PSC Partners Seeking a Cure Announces 2008 AASLD Awards 2008

PSC Partners Seeking a Cure is pleased to announce that there will be two 2008 PSC Partners Seeking a Cure AASLD Awards this year. Drs. I. Tornai and P.G. Blanco will each receive $3,000 at the upcoming AASLD meeting in San Francisco, CA, October 31-November 4, 2008.

Congratulations Drs. Tornai and Blanco! Their award-winning abstracts are shown below.

A possible role for haptoglobin polymorphism in the pathogenesis of primary sclerosing cholangitis

I. Tornai1; P. Orosz2; A. Par3; F. Szalay4; J. Harsfalvi5; M. Papp1

1. 2nd Department of Medicine, University of Debrecen, Debrecen, Hungary.
2. 2nd Department of Medicine, County Hospital, Miskolc, Hungary.
3. 1st Department of Medicine, University of Pecs, Pecs, Hungary.
4. 1st Department of Medicine, Semmelweis University, Budapest, Hungary.
5. Clinical Research Center, University of Debrecen, Debrecen, Hungary.

Introduction: Haptoglobin (Hp) is a hem-binding glycoprotein, with antioxidant, scavanger and immunomodulatory capacity. It has three major geno- and phenotypes (Hp 1-1, 2-1 and 2-2). The structure and function of these genotypes differ significantly from each other. Previous investigations have found some correlations between Hp polymorphism and the natural history of different inflammatory and autoimmune disorders. The pathogenesis of primary sclerosing cholangitis (PSC) is unknown. It has some autoimmune characteristics.

Objective: The investigation of Hp polymorphism in autoimmune liver diseases.

Patients and methods: We have collected serum samples from 72 patients with PSC, 157 patients with primary biliary cirrhosis (PBC) and 48 patients with autoimmune hepatitis (AIH). Healthy volunteers (n:384), patients with alcoholic liver cirrhosis (n:153), chronic hepatitis C (n:155) and chronic hepatitis B (n:45) served as controls. The Hp polymorphism was investigated by SDS-polyacrylamide electrophoresis followed by immunoblotting, which identifies the genotype, as well.

Results: The ratios of the Hp 1-1, 2-1 and 2-2 genotypes were 11.5 percent, 46.1 percent and 42.4 percen, respectively in the healthy controls. Similar distribution of Hp polymorphism was found in the patients with alcoholic liver cirrhosis and with both viral hepatitises. However, in patients with PSC (male/female: 52/20, mean age: 31±14 year) a complete lack of the Hp 1-1 genotype could be observed: Hp 2-1: 50 percent, Hp 2-2: 50 percent (p:0.0007). In patients with AIH (male/female: 13/35, mean age: 43±15 year) the Hp 1-1 genotype was slightly more frequent as compared to the controls (20.8 vs. 11.5 percent). In patients with PBC we found similar Hp genotype distribution than in the control groups.

Conclusions: PSC is the first disorder to date, where a complete lack of Hp 1-1 genotype has been found in a relatively large cohort of patients.

We suggest a possible protective role for Hp 1-1 genotype in PSC. However, any role of 1-1 genotype in AIH is still very questionable. The different structures of the three geno- and phenotypes might have significantly different influences on the immune reactions, modulated by the Hp molecule. Further investigations, primarily immunological tests, are needed to clarify the importance of the Hp polymorphism in the pathogenesis of PSC.

Novel therapeutic approach to Primary Sclerosing Cholangitis (PSC).

P. G. Blanco1; J. C. Keach2; J. L. Petz2; M. M. Zaman1; K. Bhaskar1; J. E. Cluette-Brown1; S. Gutam1; S. Sheth1; A. Brown1; N. H. Afdhal1; K. D. Lindor2; S. D. Freedman1

1. Beth Israel Deaconess Medical Center, Boston, MA, USA.
2. Mayo Clinic, Rochester, MN, USA.

Background: The etiology of PSC is unknown and we have previously shown that patients with PSC have an increased prevalence of CFTR dysfunction. As proof of concept, induction of colitis in CF knockout mice leads to the development of bile duct injury and can be prevented by correction of the CFTR related fatty acid defect with oral Docosahexaenoic Acid (DHA). We hypothesized that DHA might be an effective therapy for patients with PSC.

Study Design: We conducted a 12 month pilot open-label trial of DHA in the treatment of 28 adult patients with PSC. 800 mg of DHA was administered orally twice per day for 52 weeks. The primary outcome measure was change in serum alkaline phosphatase during the treatment period. Secondary outcomes included change in cholangiograms, liver biochemistry, fatty acid profile (docosahexaenoic acid, arachidonic acid), serum/plasma liver fibrosis markers, innate immune assessment, and clinical data based on signs and symptoms. Repeated measures of analysis of variance (ANOVA) were used to compare the significance of the differences in the mean serum alkaline phosphatase levels for each individual patient and among patients. Repeated Measures ANOVA was also used to determine the significance of the difference between the individual and group means for DHA levels and all of the other individual variables measured.

