

HCV ADVOCATE

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Patient or Guinea Pig? Dilemma of Clinical Trials

Denise Grady, New York Times - January 05, 1999

When pharmaceutical companies recruit sick people for studies of experimental drugs, what are the companies' obligations to the patients? And once people sign up, accepting risk but hoping for benefit, receiving free medical care and drugs, what do they owe to science, to future patients who may be helped by the research and to the company that may profit from it?

Last year, Gail Ogden, 55, from Westmoreland, Kan., confronted those questions firsthand, when she learned that she had chronic hepatitis C, a viral disease of the liver.

Although many people carry the virus for decades without becoming sick, others develop cirrhosis, liver failure or cancer. Because Ms. Ogden was ill and had signs of liver damage, her doctors recommended drug treatment.

Four million Americans are thought to be infected with hepatitis C, most of them without knowing it, and 8,000 to 10,000 people a year die of the disease. Treatment is expensive -- a six-month course of therapy costs \$6,400 to \$8,600. Ms. Ogden's health insurance would cover only part of the cost and she could not afford to make up the difference.

Her doctor encouraged her to volunteer for a study, in which she would receive medication at no cost.

In September, she entered a 48-week clinical trial at the University of Nebraska in Omaha, designed and sponsored by Schering-Plough Corp. of Madison, N.J. Ms. Ogden was at first delighted to be accepted into the study, but like many people who consent to be experimented on, she has found the transition from patient to research subject a rough one, and her experience has put her at odds with Schering-Plough.

Ms. Ogden's case and those of other people with hepatitis C have been taken up by patient advocacy groups, including some founded by people with HIV or AIDS who have had long experience in challenging drug companies over the way people are treated in clinical trials.

The experiment Ms. Ogden signed up for was to enroll 600 people at 40 to 50 medical centers around the United States.

Some participants would be given Rebetrone, a treatment approved for hepatitis C by the Food and Drug Administration. It combines two anti-viral drugs: injections of interferon and capsules containing ribavirin. Others would receive ribavirin with higher doses of interferon.

Though it was later approved for all patients, at the time the study began, Rebetrone had been approved only for people who had relapsed after treatment with interferon alone.

The purpose of the study was to test the effectiveness of Rebetrone in people who had not taken any other medication for hepatitis C, and also to find out whether the version containing higher doses of interferon would work better than the standard form of Rebetrone, which is effective in fewer than half of patients, in whom it reduces the virus to undetectably low levels.

Despite its limited effectiveness, Rebetrone is the best treatment available for hepatitis C, and Schering-Plough is its sole manufacturer. First approved last June, the drug had earned \$46 million by the end of October.

The study that Ms. Ogden entered was not "blinded," that is, both the subjects and the doctors monitoring them knew which doses they were receiving. Ms. Ogden was assigned at random to the group taking the standard form of Rebetrone.

Researchers could not promise that she would benefit from the study, but regardless of which dose she received, they knew that for the full 48 weeks she would experience formidable side

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HCV ADVOCATE

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The Treatment Advocate

Joe Shaw

This new column in the HCV Advocate will attempt to update you on important, recent studies and trends in the treatment of hepatitis C. I say "attempt" because it's hard to wade through all the information out there and provide a complete picture. Through the internet, I receive a large number of studies, reports and articles from medical journals and newspapers. This will be my attempt to wade through that information and provide the readers of this newsletter, with what I think is the most important or interesting information. Please be informed that I am not medically trained, I am just a person with hepatitis C, currently undergoing combo treatment with ribavirin and interferon. I just want to learn all I can. This is by no means a definitive look at what's going on in treatment, but I'll do my best to pass on what information I can. To that end, you may e-mail me if you have any questions about particular studies or articles mentioned in this column, and I will send you a copy. My e-mail address is joeesha@yahoo.com. Also if there's any particular topic you'd like to know about, I'll try to help you find information about that subject, if you will e-mail me. So here goes.

