

Post-Transplant Treatment for Hepatitis C



Liz Highleyman

Long-term liver damage related to hepatitis C is the most common reason for liver transplants in the U.S. Unfortunately, the hepatitis C virus (HCV) usually reinfects the new liver after a transplant. HCV recurrence typically occurs within a few weeks and sometimes in as little as 24-48 hours after transplantation, following an initial steep decline in HCV viral load. More severe recurrence is associated with high pre-transplant viral load, a liver graft from an older donor, and use of strong immunosuppressive drugs to prevent organ rejection.

Researchers are avidly studying ways to prevent and treat HCV recurrence after liver transplantation. Montserrat Garcia-Retortillo and Xavier Forns reviewed the current state of knowledge in the July 2004 issue of the *Journal of Hepatology*.

The first approach to preventing post-transplant reinfection involves attempting to eradicate HCV before the transplant is performed. If the virus can be completely eliminated from the

body, it cannot infect the new liver. Unfortunately, even among people who have achieved a sustained virological response (SVR) to treatment, HCV appears to remain in the body at very low levels. In the June 2004 issue of the *Journal of Virology*, Tram Pham and colleagues reported that HCV genetic material persists in peripheral blood mononuclear cells (a type of immune system white blood cell) for up to five years after spontaneous or therapy-induced HCV "clearance." But because rapid and severe reinfection is most likely in people with high pre-transplant viral loads, any significant reduction in HCV RNA is likely to prove beneficial.

Although HCV therapy can be risky in people with advanced cirrhosis, interferon plus ribavirin is increasingly being used in HCV patients awaiting liver transplants. For example, Gregory Everson and colleagues treated 102 HCV positive cirrhotic patients with interferon plus ribavirin. Although the SVR rate was low (20% overall, 11% for genotype 1), among the 32 patients

who underwent transplantation, HCV did not recur in any of those who achieved a sustained response. In another study, Forns and colleagues found that among 30 patients on a transplant waiting list treated with interferon plus ribavirin, HCV did not recur after transplantation in 6 of 9 patients who achieved a virological response, but did recur in all nonresponders.

Adverse side effects are common in patients with advanced liver disease, and in many cases therapy must be discontinued or dosages decreased (although use of erythropoietin or filgrastim to stimulate production of red and white blood cells, respectively, may allow some patients to stay on therapy). While HCV treatment response rates in this population are lower than those seen in individuals with milder disease, "antiviral therapy is a feasible choice in HCV-infected patients with advanced liver disease," Garcia-Retortillo and Forns concluded.

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Another approach is to use immunoglobulin (antibody) therapy starting right before the transplant operation to prevent reinfection of the new liver. In people with chronic hepatitis B, use of an immunoglobulin preparation called HBIG effectively prevents HBV recurrence. In studies to date, similar use of HCV antibodies has not prevented reinfection of the new liver. However, studies have shown that antibodies with neutralizing activity against HCV do exist, and research is continuing with new types of antibody preparations.

A third approach is to treat patients with interferon-based therapy soon after liver transplantation, while their HCV viral load is still low. Among these patients, who are typically taking high doses of immunosuppressive drugs, adverse side effects and treatment discontinuation are common. Although results have been mixed, some studies show that a proportion of patients can benefit from interferon-based therapy started within the first few weeks following transplantation. For example, in a study of 63 post-transplant patients, Vincenzo Mazaferro and colleagues reported SVR rates of 13% among post-transplant patients treated with standard interferon monotherapy and 33% among those treated with interferon plus ribavirin. Studies also suggest that early treatment helps reduce the risk of reinfection.

