who with PBC will and who will not develop progressive disease. Current therapy for PBC only delays progression; it does not induce regression. Current thinking in the field of autoimmunity is that aggressive treatment should be given at the time of initial presentation to prevent progression. However, any “aggressive” therapy is not without untoward consequences. Thus, it is imperative to establish valid markers of disease progression.

A retrospective study of 91 patients with PBC who were asymptomatic at initial presentation and followed for up to 20 years did not reveal any specific features at presentation, which predicted subsequent outcome.
Features examined included liver biochemistry and histology as well as physical features on clinical examination. A publication by Balasubramaniam et al.\textsuperscript{18} at the Mayo Clinic had suggested that presence of other autoimmune diseases was more common in those with subsequent disease progression. This finding could not be confirmed by Springer et al.\textsuperscript{17}

For those with symptomatic disease, Shapiro et al.\textsuperscript{19} in 1979 showed that height of bilirubin reliably predicts subsequent outcome. The Mayo risk score is a composite score that includes both clinical and laboratory features and was developed to predict timing for referral to liver transplantation.\textsuperscript{20} The serum bilirubin is always normal in asymptomatic PBC, and the Mayo score has not been validated in asymptomatic disease. A study by Donaldson et al.\textsuperscript{9} suggested that a particular HLA pattern may predict those who will not develop progressive disease. In this study, 164 individuals with PBC with a wide range of disease severity were tested; only one of the 35 patients who had been shown to have nonprogressive PBC on long-term follow-up was DRB1*0801 positive compared to 24\% of the 88 with late-stage disease, none had DQB1*0401 compared to 23\% with late stage disease, and only 1 was DQB1*0402 positive, as compared to 24\% with the late stage disease. So it is possible that class II HLA DR and DQ testing may help to distinguish patients in whom disease is likely to progress from those in whom it will not.

In another retrospective study, Zuchner et al.\textsuperscript{21} examined 120 patients with PBC for the subspecies of antinuclear antibodies, SP100 and antipromyelocytic leukemia protein. An association with progressive disease was seen with those who tested positive (73\%), whereas only 35\% of those who did not progress tested positive. Other non-organ-specific antibodies, namely AMA and ANA, have been shown not to predict outcome.\textsuperscript{22}

A liver biopsy is not essential to make a diagnosis of PBC in an individual who tests AMA positive and has an elevated activity of serum alkaline phosphatase, but biopsy is considered wise to establish the severity of the disease seen on histological examination of the liver. Roll et al.\textsuperscript{23} showed that the presence of cirrhosis is associated with a worse outcome. Corpechot et al.\textsuperscript{24} have shown that piecemeal necrosis (predominantly lymphocytic) is associated with more severe disease. In a study of 4 case reports from Vleggaar et al.,\textsuperscript{25} individuals with marked ductopenia developed liver failure, even prior to the onset of cirrhosis; thus, liver histology may help to predict outcome. To date, no molecular array studies in liver tissue from patients with early PBC have been reported; it is possible that certain “signature profiles” could be found to predict the likelihood of progressive disease in asymptomatic individuals with early disease.

### Pathogenesis of Fatigue in PBC

**Mark G. Swain**

The majority of patients with PBC experience fatigue, often being so severe as to be incapacitating. The etiology of fatigue in PBC, however, is unknown. Moreover, the study of fatigue is further hampered by its subjective nature. Fatigue in PBC does not appear to correlate with disease severity, is central (i.e., within the brain) and not peripheral (i.e. neuromuscular) in origin, and correlates closely with mood disorders (e.g., depression).\textsuperscript{26}

