Ursodiol Formulations

(by David Rhodes)

Ursodiol is the “generic” name for ursodeoxycholic acid (UDCA), a bile acid commonly prescribed for the treatment of cholestatic liver diseases, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). In the U.S.A., ursodiol is available under two trade names; Actigall (typically available as 300 mg gelatin capsules with a pink cap and white body containing a white/yellowish powder), and URSO (typically available as white 250 mg tablets) [URSO 250].

Actigall was developed by Novartis Pharmaceuticals Corporation and is now marketed by Watson Pharmaceuticals: http://www.watsonpharm.com/

The Actigall capsules also contain as inactive ingredients: colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, starch (corn), and titanium dioxide.

URSO is marketed by Axcan Pharma: http://www.axcan.com/

Axcan Pharma has recently developed a 500 mg tablet marketed as URSO Forte. The inactive ingredients of URSO are: microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, ethylcellulose, dibutyl sebastic, carnauba wax, hydroxypropyl methylcellulose, PEG 3350, PEG 8000, cetyl alcohol, sodium lauryl sulfate, and hydrogen peroxide. According to Levy and Angulo (2004) “Milligram per milligram, the bioavailability of Actigall preparation is about two-thirds that of the URSO 250 tablet available in the United States”

According to Axcan Pharma “URSO Forte and URSO 250 are the only ursodiol s approved by the Food and Drug Administration for the treatment of patients with Primary Biliary Cirrhosis (PBC), a chronic liver disease that slowly destroys the ducts that drain bile in the liver. The recommended adult dosage for URSO Forte and URSO 250 in the treatment of PBC is 13-15 mg/kg/day administered in two to four divided doses with food."

Ursodiol is currently not “indicated” for treatment of PSC in the U.S.A; nevertheless, many doctors prescribe it for this condition, and at a higher dose than in PBC (typically 20 - 30 mg/kg/day for PSC) because preliminary results suggest that it improves liver biochemistry in PSC patients, and it may also offer protection against the development of colon cancer and cholangiocarcinoma (see p. 2 of this issue).

In Australia, ursodiol is available as Ursofalk (Dr Falk Pharma GmbH) as white, opaque, hard gelatin capsules. Each Ursofalk capsule contains 250 mg of ursodeoxycholic acid. These capsules also contain maize starch, silicon dioxide, magnesium stearate, gelatin and titanium dioxide as inactive ingredients. A liquid formulation of Ursofalk has recently been developed for pediatric patients (Setchell et al., 2005).

References


Ursodiol (Jackson Gastroenterology Patient Education) http://www.gicare.com/pated/ursodiol.htm

### 2001


In PSC, high-dose ursodiol (20 mg/kg/d) is associated with:
- significant improvement in liver biochemistry,
- significant reduction in progression in cholangiographic appearances,
- significant reduction in liver fibrosis as assessed by disease staging.

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In PSC, high-dose ursodiol (25-30 mg/kg/d) is associated with:
- a marked improvement in liver biochemistry,
- changes in Mayo risk score that would be expected to translate to differences in survival after 4 years.

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- in PSC, ursodiol use is associated with a lower incidence of hepatobiliary malignancy,
- the main predictors of malignancy in PSC patients were: recent diagnosis of PSC, no ursodeoxycholic acid (UDCA) treatment, clinical suspicion and previous colorectal-cancer.

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The first “high-dose” ursodiol studies in liver disease associated with cystic fibrosis [note that bile duct lesions in cystic fibrosis resemble those found in PSC]. The magnitude of the biochemical improvement in serum liver enzymes was significantly greater with higher doses of ursodeoxycholic acid; at 20 mg/kg/d it was similar to that reported for patients with other liver diseases administered lower doses. Biliary ursodeoxycholic acid enrichment increased with increasing doses, attaining 42% +/- 6% of the total biliary bile acids with the highest dose.

### 2003


UDCA significantly decreases the risk for developing colorectal dysplasia or cancer in patients with UC and PSC.