Emerging Therapies for Chronic Hepatitis C Virus Infection

This is an excerpt from The Hopkins HIV Report, January 1999, put out by the Infectious Diseases Dept of The Johns Hopkins Hospital, Baltimore, MD. It represents predictions of the potential new therapies for Hepatitis C and the year in which the therapy may be available. This information could benefit those who have decided to put off treatment until better therapies are available. These timelines are only predictions.

Pegylated Interferon: Interferon chemically bound to polyethylene glycol(PEG); allows for slow, continuous release of interferon. 1999

Helicase Inhibitors: Prevents unwinding of double-stranded viral RNA during HCV replication. 2001-2003

Protease inhibitors: Prevents cleavage of large viral protein into smaller segments. 2001-2003

RNA-dependant RNA HCV genome polymerase inhibitors:Prevents replication of copying of the HCV genome. 2001-2003

IRES (internal ribosomal entry site) inhibitors: Prevents the expression of viral proteins. 2001-2003

Antisense nucleotides:Bind to interferon resistance sites. 2008

DNA vaccines: Stimulate cytotoxic T cell activity. 2008

Dominant negative mutants: Block viral protein production. 2008

Dietary Supplement Appears to Have No Affect on Hepatitis C

Complete Thymic Formula is an over-the counter dietary supplement, which the manufacturer promotes as a "supplement" but some websites promote as a cure for hepatitis. In their study, Dr. Gary A. Abrams and colleagues from the University of Alabama at Birmingham Liver Center ,tested Complete Thymic Formula, among 38 Hepatitis C patients who had not responded to or could not tolerate interferon. In the study, roughly half of the patients took the supplement for 3 months, while the other half took a placebo. After 3 months, patients taking the formula had virus levels in their blood that were just as high as those in the placebo group, the study found. A subgroup of patients who continued to take Complete Thymic Factors for three additional months had the same levels of virus in their blood at the end of the entire 6-month period as they had at the start of the study. *From: Annals of Internal Medicine 1998;129:797-800.*

Consensus Interferon Successful In Prior Hep C Non-Responders, Prior Relapsers

In a study presented at the annual meeting of the American Association for the Study of Liver Diseases in Chicago, researchers found that retreatment with 15 micrograms of consensus interferon (Infergen) three times a week for 12 months (vs. a standard dose of 9 micrograms) can eliminate Hepatitis C virus and normalise ALT levels in a significant proportion of prior relapsers, as well as some non-responders. The study results also suggest when to quit treatment. Virtually all patients who had responded to the consensus interferon were evident by week 16 of therapy. They had become HCV RNA negative by the PCR technique and their ALT levels were normal. Of all prior relapsers, 58 percent showed a sustained viral response to retreatment, versus only 13 percent of prior non-responders, indicating that a previous response to therapy predicted a higher likelihood of success to retreatment. Of those who responded, 84 percent of prior relapsers cleared the virus by week eight and 98 percent were HCV RNA negative by week 16. Among prior non-responders, 70 percent cleared the virus by week eight, rising to 94 percent by week 16. ALT levels were normal by week 16 in 99 percent of prior relapsers and in 91 percent of prior non-responders who did respond to the higher dose consensus interferon therapy. *From: Doctor's Guide to Medical News*

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After Diagnosis: How to Become Your Own Best Advocate

Part Three – On-Going Advocacy

Alan Franciscus

Last month we discussed planning your doctor visits. A doctor's visit can be an emotional experience for anyone and the first visit after your diagnosis can leave you feeling overwhelmed. You may want to seek professional help, surround yourself with friends and loved ones or simply be by yourself. At the very least, give yourself ample time to process both the intellectual and emotional information before making important health related decisions.

Your on-going advocacy is multi-faceted. Here are some tips to help you in the process:

- Review your visit and make a plan of action to be discussed with your physician.
- Keep a copy of all your lab tests and procedures – you may want to keep a journal and track your symptoms or general health.
- Keep an “open mind”. Information about HCV and treatment options is rapidly changing. Don't let your emotions or other people's opinions unduly influence your decisions.
- Investigate new drug and alternative therapies – be critical of ‘new’ therapies that promise a cure. Discuss new therapies with your doctor.
- Keep your physician informed of all medications (including herbs) you are taking.
- If you are contemplating herbs, consult with a reputable herbalist.
- Talk with other heppers about HCV – this is the most valuable resource we have. Patients often know more about new therapies, side effects etc before most professionals, but always verify information with a health care practitioner before taking action.
- Learn to trust your instincts! Sometimes you have to go with your “gut” feeling and your intuition can serve you well when it is fine-tuned.