Results: We report interim results of our ongoing study. A total of 22 subjects completed the study. There were no adverse events reported. Analysis of fatty acids revealed a mean 3.54 fold increase in serum DHA levels. The mean alkaline phosphatase (± SEM) at baseline was 326.5 ± 30.5 compared to 253.1 ± 23.7 ($p < 0.001$) after 9 months of DHA treatment. The decrease in mean alkaline phosphatase levels following DHA administration were statistically significant compared to results at baseline and at all subsequent assessments through month nine. For symptoms, we scored pruritus, fatigue and overall well being based on the Chronic Liver Questionnaire. 70% of the subjects had an improvement in fatigue and in well being. There was no change in fibrosis or apoptosis markers during this period of time.

Conclusions: These encouraging preliminary results demonstrate that an increase in serum DHA levels is possible and results in a significant decline in alkaline phosphatase and a clinical improvement in fatigue and well being. These data should prompt a more rigorous trial of DHA therapy in PSC. Supported by the Morgan Foundation for the Study of PSC.

Abstracts of Interest

by David Rhodes, Chair, Scientific/Medical Advisory Committee

RUNX, Autoimmune Diseases, and Ulcerative Colitis

The runt-related transcription factor 1 (RUNX1, also called AML1; gene map locus 21q22.3) has been identified as an important gene in determining susceptibility to several autoimmune diseases (Alarcon-Riquelme, 2003; Alarcon-Riquelme, 2004; Bowcock, 2005; Coutinho, 2004).

RUNX1 interacts with the programmed cell death 1 gene (PDCD1, also called PD-1; gene map locus 2q37.3) to determine susceptibility to systemic lupus erythematosus (SLE) (Prokunina et al., 2002) and type 1 diabetes (Nielsen et al., 2003).

In addition, RUNX1 binds to a site between SLC9A3R1 (Solute Carrier Family 9, Isoform A3, Regulatory Factor 1) and NAT9 (a member of the N-acetyltransferase family) to determine susceptibility to psoriasis (Helms et al., 2003). SLC9A3R1 is located on chromosome 17, in the same region as the psoriasis susceptibility 2 (PSORS2) gene (gene map locus 17q25).

RUNX1 also interacts with SLC22A4 (gene map locus 5q31) encoding an organic cation transporter (where SLC stands for "solute carrier"), to determine susceptibility to rheumatoid arthritis (Tokuhiro et al., 2003; Takata et al., 2008). SLC22A4 and its closely linked gene, SLC22A5, represents the IBD5 gene (gene map locus 5q31) which interacts with the IBD1 (NOD2/CARD15) gene (gene map locus 16q12), the major gene determining susceptibility to Crohn's disease (Peltekova et al., 2004).

In 2004, Brenner et al. showed that knock-out of Runx3 resulted in development of ulcerative colitis and gastric mucosal hyperplasia in a mouse model, and they suggested that RUNX3 (AML2; gene map locus 1p36) should be considered as a candidate ulcerative colitis gene in humans. The location of RUNX3 in the human genome corresponds to the IBD7 locus (gene map locus 1p36). Recently, Weersma et al. (2008) tested whether RUNX3 might represent an IBD susceptibility locus in man, and found that it is indeed an ulcerative colitis susceptibility gene, and interacts with the SLC22A4/SLC22A5 locus (IBD5). The RUNX3 gene is said to be "epistatic" with SLC22A4/SLC22A5; that is the combination of the RUNX3 and SLC22A4/SLC22A5 gene variants increases risk for ulcerative colitis. An interesting feature is that RUNX3 confers susceptibility to the pancolitis type of ulcerative colitis (Weersma et al., 2008). This type of UC is more common in PSC.

Because RUNX3 expression is frequently lost in bile-duct cancer and pancreatic cancer cell lines (Wada et al., 2004), it would seem worth evaluating whether PSC might be associated with altered expression of RUNX3 and/or polymorphisms in the RUNX3 gene.

References

Alarcon-Riquelme ME 2003 A RUNX trio with a taste for autoimmunity. Nat. Genet. 35: 299-300.

Alarcon-Riquelme ME 2004 Role of RUNX in autoimmune diseases linking rheumatoid arthritis, psoriasis and lupus. Arthritis Res. Ther. 6: 169-173.

Brenner O, Levanon D, Negreanu V, Golubkov O, Fainaru O, Woolf E, Groner Y 2004 Loss of Runx3 function in leukocytes is associated with spontaneously developed colitis and gastric mucosal hyperplasia. Proc. Natl. Acad. Sci. U.S.A. 101: 16016-16021.

Bowcock AM 2005 The genetics of psoriasis and autoimmunity. Annu. Rev. Genomics Hum. Genet. 6: 93-122.

Coutinho J 2004 RUNX1: transcription factor scores a hat-trick of autoimmune diseases. Clin. Genet. 65: 180-182.

Helms C, Cao L, Krueger JG, Wijsman EM, Chamian F, Gordon D, Heffernan M, Daw JA, Robarge J, Ott J, Kwok PY, Menter A, Bowcock AM 2003 A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis. Nat. Genet. 35: 349-356.

Nielsen C, Hansen D, Husby S, Jacobsen BB, Lillevang ST 2003 Association of a putative regulatory polymorphism in the PD-1 gene with susceptibility to type 1 diabetes. Tissue Antigens 62: 492-497.

