

FDA: NM-283 on Hold



Alan Franciscus, Editor-in-Chief

On July 13, 2007 Idenix announced that the Food and Drug Administration had placed the clinical trial development of valopicitabine (NM-283) on hold. The decision was based on the FDA analysis of the the data from the phase II clinical trials with respect to the drug's overall risk-benefit profile. The drug is being developed by Idenix in collaboration with Novartis.

RISK-BENEFIT ANALYSIS

The overall risk-benefit profile is a comprehensive analysis of whether the risk of taking a new drug is acceptable when compared to the potential benefits. In this case the FDA conducted an independent risk-benefit analysis based on the entire clinical program of valopicitabine (including the clinical trial data from the retreatment study and the current study of treatment naïve patients) and concluded that the benefits of valopicitabine did not outweigh the gastrointestinal toxicities (nausea, vomiting and diarrhea).

The FDA action was a surprise given the encouraging preliminary results on valopicitabine that were released in June (see July 2007 *HCV Advocate* newsletter). The preliminary results found that 72.2% of the patients in the triple arm (valopicitabine, pegylated interferon and ribavirin) achieved undetect-

able HCV RNA (or viral load levels less than 20 copies/mL). In this study only 1 person discontinued therapy due to adverse events (gastrointestinal side effects) related to valopicitabine. According to Idenix there were two other patients who discontinued treatment, but these discontinuations were pegylated interferon/ribavirin related.

It seems as if Idenix was caught off guard as well. Jean-Pierre Sommadossi, chairman and chief executive officer of Idenix commented that "I have to tell you that we were very surprised – Idenix and Novartis – by their perspective." Idenix has put all their clinical trials of valopicitabine in the United States on hold and they are in discussion with Novartis about the future development of valopicitabine.

SIDE EFFECTS

Valopicitabine has had its problems with gastrointestinal side effects from the beginning. Last year the FDA revised the clinical trial study of treatment naïve patients to reduce the dose of valopicitabine from 800 mg to 200 or 400 mg/day.

In the June issue of the *HCV Advocate* newsletter, I also wrote about various next steps that Idenix was proposing in the clinical development of valopicitabine. These steps included the use of anti-vomiting medications to ease up some of the gastrointestinal side



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effects, and the possible use of another direct HCV antiviral. Idenix was also planning a new phase IIb dose ranging study (200 and 400 mg) of valopicitabine in combination with pegylated interferon plus ribavirin that they believed would give some concrete answers to the side effects and effectiveness of the lower doses.

THE FUTURE OF NM-283

It is apparent that the future development of NM-283 is in doubt. Mr. Sommadossi commented that, "We're evaluating our options for the program, but I want to tell you up front that I am not optimistic about further development of valopicitabine in the future." Mr. Sommadossi went on to state that he does not personally see any further development of NM-283, but that the final decision will be made after discussions with Novartis.



Mitochondrial Toxicity



Liz Highleyman

Mitochondrial toxicity refers to drug-induced damage to the mitochondria, small structures within cells that act as the body's "power plants." Ribavirin, a component of standard combination therapy for hepatitis C, is among the drugs known to be toxic to mitochondria.

While severe mitochondrial toxicity is uncommon among people with hepatitis C virus (HCV) infection alone who take ribavirin as part of an interferon-based regimen, it is a greater concern for HIV/HCV coinfecting patients who also take certain antiretroviral drugs.

WHAT ARE MITOCHONDRIA?

Each cell contains hundreds or thousands of mitochondria, which process fats and sugars from food and combine them with oxygen to create energy-storage molecules called adenosine triphosphate (ATP); when needed, the ATP is broken down to release the stored energy.

Mitochondria carry their own supply of genetic material – known as mitochondrial DNA, or mtDNA – which is distinct from the normal DNA found in a cell's nucleus. When mitochondria reproduce, mtDNA mutations may occur. When too many mutations accumulate, the genetic material deteriorates and the mitochondria cannot perform their normal functions, leading to a wide range of potential symptoms.

A variety of factors can cause mitochondrial damage, including toxic substances, oxidative stress

(generation of reactive "free radical" molecules), and the accumulation of mtDNA mutations as part of the normal aging process. Some research suggests that HCV and HIV themselves may contribute to mitochondrial dysfunction. One recent study, for example, found an inverse relation between HCV viral load and the amount of mtDNA in peripheral blood mononuclear cells.