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Multiple mechanisms of action of UDCA in cholestatic liver diseases are reviewed:
- protection of injured cholangiocytes against toxic effects of bile acids,
- stimulation of impaired biliary secretion,
- stimulation of detoxification of hydrophobic bile acids,
- inhibition of apoptosis (cell death) of hepatocytes.

### 2004


- in PSC, ursodiol use is associated with a lower incidence of hepatobiliary malignancy,
- the main predictors of malignancy in PSC patients were: recent diagnosis of PSC, no ursodeoxycholic acid (UDCA) treatment, clinical suspicion and previous colorectal-cancer.

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The immunomodulatory activity of ursodiol is associated with activation of the glucocorticoid receptor, which then suppresses nuclear factor-kappaB-dependent transcription.

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In the rat liver, ursodiol treatment alters the expression of a large number of genes. Over 440 genes were modulated with UDCA by >1.5-fold; approximately 25% were significantly different from untreated controls.
Inflammatory Bowel Disease Genetics (Part 3)
(by David Rhodes)

In previous articles in this series (Vol. 1 Issues 2 and 3) we have discussed some of the progress being made in understanding the genetic basis of inflammatory bowel disease (IBD); Crohn's disease and ulcerative colitis (UC). Research in this area continues at a rapid pace. Here are some of the articles on this subject that have appeared in the literature in the last few months:

It was recently confirmed that the polymorphisms in the organic cation transporter cluster (OCTN = the SLC22A4/22A5 gene cluster on chromosome 9q31, corresponding to the IBD5 gene locus), are weakly associated with an increased Crohn's disease risk, and this risk is greater in the presence of CARD15/NOD2 mutations (CARD15/NOD2 is localized on chromosome 16, and represents the IBD1 gene, the first IBD gene to be identified). Genotype-phenotype analysis revealed that this association was particularly strong in patients with colonic disease (Torok et al. 2005).

In this study by Torok et al. (2005), no association between ulcerative colitis or Crohn's disease was found with DLG5 gene polymorphisms (Torok et al., 2005). DLG5 polymorphisms were also not found to be associated with Crohn's disease in the Scottish population (Noble et al., 2005). [DLG5 encodes a scaffolding protein involved in the maintenance of epithelial integrity. It is known to be located in a linkage region for IBD on chromosome 1q23. Genetic variants in DLG5 associated with IBD (ulcerative colitis and Crohn's disease) were initially found by Stoll et al. (2004)].

Despite the failure to find an association between DLG5 and IBD by both Torok et al. (2005) and Noble et al. (2005), Daly et al. (2005) were able to confirm the proposed association between IBD and certain variants of DLG5 in two out of three studies, providing support for the hypothesis that DLG5 constitutes a true IBD risk factor, but with modest effect.

Brand et al. (2005) have shown that polymorphisms in Toll-like receptor 4 (TLR4) are associated with Crohn's disease in the German population, and that TLR4 and CARD15/NOD2 mutations may contribute to distinct disease phenotypes. The presence of the Asp299Gly polymorphism of TLR4 (in the absence of CARD15/NOD2 mutations) was a particularly strong predictor of the stricturing phenotype (Brand et al., 2005).

Fowler et al. (2005) have shown that Crohn's disease in the Australian population may be in part determined by polymorphisms in the tumor necrosis factor alpha (TNFa) and interleukin 10 (IL10) genes. When these two mutant alleles are combined, this results in stricturing behavior.

In the U.S., significantly lower frequencies of CARD15/NOD2 mutations were seen in African American and Hispanic children with Crohn's disease compared with white children with Crohn's disease (Kugathasan et al., 2005). This is consistent with other studies that suggest that the CARD15/NOD2 gene association with Crohn's disease may be more prevalent in the Caucasian population.

However, it has recently been shown that in the South African population, a certain variant of the CARD15/NOD2 gene is associated with ulcerative colitis (UC); the A725G variant (allele) was found in 4 of 35 (11%) UC patients (Zaahl et al., 2005).