Peltekova VD, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, Newman B, Oene MV, Cescon D, Greenberg G, Griffiths AM, St George-Hyslop PH, Siminovitch KA 2004 Functional variants of OCTN cation transporter genes are associated with Crohn disease. Nat. Genet. 36: 471-475.

Prokunina L, Castillejo-Lopez C, Oberg F, Gunnarsson I, Berg L, Magnusson V, Brookes AJ, Tentler D, Kristjansdottir H, Grondal G, Bolstad AI, Svenungsson E, Lundberg I, Sturfelt G, Jonssen A, Truedsson L, Lima G, Alcocer-Varela J, Jonsson R, et al 2002 A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. Nat. Genet. 32: 666-669.

Takata Y, Inoue H, Sato A, Tsugawa K, Miyatake K, Hamada D, Shinomiya F, Nakano S, Yasui N, Tanahashi T, Itakura M 2008 Replication of reported genetic associations of PADI4, FCRL3, SLC22A4 and RUNX1 genes with rheumatoid arthritis: results of an independent Japanese population and evidence from meta-analysis of East Asian studies.
J. Hum. Genet. 53: 163-173.

Tokuhiro S, Yamada R, Chang X, Suzuki A, Kochi Y, Sawada T, Suzuki M, Nagasaki M, Ohtsuki M, Ono M, Furukawa H, Nagashima M, Yoshino S, Mabuchi A, Sekine A, Saito S, Takahashi A, Tsunoda T, Nakamura Y, Yamamoto K 2003 An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis. Nat. Genet. 35: 341-348.

Wada M, Yazumi S, Takaishi S, Hasegawa K, Sawada M, Tanaka H, Ida H, Sakakura C, Ito K, Ito Y, Chiba T 2004 Frequent loss of RUNX3 gene expression in human bile duct and pancreatic cancer cell lines. Oncogene 23: 2401-2407.

Weersma RK, Zhou L, Nolte IM, van der Steege G, van Dullemen HM, Oosterom E, Bok L, Peppelenbosch MP, Faber KN, Kleibeuker JH, Dijkstra G 2008 Runt-related transcription factor 3 is associated with ulcerative colitis and shows epistasis with solute carrier family 22, members 4 and 5. Inflamm. Bowel Dis. Jul 30 [Epub ahead of print].

Vitamin A and the Immune System

A topic of considerable interest to me is the effect of vitamins on the immune system. Vitamin A and D seem to be particularly important. At the outset, it is worth noting that deficiencies of vitamins A and D are commonly found in primary sclerosing cholangitis (PSC), and can become more pronounced as the disease progresses:

"In patients in the therapeutic trial*, vitamin A deficiency was seen in 40 percent, vitamin D deficiency in 14 percent, and vitamin E deficiency in 2 percent of those tested. More prominent deficiencies of fat-soluble vitamins occurred in the pretransplant group of patients, with 82 percent deficient in vitamin A, 57 percent deficient in vitamin D, and 43 percent deficient in vitamin E. We conclude that hypercholesterolemia and fat-soluble vitamin deficiencies are frequent in patients with PSC and are more common with more severe disease. Patients with PSC, especially with advanced liver disease, should be screened for fat-soluble vitamin deficiencies and supplemented accordingly." (Jorgensen et al., 1995).

Several recent papers outline the central importance of vitamins A and D in regulating the immune system (Holick and Chen, 2008; Kim, 2008; Manicassamy and Pulendran, 2008; Mora, 2008; Mora et al., 2008), and collectively emphasize the importance of maintenance of vitamin A and D levels to avoid health problems. The present article will focus mostly on vitamin A. Vitamin D will be discussed in a future article in a subsequent newsletter.

Vitamin A has been shown to be an important factor in maintaining gut integrity (Osanai et al., 2007). Specifically, all trans-retinoic acid, a key metabolite of vitamin A, is required for the expression of proteins (tight junction proteins) essential for maintaining the gut epithelial barrier. Tight junction proteins keep the cells of the epithelial barrier tightly held together. Experimental colitis in mice is characterized by increased gut permeability, and retinoic acid affords some protection against this colitis-induced change of gut integrity (Osanai et al., 2007).

* a randomized, placebo-controlled trial evaluating ursodeoxycholic acid

Vitamin A is particularly important in regulating the balance between inflammatory T cells (notably Th17 cells) and anti-inflammatory regulatory T cells (Tregs) in the gut. The gut associated lymphoid tissue (GALT) contains dendritic cells that convert vitamin A (retinol) to retinoic acid. Retinoic acid produced by the dendritic cells then regulates the differentiation of naive T cells, favoring Treg production at the expense of Th17 cell production (Kim, 2008).

The retinoic acid also imprints the T cells with gut-homing receptors. Moreover, the retinoic acid produced by the dendritic cells in the GALT, regulates immunoglobulin A (IgA) secretion by B cells, and imprints B cells with gut-homing receptors (Kim, 2008; Manicassamy and Pulendran, 2008; Mora, 2008; Mora et al., 2008). This vitamin A deficiency could potentially contribute to gut inflammation, and homing of pro-inflammatory immune cells to inappropriate sites.

