

## Update from EASL



Alan Franciscus, Editor-in-Chief

The European Association for the Study of Liver Disease recently held its annual conference in Berlin, Germany. The majority of noteworthy clinical data on current treatment options have been previously reported in the press or at other conferences. This report will mainly focus on experimental therapies for treating chronic hepatitis C and one report on the treatment of acute hepatitis C.

This year's EASL conference highlighted many new compounds under study for treatment of hepatitis C. It is important to remember that most drugs in clinical trials will never be approved by the FDA for marketing. Generally, new therapies in clinical trials are divided into three phases - (see side bar - page 4). Phase IV trials are usually considered post-marketing studies after the initial FDA approval of the new drug. The further along a drug is in testing or clinical phase the more likely the drug will be FDA approved for marketing.

### EXPERIMENTAL THERAPIES

#### Albuferon

Albuferon (XTL Biopharmaceuticals Ltd) is a form of interferon that is fused with human serum albumin allowing the interferon to remain in the body for a longer period of time.

A clinical trial by V. Balan and colleagues studied the safety, pharmacokinetics and pharmacodynamics of Albuferon in single and double dose-escalation in hepatitis C positive individuals who did not respond to a previous course of interferon containing medications. Ninety-seven percent of the trial participants were genotype 1 (the hardest to treat). Adverse events or side effects were mild to moderate and were not dose dependent. The preliminary analyses suggest a median terminal half-life (how long it stays in the body) of 143 hours in the two

**Hemolytic Anemia:** *too few red blood cells in the bloodstream as a result of the destruction of red blood cells*

**Pharmacokinetics:** *the action of drugs in the body, including the processes of absorption, metabolism, distribution to tissues, and elimination*

**Pharmacodynamics:** *how the drug is distributed in the body*

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highest single injection groups. Reduction in HCV viral load (> 0.5 log reduction) was observed in 62.5% (25/40) of the participants in the single injection group (120-160 mcg). The authors of this study concluded that "Albuferon was safe and well-tolerated. Dosing every 2-4 weeks is supported by pharmacokinetics. Anti-viral response was observed in the higher single dose groups."

#### Merimepodib

Merimepodib (MPB) (VX-497) is a selective inhibitor of IMPDH. In a study by P. Marcellin and colleagues, 31 patients with genotype 1 who were nonresponders to prior interferon and ribavirin therapy were enrolled. The participants were randomized to receive VX-497, 25 or 50 mg every twelve hours, or a placebo drug in combination with pegylated interferon plus ribavirin for 24 weeks. Trial participants with no detectable viral load at 24 weeks received treatment for an additional 24 weeks. All participants were then followed post-treatment to determine sustained virological response.

The report for the 24 weeks

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# Fibromyalgia and Hepatitis C



Liz Highleyman

Many people with hepatitis C experience symptoms such as fatigue, muscle and joint aches, "brain fog," and depression, either due to HCV itself or as side effects of treatment with interferon. But some hepatitis C patients also have fibromyalgia (FM), a condition marked by widespread bodily pain. An estimated 3-6 million Americans have FM, and the condition is most common in middle-aged women.

Fibromyalgia (FM) refers to pain in the muscles, tendons, and ligaments. It is characterized by pain and stiffness throughout the body, but especially at tender points located mostly over muscles and tendons (e.g., the base of the jaw, the back of the neck, the upper and lower back). FM does not involve inflammation or muscle damage and is not progressive (although it is chronic). Pain may range from mild to severe and typically waxes and wanes over time, exacerbated by factors such as stress, physical exertion, and inadequate sleep.

Most people with FM have various other conditions including:

- fatigue
- sleep disturbances
- headaches
- cognitive impairment or "fibro fog" (e.g., problems with memory or concentration)
- paresthesias (numbness, tingling, or burning sensations)
- restless leg syndrome (involuntary muscle jerking during sleep)
- irritable bowel syndrome
- severe premenstrual syndrome

(PMS) or menstrual cramps

- unusual sensitivity to heat, cold, noise, light, and/or odors
- neurally mediated hypotension (low blood pressure when standing or sitting upright)

## CAUSES OF FIBROMYALGIA

Despite years of research, the cause of FM is not fully understood. Because symptoms are usually invisible, many FM patients have been told the condition was "all in their heads." But today most doctors understand that FM is not a psychosomatic disorder. Although many people with FM have anxiety or depression, these generally arise due to the pain and functional limitations associated with the condition.