Your on-going therapy is a whole process in and of itself. It can be a lot of work to try to stay on top of all the latest information. But it is your health and that makes it worth all the time and effort required.

[Treatment Advocate - continued from page 2](#)

High Dose Consensus Interferon Produces Better Results

In previously untreated HCV patients, high dose consensus interferon (Infergen) given five days a week resulted in significantly more responses than did the same drug given three times a week. Seventy-three percent of patients who received 15 micrograms of drug five times per week cleared the virus from their blood after twelve weeks of therapy, compared to 38% of patients taking the three day a week dose. *The study was conducted by Dr. Carl Jones, gastroenterology fellow at Allegheny General Hospital, Pittsburgh, Pennsylvania, who found that of the genotype-1 patients who took the drug three times a week, 27% became HCV RNA negative, and 62% of those on the five times a week dose became HCV RNA negative by the end of month three.*

New Website Will Provide Information About Dietary Supplements

The National Institutes of Health Office of Dietary Supplements has begun new website at <http://dietary-supplements.info.nih.gov> which will provide the public with access to information from more than 250,000 scientific research reports on the effects of 50 of the most popular dietary supplements.

New Experimental Therapy: Iron Reduction

A data study done by doctors at the *Oklahoma Transplant Institute Baptist Medical Center of Oklahoma Oklahoma City, OK*, suggest that a reduction in hepatic iron stores by phlebotomy may be an effective way to enhance the response rate achieved with currently available agents used to treat viral hepatitis. Specifically, addition of iron-reduction therapy to cz-interferon, either alone or with other agents such as cytokines (GCSF, GM-CSF), antivirals (acyclovir, ganciclovir, ribavinn), or an NSAID (indomethacin), should only enhance the common desired effect of such therapies, namely viral clearance.

HealthWise

Lucinda Porter, RN

Liver Lab Panel Basics

Included on my top ten list of recommendations for patients with chronic hepatitis C infection is this: keep copies of your lab and biopsy results. Even if you are unable to understand what they mean, it is more convenient to have them if you are seeking another medical opinion. However, most of us register some anxiety when we see abnormal results. The aim of this article is to give some general background regarding liver function tests and to identify what is cause for concern.

In general, the liver or hepatic panel test is the most common test ordered to monitor the status of our liver. The term "liver function test" (LFT) is also used. Not all liver panels include the same tests, but basically they are similar. Normal ranges can vary from lab to lab. Accuracy can vary from lab to lab. These factors can be very frustrating. My approach is to check out the facts before assuming an abnormal lab is cause for concern. This is hard to do, but pays off in terms of reducing the amount of stress one has to manage.

All liver panels include a measurement of liver enzymes, ALT (alanine aminotransferase) and AST (aspartate aminotransferase). These are frequently elevated in those with chronic hepatitis C infection. Along with their age, most hep C patients can tell you their last ALT or AST results. Those who have had hepatitis C long enough know that in general, mild to moderately elevated ALT/AST is not significant. However, the first few "abnormal" aminotransferases often send up a wave of unnecessary panic. The ALT and AST are enzymes produced in the liver. When the hepatitis C virus (HCV) causes inflammation in the liver, these enzymes spill over into the blood. This is often the earliest indicator that motivates a health practitioner to order diagnostic tests to see if a person has HCV (or other liver diseases).

Alkaline phosphatase is found in many tissues, with high concentrates in the liver and biliary tract. An abnormal finding can be an indicator of many states, such as cirrhosis, bile duct blockage, third-trimester pregnancy, rheumatoid arthritis, and healing bone fractures. Gamma-glutamyl transpeptidase (GGT) is used as a confirmatory test if the alkaline phosphatase is elevated. The highest concentrations are found in the liver. An elevated GGT is sometimes a marker for alcohol and drugs effect on the liver.