DRUGS TOXIC TO MITOCHONDRIA?

Nucleoside analog drugs are particularly likely to cause mitochondrial damage. These agents resemble defective nucleotides, the natural building blocks of genetic material. The four DNA building blocks are adenine, cytosine, guanine, and thymine; in RNA, uracil is substituted for thymine.

Ribavirin is a guanosine nucleoside analog, meaning it resembles the natural nucleotide guanine. Taribavirin (Viramidine) is a pro-drug of ribavirin, which is converted to ribavirin in the liver. Some of the experimental HCV polymerase inhibitors now in clinical trials are nucleoside analogs as well, including valopicitabine (NM283), R-1626, and MK-0608. HCV-796 is also a polymerase inhibitor, but it works by a different mechanism and is not a nucleoside analog. Telaprevir (VX-950) and boceprevir (SCH 503034) are HCV protease inhibitors, a class of drugs that has not been linked to mitochondrial toxicity.

Several of the antiretroviral drugs used to treat HIV are also nucleoside analogs, including AZT

(Retrovir), ddI (Videx), d4T (Zerit), lamivudine (3TC, Epivir), and abacavir (Ziagen). Another anti-HIV drug, tenofovir (Viread), is a nucleotide analog, which means it requires fewer processing steps in the body to attain its active form. Along with lamivudine, two other drugs approved to treat hepatitis B virus (HBV) infection – telbivudine (Tyzeka) and entecavir (Baraclude) – are nucleoside analogs as well, while adefovir (Hepsera) is a nucleotide analog.

HOW DO DRUGS DAMAGE MITOCHONDRIA?

When viruses replicate, a process that involves building new chains of genetic material, viral enzymes (RNA-dependent RNA polymerase in the case of HCV, reverse transcriptase in the case of HIV, and RNA-directed DNA polymerase in the case of HBV) may mistakenly add a nucleoside or nucleotide analog onto the chain instead of a normal nucleotide, causing the process to grind to a halt. (While ribavirin is a nucleoside analog, it is not completely clear how it works against HCV, since it does not seem to act as a polymerase inhibitor.)

Unfortunately, nucleoside analogs can also interfere with the production of DNA in human cells, which accounts for some of their side effects. This is especially likely with mtDNA, since mitochondria use a special enzyme to copy their genetic material (polymerase-gamma), which is more likely than the enzyme that copies regular DNA in the cell nucleus (DNA polymerase) to accidentally use nucleoside/nucleotide analogs. And, unlike nuclear DNA, mitochondria have no mechanism for detecting and fixing such errors.

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MITOCHONDRIA

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SYMPTOMS OF MITOCHONDRIAL TOXICITY

Mitochondrial damage has been linked to a wide range of symptoms. The clearest association is with hyperlactatemia, an elevated level of lactic acid in the blood. Normally, mitochondria use oxygen to produce ATP. When the mitochondria are damaged, however, an alternative energy pathway known as anaerobic metabolism kicks in, which produces lactic acid as a by-product. Hyperlactatemia is characterized by fatigue, nausea, muscle pain, and shortness of breath. In severe cases, this can progress to life-threatening lactic acidosis, in which the blood becomes too acidic.

Several other manifestations have been linked to mitochondrial toxicity, primarily in people with HIV who have taken ddI, d4T, or especially the two drugs together. These include nerve damage (peripheral neuropathy), lipoatrophy (fat wasting in the face and limbs), and pancreatitis (inflammation of the pancreas). There is also increasing evidence that mitochondrial toxicity may contribute to metabolic abnormalities such as type 2 diabetes.

In addition, mitochondrial damage is thought to be responsible for one type of liver toxicity, in which tiny fat droplets accumulate in hepatocytes. This so-called microvesicular steatosis is distinct from the more common macrovesicular steatosis (accumulation of larger bubbles of fat) often seen in people with chronic hepatitis C, especially genotype 3. People with pre-existing liver disease are at higher risk of drug-induced liver toxicity, and mitochondrial damage

may help explain the high rates of steatosis—69% in one study—seen in HIV/HCV coinfecting patients, especially those taking ddI and/or d4T.

There is no definitive treatment for mitochondrial toxicity besides stopping the offending drugs. However, several nutritional supplements have been studied to alleviate mitochondrial damage, including B complex vitamins, antioxidants, N-acetyl-cysteine, L-carnitine, alpha-lipoic acid, mitoquinone (MitoQ), and mitocnol (Nucleo-maxX).