More commonly, HCV treatment is initiated months or years

after liver transplantation, once signs of damage to the new liver are apparent. By this time, patients are usually healthier overall and taking lower doses of immunosuppressive drugs, enabling them to better tolerate HCV therapy. In general, studies have found SVR rates for this population to be around 20-25% using standard interferon plus ribavirin. Rates are somewhat higher using pegylated interferon. In the July 2004 issue of *Liver Transplantation*, for example, R. Todd Stravitz and colleagues reported on a retrospective evaluation of interferon therapy in 23 post-transplant patients with recurrent HCV. The subjects completed at least six months of interferon-based therapy, 83% with Peg-Intron; however, only four were able to tolerate ribavirin. After six months of treatment, 11 patients

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(48%) had undetectable HCV RNA; of these, eight (35% of the total) achieved SVR. Liver biopsies performed two years after HCV became undetectable showed decreased necroinflammatory activity, and 6 of 11 patients showed histological improvement on follow-up liver biopsies. Although SVR rates for transplant recipients are lower

than those seen in non-transplant patients, treatment can keep HCV under control in some individuals, and those who respond may experience decreased fibrosis progression.

Caution is necessary, however, because interferon therapy appears to increase the risk of liver rejection. In the same issue of *Liver Transplantation*, Sammy Saab and colleagues reported that five of 44 liver transplant recipients treated with interferon (11.4%) developed acute liver rejection, a rate higher than that seen in liver transplant patients not receiving interferon. These five started interferon an average of 42 months (and up to 83 months) after transplantation, and were treated for an average of three months before rejection set in. Three were successfully treated with intensified immunosuppressive drugs, one required a second liver transplant, and the fifth died from sepsis. In Stravitz's study, eight (35%) of the 23 transplant recipients treated with interferon showed evidence of liver rejection and two required a second transplant. Further study is needed to determine the best immunosuppressive regimens for post-transplant patients with HCV. Whenever

transplant recipients are treated for hepatitis C, care must be taken to minimize interactions and synergistic side effects between HCV therapy and immunosuppressive drugs.

As is true for all individuals with HCV, post-transplant patients do not need to be treated until they show signs of liver disease

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How to Start an HCV Support Project: *Part 1*



Alan Franciscus, Editor-in-Chief

Living with hepatitis C is not easy! In order for people with HCV to successfully manage this condition it is important that they receive good medical care and support from as many different areas as possible—medical professionals, family and friends as well as from others living with hepatitis C. Peer support in the form of a support group is one of the critical links in helping HCV positive people face the issues in their everyday lives. Education, support, care and services available to HCV positive people will help them make the best possible choices to effectively manage their lives.

I was diagnosed in 1996 when relatively little was known about hepatitis C. The information on hepatitis C was scarce, with more misinformation than accurate information available. Shortly after I was diagnosed, I asked my doctor to recommend a support group in my area, but to my surprise he told me that there were no support groups in my area specifically geared toward people living with hepatitis C. I did attend a local liver support group that was geared towards any type of liver disease, but I didn't feel like it addressed my specific needs for information and peer support on various issues I was struggling with at that time.

A few months after I was diagnosed with hepatitis C, I began interferon monotherapy. It became clear to me early into treatment that I was not prepared to deal with the

physical and psychological side effects related to interferon treatment. I became anxious and depressed! Worst of all I did not recognize the subtle changes in my personality. I also realized how much I needed some form of peer support to help me through treatment. It was during this period that I made a promise to myself that I would start a support group after I completed therapy. Shortly after I completed treatment, I enlisted help from a friend and we started the first HCSP support group in the area. To prepare for facilitating a support group I took a 3 day course about support group facilitation from a local health agency that gave me some valuable information and resources. It wasn't particularly difficult to set up and maintain a support group, but a lot of what I needed to know specific to hepatitis C was learned by hit and miss, and it would have been much easier had I been able to learn from others who were experienced with running a hepatitis C support group.

The importance of support groups can not be overstated. This article is part one in a series of articles designed to help others start a support group and to provide some tools to help people in the difficult job of maintaining an on-going support group. This is by no means a definitive guide for starting and maintaining a support group, but I hope it will be a helpful tool for support group leaders to use and for others to take the big step of starting a support group. The information in

this article will not be suited for everyone because different approaches may be needed for different populations. Every individual is unique, as is every support group. A support group leader must always consider the members' needs and take every opportunity available to adapt to the individual and group needs.

THE NEED

Why is there a need for support groups? A person living with hepatitis C must make daily decisions on a variety of issues about hepatitis C. Some of these issues may include disclosure, stigma, disease management, and treatment issues. Peer support is critical in providing needed advice and information to help a hepatitis C positive person successfully live with HCV.

