

# DDW 2006: Conference Highlights



Alan Franciscus, Editor-in-Chief

This year's Digestive Disease Week Conference (DDW) was held in Los Angeles, CA. Some of the information presented at DDW was already released at the European Association for the Study of Liver Disease (EASL) conference earlier this year, including data on Valopicitabine (NM 283), Viroline and Adefovir, which was covered in the June 2006 *HCV Advocate* newsletter. Part one of DDW coverage in this report will focus on the new information presented at DDW on various experimental therapies to treat hepatitis C.

This year's conference introduced new terms or concepts that will most likely be widely used in the coming years: the 'Accordion' effect and 'STAT-C.'

The 'Accordion' effect refers to individualized treatment for people with hepatitis C. Think of a person who plays an accordion – they open and close the accordion to make a sound or music. In the case of treatment for people with hepatitis C, some people may need less HCV medications for shorter treatment duration and others will need more medications for longer treatment duration. And of course others may

need less or more medications for shorter or longer durations.

**STAT-C** is an acronym for "Specifically Targeted Antiviral Therapy for HCV." This will be used in the future to refer to the new direct antiviral compounds currently in clinical development and testing.

At this year's conference, the issue of drug resistance was also a hot topic of conversation. Now that we are entering a new era of direct HCV antivirals there is a potential and concern that people being treated with the new polymerase and protease inhibitors may develop drug resistance. We have seen this in HIV and HBV, and we will have to wait until the drugs are further along in the development cycle to find out the level of drug resistance in specific direct antiviral medications. Most researchers believe that the development of drug resistance is inevitable with these newer medications, and that an HCV specific antiviral will need to be used in combination with pegylated interferon and possibly ribavirin to prevent drug resistance in the near future. As more direct antivirals are developed, a combination of the different direct



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antivirals (protease and polymerase inhibitors) will be needed to prevent or counteract drug resistance.

## ITMN 191

ITMN 191 is an HCV NS3/4A protease inhibitor being developed by InterMune. At DDW there were various poster presentations (*T1793, T1794, T1795*)<sup>1</sup> on the discovery, development, bio-availability, potency, and potential for drug resistance of ITMN 191. ITMN 191 was discovered by using a rational drug design to produce inhibitors of the HCV NS3/4A protease. As a result of the design study, ITMN 191 was identified as a preclinical candidate. Further analysis of structural design using HCV NS3/4A protease domains from genotype 1b, 1a, 2 or 3 determined that ITMN 191 was a potent inhibitor against the protease derived from

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these genotypes. But, since ITMN 191's mechanism does not affect the *genotype activation site* it may be an effective therapy across all genotypes.

The results of another study found that after a 120 minute incubation in human and animal models – rat, dog, human, or monkey liver cells – that 81%, 73%, 35%, and 19% respectively of the compound remained intact. Also after a regimen in which a human equivalent dose of 290 mg (twice a day; taken by mouth) was given for 7 days, the trough liver levels in rats and cynomolgus monkeys were 390-fold and 52-fold the EC<sub>90</sub> (90% effective concentration). In another study of ITMN 191 it was found that in rats, dogs and cynomolgus monkeys ITMN 191 produced high concentrations of the drug in the liver, which should be predictive of efficacy in humans. Finally, another study of ITMN 191 found that there was an improved resistance profile of ITMN 191 over those observed for BILN-2061, VX-950 and SCH 50304, at least in the pre-clinical studies.

### MX-3253

MX-3253 (celgosivir) is being developed by Migenix and is currently in early human clinical trials for the treatment of hepatitis C. Celgosivir and its active metabolite castanospermine are potent inhibitors of alpha-glucosidase 1, a host enzyme that alters the processing of glycoproteins. Inhibition of glycoproteins by this enzyme is believed to interfere with HCV viral assembly, replication and release. Two studies were presented at DDW (T1799, S1059).<sup>2</sup> The first study tested the pharmacokinetics

of celgosivir following oral administration in rats. Following oral administration, blood samples were collected from the portal (liver) and caudal (tail) veins at pre-determined time-points. Based on the results, the authors concluded that following administration of oral celgosivir the liver was exposed to both with the majority of the drug being converted to castanospermine prior to liver exposure. The authors also speculated that the conversion of celgosivir to castanospermine most likely occurred in the gastrointestinal tract.

The second study by E. Yoshida and colleagues found that the administration of celgosivir in 43 genotype 1 patients who were treatment naïve or interferon-intolerant. The primary endpoints of this trial were to provide safety and efficacy data needed to advance celgosivir to combination therapy trials with pegylated interferon, with or without ribavirin.