In studying fatigue in patients with PBC, one question clearly stands out: How does the damaged liver and associated cholestatic syndrome signal the brain to ultimately result in changes in central neurotransmission, which gives rise to the perception of fatigue? Communication between the periphery and the central nervous system traditionally has been considered to involve activation of nerve projections from the periphery to the brain and/or circulating blood-borne signals.\textsuperscript{27} It is likely that both of these pathways are active in carrying signals from the diseased liver in PBC to the brain. Vagal nerve afferents can be activated by inflammatory mediators released into the liver or abdominal cavity (e.g., cytokines, endotoxin) resulting in nerve stimulation and signals being carried to the brain.\textsuperscript{28} In addition, these signals can give rise to changes in neurotransmitter systems within the brain, which have been implicated in the genesis of fatigue.\textsuperscript{29} Substances retained or released into the circulation in patients with PBC (e.g., cytokines, endotoxins) may also signal the brain by either directly activating cerebral endothelial cells via specific cell surface receptors (to produce secondary messengers, including nitric oxide and prostaglandins) or by entering the brain through areas devoid of an intact blood-brain barrier\textsuperscript{30} to ultimately result in altered central neurotransmission, likely by stimulating astroglia/microglia within the brain, which then release substances that modulate neuronal function.

Whatever mediators or pathways are involved in liver-to-brain signaling, the ultimate end result of this communication and cause of fatigue in PBC patients must involve alterations in neurotransmitter systems within the brain that underlie behavioral activation.\textsuperscript{31} A number of central neurotransmitter systems have been implicated in fatigue states in general,\textsuperscript{32} and defects in these systems have been documented in animal models of cholestasis and implicated in fatigue-like behaviors in these model systems. Specifically, the corticotrophin-releasing hor-
mone and serotonergic neurotransmitter systems have both been implicated in cholestasis-associated fatigue.33,34

Therefore, the ultimate delineation of the important communication pathways between the liver and the brain in PBC patients, as well as the identification of neurotransmitter systems within the brain that are altered as part of the cholestatic syndrome and drive the development of fatigue in these patients, should allow for specific targeting of therapies to treat this common disabling symptom.

Measurement of Fatigue and Its Impact on Quality of Life in PBC (David E. J. Jones)

It is increasingly being acknowledged that PBC adversely affects patients’ quality of life, with fatigue being a particularly relevant contributing factor.26,35 Study of health-related quality of life (HRQOL) in PBC (as in any disease) provides key information regarding the way in which disease affects the lives of sufferers. Approaches that are able to quantify HRQOL also provide valuable tools for use in the study of disease mechanisms responsible for poor life quality (permitting identification of symptomatically affected and unaffected patient subgroups) and in the development and testing of therapies that may improve life quality. Although some symptoms typical of PBC (exemplified by pruritus) are best assessed using objective measures (scratching activity in the case of pruritus36 the global assessment of HRQOL is typically carried out using more subjective approaches. The simplest approach to the subjective assessment of HRQOL is the Likert scale (e.g., “on a scale of 1 to 5 how would you rate the quality of your life?”), which can be converted into a continuously variable scale (e.g., a visual analogue scale). Such approaches lack sensitivity, however, and require the patient and questioner to have the same understanding of what is meant by the concept of quality of life. A much more sensitive approach is to use questionnaire-based HRQOL assessment tools. Such tools break down the concept of HRQOL into easily answerable individual questions, the results of which are integrated to give assessment of global HRQOL, thereby removing the need to ask patients themselves score the abstract concept of life quality. In using individual questions to build a composite model of HRQOL it is fundamentally important, however, that the questions used are relevant and appropriate to the disease being studied. In general terms, the more generic the measure the less relevant it will be to any individual disease group and the less sensitive it will be at identifying subtle variations between patients, and responses to therapy. What options present themselves when identifying an HRQOL measure for use in PBC?37 The first option is a fully generic measure (e.g., the SF36). Such generic measures are useful in allowing comparison of disease burden between PBC and other disease patients and controls but are of limited use in the clinical trials setting because of low disease sensitivity. The second option is a liver disease–specific measure such as the CLDQ, which allows limited interdisease comparison and increased sensitivity. The third option would be a PBC-specific HRQOL measure derived entirely within the PBC patient population. A completely disease-specific measure would be of no use for interdisease comparison but would offer the greatest sensitivity in the clinical trial context. One such measure, the PBC-40, has been derived and validated by our group.

It is concluded that sensitive tools are increasingly becoming available for the measurement of quality of life and the factors that impair it in PBC. The advent and validation in this disease setting of such measures will transform the future study of the pathogenetic mechanisms underpinning symptom development and their therapeutic modulation in PBC.

