

PSC Partners Seeking a Cure

Newsletter

Vol. 1, Issue 1, Jan 2005

Edited by David Rhodes and Ricky Safer



Working together to provide research, education, and support for people affected by Primary Sclerosing Cholangitis.

Introduction

Don and Ricky Safer

The Primary Sclerosing Cholangitis (PSC) support group is pleased to announce the formation of a new foundation; PSC Partners Seeking a Cure. The three-fold purpose of the PSC Partners Seeking a Cure foundation is to:

- (i) raise funds with which to research the causes and cures of PSC,
- (ii) promote PSC and organ donation awareness, and
- (iii) provide education and support to PSC patients and their families.

The foundation's Attachment to the Articles of Incorporation can be found on page 2 of this newsletter. We will hold our first conference in Denver, CO, April 29 – May 1, 2005 (see details below).

Partners Seeking a Cure – 2005 Conference

The "PSC Partners Seeking a Cure" foundation is pleased to announce that it will be holding its first annual conference in Denver, Colorado from April 29 - May 1, 2005.

Sponsored by Axcan Pharma, Procter & Gamble, and University of Colorado Health Sciences Center

Friday, April 29, 2005:

5:30 PM - 7:00 PM Reception; Welcoming Remarks (Don and Ricky Safer; PSC Support Group)
7:00 PM Dinner on your own (a list of restaurants within walking distance will be provided)

Saturday, April 30, 2005:

7:00 AM - 8:30 AM Continental Breakfast
8:00 AM - 8:15 AM Opening Remarks (Don Safer and Arne Myrabo; PSC Support Group)
8:15 AM - 10:00 AM
Dr. Gregory T. Everson (Introduction to PSC: The Top Ten Clinical Issues for Patients and Families) 20 minute talk
Dr. James F. Trotter (Non-Surgical Management of PSC) 20 minute talk
Dr. Joel Levine (IBD in Patients with PSC) 20 minute talk
Panel (Dr. Everson, Dr. Trotter, Dr. Levine) Q and A for 45 minutes
10:00 AM - 10:15 AM Break/snacks
10:15 AM - 12:00 Noon
Dr. Igal Kam (Transplantation for PSC) 20 minutes
Dr. Lisa Forman (Post-Transplant Issues) 20 minutes
Chris Klug (To the Edge and Back: My Story from Organ Transplant Survivor to Olympic Snowboarder) 20 minutes
Panel (Dr. Kam, Dr. Forman, Chris) Q and A for 45 minutes
12:00 Noon - 1:00 PM Box Lunch
1:00 PM - 2:30 PM
Dr. Robert A. Gleser (Integrated Healing) 20 minute talk
Dr. Lisa Corbin (CAM Therapies) 20 minute talk
Georgeane Vigue (Nutrition and Supplements) 20 minute talk
Panel (Dr. Gleser, Dr. Corbin, Georgeane) Q and A for 30 minutes
2:30 PM - 3:15 PM Marlene Murphy (Overview of Donor Awareness)
3:15 PM - 3:30 PM Break/snacks
3:30 PM - 5:00 PM
Dr. Stefan D. Holubar (PSC: Perspectives from a PSC Patient and M.D.) 20 minute talk
David Rhodes (PSC: Perspectives from a Care-Giver) 20 minute talk
Dr. Aubrey Goldstein (PSC: Perspectives from a Transplant Recipient and M.D.) 20 minute talk
Panel (Stefan, David and Aubrey) Q and A for 30 minutes
5:00 PM Dinner on your own (a list of restaurants within walking distance will be provided)

Sunday, May 1, 2005:

7:00 AM - 8:30 AM Continental Breakfast
8:00 AM - 9:30 AM Round-Table Discussions (Funding Opportunities and Challenges; Discussion Leaders - Lee Bria and David Rhodes (PSC Support Group))
9:30 AM - 10:00 AM Coffee Break/Snacks
10:00 AM - 12:00 Noon Round-Table Discussions (Education, Support, Increasing Donor Awareness; Discussion Leaders - Ricky Safer and Lee Bria (PSC Support Group))
12:15 PM Adjourn

When:

April 29, 2005 (5:00 PM) – May 1, 2005 (Noon)

Where:

Grand Hyatt Denver
1750 Welton Street, Denver, Colorado, 80202
USA

<http://www.hyattdenver.com>

Call 1 800 233-1234 to obtain a special PSC group rate (\$89 plus tax).