The patients were randomized into one of three arms: 200 mg once daily, 400 mg once daily or 200 mg twice daily. Thirty five (81%) of the patients completed 12 weeks of therapy. Two patients (5%) had peak viral load reductions of at least 1 log during treatment, but dropped out due to non-compliance. It was noted that there were mild to moderate gastrointestinal symptoms – flatulence (67%), nausea (26%) and diarrhea (49%). Elevated serum creatine kinase levels (an indication of possible muscle damage) were noted in all groups (47% of patients) and appeared to be dose-related. The elevations were asymptomatic, reversible and returned to baseline levels within weeks post-treatment. No serious adverse events were reported, but 4 patients discontinued treatment for adverse events. Another 4 patients did

not complete treatment, but it was not due to treatment-related side effects. The authors concluded that “celgosivir, used as monotherapy in chronic HCV infection, was well-tolerated in all treatment groups with a modest antiviral effect. Based on non-clinical synergy data, combination therapy of celgosivir with peginterferon alfa-2b with or without ribavirin may produce more significant antiviral activity and is the subject of an on-going study.”

### CPG 10101

CPG 10101 (Actilon) is a toll-like receptor (TLR9) agonist that stimulates cytokines, affects the adaptive immune response and appears to have antiviral activity against HCV. Preliminary data from a study by J. McHuchison and colleagues on CPG 10101 in combination with peginterferon plus ribavirin (S1062) were presented. In the trial 74 HCV genotype 1 patients who relapsed after an initial treatment of pegylated interferon plus ribavirin were randomized equally into five treatment arms (within a 6 month period after stopping the prior pegylated plus ribavirin therapy)\*:

1. Peginterferon plus ribavirin
2. CPG 10101 plus peginterferon plus ribavirin
3. CPG 10101 plus peginterferon
4. CPG 10101 plus ribavirin
5. CPG 10101 monotherapy

\*doses: CPG 10101 = 0.2 mg/kg (weekly injection), peginterferon = 1.5 µg/kg (weekly injection); ribavirin = 800-1400 mg (oral-twice daily)

The safety data at week 12 showed that CPG 10101 was generally well-tolerated and most of the adverse events were transient and consistent with the drug mecha-

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# HealthWise:

## *Healthy Living with HCV Series*

### *Part 3: Weight Management*



Lucinda K. Porter, RN

The prevalence of overweight and obese Americans is increasing. Approximately two out of every three Americans are overweight or obese. The Surgeon General estimates that 300,000 obesity-related deaths occur annually in the United States. This is thirty times greater than the rate of death related to hepatitis C (HCV).

Obesity is associated with an increased risk in a number of medical conditions including heart disease, stroke, high blood pressure, arthritis, sleep apnea, type 2 diabetes, gall bladder disease and depression. Overweight individuals are prone to *non-alcoholic fatty liver disease* (NAFLD). NAFLD is a spectrum of fat-related liver conditions, ranging from simple steatosis (fatty liver cells) to a more severe form, *non-alcoholic steatohepatitis* (NASH). NAFLD is the most common liver disease in the United States.

People living with chronic hepatitis C virus (HCV) infection may have additional reasons to be concerned about body weight. Obesity may be a negative-predictor for response to HCV therapy. Obesity is a risk factor for cirrhosis-related death and may increase the risk for fibrosis.

Although there is minimal prospective data looking at the relationship between obesity and liver disease, what is available is compelling. Patients with NAFLD, with or without HCV, are likely to improve their health after losing weight and/or body fat. Research showed improvements in lab results, liver biopsy reports and quality of life measurements.

If you are overweight, with or without HCV, consider making some changes. Skip any “all or nothing” thinking – the loss of even a few pounds may benefit your health. Start with an honest assessment. The generally acceptable parameters for overweight and obesity use Body Mass Index (BMI). BMI is a measurement based on the ratio of weight-to-height.

Individuals with a BMI of 25 to 29.9 are considered overweight, while individuals with a BMI of 30 or more are considered obese. You can calculate your BMI by dividing your weight in kilograms by the square of your height in meters. The mathematical formula for BMI is  $BMI = Kg/(m)^2$ . You can estimate your BMI by (1) multiplying your weight (in pounds) by 703, (2) multiply your height in inches by itself, then divide the answer in (1) by the answer in (2). For those with computers and who want to avoid the math, try [www.umm.edu/healthcalculators](http://www.umm.edu/healthcalculators)

BMI is not the only indicator of body fat. You can be underweight and fat, overweight and muscular. Your weight may be normal, but you may have problems with high blood pressure, unhealthy cholesterol levels, diabetes or other conditions associated with excess body fat. In the November 5, 2005 issue of *The Lancet*, Yusef and colleagues reported results from a large international study suggesting that the best indicator of cardiovascular risk is waist-to-hip ratio (WTHR). The bigger the ratio, the higher the risk. The researchers for the WTHR study were so convinced by the results, that they recommended that WTHR should replace BMI for cardiovascular risk assessment.