AVOIDING MITOCHONDRIAL TOXICITY

As noted, most people with HCV alone do not experience mitochondrial toxicity while using ribavirin in combination with pegylated interferon. The major side effect associated with ribavirin, hemolytic anemia, does not appear to be related to mitochondrial dysfunction.

HIV/HCV coinfecting patients, however, should be cautious about combining ribavirin with anti-HIV agents that can also cause mitochondrial damage, since toxicity is much more likely when such drugs are used together. Evidence of symptomatic mitochondrial toxicity was observed in about 5% of coinfecting subjects in the APRICOT and RIBAVIC trials of pegylated interferon plus ribavirin, especially those who were also taking ddI. In a more recent Spanish trial, 18% of participants developed hyperlactatemia; two patients died, and four were forced to discontinue ribavirin for this reason.

In 2003, the U.S. Food and Drug Administration warned that ddI and ribavirin “should be co-administered with caution” after the agency’s Adverse Events Reporting System revealed a five-fold increase in manifestations of mitochon-

drial toxicity in patients taking this combination. The authors of the latest international guidelines for the management of HIV/HCV coinfection went further, stating that ddI “should never be used” with ribavirin.

Although there is less evidence of increased mitochondrial toxicity risk in people using d4T plus ribavirin, many experts think it’s wise to avoid this combination as well. Among the anti-HIV nucleoside/nucleotide analogs, abacavir, and tenofovir are least likely to cause mitochondrial damage. (The combination of AZT and ribavirin should be avoided too, since both drugs can cause anemia). But one recent study found that while hepatitis C treatment led to improved mtDNA levels in coinfecting patients, this did not hold for those on antiretroviral therapy, even though none were taking ddI and just 16% were taking d4T. These results led the investigators to suggest that, if possible, anti-HIV therapy should be deferred until after hepatitis C treatment is completed.

In studies to date, there has been little evidence that experimental anti-HCV nucleoside analogs such as valopicitabine and R-1626 cause mitochondrial toxicity. However, the potential exists for additive toxicity if these drugs are used with ribavirin, or with each other, and this is something researchers should look for as trials continue. Caution will also be warranted when these agents are tested in HIV/HCV coinfecting patients using antiretroviral drugs from the same class.

References

<http://www.hcvadvocate.org/news/newsLetter/2007/advocate0807.html>



Doing your Pre-Disability Homework



Jacques Chambers, CLU

If you are dealing with hepatitis C, chances are you won't wake up one day and realize you can no longer go to work. For most people, the infection makes a more gradual progression toward disability. Because of the emotional issues involved, it can be difficult to judge when the right time is to go out (see "The Emotional Impact of Leaving Work on Disability," in the July, 2007 *HCV Advocate* Newsletter). Most people realize that disability is coming sometime in the future.

Before actually leaving work looms too close on the calendar, you should check your safety net, and know what programs are in place to continue your health insurance and provide a monthly income. This includes benefits from your employer, insurance you carry personally, and public benefits programs.

EMPLOYEE BENEFITS YOU WILL WANT TO LEARN MORE ABOUT:

1. Paid Sick Leave Policy (and other paid time off): How is it accumulated and how much do I currently have available? Ignore vacation time unless your company provides only one type of Paid Time Off; vacation benefits are vested, and you will receive payment for them in full if you are terminated which is not the case with sick leave days.

2. Company Medical Leave of Absence Policy: Primarily, what you need to know is how long the company will continue your bene-

fits, especially the health insurance, and protect your position while you are out on disability.

3. Short Term Disability Plan (STD): When does it start? How much does it pay? Does it require you to use up your sick leave first or can you use remaining sick leave to pay the gap between the percentage paid by STD and your full salary? Who handles the claims, the employer or an outside administrator? How does the plan define Total Disability?

4. Long Term Disability Plan (LTD): What is the waiting period before benefits begin (usually timed to start after the STD benefits are exhausted)? How much does it pay? What is the definition of Total Disability? Are there limits on how long they will pay for your condition (such as a limit on mental/nervous disabilities or disability due only to "subjective" symptoms)?