Registration Information:

If you wish to attend the Conference, please print, complete and mail the Registration Form:

<http://www.pscpartners.org/RegForm.htm>

Please print as many copies as you require.

Costs:

- round trip shuttle service from the airport to the Hyatt (PSC group rate) is \$28 per person.

- special PSC group rate of \$89 per night for hotel room (single or double occupancy) if reservations are made BEFORE March 31, 2005.

- early-bird conference fee = \$160 per person (or \$300 per couple) [if you register before 03/31/2005].

- late conference fee = \$170 per person (or \$320 per couple) [if you register after 03/31/2005].

- conference fee includes costs of group meals and snacks.

For further details, please visit:

<http://www.pscpartners.org/>

ATTACHMENT TO ARTICLES OF INCORPORATION OF PSC PARTNERS SEEKING A CURE

Elissa Safer Deitch

ARTICLE I: MEMBERS

PSC Partners Seeking a Cure (the "Corporation") shall have non-voting members. The designation of classes of members, the manner of election or appointment, the duration of membership and the benefits of members of each class are set forth in the Bylaws of the Corporation.

ARTICLE II: PURPOSES

The Corporation is organized exclusively for charitable, scientific and educational purposes within the meaning of Section 501(c)(3) of the Internal Revenue Code of 1986 (or the corresponding provision of any future United States internal revenue law)(the "Code") ("Section 501(c)3"), as an organization to: (i) raise funds to support education and research that lead to identifying a cure and/or the causes of Primary Sclerosing Cholangitis ("PSC"), (ii) promote awareness of PSC and organ donation, (iii) provide education and support to patients with PSC and their families and friends, and (iv) subject to the foregoing, do anything permitted of a nonprofit corporation under the laws of the State of Colorado. To this end, the Corporation shall at all times be operated exclusively for charitable, scientific and educational purposes within the meaning of Section 501(c)(3), including for such purposes, the making of distributions to organizations that qualify as exempt organizations under Section 501(c)3. All funds, whether income or principal, and whether acquired by gift or contribution or otherwise, shall be devoted to said purposes.

ARTICLE III: EXEMPTION REQUIREMENTS

No part of the net earnings, gains or assets of the Corporation shall inure to the benefit of or be distributable to its directors, officers, members or other private individuals, or organizations organized and operated for a profit, except that the Corporation shall be authorized and empowered to pay reasonable compensation for services rendered and to make payments and distributions in furtherance of the purposes set forth herein. Any and all property, both real and personal, which may be owned by the Corporation at any time, is and shall always be exclusively and irrevocably dedicated to the charitable, educational and scientific purposes of this organization.

No substantial part of the activities of the Corporation shall be the carrying on of propaganda or otherwise attempting to influence legislation, and the Corporation shall be empowered to make the election authorized under Section 501(h) of the Code. The Corporation shall not participate in or intervene in (including the publishing or distribution of statements) any political campaign on behalf of or in opposition to any candidate for public office.

Notwithstanding any other provision herein, the Corporation shall not carry on any other activities not permitted to be carried on:

- (a) by an organization exempt from federal income tax under Section 501(c)(3); or
- (b) by a corporation contributions to which are deductible under Section 170(c)(2) of the Code.

The Corporation will distribute its income for each tax year at such time and in such manner so that it will not become subject to the tax on undistributed income imposed by Section 4942 of the Code.

The Corporation will not engage in any act of self-dealing as defined in Section 4941(d) of the Code.

The Corporation will not retain any excess business holdings as defined in Section 4943(c) of the Code.

The Corporation will not make any investments in any manner that would subject it to tax under Section 4944 of the Code.