All you need is a soft measuring tape and a simple formula to determine your WTHR. Measure your waist at its narrowest point and your hips at their widest point. Divide the first number by the second. The cut-off numbers for increased risk is a WTHR greater than 0.8 for women and 0.95 for men. A calculator can be found at [www.umm.edu/healthcalculators](http://www.umm.edu/healthcalculators)

Weight control is simply a matter of energy use. If what you eat equals what you use, then your weight stays the same. If you eat more than you use, your

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weight will increase; burn more than you consume, your weight will decrease. In short, food is fuel for the human machine.

If you want to lose weight, then you need to eat fewer calories, burn more calories, or both. Although a simple concept, weight management can be difficult to practice. At any given moment, half the female and a quarter of the male population are on some sort of diet. Pick up any health or women's magazine and you are likely to find an article about weight management. Weight-loss industry profits are growing along with our waistlines.

Consumers want to know what the best diet is. If you are going to make the commitment, you want to be sure that it will work. With so many diets to choose from, how do you choose one? Most of us are looking for a diet that is quick, easy, and painless. However, diets do involve time and effort. There is little immediate gratification and although it does not have to be painful, weight management involves change. Many of us resist change.

The most effective weight loss programs combine calorie reduction with increased physical activity. It is hard to lose weight simply by increasing physical activity, although it can be done. As for the diet, the total intake of calories is more important than the composition of the diet. Here are some tips for comparing diet plans:

- Avoid extreme diets. Restricting daily calories to less than 1,100 is potentially dangerous and should not be done unless under strict medical supervision.

- Pick a diet that is low in fat. Some fat is essential, but restrict fat consumption to 30% of daily intake.

- Select a weight management plan that maximizes fiber.

- Opt for diets that emphasize fresh fruit, vegetables, and whole-grains.

- Resist fad diets. Look for a diet that has a record of long-term success.

- Choose a diet you can live with and maintain.

- Skip deprivation. Deprivation may be endured for short periods, but it usually sabotages the best intentions.

- Be skeptical of wild claims. Beware of products, such as herbs and supplements, that promise weight loss without diet or exercise.

*Note: Consult with a medical professional before starting a weight loss plan. If you are seriously obese, look for a specialist in the field of bariatrics.*

Unless your doctor has advised you otherwise, the basic heart healthy diet works for individuals with chronic HCV infection. There is a common misconception that protein is bad for the liver. On the contrary, a diet with adequate protein is recommended for HCV patients. Exceptions to this general rule are for those with very advanced liver disease or with a compounding medical condition. Depending on symptoms, these folks may tolerate plant-based proteins better than animal protein. Sodium, dietary fat and fat-soluble vitamins may be a problem for those with bile duct disease or advanced cirrhosis. In these situations, it is advisable to work with your doctor and a nutritionist for a diet tailored to your needs.

Alcohol consumption should

be avoided by anyone with liver disease. If you cannot completely abstain from alcohol, reduce your intake and get help for your drinking. This change could save your life. For more information about this, check out the *Factsheets* at [www.hcvadvocate.org](http://www.hcvadvocate.org)

**A word to smokers:** if you are reluctant to quit smoking because you are afraid of weight gain, reconsider your thinking. Not everyone gains weight after quitting smoking. Those who do, gain less than 10 pounds and often lose it later. Compare this with the facts – nearly half a million people die annually in the U.S. because of smoking. Smokers who continue to smoke have a fifty-fifty chance of dying a smoking-related death. Smokers with HCV are at a much higher risk of death from smoking than from HCV. For more information about this, check out the *Factsheets* at [www.hcvadvocate.org](http://www.hcvadvocate.org)

Weight management is more than how good you look – it is about how good you feel and how long you may live. If you struggle with your weight, perhaps now is the time to make a change. Your liver, heart and arteries will thank you.

*Next Month: Tipping the Scales towards Successful Weight Loss.*

### Resources

For more information, look under the *Resource* sections of previous “Healthy Living with HCV Series” *Healthwise* columns

- Family Doctor – [www.family-doctor.org](http://www.family-doctor.org) For weight management information, click on Food and Nutrition under the Healthy Living subtitle.