5. Health, Dental, Vision Plans: Chances are you have already been using these benefits so you will have an idea how they work. How long they will continue will depend on the company's Medical Leave of Absence policy. Do you make contributions out of your paycheck for any of these benefits? If so, you will need to make arrangements to continue paying them when the paychecks stop.

6. Group Life Insurance: Although you don't plan on using it any time soon, you should check to see if the plan provides for a Disability Waiver of Premium which would continue the coverage without

premium payment as long as you remain on disability.

7. 401(k) and Other Retirement Plans: What are the provisions for early withdrawal due to disability? Can they be withdrawn without penalty (usually the case)? Can they be withdrawn in periodic payments? If you have a defined benefit pension plan, you need to know if there is an Early or a Disability Retirement available to you.

8. Any Other Benefit Plans Your Employer Offers: Most other benefits provided by employers end when active work starts, but it never hurts to doublecheck.

9. Your Company's Actual Practice in Other Disability Situations: It also helps to know if a company has ever made exceptions to their written policies and, if so, what the circumstances were. The larger the employer, the more likely they will stick to the written company policy. With smaller employers, however, sometimes the only indication of how they handle items like Sick Leave and Medical Leave of Absence are by knowing what they have done in the past, if ever.

NOTE: When you do leave work, it's also a good idea to also have a friend at the employer's who can keep you apprised of changes once you have left work. Many companies overlook disabled employees when making changes in their benefits package, and you need to know about them.

WHERE TO FIND THIS INFORMATION.

The literature that will contain this information will come in various forms and your company prob-

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HealthWise:

A Very Big Four-Letter Word



Lucinda K. Porter, RN

Earlier this year, I wrote an article about the power of language (January 2007 *Healthwise*). I am a writer, so naturally I believe that words are powerful tools. Perhaps language is not as strong as medicine, but it is available without a prescription.

This month, I want to look at one small but controversial word – *cure*. If you get strep throat, take the prescribed antibiotics, and the infection resolves, you are cured. This is a traditional Western model. Get a disease, get treated, and then get cured. Fortunately for us, many diseases can be cured.

Viral diseases are somewhat tricky. The virus that causes genital herpes doesn't have a cure. Although there is medication that can reduce the severity of the disease, herpes is a lifelong inhabitant. Since the virus remains dormant and can be activated at any time, it is not a curable condition at this time.

Some viruses, such as those that cause mumps and measles resolve on their own. The result is immunity from these diseases. These viruses don't remain dormant. Our bodies naturally cure us of these diseases. **Note:** In some, measles, mumps and other childhood diseases can be very serious, especially for adults. There are vaccines against these diseases.

Chronic hepatitis C virus infection (HCV) acts like a renegade when it comes to the *cure* word. The ideal outcome for HCV treatment is called a *sustained viral response* (SVR). This means that HCV is non-detectable in the blood for at least six months after the last treatment dose. Approximately one-half of those who complete treatment will have this best possible outcome – no evidence of HCV.

If you can't measure HCV any longer – does this mean you are cured? Probably maybe yes. We dance

around this question because we are not completely certain. Medicine has its own well-intentioned jargon that helps us remain precise when we do not have an exact answer. Therefore, we will use terms such as SVR because it helps us to describe what we know without committing to what we don't know. We believe that HCV does not remain dormant, but we won't know this for sure until we have irrefutable evidence.

However, this may be about to change. In May 2007, a poster presented at Digestive Diseases Week (DDW) looked at five-year treatment follow-up data. Swain et al looked at 997 people with SVRs who had undergone treatment with peginterferon alfa-2a alone or in combination with ribavirin. They concluded that an SVR under these circumstances is durable in about 99% of chronic HCV patients, validating the concept of 'clinically cured.'¹ There it is, in black and white – a validation of the *cure* word.

By the way, of the eight subjects who tested HCV-positive during follow-up, one had a different genotype, indicating re-infection rather than return of the initial infection. The other seven patients were lost to follow-up leaving some uncertainty about the true nature of their HCV status.

Leaving science out of this, let's look at the word *cure* from another point of view – that of the Oxford English Dictionary. *Cure* comes from the Latin *care*. The very first meaning of the verb *cure* is (to) “relieve (someone) of the symptoms of a disease or condition.” The ending of a disease is the second definition of the verb. As a noun, *cure* means “restoration to health.”

One could argue that an SVR is a cure based on the definition of the word alone. Perhaps this is what

“Chronic hepatitis C virus infection (HCV) acts like a renegade when it comes to the cure word. The ideal outcome for HCV treatment is called a sustained viral response (SVR).”

