PSC Partners Seeking a Cure

Newsletter

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Edited by David Rhodes and Ricky Safer

www.pscpartners.org

Bulletin from Bethesda

(by David Rhodes)

Congratulations to the organizing committee (Dr. Dennis Black, Dr. Benjamin Shneider, Dr. Nicholas LaRusso, Dr. Edward Doo, and Dr. Jay Hoofnagle), the NIH/NIDDK, Office of Rare Diseases, and the Morgan Foundation for a superb conference. It was a great honor for me to be able to attend, to meet all of the leading PSC researchers from around the world, to see and hear their presentations, and to have the opportunity to talk with them one-on-one during the breaks. It was a particular delight to meet and listen to the grandmasters of PSC research....Drs. Keith Lindor, Roger Chapman, Marshall Kaplan, and Adolf Stiehl (to name but a few). We are all familiar with the wonderful research that they have done throughout the years. It was a rare opportunity to glimpse the current status of PSC research, and hear what the leaders in the field consider to be the gaps in knowledge, and challenges for the future.

For me, a major highlight of the conference was Dr. Michael Trauner's talk on his recent work on bile transporters in an animal model of PSC. Mice that are deficient in the Mdr2 gene develop sclerosing cholangitis. The equivalent gene in humans is the MDR3 gene. Mutations in this gene are known to be associated with progressive familial intrahepatic cholestasis. Dr. Trauner has discovered that a modified type of ursodeoxycholic acid (UDCA), called norUDCA, which has a shortened side-chain and is less hydrophobic (i.e. more hydrophilic, or water-loving) than regular UDCA, is able to prevent development of sclerosing cholangitis in the mouse model. Moreover, norUDCA seems to promote healing, and reverses liver damage in the mice. Dr. Trauner suggests that its therapeutic mechanisms may involve: 1) increasing hydrophilicity of biliary bile acids; 2) flushing of injured bile ducts by

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In This Issue:

This issue of the PSC Partners Seeking a Cure Newsletter is devoted to a brief description of the Primary Sclerosing Cholangitis Research Workshop, held at the National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland, from September 19-20, 2005. The workshop was attended by many of the leading PSC researchers from around the world. It was sponsored by the NIH, NIDDK, Office of Rare Diseases, and the Morgan Foundation (**http://www.pscfoundation.org/**).

All of the presentations and discussions were videotaped, and the videocasts are available for viewing at the following URLs:

Primary Sclerosing Cholangitis Research Workshop (Day 1)
http://videocast.nih.gov/ram/niddk091905.ram
Time: 6h:35min
Format: RealVideo

Primary Sclerosing Cholangitis Research Workshop (Day 2)
http://videocast.nih.gov/ram/niddk092005.ram
Time: 5h:42min
Format: RealVideo


Dr. Jay Hoofnagle


Dr. Nicholas LaRusso


Dr. Roger Chapman


Dr. Michael Trauner


Dr. Adolf Stiehl


Dr. Marshall Kaplan

There is really no substitute for viewing and listening to these 12 hours of informative presentations and discussions! You will need to install RealPlayer software on your computer in order to view these videocasts. The Free RealPlayer software is available from:

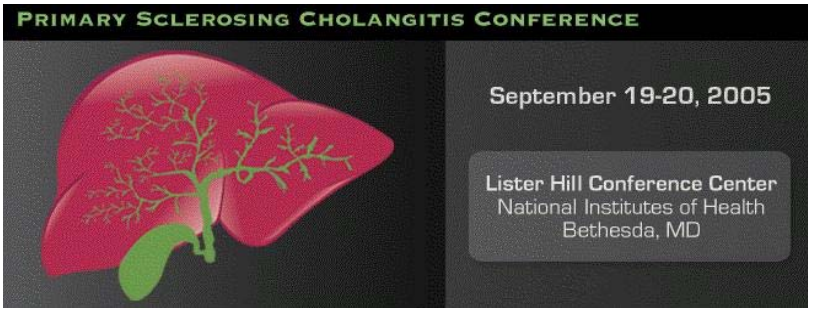
http://videocast.nih.gov/

You might wish to print off the agenda for the two days of talks to help guide you during the videocasts. The agenda is available from:

https://www.niddk.nih.gov/fund/other/primarysclerosing/

The organizing committee plans to publish an outline of the conference in a future issue of the journal “Hepatology”.

Again, congratulations to the organizing committee, the NIH/NIDDK, Office of Rare Diseases and the Morgan Foundation for putting on this important event. It represents a significant milestone in PSC research, and a major advance in the coordination of research efforts in this chronic liver disease.



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bicarbonate-rich bile, and 3) induction of detoxification enzymes and alternative pumps for bile acids.

A second personal highlight was the talk by Dr. David Adams on T cell immunity and PSC, and his recent work on long-lived mucosal T cell migration between gut and liver. The migration of these cells may be responsible for sustaining PSC. His discoveries in this area, if corroborated by others, may lead to some novel approaches to PSC treatment.