Studies with mice show that knocking out the Mdr1a gene (implicated in ulcerative colitis in humans), results in colitis in mice. Surprisingly, this was affected by infection with Helicobacter species. Helicobacter bilis accelerates development of colitis, while Helicobacter hepaticus delays disease development in the Mdr1a-deficient mice. Also surprisingly, dual Helicobacter infected Mdr1a-deficient mice eventually developed colorectal cancer (Maggio-Price et al., 2005). The Mdr1a-deficient mouse is considered to be a valuable model of human inflammatory bowel disease (Wilk et al., 2005).

References


Understanding the complex genetic basis of IBD is important for PSC because over 75% of PSC patients also have IBD (mostly ulcerative colitis, and sometimes Crohn's disease).
JUNE JOURNAL

The lazy days of summer have arrived. Although my life has slowed down a bit, PSC Partners Seeking a Cure continues to grow quickly in many directions. We continue to receive donations and in-kind services. New projects have been started, and many others are in the making, thanks to your creative suggestions. I can’t believe that it has only been six months since we came into existence. Thanks to all of you who continue to support us in every way. I know that I am thriving on the strength of the friendships that started at our conference and also on the online group. I can see that many of you feel the same way.

A huge thank you to Dave Rhodes who created the wonderful CD that summarizes the information and ambiance of our inaugural conference in April. It includes Power Point presentations and additional handouts and suggested reading materials provided by the speakers, some movies of transplant surgeries, and some photographs taken at the conference. A complimentary copy has been mailed to all conference participants. For all PSCers and caregivers who would like to purchase a copy of the CD, please go to our website at www.pscpartners.org and click on “2005 Conference CD.” It is an invaluable resource for all of us. Thanks, David, for all your expertise and time that you have donated to this project.

Lee Bria continues to be the dynamo behind all our fundraising efforts. She follows every lead and then coordinates every project for us. Thanks to Bill Wise who has spearheaded and continues to run the wristband project with great enthusiasm, we have netted great profits so far! The wristbands continue to be a hit. Lee started the Krogers rechargeable card project recently, and after just one month, we are seeing results. We hope that some of you will consider ordering a card. There is no expense involved, the card can be used at many participating grocery chains, and you will earn 5% of all money spent with the card to PSC Partners Seeking a Cure. Our newest project is a recycling program with AAA Environmental Company. If you mail in a used cell phone or ink jet cartridge in a free package provided by AAA Environmental, then PSC Partners Seeking a Cure will receive a rebate. Details of all three projects can be found at www.pscpartners.org, so please take a minute to look into how you can help. Other projects are being considered, and we’ll keep you updated. If you have any ideas, feel free to contact Lee at ldbria@comcast.net.

Many of you have mentioned the need for a foundation brochure, so you’ll be glad to know that Deb of VA has been working on the text of the brochure for us. The first draft looks terrific so far! Once we have the final product finished and printed, we’ll let you know, so that you can hand out the brochures to your physicians or other interested people. We hope to have these brochures ready to hand out at the NIH Conference on PSC next September.

We are starting to plan our second annual conference for the end of April, 2006. We have posted several messages requesting conference proposals from anyone who is interested in hosting the conference. We have two excellent options, and the board will weigh the pros and cons, and make a decision soon.

Don and I were in Scandinavia last month (celebrating my big birthday), and we were happy to have the opportunity to meet with Dr. Ulrika Broome at the Karolinska Institute in Stockholm. Dr. Broome has been doing PSC research since 1988, and it is a passion of hers. (Her research is listed in the PSC literature site of pscpartners.org) She has been doing PSC genetic studies in Sweden and plans to do family cluster studies in the future. She will keep us updated about any progress in her research that can be of value to us. Dr. Broome was very excited to hear that our foundation and the PSC online support group exist, because there is no existing group in Sweden right now. Dr. Broome is going to suggest that her PSC patients think about joining the online support group and accessing our foundation website. She also wants us to keep her updated about next year’s conference, so that she can suggest that option to her PSC patients as well. I am excited that PSC Partners Seeking a Cure now has contacts in Sweden as well as in Canada (Aubrey Goldstein) and in England (Ivor Sweigler).