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it will take – not clinical evidence, but an emotional response to the uncertainty of living with a virus that we are gathering evidence about.

In the second paragraph, I labeled our model of “get a disease, get treated, and then get cured” as a Western approach. Other traditions do not focus on the disease – they focus on the person. Although being human always has a fatal outcome, being human is not a condition that requires “curing.” Curing is for bacon, ham, and diseases. Western medicine is slowly integrating some of these holistic practices from other healing disciplines. Other disciplines are also taking some of the best that Western medicine has to offer. This is one of the advantages of living in a global society.

If we look to the non-Western models, we can see that discussion of the word *cure* is irrelevant. What if we took this notion to a radical level and stopped looking outside ourselves for documentation of our health. Are we brave enough to declare the state of our own health? I am not suggesting that we start diagnosing and treating ourselves. What I am suggesting is that we can set the terms of who tells us if we are in a state of disease or health. It is, after all, our body and our future.

A final note to those of you who undergo treatment and hear those lovely words, “you are cured.” It may take you awhile to believe this. Health is a process, whether we are getting sick or getting well. Sometimes good news is as hard to digest as bad news is. This is normal.

If you are in a support group,

it may be hard to talk about your feelings. Patients who have an SVR may feel awkward talking about their ambivalence. We tend to compare ourselves to others and may negate our feelings. We may tell ourselves that the people who are in obvious pain or in the middle of treatment have more important problems than we do. If you can, avoid minimizing your feelings. Talk to the group or to someone, even if it is only for a few minutes. What you share today may be exactly what someone else will need in the future.

Reference

¹ M. G. Swain; M. Lai; M. L. Shiffman; W. E. Cooksley; A. Ab-ergel; A. Lin; E. Connell; M. Diago Sustained Virologic Response (SVR) Resulting From Treatment with Peginterferon Alfa-2a (40KD) (PEGASYS®) Alone or in Combination with Ribavirin (COPEGUS®) is Durable and Constitutes a Cure: an Ongoing 5-year Follow-up Poster # 444 DDW May 2007.



NEW FACTSHEETS FROM HCSP

Extrahepatic Manifestations of HCV

- *Cryoglobulinemia*
- *Essential Cryoglobulinemic Vasculitis*
- *Systemic Lupus Erythematosus*
- *Waldenstrom Macroglobulinemia*

To view these and other factsheets go to:

<http://www.hcvadvocate.org/hepatitis/factsheets.asp>

Disability Programs from Social Security

A new HCSP Training Module

This July, the first of a new series of HCSP Training Modules focussing on Disability, Insurance and Benefits issues was posted to the HCV Advocate website.

The online modules have been designed and written by Jacques Chambers, CLU, a Benefits Consultant and Counselor, who has been a contributing writer at the HCV Advocate for many years.

Jacques has spent the last ten years helping people dealing with disabilities understand and access their benefits. Prior to that he spent twenty-five years in the insurance industry, designing, selling, and servicing employee benefits programs.

Disability Programs from Social Security, will focus on

- Differences and similarities between Social Security Disability Insurance (SSDI or SSD) and Supplemental Security Income (SSI)
- Definition and determination of disability
- Financial eligibility requirements
- Navigating the application process
- Dealing with a claim denial
- Appealing a decision

To take this module, go to www.hcvadvocate.org and follow the instructions.

DDW 2007 Highlights: Part 2



Alan Franciscus, Editor-in-Chief

At this year's Digestive Disease Weekly (DDW) Conference one of the most interesting presentations was given by Dr. Stephen Harrison about metabolic syndrome and HCV, and more specifically, the affect of insulin resistance on HCV treatment outcomes.

Before we delve into the affects of metabolic syndrome and insulin resistance on HCV disease progression and treatment outcome it is important to understand or define these conditions, the factors that cause the conditions, and the various steps that people can take to control, manage and even improve these conditions.

WHAT IS METABOLIC SYNDROME (MS)?

Metabolic syndrome is a group of conditions or risk factors that increase the chances of developing heart disease, stroke and diabetes.