A third highlight was meeting Dr. Chris Bowlus and Dr. Chris Aoki from U.C. Davis, and hearing more about their work on PSC genetics, and the p-ANCA antibodies associated with PSC. Dr. Bowlus is particularly interested in contacting twins with PSC (one or both of whom are affected) to assist in identifying genetic factors. Please visit **www.psc-literature.org** for contact information for PSC genetic studies underway at both U.C. Davis and Mayo Clinic.

A fourth highlight was meeting Dr. Steven Freedman and his colleague, Dr. Harpreet Pall, and learning more about their recently initiated trial on DHA in PSC. DHA (docosahexaenoic acid; an omega-3 fatty acid found in fish oil) has shown benefit in cystic fibrosis patients, and in a mouse model of sclerosing cholangitis: the cystic fibrosis transmembrane conductance regulator (CFTR) deficient mouse. When given colitis, these CFTR-deficient mice develop sclerosing cholangitis, and are significantly protected from bile duct injury by oral DHA supplementation.

A fifth highlight was the announcement, by Dr. Dennis Black, concerning the initiation of a PSC registry which will greatly facilitate future collaborative research. This registry will consist of a databank of PSC patient history and DNA to facilitate studies on the genetics of PSC. The Morgan Foundation is taking the lead on this important initiative.

Dr. Roger Chapman discussed pathogenic mechanisms in PSC and concluded that it is probable that multiple interacting genetic and environmental factors contribute to the development of PSC, but the question of whether it is a true autoimmune disease remains unanswered. The male predominance and the association with lack of smoking remain unexplained.

Dr. Peter Donaldson gave an update on PSC genetics. He explained the established importance of the major histocompatibility complex (MHC) genes in determining the risk of developing PSC, and then discussed additional genes as candidate susceptibility genes, including the bile transporters (BSEP and MDR3), CFTR, and the CARD genes (CARD4 and CARD15) implicated in inflammatory bowel diseases.

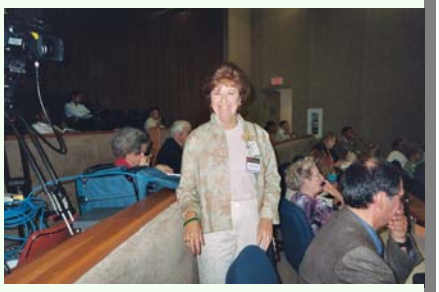
There was much discussion about whether or not pediatric PSC is a different disease from adult PSC. Both Dr. Eve Roberts and Dr. Giorgina Mieli-Vergani noted that the presentation in children often looks much more like autoimmune hepatitis. Dr. Giorgina Mieli-Vergani suggested that sclerosing cholangitis in children be termed “autoimmune sclerosing cholangitis” (ASC).

Dr. Ann Fulcher gave a detailed overview of how “MRCP has emerged as a technique that depicts the biliary tract, pancreatic duct, and gall bladder as high signal intensity structures without contrast material” non-invasively. When MRCP is combined with conventional MR, it can yield cross-sectional information similar to CT. There was much interest in the possibility of adopting MRCP as a standard diagnostic tool, and perhaps using it in the future to routinely determine the three-dimensional volume of the biliary tree in order to track disease progression and responses to therapies.

Both Dr. Adolf Stiehl and Dr. Anthony Kalloo stressed the importance of managing dominant strictures/stenoses in PSC patients using ERCP and balloon dilatation. Dr. Keith Lindor described some innovative approaches to the treatment of PSC, including the use of antibiotics, the use of minocycline to suppress nitric oxide synthesis and inflammation, the use of oral DHA (as mentioned earlier), and the possibility of targeting nuclear receptors that control enzymes of bile acid detoxification and transport.

While it was recognized that there is still a great need for the development of better markers for early detection of cholangiocarcinoma, it was noted that preliminary data suggests that ursodiol (UDCA) may be protective against this dreaded complication of PSC. The evidence for a protective effect of UDCA against colon cancer appears stronger.

Last, but by no means least, it was a great delight to see Ricky Safer, Don Safer, Lee Bria, Yolanda (Reggie) Belmont and other 'PSC Partners' again.



Ricky Safer at the PSC Research Conference in Bethesda (photo courtesy of Lee Bria; Lee’s husband, William Bria, is on the right).

In conclusion, it is no longer possible to say that PSC is an "orphan" disease; it has clearly been "adopted" by a tremendous group of researchers. I wish them great success in their future research endeavors and collaborations.

PSC Partners Seeking a Cure presented a poster at the conference. The poster can be viewed at:

http://www.pscpartners.org/PSCPartnersPoster.pdf

Visitors to the poster were given our new brochure “Living with PSC”:

http://www.pscpartners.org/PSCBrochure.pdf

a wristband, and a PSC Partners Seeking a Cure pen.