- MedicineNet – [www.onhealth.com](http://www.onhealth.com)

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# Extrahepatic Manifestations: *Fibromyalgia and Hepatitis C*



Alan Franciscus, Editor-in-Chief

It is estimated that 3 to 6 million people in the United States have Fibromyalgia (Fibro or FM for short) and while a direct link between Fibromyalgia and hepatitis C hasn't been established there are more people living with hepatitis C who are also living with Fibromyalgia than the general population. Hepatitis C and Fibromyalgia also share many symptoms such as fatigue, and muscle/joint pain.

Fibromyalgia is a condition (rather than a disease) which causes widespread muscle pain, fatigue and multiple tender points in specific parts of the body. The pain has been described as aching or burning. Fibromyalgia affects people differently and the symptoms or severity of symptoms can not be predicted. Like most autoimmune conditions, more women than men develop Fibromyalgia. Fibromyalgia is a chronic condition – that is it is a life long condition for most people, but it is not a progressive disease and does not shorten normal life expectancy. It can, however, greatly reduce the quality of life of those who suffer from this condition.

Fibromyalgia is sometimes referred to an arthritis-related condition, but Fibro is not a true form of arthritis because it does not cause inflammation or damage to the muscles, joints or other tissues involved. It is, however, considered a rheumatic condition that impairs the joints and/or soft tissues and

causes chronic pain.

## THE HCV CONNECTION

The association or direct link between hepatitis C and Fibromyalgia has not been discovered, but most experts believe that HCV may act as a trigger to the onset of Fibromyalgia. Of interest, one study found that people with Fibromyalgia and HCV exhibit symptoms such as inflammation around a joint, bursa (sac containing fluid for lubrication of joints) and/or tendon, and vasculitis (blood or lymph vessel inflammation) that are not seen in HCV negative people with Fibromyalgia.

The prevalence of Fibromyalgia in people with hepatitis C has been found to be much higher than in the general population – 15 to 19% compared to approximately 2% of the general U.S. population.

## SYMPTOMS

The symptoms of Fibro vary from person to person. The most common symptoms and conditions associated with Fibro include:

- *Fatigue* that can range from mild to severe
- *Sleep disturbances* such as trouble falling asleep, staying asleep and/or waking up feeling exhausted (non-refreshing or non-restorative sleep)
- *Restless legs syndrome* is a disorder of the nervous system that affects sensation and movement in the legs and causes a strong urge to

move the legs. Restless legs syndrome can also interfere with sleep since the symptoms are usually worse at night.

- *Stiffness* when waking or after remaining in one position for a prolonged period of time
- *Irritable bowel syndrome* is a condition characterized by stomach pain and bloating and frequently alternating constipation and diarrhea in the absence of any disease
- *"Fibro Fog"* symptoms including difficulty concentrating, forgetfulness, mixing up words when speaking or reading (similar to HCV "Brain Fog")
- *Headaches* that are usually caused by tight neck and shoulder muscles or from the pain associated with Fibromyalgia
- Hyper-sensitivity to light, noise, touch and temperature
- *Numbness or tingling* of the extremities (legs and arms )
- *Anxiety, depression and irritability* due to pain, isolation and the unpredictability of the symptoms
- *Painful menstrual periods* in the absence of an infection
- *Light-headedness and balance problems* such as trouble with balance while standing and difficulty in visual tracking

## CAUSES OF FIBROMYALGIA

The exact cause of Fibro has not been established, but it is believed that Fibromyalgia may be caused by a physically or emotion-

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## FIBROMYALGIA

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ally stressful or traumatic event, repetitive injuries, illness (such as HCV?), rheumatoid arthritis or another type of autoimmune disease. Fibro may also be influenced by a person's genes and may run in families. In the past, it was believed that Fibro was a disease of the muscles and soft tissues, but researchers have documented brain and central nervous system abnormalities. Another theory is that people with Fibromyalgia may have a gene that causes them to react strongly to certain stimuli that others might not perceive as painful.

### DIAGNOSIS

Currently, there is no simple blood test for diagnosing Fibromyalgia. Because the symptoms are generalized they can overlap many other conditions so other diseases or conditions should be ruled out. If a physician is not well-versed in Fibromyalgia the diagnosis may be overlooked. Physicians who are familiar with Fibromyalgia can make a diagnosis based on criteria established by the American College of Rheumatology (ACR):

- *Widespread pain* (right and left side body pain above and below the waist) that lasts for more than 3 months
- *11 or more tender points* (out of 18) standard possible sites on the body

### MANAGEMENT

There is no cure for Fibromyalgia, but there are many strategies to manage the condition.