Recently Reported Adjuvant Therapies for PBC (Keith M. Lindor)

Current recommendations by the AASLD and the Food and Drug Administration are for the use of UDCA as first-line therapy for primary biliary cirrhosis.38 Among patients treated with UDCA, 20% will have complete biochemical normalization after 2 years and 35% after 5 years of therapy. This finding leaves a substantial number of patients with ongoing biochemical abnormalities and, hence, it is an impetus for the development of adjuvant therapies. A variety of approaches for adjuvant therapy have been considered including induction of oral tolerance, treatment of potential inciting infections, use of dietary supplements, herbal therapy, and immunosuppression.

In an attempt to induce oral tolerance to pyruvate dehydrogenase, the antigen recognized by the antimitochondrial antibody,39 6 patients with PBC were fed 5 mg of purified bovine pyruvate dehydrogenase every day for 6 months.40 Inducing oral tolerance has been attempted in a variety of other conditions, such as allergic encephalitis and arthritis,41 and it seemed a reasonable goal in PBC. Unfortunately, there were no changes in liver tests or AMA titers over the course of therapy, and 1 patient developed a rash.40 The lack of efficacy in this study does not refute this mechanism as potentially valuable in treating early PBC. If oral tolerance could be induced in such a way, this approach has the potential to be curative. Further research in this area would seem to be warranted.

Two lines of evidence have been recently proposed as suggestive of an infectious process in the pathogenesis of...
PBC.\textsuperscript{2,3,6} The finding of HBRV (reviewed by A. M., above) in patients with PBC was followed by a pilot study of Combivir (lamivudine plus zidovudine) for the treatment of PBC in 14 patients.\textsuperscript{6} Five of the 10 patients who completed the study normalized the serum activity of alkaline phosphatase and of these, 4 normalized the activity of the alanine and aspartate transaminases.\textsuperscript{6} None of the 4 who dropped out of the study had serious adverse events. Normalization of the serum activity of transaminases was sustained in 2 patients for at 6 six months after stopping the drug. This study was followed by a controlled, randomized trial being conducted at present. Another organism, \textit{Chlamydia pneumoniae}, was detected with high prevalence in the liver grafts and liver biopsy tissues from patients with PBC, but rarely in controls.\textsuperscript{42} A study of tetracycline, used to treat infections caused by this bacterium, at a dose of 500 mg 4 times a day for 3 weeks in 15 patients with PBC did not lead to changes in serum liver profile;\textsuperscript{43} however, the lack of response to the treatment may have been due to suboptimal choice of drug, dose, and/or duration of treatment.

Silymarin, the active ingredient of milk thistle, has been identified as having antioxidant, anti-inflammatory, and antifibrotic effects.\textsuperscript{44,45} In a study of 27 patients with PBC who had a suboptimal response to UDCA, silymarin treatment for 1 year led to no change in serum activity of alkaline phosphatase, AST, serum bilirubin, albumin, or Mayo risk score.\textsuperscript{46}

Bezafibrate is used to treat hyperlipidemia.\textsuperscript{47} This drug facilitates mdr2 expression in mice, promoting biliary secretion;\textsuperscript{48} in addition, it is a PPAR \( \alpha \) and \( \beta \) ligand.\textsuperscript{49} In a study of 22 patients with PBC in which half received low-dose of UDCA, 600 mg per day, and the other half bezafibrate, 400 mg per day, for 6 months, there was substantially more improvement in liver biochemistries in the patients receiving bezafibrate than in those receiving UDCA.\textsuperscript{50} The results of this pilot study certainly warrant further work.