Many (but not all) FM patients report that their symptoms began after a physical injury, surgery, viral or bacteria infection, exposure to a toxin, or an emotionally stressful event. FM has not been linked to any specific pathogen such as Epstein-Barr virus (EBV), mycoplasma, or human herpesvirus 6 or 7 (and there is no evidence it can be transmitted from person to person). These triggering events do not seem to directly cause FM, but rather set in motion physiological processes that lead to symptoms. This may occur in people who have a genetic predisposition, since FM runs in families.

These processes may involve changes in immune, endocrine, or neurological function. Some studies

have shown immune changes in people with FM such as altered cytokine (chemical messenger) levels and decreased natural killer cell activity, but data is conflicting. FM does not appear to be due to either immune suppression or autoimmunity. Research indicates that people with FM have certain endocrine abnormalities, including low levels of growth hormone and cortisol, a hormone produced by the adrenal glands when the body is under stress. FM also appears to involve changes in the way the central nervous system processes pain. Imaging and EEG studies show that people with FM have altered activity in pain-processing parts of the brain. They also have elevated levels of substance P, a chemical that transmits pain signals. These changes may cause hyperalgesia, or heightened sensitivity to pain (and sometimes other types of stimuli as well).

Most people with FM have sleep disturbances including trouble falling asleep, waking during the night, or restless leg syndrome. Brain wave studies show that people with FM may not enter the deepest stages of sleep. Thus, despite being in bed for 8 - 10 hours, they may still feel exhausted in the morning (called non-refreshing or non-restorative sleep).

It is likely that FM involves the interaction of multiple factors. Once symptoms develop, patients may

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# HealthWise:

## Herbs and Hepatitis C: Part 1



Lucinda K. Porter, RN, CCRC

Over 5 years ago I wrote an information pamphlet called *Herbs and Hepatitis C*. Interest in herbs continues to be on the rise and since more information is available, it became clear it was time to update *Herbs and Hepatitis C*. The revised edition can be read in its entirety at [www.hcvadvocate.org](http://www.hcvadvocate.org). I have reformatted *Herbs and Hepatitis C* into a 3-part series for this newsletter. This article is not meant to be the final word on the issue of herbs. I hope the reader will use this as a tool towards gaining more insight and knowledge about the world of herbs. Of course, this information is not meant to be used for medical care. Always talk to your primary health provider before using herbs.

The use of herbs for medicinal purposes has a long and interesting history. The origins of some modern medications are actually plants, such as aspirin from white willow bark, digitalis from foxglove, morphine from poppies and warfarin (Coumadin) from sweet clover. Many cultures use indigenous plants for healing purposes. The use of herbs, however, is controversial in contemporary western medicine due to the lack of evidence-based research to support safety and efficacy. Couple this with the potential harm these substances can inflict and it is easy to see why physicians are reluctant to endorse herb use. Some patients are interested in alternative methods to use with or instead of the treatment their physicians have prescribed. This is particularly true for patients living with chronic hepatitis C virus (HCV). Although huge progress has been made in the HCV treatment arena, current antiviral therapy has many side ef-

fects and is not always effective. Add these elements to the symptoms some people experience from HCV and it is no wonder that herbs seem attractive.

Although herbs and other supplements may seem appealing, a number of herbs can cause harm. Some herbs are known to have potentially carcinogenic properties and to cause neurological damage. There are herbs that can be particularly harmful to the liver and can cause damage and death. It is because of the potential for hepatotoxicity (poisoning of the liver) that HCV patients are advised to avoid herbs or to use them cautiously.

The Food and Drug Administration (FDA) is the federal agency responsible for drug and food safety.

Drugs undergo years of rigorous testing on animals and humans before the FDA allows them to be marketed. Herbs and supplements, on the other hand, are considered to be dietary supplements. This means that they are regulated by a different set of standards, as set out in the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under this act, it is the manufacturer that ensures the safety of the dietary supplement. In general, the supplement manufacturers do not need FDA approval and do not need to register their product. They are required, however, to label the supplement in a truthful manner.