Serum albumin and prothrombin time are true liver function tests. Albumin is a protein synthesized in the liver. Decreased albumin levels is sometimes seen in chronic liver disease. The more advanced the disease, the lower the albumin levels. Prothrombin time (Protime or PT) evaluates blood-clotting speed. Since blood-clotting factors are manufactured in the liver, an increase clotting time can indicate liver dysfunction. Bilirubin levels are also measured to assess for liver function. Bilirubin is a pigment formed by the breakdown of red blood cells. The liver takes it from the blood and processes it. Elevated bilirubin levels can cause jaundice (yellow eyes and skin).

Interferon treatment, with or without ribavirin can alter lab results. This is also true for many medications as well as alcohol. Since this was a very basic overview of some routine liver tests, please do not try to evaluate your own lab results. A little information can be dangerous and unless you are qualified to interpret tests, please seek opinions of experts you trust. Do not lose a night's sleep because of an out-of range lab result.

Next month: More lab basics

For more information about hepatitis C, please contact the following organizations:

- American Liver Foundation 800-223-0179 <http://www.liverfoundation.org/>
- Hepatitis Foundation International 800-891-0707 <http://www.hepfi.org/>
- Hep C Connection 800-522-4372 <http://www.hepc-connection.org>

effects: fever, headaches, nausea, fatigue, aches and pains, anemia, and mental symptoms including depression and sometimes suicidal thoughts.

Nonetheless, Ms. Ogden said: "I was grateful to get into this treatment. I was delighted. I went into it thinking that not only was I going to help myself, I'd help others coming after me. I was all fired up. I thought this is a good thing to be doing."

Her plan was to watch her test results closely, particularly her viral load, a measurement of virus levels in the bloodstream. If it did not drop within a few months, and if the side effects were severe, she would consider dropping out of the experiment.

Three months into the study, she is bitter. Only after it began, she said, did she find out that Schering would be withholding viral-load information until the study was finished. "I had no idea the extent these people would go to get their drugs to the market. It's absolutely disgusting, the corporate greed in America."

Robert Consalvo, a spokesman for Schering-Plough, said that the company was motivated not by greed but by the need to determine the best treatment for hepatitis C. In this case, he said, the company decided to withhold viral loads in the hopes of keeping patients from dropping out of the study. Too many dropouts would make it hard to complete the research.

In any event, Consalvo said, being a subject in a study is not the same as being a patient treated by a personal doctor. But, he acknowledged, drug companies may need to do a better job of communicating that to people who participate in experiments.

Ms. Ogden's objections to the study, echoed by other participants, reflect a tension that has always existed between researchers and their subjects. People who volunteer for studies are told that the purpose of the study is not to help them, but to gather information that may eventually help others. Participants themselves may or may not benefit, and must accept the risks and the possibility of side effects that are part of any experiment.

But few people sign on out of pure altruism. They want the experimental drugs a study provides, often regarding them as "treatment" even when their safety and effectiveness have not yet been proved. Even the most unselfish cling to the hope that an experiment will help them. And people who are feeling sick and vulnerable, trying to beat a disease that might kill them, may resent the feeling that their needs come second to a heartless quest for data.

"Sick people can't think of themselves as research subjects," said George Annas, chairman of the health law department at the Boston University School of Public Health. "They don't want to feel like they're being used as guinea pigs. They want to feel like patients. But they're not. They're guinea pigs."

Those like Ms. Ogden who enter studies because they cannot afford treatment are in the worst position, he added, as they feel at the mercy of whoever is doling out the medication.

Her antagonism over the viral-load test developed in part because the consent form she signed did not mention what would be done with the results, but she assumed that they would be reported to her, and she was counting on them to gauge her progress.

"This treatment is tough," she said. "It makes you sick. I want to know if I'm showing signs of getting better or if nothing's happening, and I need to make a decision about whether I continue putting this toxic stuff into my body."