A comprehensive approach with many different health providers (doctor, physical therapist and others) seems to work best – this

includes the person suffering from Fibromyalgia.

### PAIN MANAGEMENT

There are no drugs approved by the U.S. Food and Drug Administration to treat Fibromyalgia, but many medicines have been found to help with Fibromyalgia-related pain and fatigue. Antidepressants have been found to help with managing Fibromyalgia. In addition to treating mood disorders, antidepressants are now widely used to manage pain and fatigue. Over the counter pain relievers such as acetaminophen (Tylenol), aspirin, ibuprofen and other medications are used to treat the pain. For more severe pain, stronger medications and narcotics can also be used, but long-term use should be avoided due to the high risk of physical or psychological dependency. Low-impact exercise and stretching can help with pain, stiffness and mood.

Medications used to help with sleep disorders; restless legs syndrome and other conditions associated with Fibromyalgia can help manage symptoms.

*Exercise* – Research has clearly found that aerobic and flexibility exercises are some of the best tools for managing Fibromyalgia. Try gentle exercising like walking. Be sure to stretch before and after exercise. New research is examining strength training exercises. Physical therapy has also been found to improve the symptoms.

*Sleep* – Getting the right type and enough sleep is very important. This can be difficult for people with Fibromyalgia since pain and restless legs syndrome can greatly interfere with amount and quality of sleep. Talk to your medical provider about medications to treat sleep disorders, pain management and restless legs syndrome

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*wedmd.com* Check out the Healthy Living section of this website.

- Merck – *www.mercksource.com* Although owned by a pharmaceutical company, there is no advertising and good information. Free sign-up is required in order to access some of the information, such as the Body Mass Index Calculator.

- The Obesity Society, NAASO – *www.naaso.org/consumers* Accurate information about the disease of obesity.

- Partnership for Healthy Weight Management – *www.consumer.gov/weightloss* This coalition is packed with weight management resources.

- University of Maryland Medical Center – *www.umm.edu/healthcalculators* Provides tools to calculate BMI and WTHR

- Weight-control Informational Network (WIN) – *www.win.niddk.nih.gov/index.htm* This service is brought to you by the National Institute of Diabetes and Digestive and Kidney Disease Center (NIDDK)

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nism. There were 6 withdrawals (2 drug-related adverse events; 2 patients lost to follow-up; 1 patient withdrew consent; 1 for non-compliance). There was one additional serious adverse event – CPG 10101 serious adverse event (CPG 10101 hypersensitivity). It was also noted that there were no exacerbations of hematologic (blood disorders) or ALT flares with CPG 10101 in combination with pegylated interferon plus ribavirin.

The authors concluded that CPG 10101 improves early antiviral activity of pegylated interferon plus ribavirin in the treatment of prior pegylated interferon plus ribavirin relapsers. An additional study of 90 treatment non-responders to a previous course of therapy is underway.

### HCV-796

HCV-796 is a non-nucleoside viral polymerase inhibitor that is being developed by ViroPharma and Wyeth. Preliminary results from an on-going trial of 16 treatment naïve patients (12 patients received HCV-796; 4 patients received placebo) for a 14 day dosing period with HCV-796 monotherapy (#1)<sup>3</sup> was presented. The patients were mostly genotype 1 (72%) and received oral doses of HCV-796 ranging from 50 to 1500 mg twice daily.

It was found that the 500 to 1500 mg twice daily dose achieved the highest HCV RNA or viral load reductions of 96 to 97% with substantial reductions in ALT levels – a marker of liver inflammation. The most common adverse event was mild to moderate headache. Three patients discontinued treatment due to adverse events – one

patient because of hypertension (in the placebo group), one due to elevated TSH level (thyroid) and one patient for elevated unconjugated bilirubin (returned to normal levels after treatment was discontinued). There were no serious treatment-related adverse events and no dose-limiting toxicities across the range of doses studied. Information on genetic sequencing for possible drug resistance is being collected. It was concluded that “HCV-796 demonstrated antiviral activity and was generally safe and well-tolerated given for 14 days.” HCV-796 is also undergoing clinical trials in combination with pegylated interferon.