Reggie Belmont in Connecticut has started another exciting first for us, our first local chapter of PSC Partners Seeking a Cure. After Reggie attended the conference, she returned home and began contacting local chapters of CCFA (Crohn’s and Colitis Foundation of America) and ALF (American Liver Foundation), as well as local GIs and medical advisory groups to tell them about our foundation. On Saturday, June 18, they held their first meeting, which was a combination support group meeting and planning session for the future. Their group plans to meet monthly, expand their membership, do outreach to area doctors, and possibly form a fundraising team for the Liver Walk in September. Thank you Reggie, for all your work. I hope to start a local Colorado chapter sometime this summer. If anyone else is interested in starting a chapter in your area, please contact me at pscpartners@yahoo.com and I will work with you.

I hope that the foundation continues to meet your needs as we continue to grow. Please write in with any suggestions that you have or with any volunteering offers. We greatly appreciate everyone’s input and ongoing support!

Ricky Safer

Thanks

We would like to thank these people who have helped with wristband sales: Pioneer Theater Guild and Friends of The Pioneer Choirs (Ann Arbor, MI), St. Mary’s School (Richland Center, WI), Camp Henry (North Carolina), Bill Wise, JD Krmpotich, Denny and Joanne Mayer, Jason and Jennifer Drasner, Melanie Scherder, Norm Cable, J and S Professional Pharmacy, Jeffrey Brown, Lee Bria, Ricky and Don Safer, Madeleine and Riad Al-Awar, Deb and John Wente, Linda Bullard, Joanne Grieme, Claudia Chaille, Douglas and Nancy Honig, Ellen Chenchinsky Deutsch, Mark and Julie Glassman, Stephen and Cynthia Althoff.
Some facts about PSC
(by David Rhodes)

According to Dr. E. Orfei, primary sclerosing cholangitis was first recognized by Delbet in France in 1924, and described as "Irregular Fibrosis and Stenosis of the Biliary Tree", to be distinguished from Secondary Sclerosing Cholangitis. (REVIEW OF PATHOLOGY OF THE LIVER. li-11-6. PRIMARY SCLEROSING CHOLANGITIS, by Dr. E. Orfei):


In the original descriptions, and up until the mid-1980s, 85-93% of patients were highly symptomatic at presentation. Although asymptomatic PSC was recognized, it was relatively rare. Between 1988 and 2002, however, over 47% of patients were asymptomatic. Most (74%) were diagnosed following presentation with elevated alkaline phosphatase and very few other signs and symptoms. Only 26% of patients were diagnosed because of abdominal pain, jaundice or hepatomegaly. The identification of PSC patients before the development of end-stage liver disease may allow earlier medical intervention (Abboud et al., 2002).


Our PSC Literature web site provides a compilation of articles and research abstracts on PSC and allied disease. It was established with its present domain name (www.psc-literature.org) in November 2004. Google has very kindly provided a free (public service) search engine for the site, delivering search results without any advertisements. In May, 2005, the site received 34,292 successful requests, with an average of 1,016 successful requests per day. Average data transfer per day was 113.4 megabytes, totaling 3.43 gigabytes for the entire month of May. The site served 8,073 distinct hosts in May 2005. The hosts were located in the following countries (listed in approximate order of greatest use):

- USA
- UK
- Netherlands
- Japan
- Canada
- Italy
- Germany
- Australia
- New Zealand
- Israel
- Mexico
- France
- Belgium
- Brazil
- India
- Greece
- Hungary
- Turkey
- Austria
- Poland
- Spain
- Argentina
- Saudi Arabia
- Singapore
- Peru
- Switzerland
- Sweden
- Slovakia
- Denmark
- Taiwan
- Czech Republic
- Norway
- Iran
- Russia
- Ireland
- Romania
- Portugal
- Philippines

We hope that we are delivering useful information that may help assist PSCers around the world in their search for answers to their questions. We hope that some of these visitors will join the PSC Support Group(s), and will spread the word about the PSC Partners Seeking a Cure Foundation.