The point at which the FDA may become involved with herbs is after marketing. The FDA may monitor product labeling, information, and safety. Adverse event reporting is voluntary. Whether the FDA should regulate supplements is a hotly debated issue. The FDA has been criticized both for regulating and under-regulating dietary supplements. For a variety of reasons, the FDA's involvement with herb use has been minimal. To date, the notable excep-

***For a variety of reasons, the FDA's involvement with herb use has been minimal.***

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## EASL

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(preliminary results) found that the highest dose of VX-497 when combined with pegylated interferon plus ribavirin produced the highest number of patients with undetectable viral load—85%. The authors concluded that “the addition of VX-497 at a dose of 50 mg to pegylated interferon and ribavirin was well-tolerated and showed an enhanced anti-viral effect at 24 weeks in the interferon/ribavirin non-responder population.” The post-treatment follow-up SVR’s are eagerly awaited.

### Viramidine

Viramidine is a prodrug of ribavirin. Ribavirin is well known to produce hemolytic anemia for many patients on combination interferon plus ribavirin therapy. It is believed that since viramidine directly targets the liver there should be less drug induced hemolytic anemia. In a study conducted by Robert Gish and colleagues 180 patients were enrolled to evaluate viramidine as a safe substitute for ribavirin. Patients were randomized to receive pegylated interferon alpha-2a (Pegasys) 180 µg/week in combination with viramidine at 400mg, 600mg, 800 mg twice daily or ribavirin 1000/1200 mg daily. In this study, 64% of participants were male, the mean age was 48 years, 76% were Caucasian, and the mean viral load was 6.5 log<sup>10</sup> copies/mL. Following 24 weeks of treatment there was no significant difference between the viramidine group (800-1600mg/day) vs. ribavirin group in the proportion of patients with undetectable viral load or a decrease in viral load of 2log or more (83% vs. 83%).

Very few patients in the viramidine groups developed hemolytic

anemia compared to the group treated with ribavirin (2% vs. 24%;  $p < 0.001$ ). The other adverse events were similar among the different treatment groups. The authors concluded that “Viramidine demonstrated antiviral activity comparable to that of ribavirin when used in combination with peginterferon alfa-2a but with a significantly lower incidence of hemolytic anemia.

### NM283

NM283 is a polymerase inhibitor. A phase I/II study by E. Godofsky and colleagues assessed the tolerance, pharmacokinetics, and anti-viral activity of NM283. Twelve patient groups were randomized to receive NM283 (range 50-800 mg/day) or placebo. The study reported that the reported side effects were transient in nature. All patients completed treatment. It was found that that NM283 was well absorbed, with dose-proportional plasma drug levels. The authors noted that the next study would look at the use of NM283 in combination with peg-interferon.

### TREATMENT OF ACUTE HEPATITIS C

In recent studies the use of conventional interferon to treat acute hepatitis C has been highly successful, with sustained virological response rates up to 98%. However, the optimal treatment regimen and timing of treatment have remained undefined.

A study on the use of pegylated interferon alfa-2b (Peg-Intron) (1.5 mcg/kg weekly for 3 months) for treating acute hepatitis C was reported. In the study, Calleri and colleagues reported on the preliminary results of 15 patients currently enrolled in 6 centers in Italy (one patient dropped out due to logistical reasons). Treatment with Peg-Intron was started within 4-90 days after initial infection of hepatitis C. The study found that treatment was well-

tolerated with no severe adverse events or ALT flares. HCV viral load dropped to undetectable levels in 13 of 14 patients enrolled during the first month of therapy, and all fourteen were negative after 3 months of therapy. Eight of 14 patients remained virus negative during the follow-up period (median 3 months, range 1-12). Genotype 1 patients were more likely to relapse during and following treatment.

The authors concluded that treatment with “Pegylated interferon is well tolerated in acute hepatitis C. After a prompt clearance of HCV, a relapse is frequent in genotype 1 patients. A more aggressive treatment, possibly including ribavirin, or prolonged course, is probably desirable at least in genotype 1.”



### STUDY PHASES

In **Phase I** clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In **Phase II** clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In **Phase III** studies, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

In **Phase IV** studies, the drug is already on the market for a particular indication, but is now being tested for a different indication, use, or disease.