The Corporation will not make any taxable expenditure as defined in Section 4945(d) of the Code.

ARTICLE IV: DISSOLUTION

In the event of dissolution, or final liquidation of the Corporation, the board of directors shall, after paying or making provision for the payment of all the lawful debts and liabilities of the Corporation, distribute all the assets of the Corporation to one or more of the following categories of recipients as the board of directors of the Corporation shall determine:

- (a) a nonprofit corporation or organization which may have been created to succeed the Corporation, as long as such corporation or organization then qualifies as an organization exempt from taxation under Section 501(a) of the Code as an organization described in Section 501(c)(3); and/or
- (b) a nonprofit corporation or organization having similar aims and objects as the Corporation and which may be selected as an appropriate recipient of such assets, as long as such corporation or organization then qualifies as an organization exempt from taxation under Section 501(a) of the Code as an organization described in Section 501(c)(3).

Any of such assets not so disposed of shall be disposed of by the District Court for the City and County of Denver, Colorado exclusively for such exempt purposes or to such organization or organizations which are described in Section 501(c)3 as said Court shall determine which are organized and operated exclusively for such exempt purpose.

ARTICLE V: INDEMNIFICATION

The Corporation shall, subject to the provisions of the Bylaws of the Corporation, indemnify and hold harmless any and all of its directors, officers, employees, fiduciaries and agents to the fullest extent provided by the laws of Colorado.

ARTICLE VI: LIMITATION ON DIRECTOR LIABILITY

A director of the Corporation shall not be personally liable to the Corporation or to its members for monetary damages for breach of fiduciary duty as a director; except that this provision shall not eliminate or limit the liability of a director to the Corporation or to its members for monetary damages for: (i) any breach of the director's duty of loyalty to the Corporation or to its members; (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law; (iii) acts specified in Section 7-128-403 or 7-128-501(2) of the Colorado Revised Nonprofit Corporation Act, as amended from time to time (the "Nonprofit Act"); or (iv) any transaction from which the director directly or indirectly derived an improper personal benefit. If the Nonprofit Act is hereafter amended to eliminate or limit further the liability of a director, then, in addition to the elimination or limited liability provided by the preceding sentence, the liability of each director shall be eliminated or limited to the fullest extent to the fullest extent permitted by the Nonprofit Act as so amended. Any repeal or modification of this Article VI shall not adversely affect any right or protection of a director of the Corporation under this Article VI, as in effect immediately prior to such repeal or modification, with respect to any liability that would have accrued, but for this Article VI prior to such repeal or modification.

If you would like to contribute an article to a future issue of this Newsletter, please e-mail it to David Rhodes:

rhodesdavid@insightbb.com

- PSC patients must be closely monitored to detect cancer.
- It is not only the risk of colon cancer that is elevated in PSC patients. Patients also exhibit a higher risk for cholangiocarcinoma and carcinoma of the gallbladder. The risk of pancreas carcinoma is about 14 times higher than in the general population.
- Prognosis is poor for patients who develop cholangiocarcinoma, with a mean survival of six months.
- It appears that chronic inflammation is associated with an increased risk of developing malignancy.
- It would be advisable for patients with a high risk of cholangiocarcinoma or another malignant disease entity to undergo early transplantation. This concept, however, due not least to the continuing scarcity of donor organs, remains unrealistic.
- Serum levels of the tumor markers CEA and CA 19-9 play a certain role in recognizing cholangiocarcinoma. But diagnosis is only reliable when more than one method or marker is combined. Methods include brush cytology.
- Preliminary data suggests that UDCA reduces the risk of developing not only colon cancer but also cholangiocarcinoma.