One wonders whether aberrant expression of gut-homing receptors by immune cells associated with vitamin A deficiency might contribute to the extra-intestinal manifestations commonly associated with inflammatory bowel disease (e.g. migration of pro-inflammatory immune cells to sites outside of the gut, such as the eyes, skin, joints and liver)? Indeed, Eksteen et al. (2008) suggest that aberrantly expressed gut-homing molecules in T cells may potentially contribute to liver (as well as gut) inflammation in PSC patients. Eksteen et al. (2008) conclude their paper with the statement: "The discovery that retinoic acid imprints selective gut homing provides an important tool with which to make ex vivo regulatory cells that can be selectively targeted to the gut as a therapeutic intervention to deliver long-lasting remission" (Eksteen et al., 2008).

References

Eksteen B, Liaskou E, Adams DH 2008 Lymphocyte homing and its role in the pathogenesis of IBD. Inflamm. Bowel Dis. 14: 1298-1312.

Holick MF, Chen TC 2008 Vitamin D deficiency: a worldwide problem with health consequences. Am. J. Clin. Nutr. 87: 1080S-1086S.

Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH 1995 Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. J. Clin. Gastroenterol. 20: 215-219.

Kim CH 2008 Regulation of FoxP3 regulatory T cells and Th17 cells by retinoids. Clin. Dev. Immunol. 2008: 416910.

Manicassamy S, Pulendran B 2008 Retinoic acid-dependent regulation of immune responses by dendritic cells and macrophages. Semin. Immunol. Sep 6 [Epub ahead of print].

Mora JR 2008 Homing imprinting and immunomodulation in the gut: role of dendritic cells and retinoids. Inflamm. Bowel Dis. 14: 275-289.

Mora JR, Iwata M, von Andrian UH 2008 Vitamin effects on the immune system: vitamins A and D take centre stage. Nat. Rev. Immunol. Aug 8 [Epub ahead of print].

Osanai M, Nishikiori N, Murata M, Chiba H, Kojima T, Sawada N 2007 Cellular retinoic acid bioavailability determines epithelial integrity: role of retinoic acid receptor alpha agonists in colitis. Mol. Pharmacol. 71: 250-258.

Vitamin A Deficiency was First Noted to Affect the Immune System in 1924

"The disease [vitamin A deficiency] is ushered in by failure to gain weight. These children are liable to be attacked by some infectious disease. These infections are extraordinarily persistent and often have a fatal issue. An increased susceptibility and a diminished power of resistance to infections are therefore present. The eye lesion does not appear as a rule until late in the disease." - CE Bloch (1924)

Bloch CE 1924 Blindness and other diseases in children arising from deficient nutrition (lack of fat-soluble A factor). Am. J. Dis. Child. 27: 139-148.

Foxa2: A New Piece of the PSC Puzzle?

A recent paper published in Nature Medicine (published in August, 2008) shows that a gene called Foxa2 is important in controlling bile acid levels, and preventing liver injury caused by dietary cholic acid in mice (Bochkis et al., 2008). The authors (from the University of Pennsylvania School of Medicine) deleted the Foxa2 gene specifically from the hepatocytes of mice and show that this reduces the expression of genes encoding several bile acid transporters on both the basolateral and canalicular membranes, resulting in intrahepatic cholestasis, especially when the mice were fed with cholic acid (Bochkis et al., 2008). More interestingly, the authors went on to show that the expression of the equivalent gene in humans, FOXA2, is markedly reduced in the livers of adult patients with primary sclerosing cholangitis (PSC), and children with biliary artresia (Bochkis et al., 2008).

The Nature Medicine paper by Bochkis et al. generated considerable interest in the popular scientific press in early August, 2008, as can be seen in these news articles:

Penn Researchers Find a New Role for a 'Foxy Old Gene'
http://www.uphs.upenn.edu/news/News_Releases/2008/08/foxa2-bile-gene.html

Penn researchers find a new role for a 'Foxy Old Gene'
http://esciencenews.com/articles/2008/08/01/penn.researchers.find.a.new.role.a.foxy.old.gene

Researchers find a new role for a 'Foxy Old Gene'
http://www.physorg.com/news136808930.html

Gene found to protect liver
http://www.scientistlive.com/lab/?/Genetics/2008/08/04/20833/Gene_found_to_protect_liver/

Penn researchers find a new role for a 'Foxy Old Gene'
http://www.newsguide.us/education/science/Penn-researchers-find-a-new-role-for-a-Foxy-Old-Gene/

Implications for treating liver diseases
http://www.huliq.com/65647/implications-treating-liver-diseases

FOXA2 may be acting in a manner similar to the nuclear receptor PXR (pregnane X receptor), also controlling the expression of a number of enzymes of bile acid metabolism/conjugation and transport in the liver. PXR regulates lithocholic acid detoxification in the liver, while FOXA2 appears to be key to cholic acid detoxification (Bochkis et al., 2008). As has been mentioned in previous newsletters, PXR has been implicated in susceptibility to ulcerative colitis, and rate of progression of PSC. Perhaps FOXA2 should now be examined as a candidate susceptibility gene in PSC?