### VX-950

VX-950 is an HCV protease inhibitor that has garnered the most attention of the new direct HCV antivirals. At DDW preliminary 12 week follow-up data from a 28 day dosing period of VX-950 in combination with pegylated interferon (Pegasys) and ribavirin of 12 patients (treatment naïve) was presented (*abstract 686f*). All patients received 750 mg (oral tablet) every 8 hours of VX-950, 180 µg of Pegasys (weekly injection), and ribavirin in two oral doses for a total of 1000 or 1200 mg daily. Patients received VX-950 for 28 days. At the end of the VX-950 treatment period, all 12 patients continued to receive Pegasys and ribavirin for the standard duration of treatment.

The combination of VX-950, Pegasys and ribavirin was well-tolerated with no serious adverse events. No patients discontinued treatment. The most common side effects reported were fatigue, headache, nausea, anemia, depression, itching and rash. One patient had a headache that was graded as severe, but in general the side effects reported were what you would

expect from interferon plus ribavirin therapy.

The authors reported that there was a highly significant reduction in HCV RNA or viral load levels with all 12 patients achieving undetectable levels (less than 10 IU/mL). The viral load for one patient became detectable two weeks after stopping VX-950, undetectable for the next 8 weeks, but again became detectable after 12 weeks of continued pegylated interferon plus ribavirin therapy. At week 16 of follow-up the viral load for this patient was 490 IU/mL. Blood work from this patient is undergoing viral sequencing for possible drug resistance and the patient continues to receive Pegasys plus ribavirin therapy.

The lead investigator, Dr. Lawitz, commented that 28 days of therapy with the combination of VX-950, Pegasys and ribavirin resulted in unprecedented antiviral activity, with all 12 genotype 1 patients reaching viral levels below the limits of detection at the end of dosing at 28 days; the combination of pegylated interferon plus ribavirin will hopefully preserve the response in these patients. For more information about this trial and the initiation of two large Phase II studies of VX-950 please see our “Special Report on VX-950” at [www.hcvadvocate.org/news/reports/DDW\\_2006/spec\\_rep\\_VX950.htm](http://www.hcvadvocate.org/news/reports/DDW_2006/spec_rep_VX950.htm).

### References

- <sup>1</sup> S. Seiwert et. al., K.R. Condroski et. al., and R. Rieger et.al. respectively.
- <sup>2</sup> E. Rubinchik and colleagues.
- <sup>3</sup> S. Villano and colleagues



# Steatosis and the Metabolic Syndrome in People with Hepatitis C



Liz Highleyman

Steatosis, or accumulation of fat in liver cells, is associated with progressive liver fibrosis, development of liver cancer, and poorer response to interferon-based therapy in people with hepatitis C. It is increasingly recognized that fatty liver disease is associated with metabolic disorders, including type 2 diabetes – a growing concern given the epidemic of obesity in the United States.

## FATTY LIVER AND THE METABOLIC SYNDROME

Nonalcoholic fatty liver disease (NAFLD) and its more severe form, nonalcoholic steatohepatitis (NASH), are common in people with and without hepatitis C virus (HCV) infection. In the February 2006 *Hepatology* supplement, G. Farrell and C. Larter noted that NAFLD and NASH were barely recognized 25 years ago, but now affect as many as one-third of Americans.

The prevalence of fatty liver has risen in parallel with the metabolic syndrome, and what Farrell and Larter refer to as “overnutrition and underactivity.” This poorly defined cluster of conditions includes abdominal fat accumulation, high blood pressure, elevated blood fats (cholesterol and triglycerides), and insulin resistance (inability of the cells to respond properly to the action of insulin), which can lead to elevated blood glucose and type 2 diabetes (sometimes called “adult onset,” though it is increasingly

seen in children as well).

As M.R. Charlton and colleagues discussed in a review article in the June 2006 issue of *Hepatology*, obesity is associated with insulin resistance, steatosis, fibrosis progression, and decreased effectiveness of interferon-based therapy in patients with hepatitis C. The mechanisms by which obesity and metabolic abnormalities promote fatty liver are not well understood, but inflammation, autoimmunity, and altered levels of cytokines and hormones such as leptin and adiponectin may play a role.

## HCV, STEATOSIS, AND DIABETES

Rates of fatty liver disease are substantially higher among individuals with hepatitis C, reaching 50%-75% in some studies. At the Digestive Disease Week 2006 (DDW) conference in Los Angeles in May, P.K. Pandya and colleagues (*abstracts 173 and S1915*) reported that half of veterans with chronic hepatitis C had the metabolic syndrome, and these patients were significantly more likely to have evidence of steatosis and fibrosis.