Metabolic syndrome is defined by the National Cholesterol Education Program as the presence of any three of the following conditions:

- excess weight around the waist (waist measurement of more than 40 inches for men and more than 35 inches for women)
- high levels of triglycerides (150 mg/dL or higher)
- low levels of HDL, or "good," cholesterol (below 40 mg/dL for men and below 50 mg/dL for women)
- high blood pressure (130/85 mm Hg or higher)
- high fasting blood glucose levels (110 mg/dL or higher)

**Source: National Cholesterol Education Program, Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), National Heart, Lung, and Blood Institute, National Institutes of Health, May 2001*

WHAT IS INSULIN RESISTANCE (IR)?

The pancreas produces and releases insulin after a meal so that cells can absorb and convert glucose (carbohydrates/sugar) into energy. In an individual with insulin resistance the normal levels of insulin do not trigger the absorption of glucose into cells, which leads to an excess of glucose in the bloodstream. When this happens the pancreas makes and releases even more insulin as a way to compensate, but the result is high levels of insulin and glucose in the bloodstream. Insulin resistance is also a condition that is considered pre-diabetes. It is estimated that when someone becomes insulin resistant they will develop diabetes within 10 years unless lifestyle modification can be made.

There are a variety of tests used to diagnose insulin resistance including glucose tolerance testing, hyperinsulinemic euglycemic clamp, and most recently the Homeostatic Model Assessment (HOMA) test and the QUICKI.

Treatment of metabolic syndrome and insulin resistance is usually in the form of lifestyle modifications, such as diet and exercise and the use of prescribed medications to lower and control blood pressure, cholesterol, and blood sugar levels. Studies have found that diet modification and exercise can prevent the onset of type 2 diabetes and other complications of insulin resistance

and metabolic syndrome by losing 5 to 7% of body weight alone.

THE OBESITY FACTOR

Understanding the increase in obesity in this country is important for understanding the increase of metabolic syndrome and insulin resistance. In the past 14 years there has been a significant increase in obesity in this country. In 1991 a random sampling of states found that obesity was limited to about 15% of the population. But in 2004 it was found that in many states the rates of obesity increased up to 25%. Today, obesity rates are greater than 30% in most states and 65% of the entire U.S. population is believed to be overweight. World wide obesity is no less of a problem, with estimates of obesity ranging from 40 to 65%.

The problem is that obesity leads to many health problems including metabolic syndrome. For example, the obesity rates in the United States can be directly correlated with an increase in insulin resistance and diabetes, both of which contribute to metabolic syndrome. Metabolic syndrome's affect on the liver is to contribute to the formation of fatty infiltrates in the liver leading to fatty liver or steatosis. But it is unclear if steatosis leads to insulin resistance or if insulin resistance leads to steatosis.

THE HCV FACTOR

There are many new HCV therapies under development for the treatment of hepatitis C. The current standard of care for treating hepatitis C is the combination of pegylated interferon plus ribavirin. Now is a very exciting time in drug development, with the hope that newer therapies will be able to successfully treat more people without

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DDW HIGHLIGHTS

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some of the undesired side effects of current therapy. However, it has become clear that the use of pegylated interferon plus ribavirin is going to be used in combination with the new HCV medicines at least for the foreseeable future. In recent years we have learned that many factors influence treatment outcome such as race, gender, genotype, viral load, age, steatosis, the amount of liver damage, metabolic syndrome and insulin resistance.

The relationship between treatment outcome and metabolic syndrome and/or insulin resistance on treatment outcome is important for medical providers and patients to know because these conditions can be greatly improved by lifestyle modifications such as a healthy diet and exercise program.

Improving these conditions will help to increase the likelihood of successful treatment outcome without having to wait for the clinical trials, testing and the Food and Drug Administration (FDA) approval of the drugs that are currently in clinical development. These strategies are very important for people who can not wait for the newer medications because they have serious disease progression since it is clear that successful treatment can slow down, stop or even reverse disease progression – even if an SVR is not achieved. Since pegylated interferon and ribavirin therapy will most likely be the backbone of HCV therapy for many years to come these strategies will also help to improve future treatment outcomes.

STEATOSIS (FATTY LIVER)

A direct viral connection has not been found between the hepatitis C virus and steatosis, although it is

more common in people with hepatitis C than the general population. The exception is in HCV genotype 3 patients – most experts believe that genotype 3 of the hepatitis C virus directly causes steatosis. We can connect the dots on this theory because it has been found that when HCV genotype 3 individuals are successfully treated (and even some who do not respond to treatment) the steatosis levels are reduced and in some instances completely resolved. This is not the case in people with HCV genotype non-3.