Cholic acid is a bile acid that is synthesized from cholesterol in the liver, but can become toxic to the liver because it gets converted to deoxycholic acid in the intestine by bacteria, and then recycled to the liver. The deoxycholic acid can cause cell damage not only in the liver, but also in the colon, and may contribute to development of colon cancer. Mouse models have previously been used to show that ursodeoxycholic acid (UCDA, Actigall) protects against colon cancer caused by cholic acid feeding (Loddenkemper et al., 2006). The 'normal' amount of cholic acid in the bile of PSC patients not treated with ursodeoxycholic acid (UDCA) is 61 percent of the total bile acids (Rost et al., 2004). This amount of cholic acid in the bile is reduced to about 16 percent of the total bile acids when PSC patients are treated with 22-25 mg/kg/day of ursodeoxycholic acid (Rost et al., 2004).

The other major bile acid produced in the liver in humans is chenodeoxycholic acid. This is also derived from cholesterol, and is converted to the toxic bile acid, lithocholic acid, by bacteria in the intestines. Both lithocholic acid and deoxycholic acid are considered to be secondary bile acids. Perhaps the combined action of PXR and FOXA2 co-ordinately controls the detoxification of these secondary bile acids to prevent liver and colon injury? FOXA2 and PXR seem to share some control of the genes that they regulate ... that is the two transcription factors are said to "cross-talk" with one another (Nakamura et al., 2007).

FOXA2, also known as hepatocyte nuclear factor 3 beta (HNF3beta), has previously been shown to play an important role in regulating liver and pancreas development and metabolism.

References

Bochkis IM, Rubins NE, White P, Furth EE, Friedman JR, Kaestner KH 2008 Hepatocyte-specific ablation of Foxa2 alters bile acid homeostasis and results in endoplasmic reticulum stress. Nat. Med. 14: 828-836.

Loddenkemper C, Keller S, Hanski ML, Cao M, Jahreis G, Stein H, Zeitz M, Hanski C 2006 Prevention of colitis-associated carcinogenesis in a mouse model by diet supplementation with ursodeoxycholic acid. Int. J. Cancer 118: 2750-2757.

Nakamura K, Moore R, Negishi M, Sueyoshi T 2007 Nuclear pregnane X receptor cross-talk with FoxA2 to mediate the drug-induced regulation of lipid metabolism in fasting mouse liver. J. Biol. Chem. 282: 9768-9776.

Rost D, Rudolph G, Kloeters-Plachky P, Stiehl A 2004 Effect of high-dose ursodeoxycholic acid on its biliary enrichment in primary sclerosing cholangitis. Hepatology 40: 693-698.

Additional references on FOXA2 can be found at:
http://www.psc-literature.org/FOXA2.htm

Foundation Website Recognition in *Current Hepatitis Reports*

by David Rhodes

Our two web sites (Primary Sclerosing Cholangitis Literature and PSC Partners Seeking a Cure Foundation) were recently recognized in the "Web Alert" sections of *Current Hepatitis Reports*:

Current Hepatitis Reports Volume 7, Issue 2: June 2008; pp. 47-48
Web Alert
Editor Naishadh Raghuwanshi, MD MBA
Saint Louis University School of Medicine, Division of Gastroenterology
and Hepatology, 3660 Vista Avenue, St. Louis, MO 63110, USA.
E-mail: nraghuwa@slu.edu

Primary Sclerosing Cholangitis Literature
http://www.psc-literature.org/

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease involving inflammation, fibrosis, and stricturing of medium-size and large ducts in the intrahepatic and extrahepatic biliary tree. Because the etiology of PSC is unknown, the disease's progression is unpredictable, and therapeutic options are limited, patients and their families are constantly looking for more information to help them cope with the disease. This website was constructed by a family whose son was diagnosed with PSC after high school. The website is designed to provide easy access to scientific literature regarding PSC, and through its "www.Resources" link it provides a well-organized alphabetical list of related websites. The wealth of scientific literature that can easily be accessed from this website makes it a good resource for physicians looking for the latest published information relating to PSC.

Current Hepatitis Reports Volume 7, Issue 3: August 2008; pp. 93
Web Alert
Editor Naishadh Raghuwanshi, MD MBA
Saint Louis University School of Medicine, Division of Gastroenterology
and Hepatology, 3660 Vista Avenue, St. Louis, MO 63110, USA.
E-mail: nraghuwa@slu.edu

Primary Sclerosing Cholangitis Foundation
http://www.pscpartners.org/

The mission of the nonprofit PSC Partners Seeking a Cure Foundation is to find a cure for primary sclerosing cholangitis (PSC). Despite advancements in medicine and technology, PSC remains one of the few conditions afflicting the liver for which there is no curative treatment. The primary goals of the foundation are to raise research funds, promote organ donation awareness, and provide a support system for patients suffering from PSC. "Living with Primary Sclerosing Cholangitis (PSC)," a brochure tailored to those who want a brief synopsis about PSC, can be downloaded in PDF format by clicking on the link on the home page. Although this website contains little scientific data, it provides a forum to help advance PSC education and research and raises awareness of this disease.