Primary Sclerosing Cholangitis (PSC)

<http://www.falkfoundation.com/pdf/FSK136-137e.pdf>

Highlights from: Congress Short Report Falk Symposia

Falk Symposium No 136

Cholestatic Liver Diseases: Therapeutic Options and Perspectives

Falk Symposium No 137

Liver Diseases: Advances in Treatment and Prevention

Freiburg (Germany), October 15–19, 2003

- In the majority of cases, the disease involves both intra- and extrahepatic bile ducts. In only 5% of patients, PSC affects only the intrahepatic bile ducts (small duct PSC); this is thought to be a benign variant of the disease.
- In general, PSC progresses through four separate disease stages: stage 1 with portal hepatitis; stage 2 with periportal hepatitis; stage 3 with cellular necroses and septal fibrosis; and stage 4 with manifest cirrhosis.
- In PSC, a frequent histologic finding is that the bile duct is completely encased in connective tissue. In later stages, this may progress so far that the original bile duct is completely replaced by connective tissue.
- PSC predominantly affects males and usually becomes manifest between the ages of 35 and 40 years. 43% of those affected are asymptomatic at the time of diagnosis. In 57% of cases, however, patients do present with symptoms, with jaundice and pruritus occurring in 27% and 24%, respectively. Within four years of diagnosis, however, 84% of patients report complaints. Patients' average survival is 12–18 years; cholangiocarcinoma occurs in about 10% of cases.
- In N. Europe and N. America, about 80% of patients with PSC concomitantly suffer from an inflammatory bowel disease (IBD). About 60% suffer from ulcerative colitis, 10% from Crohn's, and 10% from indeterminate colitis. Only 3.4% of IBD patients also suffer from PSC.
- The epidemiology of PSC is poorly understood. Worldwide prevalences of PSC range from 0 to 8.5 cases per 100,000 persons.
- The clinical course in patients with PSC is quite variable, but there are certain parameters that point to an unfavorable prognosis. The most important of these is elevated bilirubin levels. Other potential risk factors include advanced patient age, elevated levels of aspartate aminotransferase and alkaline phosphatase, reduced albumin levels, advanced histologic disease stage, bleeding esophageal varices, and hepato- and/or splenomegaly. The outlook is less favorable in patients who suffer simultaneously from IBD or who show low blood hemoglobin concentrations.
- Much of the available data suggests a strong immunologic component in the development of PSC. This includes the association of the disease with certain HLA haplotypes (B8, DRB3, DRB5), the occurrence of autoantibodies and the association with IBD. Even more data, however, conflict with the hypothesis that PSC is an autoimmune disease, including the predominance of males, the failure to respond to immunosuppressants, the absence of disease-specific epitopes for autoantigens and the fact that the transfer of autoantibodies in animal experiments does not result in disease development. Certain researchers are not convinced that PSC is an autoimmune disease since the key components of an autoimmune disease are notably absent.
- The pathogenesis of PSC is certainly affected by many factors, including genes and the environment. There are, however, very few corroborating data. Similar to PBC, however, PSC appears to develop in individuals with an elevated genetic susceptibility. The disease is unlikely to involve just a single gene.
- The disease may become manifest in association with a viral or bacterial infection. Among the viruses that may be involved in the pathogenesis of this disease, may be type 3 reoviruses (neonatal atresia), cytomegalovirus and retroviruses. Bacteria that may have a role in the pathogenesis of PSC include *Chlamydia* and *Helicobacter pylori*.
- In addition, other immunological disorders occur with increased frequency in patients with PSC. In many cases, these are autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, spondyloarthritis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, systemic sclerosis, sarcoidosis, polyposis, celiac disease and thyroiditis.
- The clinical course of PSC differs between children and adults. The clinical picture often presents as a kind of overlap syndrome showing features of both autoimmune hepatitis and PSC. For this reason, it is also termed autoimmune sclerosing cholangitis (ASC). The association between PSC and IBD is also high in children, standing at about 45%. Unlike adults with PSC, however, children with ASC as a rule, respond well to immunosuppressants, similar to patients with autoimmune hepatitis. It is possible that cases of PSC in adults may simply represent "burnt out" cases of ASC.