A decision to drop out would be inconvenient for the drug company, which wants as many people as possible to finish the study. But from a patient's point of view, quitting is logical. "If they see it's not helping, they want to get out," Annas said. "I don't blame them."

After just four weeks on Rebetron, Ms. Ogden said, she developed such severe anemia, a side effect of ribavirin, that her doctor halted the drug temporarily, and then resumed it at a lower dose. She also had problems with her eyesight, and the other side effects have been so debilitating that she has taken a disability leave from her job as business manager for a stock broker.

Six or eight weeks into the study, Ms. Ogden and the doctor assigned to her in the study received her test results: everything except her viral load. When Ms. Ogden asked for it, she said, she was told that Schering was withholding it from patients -- precisely to keep them from quitting the study.

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Like any subject in a medical study, she had the right to quit whenever she wanted, but the company would not give out information that might lead people to exercise it. Ms. Ogden was outraged. "It's not up to them to decide whether I stay in the study," she said. "I'm adamant. These are my civil rights here. Having knowledge about your health should be a partnership. They know what's going on. I should be informed."

She was further incensed when she learned that the viral-load numbers were not being given to her doctor, either. "How can he take care of me if he doesn't even know?" she asked. She could not afford to have repeated viral tests on her own: The test costs \$250.

Consalvo confirmed that other patients and doctors had also requested the viral-load data. And he said the information was indeed withheld to keep patients from quitting the study. "It's for no reason other than to keep the viability of the clinical trial, which is to prove safety and efficacy of the product," he said. If patients drop out, he said, "it jeopardizes the data." Dropouts must be counted as treatment failures, he said, but they may not really be failures, because some may quit before the drug has a chance to work.

"You may be spiting yourself by getting out of the study early," Consalvo said, adding that patients were no more qualified scientifically to decide when to quit than they were to decide what drug doses should be tested.

But Annas said he believed patients like Ms. Ogden had a right to receive viral-load test results, particularly because the consent form for the trial did not say the information would be withheld. To withhold them under those circumstances, he said, was "just blatantly unethical."

Annas added that he was surprised that the group overseeing research ethics at the university medical center, the institutional review board, would allow it. But the board at the University of Nebraska did give permission for the study.

Dr. Bruce Gordon, chairman of the review board, said the group had discussed the issue because another study subject had already raised it. But researchers convinced the board that it was reasonable to withhold the viral load because subjects should not be basing their decisions on it.

Ideally, Gordon said, "the investigator should be able to sit down with the patient and say, 'OK, you want this number, you can have it, but let me try to convince you that it's not important.'" He said the board had urged doctors involved in the study to communicate better with participants. But, he said of Ms. Ogden's situation, "It's a tough ethical problem. Her point of view is valid. The investigator's is, too."

Consalvo said that in earlier studies, Schering had released viral-load data, but stopped when it realized patients were using the data to decide whether to remain in the study. "Patients have become much more sophisticated," he said.

Current consent forms state clearly that viral loads will not be revealed, Consalvo said, and medical centers enrolling patients have been sent amendments explaining the policy, though Ms. Ogden said she never received one.

Annas said it was not reasonable to amend a study that was already under way. Stating the policy up front before a patient joins a study is defensible, he said, but he added, "even then I'd say it's not right."

Like many people with chronic diseases, Ms. Ogden had been communicating with other patients on the Internet, and now she sought help from an advocacy group, the Hepatitis C Action and Advocacy Coalition, which is based in San Francisco, with chapters in half a dozen cities in the United States.

Brian Klein, one of its founders, said the group was formed in the spring of 1998 by patients seeking to force Schering-Plough to reduce the price and alter the marketing of its hepatitis drugs. At the urging of Ms. Ogden and other study participants, the group added the viral-load question to its agenda.

In an HIV study, withholding viral-load data "would be unconscionable," said Klein, who is infected with both HIV and hepatitis C. "It's never done." One reason for that, he said, is that people with HIV are better organized and more experienced at protesting than those with hepatitis C. Many with HIV are also well enough to fight, unlike hepatitis C patients sick enough to need treatment.