International Scientific Conference on PSC Announced: Olso, June, 2009

Next June in Oslo the European Association for the Study of the Liver (EASL) will hold a conference on the state of PSC research. Scientists will focus on epidemiology and natural history of PSC, pathogenesis of the disease, overlap syndrome and autoimmunity.

Attending will be US and European researchers, who will share studies and discuss trends. Ricky and Don Safer will attend to support international research efforts and to inform the EASL group about the availability of research grants from PSC Partners.

Photo Caption Contest!

This photo was sent to PSC Partners by Dr. Tom Karlsen of Oslo, a speaker at the May conference in Jacksonville. On a mountain jaunt in Norway, Dr. Karlsen set down his PSC Partners sport bottle and took in a glorious view of the scenic peaks.

This photo cries out for a humorous caption, but your editor is stumped, breathless from the altitude.

What's the contest prize? Your name in the newsletter! Respect, fame, and honor among fellow PSCers!

Send your caption ideas to newsletter@pscpartners.org. We'll announce the winners in the next issue.

What I learned from the Transplant Experience

The recent annual conference featured a session on transplant. We wanted to explore the topic a bit more so we asked a few member recipients to answer one more question. We asked them what they'd learned from the experience, what they'd pass on to others.

Dr. Aubrey Goldstein, transplanted May 10, 1998

My liver transplant was on May 10, 1998, Mothers Day. A big blessing for me, my wife and my mother. I had been unwell for 18 years prior to my transplant. Five days before my surgery I almost bled to death from esophageal varices. Surprisingly, that wasn't a frightening or scary event. I was just light headed and a bit more tired. I was expecting something like this to happen for a while. And having had a previous bleed from an ulcer I knew what was going on.

While I hadn't given up hope of having a tx, I was tired of being tired. Of not being able to do what I wanted to do when I wanted to do it. I was frustrated by the wait. But upon waking up in the ICU I knew I had a new liver inside me. I felt better despite having gone through 5 hours of surgery and still being on a ventilator to help me breathe.

I've learned not to give up on doing the things I enjoyed before my transplant. I continued to do them when I was sick. I'm doing them again with more energy now that I'm well. I learned to slow down a bit; to be kinder to myself. Expect a bit less and be more realistic. I think this helped me be kinder to others. The world doesn't necessarily make accommodations if you have a disability. Especially if they can't see it. You need to let people know you're hurting so that they can help you. I learned this as well.

Having a second chance at life made me appreciate everything we experience a bit more. That is not to say that I don't get frustrated or lose my temper. Just ask Caroline about that. But I do see and appreciate the beauty in the world around me. I enjoy being able to be active again, to cross country ski in the fresh fallen snow, to canoe in the wilderness, to carry my fair share of the load during a canoe trip, to go to the gym, to ride my bike around town, to listen to and enjoy music, to help others in my job as a physician, and especially to experience the love of my family, my friends, and especially my wife. I would have missed out on all these things.

I also learned that I can cope with not being perfect. The transplant changes you. I'm not the same person now. I'm healthier, but the meds and the surgery changed me. I had to learn to cope with the side effects of the medications. And I had to accept that they wouldn't go away. But that is the trade-off. I'm alive and enjoying a new life. Ten years and counting.

Aubrey and his wife Caroline Vanneste attended the conference in May

Melanie Sherder, transplanted January 7, 2008

On Monday, January 7, at 8:24 a.m., my Caring Bridge entry stated, "I made it home safe and sound (from Cleveland Clinic Foundation) and I'm currently enjoying the feel of my sweats and warm coffee. When I spoke to my coordinator, Paula (at CCF), on Friday, she informed me that my MELD score is a 15 and my INR was only 1.1. That means that it's no longer my INR that is raising my MELD score. I didn't even think to ask her what was driving it this time – my bilirubin or my creatinine. I plan to send her an email and ask her; I'm curious. A MELD of 15 puts me in the running for a cadaveric liver, but it's not likely that I will get the call. I could get the call for a split liver around 17, I'm told, but that's not an issue, now."

Later that same day, at 6:51 p.m. my dear friend, Ali, posted, "Hi everyone, I am updating for Melanie because she might be on her way to transplant this evening!!!!!! They have a split liver for her so if everything checks out she should be in surgery in an hour or so. She's totally surprised and happy and amazingly calm. I just got off the phone with her and she seems ready to go. Barnes-Jewish can you believe it?"

Minutes after that conversation with Ali, I was on my way to the operating room at Barnes-Jewish, in St. Louis. I remember climbing on the operating table, with the lights blurred and….woke up in ICU, without a ventilator. In the absence of the ventilator, my first thought was that they had not been able to perform the surgery, but in a split second my intuition told me that they had. No, I did not feel pain, I felt joy and peace. The greatest joy came when I asked the surgeon how the infant, who now shared this gift with me, was doing, and he said, "Resting well in ICU." The peace was in knowing that I now have a chance at a life, certain to end without this great gift – my new liver.

Mark your calendar!!!

Next year's
PSC Partners Seeking a Cure
Conference

With Northwestern Memorial
Hospital
Chicago, May 1-3, 2009

Together in the fight,
whatever it takes!

Melanie Sherder came to the 2008 conference just four months after her transplant!