PSC Literature use has shown steady growth over the last 6 months:
Update on Donations to PSC Partners
Seeking a Cure
(by Ricky Safer)

Here is a list of our recent individual donors (since May 2005)

In honor of: Donor:
Jason Drasner Jeffrey and Leslie Rich
Everett and Joan Walters
Jordan Rose
Shane Ore Dick and Kathleen Kynett
Judith Ore
William F. Bria III Dr. Rosemarie Bria-Levine
Terence and Nanette Weaver
G.K. and V.M. McMaster
Daniel Kantor Dorothy Kantor
Elaine Meshell
Paula and Herbert Margolin
Wendy and Mark Cimino
Marco Ginefra Diane and Angelo Paris
Rose de Santis
Denise Boyd Jenkins Donnie and Marjorie Marston
Aubrey Goldstein Dr. D. and Marcia Wolochow
Lonnie Smith Daniel and Nancy Wisley
Anonymous Donald and Betty Nygaard
Rob Lathrop and all those who were too ill to attend the conference

In memory of: Donor:
Justin, Billy, Mike, Barb Henshaw (Barb in Texas)
Richard, Laurie, Mette, Norm, Pat, Ed,
Art, Dan and Shauna, and all members of PSC-Support
who have passed on
Helen Elizabeth Eleanor G. Hubbs
Cavanagh

Thank you to all our donors for helping us reach our ultimate
goal of finding a cure for PSC!

Thank you to our new bronze level sponsor:
Barb Henshaw (Barb in Texas)

PSC/UC 30 Years Ago
(by David Rhodes)

It’s interesting that just 30 years ago, ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) were considered to be a “rare combination”:


This is a report on a 36-year-old male patient presenting with a rare combination of ulcerative colitis and primary sclerosing cholangitis. The disease of the biliary tract was suspected on the basis of the endoscopic retrograde representation of the common bile duct, and serologically differentiated from a chronic destructive, non-suppperative cholangitis on the basis of a lack of antimitochondrial antibodies. Subsequently, a hepaticojejunostomy was carried out to normalize the bile flow. PMID: 1211068.

It’s now estimated that of the patients with UC, 3% to 7.5% have PSC. Approximately 70% of patients with PSC have or will develop UC.

(Primary Sclerosing Cholangitis (Best Practice of Medicine: Hepatology: Chronic Choelstatic Liver Disease in Adults (MerckMedicus)) by Claudia Ortiz Zein, MD and Keith D Lindor, MD; January 2000. Last modified February 15, 2002)

Making Donations to PSC Partners Seeking a Cure

Tax-deductible donations can be sent to:

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

with a check made out to:

PSC Partners Seeking a Cure

Alternatively donations can be made on-line via PayPal (https://www.paypal.com) to pscpartners@yahoo.com

Please include a note to indicate who the donation is in honor and/or in memory of, and your return address.

We offer several levels of sponsorship

- Platinum level: $10,000
- Gold level: $5,000
- Silver level: $2,500
- Bronze level: $1,000
- Copper level: $500

Thank you for your generosity!
Kroger's Gift to PSC Partners

Right now our first batch of 20 Kroger gift cards has all been sold. I will be picking up 20 more this weekend so please contact me if you can use one. I have sold eleven of them so far to neighbors and friends who are only too happy to help out with this great program.

Thanks to the members from our support group who have also come forward to help so far:

- Tim Romlein
- David Rhodes
- Judy Rhodes [4]
- Dike Ajiri
- Kathy Smith [2]
- Nancy Brock
- Mary Wells
- Johnathan George
- Ricky Safer.

We know that not all of you can participate if you live in an area without any of the above stores.

We are working on starting a similar program back east and we will let you know when we are ready. If you live in another part of the country with a large grocery chain, please ask them if they also have a program and maybe we can start another one in your area. These generous corporate dollars make it easier on all of us.