Several studies have shown that type 2 diabetes is also more common among patients with hepatitis C – as much as four times more common – compared with the population as a whole. In a 434-person study by G.V. Papatheodoridis and colleagues published in the May 2006 *Journal of Viral Hepatitis*, 13% of subjects with hepatitis C and 14% with hepatitis B had diabetes. Diabetes was seen significantly more often among patients

with higher fibrosis scores (29% for scores of 5-6 vs 8% for 0-2). The presence of diabetes was independently associated with more severe fibrosis, cirrhosis, steatosis, and increased triglyceride levels.

## ROLE OF LIVER INFLAMMATION

In the June 2006 issue of *Gastroenterology*, G. Leandro and colleagues reported on a meta-analysis of data from more than 3000 patients with chronic hepatitis C (55% with genotype 1) at 10 clinics in Italy, Switzerland, France, Australia, and the United States. Just over half had steatosis and 88% had fibrosis. Steatosis was independently associated with older age, genotype 3 HCV, ongoing alcohol use, higher body mass index (BMI), diabetes, liver inflammation, and fibrosis. The authors concluded that steatosis is “significantly and independently associated with fibrosis in chronic hepatitis C,” and suggested that liver inflammation may mediate fibrogenesis in patients with liver steatosis.

A study by D. Prati and colleagues published in the April 2006 *Journal of Hepatology* showed that among 2881 chronic hepatitis C patients, about half of whom achieved sustained virological response to pegylated interferon plus ribavirin, alanine aminotransferase (ALT) levels – and whether ALT decreased with successful treatment – were associated with indicators of the metabolic syndrome including BMI, blood pressure, blood glucose, and

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blood fat levels. The researchers concluded that elevation of ALT – a marker for liver inflammation – “partially depends on the degree of derangement of fat and carbohydrate metabolism.”

Similarly, in a study presented at DDW 2006, K. Ario and colleagues (*abstract 553*) found that liver inflammation was strongly related to insulin resistance in patients with chronic hepatitis C. Since long-term liver inflammation may promote fibrogenesis, they suggested that management of insulin resistance may help improve fibrosis.

### IMPACT OF HCV GENOTYPE

Interestingly, different HCV genotypes are associated with steatosis by different mechanisms. Genotype 3 HCV seems to directly promote the build-up of fat in hepatocytes – though this process is not well understood – and steatosis is more common and potentially more severe in this group. Among individuals with genotype 1, steatosis appears to be linked with co-existing metabolic conditions.

In the January 2006 issue of *Hepatology*, C. Camma and colleagues reported that insulin resistance is a risk factor for moderate-to-severe steatosis in genotype 1 patients, especially men (although in this study fatty liver was common even among non-diabetic genotype 1 patients at low risk for the metabolic syndrome). In the December 2005 *American Journal of Gastroenterology*, A. Wang and colleagues reported that the relationship between insulin resistance and adiponectin (a hormone produced by fat cells that regulates insulin sensitivity) is disturbed in

patients with genotype 1, but not genotype 3.

### IMPACT OF STEATOSIS ON LIVER DISEASE PROGRESSION

Recent studies, including two presented at DDW 2006, confirm the link between steatosis and liver disease progression. K. Corey and colleagues (*abstract S1056*) conducted a retrospective review of medical records from 223 chronic hepatitis C patients who underwent liver biopsy. Steatosis of at least grade 1 (fat in less than 5% of hepatocytes) was observed in 66% of genotype 1 patients, with 27% having grade 2 (fat in 5%-33% of hepatocytes) or higher; among genotype 3 patients, the corresponding figures were 78% and 30%. Among individuals with minimal-to-moderate or severe fibrosis, and among genotype 1 patients, a significant relationship was observed between steatosis and fibrosis. The authors suggested that “efforts to control steatosis may therefore have an important role in halting HCV liver disease progression, particularly in persons who are non-responders to antiviral therapy.”

The second study, by J. Pekow and colleagues (*abstract S1016*), included 94 patients receiving liver transplants for HCV-related cirrhosis; 34% of the explants (old removed livers) showed evidence of HCC. The researchers found that 69% of livers from patients with HCC and 50% from patients without HCC showed evidence of steatosis. They concluded that steatosis is an additional risk factor for HCC, and recommended that “increased vigilance should be practiced in persons with both HCV and steatosis.” Together, these two studies suggest that HCV positive individuals with steatosis may require earlier treatment for hepatitis C.

In addition, as reported by M.S. Lai and colleagues in the June 2006 issue of *Hepatology*, a recent study in Taiwan – where the prevalence of HCV infection is high – found that type 2 diabetes was associated with a higher risk of developing HCC even among HCV negative individuals, and also among people with elevated total cholesterol.