There are generally several major reasons why people seek HCV support groups:

Newly Diagnosed

When a person is newly diagnosed it is usually a life altering event. Being told you have hepatitis C raises many questions:

- What does it mean to have hepatitis C?
- Am I going to die soon?
- What should I tell my spouse, family, employer and co-workers?
- How do I tell others I have hepatitis C?
- Do I need to start treatment immediately?

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SUPPORT GROUP

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- How do I protect others from getting hepatitis C?
- How do I take care of myself?
- How do I take care of loved ones?
- What about herbs?
- What should I avoid - alcohol/ other drugs?
- How do I cope with a potentially life-threatening disease?

Stigma

Stigma occurs when we attach negative labels to people and make generalizations about certain groups or types of people. Generalizations about people are endemic in our society because we all feel a need to categorize people and situations in order to make decisions in relation to any group. Some people find it easier to generalize about certain groups rather than to take the time and energy needed to discover and understand the differences that make up individuals. These differences may be due to religious, cultural, physical or even pathological reasons. Negative generalizations on a large scale produce prejudice, in which certain groups or populations in our society become stigmatized.

Stigma has two consistent components—the recognition of different characteristics in groups of people, and the devaluation of another human being. Feeling different is one of the reasons why people seek out support groups—they need to be with like-minded people experiencing similar situations.

Most people who have been diagnosed with hepatitis C face some form of stigma or prejudice in their daily lives. It could be a phrase like "you people," or a slight pause when you divulge your HCV status. Friends may stop calling, employers and co-workers may act differently, or it

could be as subtle as a facial expression. In any event, we all know how it feels to be treated differently based on being HCV positive. How you handle the stigma associated with HCV is an important issue because it will greatly affect the quality of life, health (both mental and physical) as well as just about every area of the life of those dealing with this condition.

Stigma and prejudice affect every one differently and could lead to:

- Withholding HCV diagnosis from family, friends, and co-workers
- Not seeking medical care for fear of being seen at a healthcare setting by others
- Loss of employment and livelihood
- Friends and family may "guard" their children from coming into contact with a person with HCV.

Disease Management

After the shock of being diagnosed with hepatitis C a person will have to make a variety of important decisions in order to manage the disease.

Individuals will seek information and advice about many issues including:

- Alcohol and other drugs
- Nutrition and exercise
- Preventing transmission of HCV to others
- Medical management
- Depression and anxiety
- Herbs, vitamins and other dietary supplements
- Disability issues
- Sexual issues
- Guidance on their everyday lives

Treatment

Issues about treatment are one of the main reasons why people seek out HCV support groups. People come to hear what others have experienced on treatment as well as

to learn from others about effective strategies to cope with the side effects of therapy.

Peer support is critical for people taking interferon-based therapy. There are a wide variety of physical and psychological side effects that people may experience on a daily basis. The potential for drug-induced psychological problems is frightening for most people to think about. During HCV medical therapy the side effects can be so subtle that only the people in close contact are able to notice any changes. Support group members who have experience with these side effects are able to help identify and help others cope with these distressing issues.

After Treatment Issues

The side effects of treatment will continue even after stopping therapy. It may take even longer to feel completely back to "normal." The uncertainty of treatment outcome will weigh heavily on most people. Until someone receives the news that their treatment was "successful" or "unsuccessful," they can become quite anxious. In addition, if the hepatitis C virus does come back after enduring a six month or year long therapy it is disappointing and makes it difficult for people to decide how to move forward.

These are some of the most important issues that I have found that have been raised in support groups, but it is by no means the entire list. The amount of support and the different issues raised by hepatitis C positive support group members is truly amazing.

Part two of this article will focus on identifying experts and resources as well as on one of the most important questions to consider: "Why do I want to start a support group"?



HealthWise:

Advocating for Health Care



Lucinda K. Porter, RN, CCRC

This month my intention was to write about Patients' Rights and the broader topic of legislated patient protection. I thought this would be a fairly straight-forward topic, requiring some research, reporting, and perhaps some analysis and recommendations. Hours later, I found that this topic consisted of more dead ends than Boston's traffic pattern.