Therapy with UDCA (ursodeoxycholic acid; ursodiol) is a main component in the management of PSC. To date, there have only been a few controlled long-term studies and the results were generally less favorable than with PBC. Preliminary results suggest that higher UDCA doses (20–30 mg/kg body weight) are superior to lower doses. According to Prof. Adolf Stiehl, Heidelberg, the results are significantly better when patients routinely treated with UDCA also undergo endoscopic dilation of significant stenoses. This method experienced a significant prolongation in pre-transplant survival. UDCA combined with endoscopic dilation of significant bile duct stenoses currently represents the treatment of choice in PSC. UDCA also possesses chemoprotective properties against colorectal cancer.

An Overview of Primary Sclerosing Cholangitis

By David Rhodes

Primary sclerosing cholangitis (PSC) is a rare liver disease that has an estimated prevalence of 20.9 per 100,000 men and 6.3 per 100,000 women in the U.S (Bambha et al., 2003). The disease has no known causes or effective treatments (Levy and Lindor, 2003). It results in progressive inflammation, blockage, and eventual destruction of the intra- and extra-hepatic bile-ducts, resulting in liver cirrhosis for which the only treatment is liver transplantation (Chapman, 2003; Portincasa et al., 2005). The disease is often accompanied by inflammatory bowel disease (IBD); mostly ulcerative colitis (UC) and sometimes Crohn's disease (Levy and Lindor, 2003). Over 75% of PSC patients have chronic ulcerative colitis (Levy and Lindor, 2003). PSC comes with a greatly increased risk of cholangiocarcinoma, and UC with a greatly increased risk of colon cancer (Levy and Lindor, 2003). Moreover, PSC is frequently associated with other complications, including gallbladder disease, chronic pancreatitis, systemic sclerosis, celiac disease, Sjogren's syndrome, lupus, thyroiditis, and bone diseases such as rheumatoid arthritis (Gow et al., 2001; Portincasa et al., 2005).

There is controversy as to whether PSC is an autoimmune disease. Some researchers argue that certain features of PSC are inconsistent with an autoimmune disease (Vierling, 2004). However, there is evidence that autoimmune hepatitis (a known autoimmune disease) can evolve into PSC (Abdo et al., 2002), and many of the conditions associated with PSC (above) have a well established autoimmune basis. It is postulated that the disease may be caused by an as yet unidentified environmental trigger in genetically susceptible individuals (Portincasa et al., 2005). Although there has been progress in identifying genes conferring susceptibility to PSC [including several genes of the major histocompatibility complex (Boberg et al, 2001; Gow et al., 2001; Mehal et al., 1994; Mitchell et al., 2001b; Norris et al., 2001; Spurkland et al., 1999), the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Sheth et al., 2003), the CC chemokine receptor 5 (CCR5) gene (Eri et al., 2004), the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene (Agarwal et al., 2000), the intercellular adhesion molecule-1 (ICAM-1) gene (Yang et al., 2004), and the matrix metalloproteinase-3 (MMP-3) gene (Satsangi et al., 2001)], much remains to be done to elucidate its complex genetic basis. It is likely that the genetics of PSC susceptibility will be further complicated by the underlying genetics of susceptibility to inflammatory bowel disease because of the tight association between IBD and PSC.

According to Cullen and Chapman (2001), "PSC may be triggered in genetically susceptible individuals by toxic or infectious agents gaining access to the liver via a diseased and permeable colon." This idea is gaining support from studies with animal models. For example, mice deficient in Mdr2 (*mdr2(-/-)*) [the mouse equivalent of the human MDR3 protein] develop sclerosing cholangitis by a multistep process involving regurgitation of bile from leaky ducts into the portal tracts. This leads to induction of periductal inflammation, followed by activation of periductal fibrogenesis, finally causing obliterative cholangitis owing to atrophy and death of bile duct epithelial cells (Fickert et al., 2004). Various infectious agents have been proposed as causing or contributing to PSC, including *Chlamydia* (Ponsoen et al., 2002), and *Helicobacter* (Nilsson et al., 2000) species.