Immunosuppressive therapy has been used because of the presumed autoimmune nature of this disease. Budesonide is a steroid with extensive hepatic metabolism such that it would theoretically have fewer side effects than prednisone.\textsuperscript{51} In one study of 22 patients with PBC who had had a suboptimal response to UDCA after a year of treatment, the addition of budesonide, 9 mg a day, led to no improvement in the liver tests and worsening of bone disease.\textsuperscript{52} In another study, patients were randomized to receive UDCA (n = 19) or the combination of ursodeoxycholic acid and budesonide (n = 20). The patients receiving the combination therapy seemed to have a superior biochemical response. Effects on bone loss were not reported in this study.\textsuperscript{53} Mycophenolate mofetil\textsuperscript{54} (CellCept), another immunosuppressive drug, has been explored in the treatment of PBC.\textsuperscript{55,56} In one study reported to date, 25 patients with a suboptimal response to UDCA were treated for 1 year with mycophenolate mofetil up to 3 g per day.\textsuperscript{57} Three withdrew due to side effects, and 8 had an adverse event requiring dose reduction. Serum liver profile improved and surprisingly, the greatest degree of improvement was found in those patients with more advanced disease and, more surprisingly, this group of patients had the fewest side effects.

Sulindac is a nonsteroidal anti-inflammatory drug reported to enhance bile flow in rats.\textsuperscript{58} In one study, 23 patients who reached a plateau after UDCA therapy were given sulindac 100 to 300 mg/day, and had a significant decrease in the serum activity of alkaline phosphatase with this therapy.\textsuperscript{59}

It is encouraging that therapeutic options are being explored for patients with PBC. Among the areas that should continue to be explored are induction of oral tolerance because of the potential development of a long-term response, further exploration of treatment for potential infectious agents involved in the pathogenesis of PBC, and clarification of the role of immunosuppressive therapy such as budesonide and mycophenolate mofetil.

\textbf{Novel Therapeutic Approach for PBC (Margaret F. Bassendine)}

PBC predominantly affects middle-aged women, but the reasons for the increased female susceptibility are unclear. We have recently reported 2 patients with PBC who showed a decrease in the activity of alkaline phosphatase while receiving tamoxifen therapy.\textsuperscript{60} Tamoxifen, a nonsteroidal triphenylethylene, is a widely utilized antiestrogen agent in the treatment and chemoprevention of breast cancer. Since it produces antiestrogenic actions in the breast but manifests estrogen-receptor agonist activity in some tissues, the term selective estrogen receptor modulator (SERM) has been used to describe this group of pharmaceuticals.\textsuperscript{61} Recent studies have examined the distribution of estrogen receptors (ER) in the liver. There are two subtypes of ER, alpha and beta, and the relative expression level of these two isoforms is thought to be a key determinant of cellular responses to agonists and antagonists. In the rat, cholangiocytes have been found to express both ER \( \alpha \) and \( \beta \), whereas hepatocytes express only ER \( \alpha \).\textsuperscript{62–64} In PBC both ER \( \alpha \) and ER \( \beta \) are expressed on cholangiocytes.\textsuperscript{65} The antiestrogen tamoxifen is a mixed agonist/antagonist on ER \( \alpha \) but a pure antagonist on ER \( \beta \). In PBC, tamoxifen may lead to a decrease in the serum alkaline phosphatase level via cholangiocyte estrogen receptors, inhibiting cholangiocyte proliferation and induc-
ing apoptosis. Tamoxifen or other SERMs may be worth evaluating further in the treatment of PBC.

It has now been established that UDCA, the drug approved for the treatment of PBC, activates the human pregnane X receptor (PXR), a promiscuous nuclear receptor that has evolved to facilitate rapid and efficient detoxification and elimination of foreign chemicals and bile acids. Its ligand binding site is large, spherical, and extremely hydrophobic and appears to be activated by a diverse collection of compounds including tamoxifen and 4-hydroxytamoxifen. Thus, it is possible that the mechanism of action of tamoxifen in PBC is not as a SERM but via PXR. PXR is a member of a nuclear receptor gene family (family NR1) that includes PPAR, FXR, CAR and LXR. All share a common heterodimerization partner, retinoid X receptor, and are subject to crosstalk with other nuclear receptors. Interestingly, the PPAR ligands bezafibrate and fenofibrate have also recently been shown to improve cholestatic liver function in PBC. The rationale for their use was that hypercholesterolemia is commonly associated with PBC and lipoprotein abnormalities are found in early PBC, and these lipid abnormalities may have pathological implications as survival in PBC is poorer than age- and sex-matched controls (excluding liver deaths). PPAR α agonists induce expression of UDP-glucuronidating UGT2B4 enzyme and so may modulate catabolism of cytotoxic bile acids and xenobiotics. Following an early report of the effect of bezafibrate in PBC, both this drug and the stronger PPAR α ligand, fenofibrate have been used alone and in combination with UDCA, and the combination looks particularly promising. These findings raise the exciting possibility that potent PXR activators, either alone or together with other heterodimeric partners such as PPAR or FXR agonists may be useful in the treatment of PBC and other diseases in which bile acids or other toxins accumulate in the liver.