Recovery was as amazing as the unexpected call, the blessed calmness as I awaited surgery, and the absence of the breathing machine. I spent a mere 12 hours in ICU, then a day in the step-down portion of the ICU. I came out of surgery on Tuesday morning, and they removed the pump for my pain medication on Friday, because I hadn't been using it, and I was released just four days after surgery.

The whirlwind of my recovery continues on with only a glitch here and there. Recuperating has gone far better than anything I could have imagined. My life, overall, still surreal so much of the time, is filled with beauty and blessings, and abundant love.

Yes, I have a love and appreciation for my donor, my donor's family, my new liver, new life and a renewed love and appreciation of God. It has been the greatest spiritual experience of my life, and I've had many. I realized within the first hours following transplant that God had taken me to, and through, the most complex part of my life and done so in truest fashion, with a surprise around every turn. Forever, I will be grateful for God's presence in my life, the donor family, and my new liver. In God's timing, and with perfect choreography, I have been given a new lease on life.

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Pat Bandy, transplanted March 21, 2002

Suddenly after years of PSC, autoimmune hepatitis, and ulcerative colitis, I had hepatocellular cancer. I learned I had to get a grip—fast, to outrace the tumor—and not let emotions make me crazy, not let myself wallow in pity or fear. I learned I had to deny denial in my situation; well-meaning friends truly didn't understand the crisis. Hopeful platitudes weren't helpful. I needed a clear and honest personal focus.

I learned to postpone *nothing* and to overcome fear with action. I pushed to get labs and other tests earlier than routine and that saved my life. I kept moving toward my goal of a transplant. I learned a new language of UNOS and MELD, as well as surgery; I learned what I could and couldn't do, what to expect. I didn't want sugarcoating.

I learned to get my support team ready, have them learn along with me, visit the doctor with me. My supportive family was wonderful. They took good care of me.

And I learned that the best medical team has the best result. Once I'd decided on them, I trusted them with my life.

I learned that an exceptional and anonymous grief-stricken family gave truly extraordinary gifts of life to many people.

And, finally, at the end, I learned I wasn't my liver or my disease. I learned I was stronger and more resilient than I'd thought.

Joanne Grieme, Caregiver to recipient and living donor, December, 2003

There are so many things I learned as an advocate and caregiver to my two sons during the living donor liver transplant experience. The emotions at times were overwhelming, but in having to choose two things that I thought would be helpful to others going through it, I would have to say: (1) it takes time to heal, and (2) make sure the insurance coverage you carry is sufficient for complications.

The transplant surgeon during the pre-op evaluation told us that it would take a good six months to fully heal. I thought, "Six months: that sounds excessive." I figured two weeks in the hospital for Todd (recipient) and one week for Scott (donor) and then things would be relatively back to normal after they both surgically healed in five to six weeks, right? Isn't that the way it works? Wrong. We never prepared ourselves fully for the bumps in the road after the transplant. Some days felt like Todd took one step forward and five steps back and that things would never return to a normal life. Although healing came slower then we anticipated it was six months later that Todd was packing up to attend college as a freshman over 1,000 miles from home. I should have listened to the surgeon's six-month time frame.

The one million dollar lifetime insurance maximum sounded sufficient, but Todd hit that after having complications with the first transplant and requiring a second transplant only 10 days after the first. Of course he didn't start out at $0 when he went in for the transplant, since PSC pre-transplant can be quite costly with doctor visits, hospital stays and many procedures along the way. Todd had a one million dollar lifetime maximum under his dad's health insurance policy and I covered him on my policy for secondary insurance, but it wasn't until after we met with the transplant financial advisor that she informed us that Pennsylvania has an insurance plan for children with life threatening illnesses (no matter what the family income) that would cover everything that wasn't covered including deductibles. That was a huge surprise to us.

We had no idea that the state we lived in had that available for children under the age of 19. We were very fortunate that Todd was fully covered.

Miss the May Conference?

Order Your Copy of 2008 Conference Presentations at:

http://www.pscpartners.org/CD2008.htm.

Itching for a Cure

Road to Chicago

PSC Partners Seeking a Cure Conference

NEW FUNDRAISING CHALLENGE: WE CAN DO IT!

Please do your part to help us meet this incredible fundraising challenge--to raise $45,000 between now and our conference May 1-3, 2009. (See Ricky's Message on page 2.)

Our anonymous donor has very graciously offered to match donations to The Road to Chicago fundraiser dollar for dollar up to $45,000. Help us turn $45,000 into $90,000 for PSC research!!! Every donation, no matter the amount, is welcome. For ideas on how you can participate in the Itching for a Cure Fundraising Challenge, go to the fundraising section of our website (http://www.pscpartners.org/RtC.htm). Animare Studio's video contribution is a happy addition to the Challenge.

Let's show our anonymous donor that we can live up to our motto: Together in the fight, whatever it takes! Let's move closer to finding that cure for PSC.

October is Liver Awareness Month

The American liver Foundation (ALF) has designated October as Liver Awareness Month. The Foundation is initiating a nationwide education initiative to teach kids about how important their liver is.