Preliminary results suggest that high doses of the bile acid ursodiol (ursodeoxycholic acid; UDCA) improve liver biochemistry in PSC patients (Chen and Glud, 2003; Mitchell et al., 2001a; Harnois et al., 2001), and may also be preventive against cholangiocarcinoma (Brandsaeter et al., 2004; Chazouilleres, 2004) and colon cancer (Pardi et al, 2003). However, the questions of whether or not high-dose ursodiol delays PSC progression, and delays time to liver transplantation, await the results of long-term high-dose ursodiol clinical trials that are currently in progress. In Europe, a mainstay of therapy for PSC is ursodiol treatment together with endoscopic intervention (Stiehl et al, 2002). In the U.S., ursodiol is not "indicated" for PSC because "there is insufficient evidence to either support or refute its clinical effects in patients with primary sclerosing cholangitis" (Chen and Glud, 2003). Liver transplantation is not a "cure" for PSC. It has been shown that PSC frequently reoccurs in PSC liver transplant recipients. The recurrence rate has been estimated to be about 37% after 36 months (Vera et al., 2002).

(please see p. 5 of this newsletter for references cited)



This newsletter is dedicated to the memory of **Shauna Saunders**, a graduate student in the Dept. of Economics at Duke University. Shauna tragically died in December, 2004 while awaiting a liver transplant. Shauna suffered from autoimmune hepatitis (AIH) as a child, and was later diagnosed with PSC and Crohn's disease. Shauna was a very active participant in the U.S. PSC forum, and was a constant source of support even while her own health was failing. She will be missed by all who had the privilege of knowing her.

The Need for Patient/Care-giver Education and Support

Because of the dismal prognosis of this disease and its numerous complications, there is a desperate need for support and education for patients and their family members (or care-givers) afflicted by this disease. In recent years and months, significant progress has been made in establishing several complementary support mechanisms:

1. An on-line PSC support group was established in 1998. This is a message board (forum) on Yahoo/Health, where PSC patients and care-givers can exchange information and lend support/advice to one another.

<http://health.groups.yahoo.com/group/psc-support/>

The membership of this group has grown to ~750. This support group is closely affiliated with the PSC support group in the U.K. (with a membership of ~300). The latter group publishes a newsletter (PSC News) and holds an annual meeting in Oxford with a leading world expert on PSC, Dr. Roger Chapman.

<http://www.psc-support.demon.co.uk/>

Many members of the U.K. support group participate in the Yahoo forum, and many members of the Yahoo forum subscribe to (or contribute articles to) the U.K. PSC News newsletter. These support groups play an essential role in helping newly diagnosed patients and their care-givers cope with the anguish of diagnosis and dismal prognosis of this disease on a day-to-day (and sometimes minute-to-minute) basis. This forum is generally the first place that patients and care-givers turn to for advice when faced with a new symptom or concern. Common symptoms include fatigue, pruritus, cholangitis attacks, and depression. Those patients in end-stage liver disease must further deal with hepatomegaly, splenomegaly, ascites, variceal bleeding, and hepatic encephalopathy.

2. To complement the support groups, a PSC Literature web site was developed in 2004 to provide PSC patients and care-givers with easy access to a vast body of information available on the internet concerning PSC and allied diseases:

<http://www.psc-literature.org/>

This site includes links to hundreds of www resources, and links to over 21,500 research abstracts (organized by keyword, authors and dates) for those interested in exploring the scientific literature in detail. This site currently serves about 870 distinct hosts per month; the hosts are located in 36 different countries.

3. In January 2005, members of the U.S. PSC support group established a non-profit foundation to foster research, education and support for PSC patients and their care-givers, and to promote organ donor awareness:

<http://www.pscpartners.org/>

This foundation, "PSC Partners Seeking a Cure", plans to hold its first patient/care-giver conference in Denver, Colorado from April 29 - May 1, 2005, and plans to develop a monthly newsletter dedicated to patient/caregiver education and support. The "PSC Partners Seeking a Cure" foundation has made contacts with the "Morgan Foundation for PSC Research" which will be holding its first PSC Research Workshop (primarily intended for researchers) in Bethesda, MD in September, 2005. It is anticipated that our two foundations will work closely together in the future.

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