**Summary of Workshop**

(*Howard J. Worman*)

This workshop on PBC occurred during the 50th anniversary of the discovery of immunological tolerance. According to Sir Peter Medawar’s Nobel lecture in 1960, “Immunological tolerance may be described as a state of indifference or non-reactivity towards a substance that would normally be expected to excite an immunological response.” The major question facing us today regarding PBC is the breakdown in immunological tolerance. In PBC, loss of immunological tolerance likely excites an immunological response against a subject’s own intrahepatic bile ducts. It also underlies the generation of autoantibodies to specific mitochondrial antigens in essentially all patients and specific nuclear antigens in some.

Two presentations at this workshop addressed environmental factors that may lead to a loss of immunological tolerance in PBC. Putative agents include a virus and a bacterium. While the preliminary results are exciting, we need to do much more to prove a cause-and-effect relationship between these agents and the pathogenesis of PBC. This reality was manifested by Dr. Mason’s presentation, which sparked a vigorous discussion about the putative role of a betaretrovirus infection in PBC and the fact that the identification of viral particles alone in subjects with PBC does not fulfill 19th-century criteria for judging whether a given infectious agent is the cause of a given disease. Other unidentified environmental factors may also be involved in pathogenesis. While environmental factors may initiate a breakdown of immunological tolerance in PBC, it is almost certain that genetic susceptibility to the disease is necessary for its development. No genetic susceptibility loci for PBC have been identified to date. In addition, no genetic variations have been found in the canalicular membrane transporter MDR3 (ABCB4), as suggested by Dr. Floreani’s unpublished data, or in canalicular membrane transporter bile salt export pump (BSEP, ABCB11). Other possible candidates may include genes involved in immune system regulation and numerous genes encoding proteins with a variety of functions may also be involved in predisposition to PBC and other autoimmune disorders.

Another topic discussed at this workshop was fatigue, one of the symptoms experienced by patients with PBC. The study of fatigue appears to be complicated by the lack of single definition and lack of objective methodology. An important question that needs to be answered is whether fatigue in PBC is disease-specific or similar to what occurs in many other chronic diseases. Future studies must have appropriate comparison groups and objective measurement standards, as has occurred for the study of pruritus, for which methodology to study scratching, the behavioral manifestation of this symptom, has been developed.

The final topic of this workshop was the treatment of PBC. The only approved treatment, UDCA, may slow the progression of liver disease but is not a cure and is probably not directed at the underlying disease process. Several clinical trials of immunosuppressive agents for PBC have been carried out or are in progress, but, as the efficacy and safety of these agents in PBC are not yet known, clinicians should not use these drugs outside of approved trials. Future clinical trials in PBC should be randomized, double-blinded, and controlled with objective outcome measurements specified at the time the trial...
is being designed. The identification of specific drug targets must await more pathophysiological studies.

Focused scientific investigations and collaborations between physicians and scientists interested in PBC should be a priority, including the creation of an international trial group for the study of PBC. Large-scale epidemiological and genetic studies should be carried out to address pathogenesis. Importantly, young basic immunologists and geneticists should be encouraged to study PBC, perhaps through initiatives championed by AASLD. In the clinical arena, it is necessary to devote the major effort to controlled studies with meaningful endpoints. The long-term goal is the identification of new drug targets through basic research that could ultimately lead to the development of novel agents for clinical trials.

References