The Love Your Liver program is targeted to elementary and high school students. The program educates students about the liver and the actions they can take to maximize their liver health and prevent liver disease. For more details go to the ALF website: http://www.liverfoundation.org/chapters/lam

Could You Help to Host the 2010 PSC Partners Conference?

It's not too early to begin thinking about helping the Foundation to host the annual conference in 2010.

Check out the hosting guidelines on the website: http://www.pscpartners.org/Conf2010Guide.htm.

IT'S ALL ABOUT THE NAP

Sandi Pearlman, a 20-30-Something who was diagnosed in 2007, takes her naps in Fredericksburg, VA, where she lives with her oversize cat, Kissinger.

It's hard enough to be in your 20s and 30s. Everyone tells you that they're the greatest times of your life: you leave home for the first time, you find a job, contemplate starting a family with that special someone, etc. It's a lot for anyone to deal with. And then you add PSC. Wet blanket, anyone?

Just at a time where we're supposed to be exploring ourselves, going out, meeting people, we PSCers face an energy crisis.

In our 20s, we're experiencing college, leaving home and living on our own for the first time. It's a time to go wild, to be free to try a million different things on the path to finding out who we are. You're supposed to fall in love with all the wrong people, shut down bars and parties, hang out at diners until the wee hours of the morning.

Only problem is, you can't seem to stay up past 8:00, you're so tired that holding a conversation is tantamount to climbing Mt. Everest and the only bedroom activity you're interested in involves you, your comforter, and some nice long Zzzzs.

As to those trips to the local bar, well, you're pretty sure eventually somebody's going to notice that the only drink that ever touches your hand is an orange soda or a rum and coke minus the rum. And pick-up lines: "Hi, I'm Jack, I can't drink, I feel the need to sleep for hours on end, I itch in the oddest places and, oh, yeah, I have an incurable disease that will most likely lead to transplant. How about I buy you a coke?"

In our 30s, we're supposed to be settling down, solidifying our careers, making lifelong commitments and starting families. Our peers are happy to trot along to the local bar for a quick pint and not make it home 'til five past midnight while we're struggling to stay awake for the 7:00 news or fighting our urge to just let the kids forage in the pantry for whatever they may find and call it dinner surprise. And that's just for those of us who even have the energy to work, leave the house or have kids.

A quick drink with the boss seems like the road to promotion, but how to explain why that's just not quite possible without giving your boss details best left private or being labeled a recovering alcoholic or prude.

And let us not forget the romantic side of things. First, we have to have the energy to go out and meet someone, not to mention hold a sparkling conversation if and when we do.

Then, that partner has to remain unfazed by the whole transplant thing and, on top of that, be more than a little understanding when we're just too tired to be in the mood. If you know someone who fits this description and has decent health insurance, by all means, send him my way and check to see how many siblings he has for the rest of us out there.

Here's the thing, it's cute to have nap time when you're in kindergarten. It's fine for execs to power nap in the afternoon. It's not so fine when you're so exhausted all the time that your version of a nap lasts three or four hours and you're still exhausted upon waking.

So, what's a PSCer to do? Do we proudly wear Ts that shout slogans like "I ❤ Naps" or warn our dates, spouses, and friends that if we fall asleep on them it really isn't the company? Should we all hang out with narcoleptics so they just won't notice?

I guess there are no easy answers, at least none that I can come up with at the moment and it is getting close to nap time . . .

Connections

ALF, the **American Liver Foundation,** sponsors several events and fundraisers to raise awareness of liver disease. The website lists culinary celebrations, outdoor activities, educational and music events in various states: http://www.liverfoundation.org/events

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Check out these recent news stories from the **Crohn's and Colitis Foundation of America** website: http://www.ccfa.org

- Crohn's disease and ulcerative colitis share genetic risk variants
- Abnormal Pap smears more likely in women with inflammatory bowel disease
- Ulcerative colitis may respond to treatment with rosiglitazone
- Inflammatory bowel disease linked to poorer outcome from C. difficile infection. Smoking may raise risk of colon polyps
- Granulocyte protein may provide marker for inflammatory bowel disease
- Mesalamine reduces risk of CRC among IBD patients
- New cancer drugs could help in autoimmune disease

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The annual National **Donor Sabbath** is traditionally held two weekends before Thanksgiving; this year the dates are November 14th through 16th. Faith communities across the country focus on the critical need for organs, tissues, marrow, and blood, and their life-enhancing capabilities. Faith leaders participate in discussions of donation with their congregants, and faith communities sponsor donation awareness activities during this 3-day celebration of life. To learn more and plan for the event in your faith community, go to this website: http://donatelife.net/ and http://www.organdonor.gov/get_involved/events.htm.

Fact-O-Rama!

PSCers: We are NOT alone

(but we're a rare group . . .)

☑ PSC occurs at rate of 1–6 people per 100,000

☑ It's more prevalent in men (60 - 70%)

☑ PSC is associated with Ulcerative Colitis (UC)

☑ 65-75 % of people with PSC have Inflammatory Bowel Disease or IBD (UC or Crohn's)

☑ 3-10 % of those with UC have PSC

Source: Dr. Winston Hewitt, Division of Transplant Surgery, Mayo Clinic Jacksonville, presentation at 2008 PSC Partners Seeking a Cure conference