## HERBS

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tion to this is the sale of dietary supplements containing ephedrine alkaloids. Ephedra, also called Ma Huang, is one of the plants that are a source of ephedrine alkaloids. Its use has been associated with an increase in blood pressure, a condition which will increase the risk of heart attack, stroke, and death.

There is very little independent research involving the use of herbs. The gold standard randomized, double blind placebo controlled studies are few in the area of botanical remedies, let alone the use of herbs and HCV. In 1991, the U.S. Congress established the Office of Alternative Medicine (OAM) within the National Institutes of Health (NIH). In 1998 The National Center for Complementary and Alternative Medicine (NCCAM) became a new center of the NIH. Responding to the need for more research concerning the safety and efficacy of herbs and supplements, NCCAM and the NIH Office of Dietary Supplements established the first Dietary Supplements Research Centers with an emphasis on botanicals. The specific subject of herbs and viral hepatitis was included in the Complementary and Alternative Medicine in Chronic Liver Disease conference in 1999 and a few clinical trials are being conducted in this area. Unfortunately funding is limited and evidence-based data about herbs and HCV is largely unavailable.

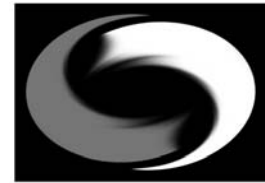
The insufficiency of independent research does not mean that there is no value in herbs.

Herbs have made a significant contribution to medicine. Herbal

practice has been around for centuries and has produced some sound observations. Indigenous practitioners relied on botanicals for medicine. In these modern times it is common for people to self-treat a mild sunburn with aloe vera, a mild stomach ache with ginger, or a mild cold with peppermint or chamomile tea. Generally these are assumed to be safe alternatives. However, the use of herbs for treatment of more serious conditions such as HCV is more complicated and raises a number of questions. For example, when choosing an herb, which part of the plant is used, when is it harvested, and how is it processed? Botanicals are not made in a lab setting. This means that the consistency of the product is at risk. Is the herbal product safe, which brands are the best, and what is the recommended dose? Next month's column will attempt to answer some of these questions and will provide some tools that can be used towards making informed choices.



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## FIBROMYALGIA

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avoid physical activity (causing their muscles to become deconditioned, or out of shape), get depressed, and have even more trouble sleeping, which in turn can make symptoms worse.

### FIBROMYALGIA, CFS, AND HCV

FM appears to be closely related to other conditions characterized by chronic pain, fatigue, cognitive impairment, and heightened sensitivity to stimuli. These include chronic fatigue syndrome (CFS, also called CFIDS), multiple chemical sensitivity (environmental illness), and Gulf War syndrome. Some experts believe these are, in fact, different manifestations of the same underlying disorder. As many as 75% of people with FM also have CFS, and vice versa. The symptoms of these conditions overlap to a large degree, but there are some differences: people with CFS are more likely to have flu-like symptoms such as fever and tender lymph nodes, while people with FM have characteristic tender spots.

Because some symptoms of FM and CFS are similar to those of hepatitis C, researchers have explored whether and how these conditions might be related. In a 250-person study, D. Buskila and colleagues found that 16% of HCV patients, 3% of patients with cirrhosis due to other causes, and no HCV-negative patients without liver disease met the diagnostic criteria for FM. Almost all of the HCV positive individuals with FM were women. Conversely, J. Rivera and colleagues detected HCV antibodies in 15% of a group of 112 patients with FM, compared with 5% in a matched groups of rheumatoid arthritis patients. More recently, E. Kozanoglu

and colleagues found that 19% of HCV patients had FM, compared with just 5% of uninfected controls. Interestingly, patients who had both HCV and FM reported more tender spots and more intense pain than those with FM alone. Interferon can cause symptoms similar to many of those associated with FM and CFS, but none of the HCV patients in Buskila's study were receiving interferon (Rivera and Kozanoglu did not report interferon use in their abstracts). In another recent study, M. Thompson and colleagues described several cytokine alterations seen in both hepatitis and FM that can cause hyperalgesia and other symptoms common to these two conditions. Buskila suggests that since there is no evidence that specific pathogens cause FM or CFS, it is more likely that infection in general, including HCV, is among the many possible triggers for these conditions.