Steatosis is also more prevalent in HCV genotype 3 patients than in HCV genotype non-3 patients. It has also been found that people with HCV genotype 3 have more extensive amounts of fatty liver tissue than in people with HCV genotype non 3 – in excess of 60% in people with genotype 3 compared to less than 30% in genotype 1.

METABOLIC SYNDROME & HCV

It is important to know that the host factors and hepatitis C contribute to metabolic syndrome. This is valuable information to know because of the relationship between these factors on HCV treatment outcome:

- Insulin resistance, steatosis and NASH (non-alcoholic steatohepatitis) **decrease** sustained virological response rates
- Steatosis **increases** fibrosis progression (a negative predictor of treatment response)
- Insulin resistance has been associated with higher viral load (a **negative** predictor of treatment response)
- Insulin resistance inhibits the innate immune response = **lower** treatment response (interferon works by increasing the innate immune response)

INSULIN RESISTANCE AND HCV TREATMENT

A study from Spain on treatment of patients with HCV genotype 1 found a dramatic decrease in the SVR rates in the patients with insulin resistance compared to patients without insulin resistance. Looking at the varying degrees of insulin resistance it was found that in the group as a whole the SVR rates for genotype 1 patients were 60% in those patients without insulin resistance compared to 30% in those genotype 1 patients with insulin resistance. Dr. Harrison pointed out that in those patients with significant insulin resistance the SVR's were further reduced to 20%.

TREATING INSULIN RESISTANCE

There have not been any conclusive studies that have found the use of lipid lowering agents, diabetic medications or other medications to be helpful in treating insulin resistance in people with hepatitis C. The only proven method we have now is from lifestyle modification using diet and exercise.

Dr. Harrison recommended that insulin resistance testing should be a part of the general battery of pre-treatment blood work for patients considering treatment and that patients should be advised of the increased or decreased chances of responding to therapy. It was pointed out that if a person could lose 5% of their body weight prior to treatment that it could dramatically improve their chances for successful treatment outcome. Even just this short term modification for three months prior to therapy can improve the chances of response to treatment.

Source: DDW 2007, *Hepatitis C-What's New Session*, Stephen Harrison, MD, Chief of Hepatology, Brooke Army Medical Center.



PRE-DISABILITY

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ably calls them something like:

- Benefit Plan Booklets
- Benefits Handbook
- Employee Handbook
- Insurance Plan Booklet/Policy
- Employee Certificate/Booklets
- Plan Descriptions
- Summary Plan Descriptions or just plain SPDs

Regardless of what your company calls them, the federal government calls them **Summary Plan Descriptions** or **SPDs** and requires employers to give them to employees when they are first covered and **whenever they request them.**

HOW WILL I KNOW A SUMMARY PLAN DESCRIPTION WHEN I SEE ONE?

A Summary Plan Description will:

- Be a complete description of the benefits. For one of the insurance coverages, that means several pages, not a paragraph or two. A Health SPD should be 20 to 30 pages or more; life insurance will generally be 5 to 10 pages; disability plans will be 8 to 25 pages.
- In an SPD, there will usually be a section, often towards the back, titled **ERISA Requirements** or **ERISA Provisions**. Whatever it's called, it will include things like:
 - Plan Name (such as Flying Carpet Mfg., Inc. Employee Health Plan)
 - Plan Number (Usually starts with 5, like 501, 502, 505)
 - Type of Plan (Insurance contract, or Self-Funded Employee Benefit Welfare Plan, etc.)
 - Plan Administrator (Usually

the insurance company or an outside plan administrator or sometimes the employer)

- "Agent for Legal Service" (This is to whom you serve with papers if you end up suing the plan). This item is a good clue as it's almost always phrased just this way, and is only found in an SPD. If you see it, you can relax. You got the Summary Plan Description.

NOTE: Even if you still have the Summary Plan Descriptions that you got as a new hire, it's a good idea to request new ones to make sure you have the most current versions.

PUBLIC BENEFIT PROGRAMS

1. **State Disability Programs** – California, Hawaii, New Jersey, New York, Rhode Island and the Virgin Islands all have state mandated disability programs that pay a weekly benefit for up to twelve months, depending on the state. Information on those programs and claim forms can be obtained from each state's employment development department.