Thank you so much to the Kroger Company for their ongoing generosity. 5% of every grocery bill purchased with the card is donated to PSC Partners Seeking a Cure.

Thank you so much to our wonderful members for supporting PSC Partners Seeking a Cure.

Lee Bria

If you would like to purchase a Kroger Gift Card, please send a check for $20.00 for each card, made out to PSC Partners Seeking a Cure and mail it to:

Lee Bria
2720 White Oak Dr.
Ann Arbor, MI 48103

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

Recycling Program

Once again, Lee Bria has beaten the bushes to find another way for PSC Partners Seeking a Cure to generate money. Along with the Kroger Cards, Lee has made arrangements with the AAA Environmental Company to compensate our foundation for the recycling of cell phones and ink jet cartridges.

The system is very easy to use and anyone with a printer at home or at work can make a difference. This is how it works. You can order envelopes from AAA Environmental (for personal use) or boxes (for larger quantities such as IT departments at the office). Ordering these self addressed postage paid items can be done by the internet:

http://www.aaaenvironmentalinc.com

or by phone 1-866-332-2234. The phone call will require you to leave a return phone number for a customer service person to get back to you. Both communication options will require the use of a code specific to our organization. The code # is:

PSC PARTNE 001

Without the code number we will not receive the compensation, so make sure to use it when reordering. The filled envelopes can be returned by mail while the larger quantity boxes will be shipped Fed Ex.

Within approximately 60-90 days we will receive our first checks and will at that time begin to get reports on the progress of this fundraiser. Cell phones that are recycled will net one dollar while the ink cartridges are subject to type and condition. We will notify everyone on the success of this effort as we receive these progress reports.

If you have any questions about this exciting new fundraising tool, please feel free to contact me at:

timwholey@cox.net

Thanks to Lee for another wonderful means to an end of PSC.

OMAHA TIM WHOLEY

http://www.pscpartners.org/Recycling.htm
This Won’t Hurt A Bit

Five words. Five lousy little words. This… won’t… hurt… a… bit. How many times have you heard that phrase? Better yet, how many times has it been true? This won’t hurt much? Maybe. This won’t hurt for long? Probably not. But, this won’t hurt a bit? Yeah, right. And Pamela Anderson can act, David Hasselhoff can sing, and Elvis just moved in next door.

So you can imagine my surprise when I heard, “Oh yeah, this is one of the more painful procedures we do.” I was in the pre-op room talking with the doc from the Interventional Radiology Department (read: Department of Sticking Things In You) and he had just answered the question, “Will this be done under general anesthesia?”

They were prepping me for a Percutaneous Transhepatic Biliary Drainage (or PTBD as his friends call him). The doc never missed a beat, but the nurse practitioner had picked up on the fact that I’d gone white beneath the yellow. See, I’d had a liver biopsy seep, and the pain from that had laid me out for a week. I’d had an ERCP backfire that swelled my gallbladder to the size of a softball and gave me pancreatitis. (Those of you who have had pancreatitis know what I mean… those of you who haven’t, I don’t recommend it). I’d given birth to three kids… no wait, that was my wife. Anyway, none of those things was supposed to hurt a bit, but they did. Now Dr. Smileypudd here was telling me that this was going to hurt worse than anything I’d ever experienced. I wasn’t exactly OK with that.

The NP was the same one who had called me the previous week to let me know what was going to happen next, when it was going to happen, and answer any questions I might have had. At the moment she was looking a little sheepish about forgetting to mention that the PTBD was also considered an effective means of extracting information in some less civilized parts of the world. Plus, there were more people in the room than for any procedure I’d ever been through. I go to a teaching hospital, so I’m used to having two of everyone in the room, but this was ridiculous. Nervous? You betcha. But hey, I’d long since stopped worrying about what happens to my body while I’m unconscious. After all, I get to sleep through the worst of it, right?