### FIBROMYALGIA DIAGNOSIS AND TREATMENT

There is a two-part definition for diagnosing FM:

- Pain in all four quadrants of the body (i.e., on both sides and above and below the waist) for at least 3 months
- Pain in at least 11 of 18 defined tender points

There are no laboratory tests that specifically indicate FM. However, FM can resemble several other conditions, which should be ruled out using appropriate tests if suspected. These include Lyme disease, lupus, rheumatoid arthritis, multiple sclerosis, and hypothyroidism (which is sometimes associated with interferon therapy).

There is no known cure for FM, so therapy is aimed at relieving symptoms and improving quality of life. Education is key to helping pa-

tients adjust their lifestyle to accommodate pain and fatigue. Many of these measures will be familiar to people living with HCV: pacing activities, simplifying tasks, scheduling time for rest, setting realistic expectations, and asking for help. Don't try to do too much on "good days," since this can lead to overexertion and a flare-up of symptoms.

"A gentle program of stretching and aerobic exercise is essential to counteract the tendency for deconditioning that leads to progressive dysfunction in fibromyalgia patients," says FM expert Robert Bennett, MD. Complete bed-rest might be tempting, but is likely to lead to worse fatigue and disability. Regular, low-impact exercise can improve muscle tone and promote deep sleep. Start slowly with just a few minutes of gentle stretching per day; if possible, work up to 20-30 minutes daily.

Many medications can help promote sleep and manage pain. For insomnia, antihistamines and melatonin may be tried first, followed by stronger medications such as zolpidem (Ambien) or temazepam (Restoril). Clonazepam (Klonopin) is used to control restless leg syndrome. Over-the-counter pain medications are not usually very effective, but low-dose tricyclic antidepressants such as amitriptyline (Elavil) or doxepin (Sinequan) can both relieve pain and improve sleep, as does trazodone (another type of antidepressant). If these measures are not adequate, stronger pain medications such as tramadol (Ultram) or narcotics (e.g., Vicodin, OxyContin) may be used. Injection of lidocaine at tender points can also help with flare-ups. Patients in constant, severe pain should consult a specialized pain

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## FIBROMYALGIA

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management clinic. Importantly, patients with FM are often especially sensitive to the effects of drugs, so it is prudent to start with low doses and increase them as needed.

People with FM often find alternative therapies helpful, including acupuncture, t'ai chi, therapeutic massage, physical therapy, hot baths, biofeedback, and relaxation techniques. In addition, many can benefit from peer support groups or professional counseling.

While FM is a chronic condition and complete recovery may not be possible, many people do experience some improvement over time. Some people are able to resume work, and if not, may be eligible for disability benefits (see "Fibromyalgia, CFIDS, HCV and Social Se-

curity Disability" [LINK: [www.hcvadvocate.org/hepatitis/hepC/Fibro\\_CFIDS.html](http://www.hcvadvocate.org/hepatitis/hepC/Fibro_CFIDS.html)]).

As with many conditions, a combination approach seems to work best. Pacing activities, gentle exercise, good sleep habits, and stress reduction can help keep pain and fatigue under control.

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Kozanoglu, E. et al. Fibromyalgia syndrome in patients with hepatitis C infection. *Rheumatology International* 23(5): 248-251. September 2003.

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*British Journal of Rheumatology* 36(9): 981-5. September 1997.

Thompson, M. and A. Abarkhuizen. Fibromyalgia, hepatitis C infection, and the cytokine connection. *Current Pain and Headache Reports* 7(5): 342-347. October 2003.

### Web Resources:

- Arthritis Foundation: 800-283-7800, [www.arthritis.org](http://www.arthritis.org)
- National Fibromyalgia Association: 714-921-0150, [www.fmaware.org](http://www.fmaware.org)
- National Fibromyalgia Partnership: [www.fmpartnership.org](http://www.fmpartnership.org)
- National Chronic Fatigue Syndrome and Fibromyalgia Association: [www.ncfsfa.org](http://www.ncfsfa.org)
- CFIDS Association of America: 704-365-2343, [www.cfids.org](http://www.cfids.org)



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