2. **Social Security Benefits** – Learn about all the Social Security Disability programs at www.ssa.gov and from articles in the archives of this website. It is imperative that you understand the application process as it will greatly increase your chances of being approved the first time around.

About three months before each birthday, Social Security sends out a statement of earnings which summarizes all of your earnings that have been reported to Social Security and gives an estimate of the amount of your retirement and disability benefit amounts. If you didn't keep yours, it can be ordered either

on line or at the Social Security number at 800-772-1213.

- a. **Social Security Disability Insurance (SSDI)** – This benefit is available to persons who have paid into Social Security through F.I.C.A. payroll taxes and are unable to work to retirement age.
 - b. **Medicare** – Medicare becomes available to disabled persons once they have collected SSDI benefits for twenty-four months.
 - c. **Supplemental Security Income (SSI)** – This is a "needs-based" benefit for persons who either didn't pay into the Social Security system for SSDI benefits or who paid so little their SSDI benefit is below the SSI floor amount, which varies from state to state. To be eligible for SSI benefits, you must have spent most of your own savings and be receiving little or no income.
 - d. **Medicaid** – This is a "needs-based" health insurance program with similar financial requirements to SSI. It will either supplement Medicare or may stand alone to help people not eligible for Medicare.
3. **Personal Insurance** – Review your policies to make sure you understand what they provide in the event of disability. If necessary, ask your insurance agent or other knowledgeable person to review it with you.

Even if disability is a year or more away, it is helpful to know just what will happen and what benefits are available to you in the event disability does occur.



National Minority Donor Awareness and Wisconsin Organ Donor Registry

August is National Minority Donor Awareness month. Minorities are underrepresented on transplant waiting lists. Patients are less likely to reject an organ that is genetically similar to their ethnic group. To avoid rejection, it is critical to get a close match between the donor organ and the recipient. There is a huge shortage of minority organs, which means that minority patients may have to wait longer for an organ. We can change that by encouraging everyone to be an organ donor. The state of Wisconsin is actively raising awareness about the need for minority organs. Perhaps the rest of the country can join them in this good cause.

www.wisconsinorganonor.org

www.wisdonornetwork.org/outreach/index.html

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Extrahepatic Manifestations: *Raynaud's Phenomenon*



Alan Franciscus, Editor-in-Chief

In someone with hepatitis C, Raynaud's phenomenon is caused by HCV-related cryoglobulinemia. The prevalence of Raynaud's phenomenon in the hepatitis C population is unknown, but it is believed to be an uncommon condition. In people with HCV related cryoglobulinemia, however, one study found that 30% of people also had Raynaud's phenomenon.

Raynaud's is a painful condition that affects the blood vessels in the fingers, toes, ears, and nose. When Raynaud's phenomenon affect the fingers is it easy to diagnose because the end of the fingers turn white. The diagnosis of Raynaud's is based on certain lab tests (for autoimmune diseases), and by physical exam.

Raynaud's affects more women than men – about 75% of all cases are diagnosed in women who are between 15 and 40 years old. It is estimated that between 5 to 10% of the U.S. population have Raynaud's Phenomenon.

There are two types of Raynaud's – primary and secondary. *Primary* is the milder form of Raynaud's that has no underlying disease or associated medical condition. *Secondary* is less common than the primary form but it is considered a more serious condition that is caused by another disease or condition.

The exact cause of Raynaud's is unknown but it is considered an autoimmune disease and has been linked to cryoglobulinemia,

hypothyroidism, scleroderma, lupus, Sjögren's syndrome as well as occupational exposure to toxins, environmental factors (exposure to cold temperature) and certain medications, and can be triggered by emotional stress.

Below are some strategies for managing Raynaud's:

- Take action as soon as possible at the first sign of an attack:
 - o Warm hands and/or feet
 - o If outside temperature is cold go inside as soon as possible to warm up
 - o Run warm water over hands and feet or soak them in warm water
 - o Reduce immediate stress
- Stop smoking – nicotine causes skin temperature to drop which can contribute to the condition
- Stress reduction – biofeedback, meditation, and deep breathing exercises
- Exercise can improve overall health and reduce stress
- Consult with and regularly visit a medical provider

Medical treatment of Raynaud's may include calcium-blockers, and various topical skin ointments. One study published in 2005 found that the use of sildenafil (Viagra) improved blood circulation and reduced the symptoms of Raynaud's.



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