"In the HIV world you also have community advisory boards at research institutions," Klein said. "This is nonexistent in the hepatitis C world. No one has reached out to patients to ask them to help design trials."

Ms. Ogden said she still hopes that the company will change its policy. At times, she describes herself as being treated like a "lab rat," and has fleeting thoughts of quitting the study. "Then I think," she said, "it's the only chance I have."

Interferon / Ribavirin Tips

- Drink all the liquids (water) you can stand - then a little more
- Moisturize your skin daily
- Eat small frequent meals
- Consider anti-depressants if depressed
- Use acetaminophen for pain management
- Get regular massage
- Rotate injection sites
- Exercise in 5-10 minute increments or whatever you can tolerate
- Meditate

And finally - **Ask for Help** when needed

MEDITATION

Alan Franciscus

Meditation is many things for many people. Some people use meditation as part of a spiritual experience. While others meditate to alleviate everyday stress. Some others, use meditation as a tool to help manage a chronic illness such as hepatitis C. It is all of these things and more.

I took up meditation while I was experiencing some psychological side effects from interferon therapy. I was severely depressed, anxious and unable to concentrate. My doctor prescribed anti-depressants for the depression, but I was still having problems concentrating and I was still very anxious. A friend of mine suggested meditation. I was amazed at the results - I was calmer and able to concentrate after only a few days of meditating. What's more, I believe the combination of anti-depressants and meditation were responsible for being able to finish one year of interferon therapy.

Why do people avoid meditation? The first reason people give is that they can't find the time to meditate. While we all have busy lives, I believe when you start to experience the benefits of meditation, finding time to meditate will not be a problem. In fact, you will look forward to the time of day when you usually meditate.

The second obstacle is that people think it is difficult to learn to meditate. Nothing could be further from the truth. If you follow some of the following suggestions, you will be well on your way to meaningful meditation.

Setting aside time to meditate - set aside a particular time of day to meditate and practice regularly. In my case, I practice in the morning before I go to work. At first, you should only practice for 5 minutes and work your meditation up to 15-20 minutes. You may decide that you want to practice twice daily, so plan your schedule and make appointments to meditate (if necessary).

Find a spot to meditate - Find a location both quiet and comfortable. Try a comfortable chair or sit on the floor with a cushion.

How to sit - try different positions- whatever is most comfortable. I usually sit in a comfortable chair with my legs crossed. Others sit in a straight-backed chair with hands resting on their legs and feet gently touching the floor. Some others like to sit in a lotus position.

Dress comfortably - wear loose fitting, comfortable clothes. Make sure that you are warm and not near any drafts.

HOW TO MEDITATE

There are many different types of meditation and you may want to try a couple of different types before settling on any one particular style. Look in your phone book for a Zen or Transcendental Meditation center near you. You can also teach yourself. Check your local bookstore or library. Personally, I practice TM, but I also incorporate other styles into my practice.

A couple of suggested techniques:

Breathing - close your eyes and concentrate on your breath. Feel your breath as it goes into and out of your lungs. Try to relax into your breath and feel your stress melt away. Once you have mastered this technique, experiment with different breathing techniques.

Candle - Light a candle in a dark, draft-free area and place it at eye level. Gaze at the flame and concentrate on your breath. Soon you will find your mind relaxed and still. *Note: this should not be practiced if you suffer from epilepsy or migraines.*

Meditation of Loving Kindness - Relax and concentrate on your breath. As you are breathing in say, "May I be well." As you breathe out say, "May others be well". This is one of my favorite practices since I can focus on well being of others and also on myself.

Chanting - Many use a Mantra to chant while meditating. TM practitioners are given a mantra when initiated into TM. Others may simply use "OM" or "AUM" while meditating. Try sitting comfortably and chant "OM". Feel the vibration while you breathe out. Stretch it out as long as you can. You will soon feel relaxed and tranquil.

These are but a few techniques out of many ways to meditate. Give it a try...you literally have nothing to lose but your stress and anxiety.

Suggested reading:

Discover Meditation by Doriel Hall, Ulysses Press 1-800-377-2542 - mention the HCV Advocate and receive a 20% discount.