### MANAGEMENT OF FATTY LIVER

In a review article in the February 2006 *Journal of Viral Hepatitis*, A. Lonardo and colleagues concluded that metabolic approaches should be evaluated in addition to antiviral therapy for hepatitis C patients with steatosis.

The mainstay of fatty liver management is weight loss and increased exercise. Studies have shown that weight loss increases insulin sensitivity and can contribute to reversal of steatosis and fibrosis. Along with these lifestyle changes, medications that treat insulin resistance, such as rosiglitazone (Avandia) and metformin (Glucophage), may also play a role; medical therapy for NAFLD was covered in a review article by K.M. Comar and R. Sterling in the January 2006 issue of *Alimentary Pharmacology & Therapeutics*.

To date, however, medications such as these have not been well-studied in people with fatty liver disease, nor in HCV positive individuals. Indeed, much remains to be learned about metabolic conditions, steatosis, and liver disease progression in people with hepatitis C – everything from biological mechanisms, to noninvasive methods of diagnosis, to optimal management. Fortunately, this is one of the most active areas of liver disease research today.



**DONOR REGISTRY: PENNSYLVANIA**

Pennsylvania is slated to begin on-line organ donor registration on July 1, 2006. Like many states, Pennsylvania utilizes drivers' licenses and state identification cards for residents to designate their wishes to be organ donors upon death. This process is for those of "sound mind" who are at least 18 years of age. Anyone between the ages of 16 and 18 may donate if they have permission from their parents or legal guardians. Parents or legal guardians of children under the age of 16 may choose to donate these especially precious organs.

Potential donors are strongly encouraged to discuss their wishes among those closest to them, such as family and friends. The people who are alive after we are gone are the ones that guard our wishes.

**For more information:**

- On-line registration [www.donatelife-pa.org](http://www.donatelife-pa.org)
- Call 1-877-PA HEALTH or 1-877-DONOR-PA to get a free organ and tissue donor card to sign and carry with you.
- Center for Organ Recovery and Education - [www.core.org](http://www.core.org) Serves western Pennsylvania
- Gift of Life Donor Program - [www.donors1.org](http://www.donors1.org) Serves eastern Pennsylvania
- Pennsylvania car owners can promote this issue by displaying a tissue and organ donation awareness license plate [www.donors1.org/news/license.html](http://www.donors1.org/news/license.html)

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## FIBROMYALGIA

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to help restore quality of sleep (see the HCSP Fact Sheet Sleep and Hepatitis C for tips on managing sleep).

**Stress** – stress can trigger or worsen the symptoms of Fibromyalgia so stress management is another important tool that a person can use to manage the symptoms. Try relaxation techniques, prayer, meditation and other techniques to lower stress.

**Work Adjustments** – it may be helpful to find out if an employer allows for flexible working schedules, improving the physical work environment with ergonomically correct equipment such as the chair, desk and computer monitor. Persons unable to work because of Fibromyalgia may be eligible for disability. If you are unable to work you may be eligible for disability benefits from Social Security or from private disability insurance. People with Fibromyalgia have some work place protections. Contact the Americans with Disability office at 1-800-949-4232 for more information.

**Complementary Medicine** – the use of acupuncture, acupressure, t'ai chi, qi quong, massage, bio-feedback and relaxation techniques can help to manage symptoms.

**Support groups** – people with Fibromyalgia, like people with HCV, can greatly benefit from professional counseling and/or a support group to deal with the emotional and physical realities of living with Fibromyalgia.

In the past Fibromyalgia was not taken seriously and there was little research conducted to find the

cause and ways to manage the condition. But as we have begun to learn more about the condition and it has been acknowledged more and more research is being done to learn about the cause, management and treatment of this potentially disabling condition. Until more information and medications are available the best advice is always advocate for the best possible care for yourself and others with this condition.

### Resources:

- HCSP Fact Sheet: *Sleep and Hepatitis C*
- HCSP: *A Guide to Hepatitis and Disability*
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health Toll free: 877-226-4267 [www.niams.nih.gov](http://www.niams.nih.gov)
- National Fibromyalgia Partnership [www.fmpartnership.org](http://www.fmpartnership.org)



### Interview with Dr. Pockros on NM283 and Other Drugs Being Developed to Treat Hepatitis C

At this year's DDW, Alan Franciscus had the chance to ask Dr. Pockros everything you ever wanted to know about future treatments. This exciting interview is now available at [http://www.hcvadvocate.org/hepatitis/hepC/Pockros\\_interview.html](http://www.hcvadvocate.org/hepatitis/hepC/Pockros_interview.html)



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The HCV Advocate offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

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