Well, the conclusion that I came to after awakening from my trip to Hell and back, was that with the possible exception of Aubrey, docs don’t have the slightest idea of what they do to people that causes pain and what they do that doesn’t cause pain. I’ll take a PTBD over pancreatitis any day. In fact, I’ll also take it over a liver biopsy, ERCP, broken bone, torn ligament, sprain, cut, scrape, razor burn, or hangnail. The reality is that even in the simplest of procedures with the best of practitioners, things can go wrong. Conversely, even a trained chimp can occasionally navigate the complexities of the human body without doing any real damage. Luck plays a factor. Sure, you can optimize your chances through your choice of hospital or doctor and your own prior experiences, but bad things still happen to good people.

Some of the finest people I’ve ever met are reading this article right now, and not a one of them deserves the lot in life they or their loved one has been dealt. But the very struggles that they’ve endured are part of what makes them what they are and who they are. Having repeatedly heard “this won’t hurt a bit” has made them stronger than anything that comes their way. It has given them the tenacity to rise above any obstacle in their path. It has galvanized them against any rain falling on their parade. It has metamorphosed them from Joe Blow and Suzie Homemaker into relentless advocates and peerless role models. So, next time your doc spits “this won’t hurt a bit” in your face, tell him to bring it on.

Bill Wise

Multi-listing, Pros and Cons

There was allot of "talk" about multi-listing among the PSC support group members, and one night as I crawled into bed I was contemplating the idea. Well, as I drifted off to sleep my mind continued on this journey...zzzz...

The phone rang, I answered. I was greeted by a friendly female voice informing me, "It's time. We have a liver for you in Italy."

In my mind's eye I saw the beautiful vineyards of the countryside, and the wonderful architecture of the cities. I saw the captivating sunset and its reflection on the water of the Grand Canal. I began to feel the breeze on my face as I lay in the gondola relaxed by the rhythm of the oar.

In that moment I decided that Italy, the country I had longed to see for so many years, would be the perfect place even if to recuperate from a transplant. After all, I remember my doc (a true Italian) talking of the abundance of hepatologists there - surely I'd be in good hands. When I snapped back to the conversation at hand, prepared to accept the liver, the voice on the line exclaimed, "Yes, we have a liver for you in Italy - Italy, Guam."

Italy, Guam?! As the visions began to fade I began to awake with the realization that it may be difficult, at times, to distinguish between the pros and the cons of multi-listing!

Melanie Scherder

* For those of you who are not confident in your knowledge of geography, no, there is not an Italy in Guam.

PERCUTANEOUS TRANSEPTATIC CHOLANGIOGRAPHY AND BILIARY DRAINAGE

“Percutaneous transhepatic cholangiography, or PTC, is a way of examining the bile duct system in the liver. This procedure is done under local anesthesia by a radiologist. During the exam, a thin needle is inserted through the skin (percutaneous) and through the liver (transhepatic) into a bile duct. Then dye is injected, and the bile duct system is outlined on x-rays (cholangiography).” “When one or more bile ducts narrows or has a blockage, bile may back up and cause problems such as jaundice, a yellowing of the skin. Or, a leak in a bile duct may allow bile to flow into the abdominal cavity. PTC allows your doctor to see on the x-rays if the ducts are partially or completely blocked. If necessary, a thin, flexible tube (catheter) may be inserted to allow the bile to drain into a collection bag outside the body, or into the small intestine. This procedure is called biliary drainage.”

As I was watching the recent Star Wars movie, “Revenge of the Sith,” I was reminded of the balance between good and evil, and the light and dark sides of life. It struck me that there is an analogy here between the battle between anti-inflammatory and pro-inflammatory signals in the body. The good, anti-inflammatory signals (leading to resolution of inflammation) are in a constant fight with the darker, pro-inflammatory signals (promoting inflammation).

The “Darth Vader (Anakin Skywalker)” of pro-inflammatory signals in the human body is thought to be the n-6 (omega-6) fatty acid, arachidonic acid (AA; C20:4n-6). AA has 20 carbons, and 4 double bonds, with the first double bond at the 6th carbon, counting from the end of the molecule (hence the term n-6). AA is converted to a series of pro-inflammatory eicosanoids. AA is obtained in the diet predominantly from meat. AA can also be produced in the human body from the n-6 (omega-6) fatty acid linoleic acid (LA; C18:2n-6) found in a number of vegetable oils; safflower, corn and soybean oils. LA has 18 carbons and 2 double bonds. Think of LA as the evil “Emperor” keeping the AA (“Darth Vader/Anakin Skywalker”) constantly replenished with the dark side of the force.

Some of the “Jedi” that counter these pro-inflammatory molecules are the n-3 (omega-3) fatty acids: the 20-carbon eicosapentaenoic acid (EPA; C20:5n-3), and the 22-carbon docosahexaenoic acid (DHA; C22:6n-3). Think of the omega-3 fatty acids, EPA and DHA as “Obe-One Kanobe” and “Yoda” [YoDHA], respectively, fighting against the dark side of the force. EPA contains five double bonds, while DHA contains six double bonds. These double bonds are all in the cis configuration; the first double bond being at the 3rd carbon from the end of the molecule (hence the term n-3). DHA is an important component of the phospholipids of human cellular membranes, especially those in the brain and retina. EPA and DHA are found at high levels in fish oils. EPA can also be derived in the diet from the omega-3 fatty acid C18:3n-3, linolenic acid (LNA), found at high levels in canola oil, walnuts, flax seed and many leafy plants.

Consuming increased amounts of long chain n-3 polyunsaturated fatty acids (LCPUFAs) results in a partial replacement of the AA in cell membranes by EPA and DHA. This leads to decreased production of AA-derived pro-inflammatory molecules. EPA and DHA competitively inhibit the conversion of AA to the pro-inflammatory eicosanoids, thus reducing their synthesis. EPA is converted to anti-inflammatory eicosanoids which inhibit inflammation, and prevent platelet aggregation; and increase vasodilation. This may lead to reduced blood clotting activity and decreased blood pressure.

EPA and DHA also inhibit the synthesis of the inflammatory cytokines TNF (tumor necrosis factor)-alpha and IL (interleukin)-1 beta. They also lower triglyceride levels by inhibiting lipid production, and by stimulating fatty acid oxidation in the liver. Stimulation of fatty acid oxidation is through activation of PPAR (peroxisome proliferator-activated receptor)-alpha. Because PPAR-alpha has anti-inflammatory actions (via inhibition of nuclear factor-kappa B), the activation of PPAR-alpha by fish oils may also contribute to their anti-inflammatory properties, and anti-cancer (cancer chemopreventive) effects.

Fish Oils are Converted to Resolvin E1

[If you are as dyslexic as me and Yoda, this spells “FORCE”!] The EPA of fish oils has recently been shown to be converted to a powerful anti-inflammatory molecule called resolvin E1, which protects against colitis in rodent models of inflammatory bowel disease. May the FORCE be with you!

Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids of approximately 1:1. However, in the current Western diet the ratio is closer to 15:1-17:1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved. Excessive amounts of omega-6 polyunsaturated fatty acids and a very high omega-6 : omega-3 ratio, as is found in today’s Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a low omega-6 : omega-3 ratio) exert suppressive effects.

Eating fish (rich in omega-3 fatty acids) once or twice per week can help to lower this ratio of omega-6 to omega-3 fatty acids. However, some fish are now known to be contaminated with mercury, and should be avoided, especially by nursing and pregnant women, and children (see article “Fish for Your Health” by Dr. C.R. Santerre (Dept. of Foods and Nutrition, Purdue University):

http://fn.cfs.purdue.edu/anglingindiana/FishAdvisory04.pdf

Fish oil dietary supplements (available as capsules) are available for those who do not eat enough fish, or other sources of omega-3 fatty acids.

Sources


2005 Conference CD

Copies of the 2005 Conference CD ($25 each in the U.S./$30 abroad; this includes shipping and handling) can be purchased from:

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

Please make checks out to: PSC Partners Seeking a Cure
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If you are planning for a year, sow rice;
if you are planning for a decade, plant trees;
if you are planning for a lifetime, educate people.

Chinese Proverb