I began my search with the topic "patients' rights." Over the years there have been a number of attempts by both the Senate and the House of Representatives to pass bills that provide more patient protection. The subject of patients' rights covers a huge arena of concepts, far more than can be discussed in this article. In particular I was interested in finding out more about the status of the Patients' Bill of Rights.

Both Republicans and Democrats endorse wider patient protection. Presidents Clinton and Bush (George W.) have both publicly supported the concept of a patients' bill of rights. The following text is from the White House web site:

"The President strongly supports the passage of a Patients' Bill of Rights that leaves medical decisions in the hands of physicians, instead of insurance companies. A Patients' Bill of Rights must include comprehensive patient protections (such as access to emergency room or specialty care); independent, binding external medical review for denials of care; and meaningful legal remedies for patients who have been harmed by an HMO's denial of medical care. The President further believes that the Patients' Bill of Rights should apply to all Americans in private health plans, but that we should give deference to the strong patient protection laws that have already been passed by many states. Patients should be guaranteed new federal appeals processes

and legal remedies to hold their health plans accountable when they have been injured by a wrongful denial or delay in medical care, but employers should be shielded from unnecessary and frivolous lawsuits and damages. Damages should also be subject to reasonable caps to avoid expensive health care premiums and unaffordable health coverage."

This sure sounds good to me. With so many elected officials in favor of strengthening the rights of patients, this issue ought to be a slam dunk, right?

Wrong. Since 2001 there have been a number of bipartisan attempts to pass legislation that would provide greater protection for patients. There were failed attempts to create a Patients' Bill of Rights. Then there was the Bipartisan Patient Protection Act of 2001 (not signed into law) followed by the Bipartisan Patient Protection Act of 2003 (also not signed into law). There were more than one version of each of these, the most famous being the one drafted by Senators Edward Kennedy and John McCain. Just prior to this year's summer recess, the Bipartisan Patient Protection Act of 2004 is still not signed into law.

The President and both branches of Congress agree on the necessity of providing legal protection for patients. The conflict arises around the issue of allowing people to sue their managed-care plans over the denial of medical treatment. Although there is bipartisan agreement that patients would need to pursue an extensive appeals process prior to bringing litigation, Bush and many House and Senate Republicans argue that

"Now is the time to become informed and involved. Find out how your elected officials stand on issues important to you."

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progression. "Given the low efficacy and poor tolerability of current antiviral therapy," Garcia-Retortillo and Forns recommend that "treatment should probably be reserved to those individuals in whom disease progression is well documented." However, liver damage progresses more rapidly in people with compromised immune systems, including those taking immunosuppressive drugs. Martín Prieto and colleagues, for example, found that HCV infection led to cirrhosis in some 30% of transplants recipients within just five years. And in Saab's study, two of the three patients whose acute rejection was successfully treated progressed rapidly to cirrhosis.

For this reason, Garcia-Retortillo and Forns suggest that frequent biopsies are indicated to monitor disease progression in the new liver.

"[A]ntiviral treatment is now fully part of the overall therapeutic strategy post-transplantation," wrote Didier Samuel in an editorial in the July *Liver Transplantation*, but "[t]he timing, the duration of treatment, the use of pegylated interferon instead of nonpegylated interferon, and the optimal dosage of ribavirin are still a matter of debate." As better therapeutic regimens emerge, more research is needed to improve outcomes for liver transplant recipients, who are among the most difficult patients to treat but who can potentially derive considerable benefit from successful therapy.

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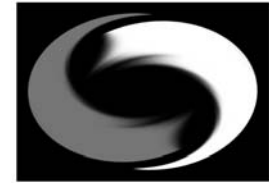
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ADVOCATING

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passage of the McCain-Kennedy bill will trigger a wave of frivolous litigation. Republicans have drafted amendments or alternative bills that would restrict this. In short, there is an impasse in the legislative process, leaving patients with weak protections, especially for those who have managed health care.

This is an election year for Congressional seats as well as for the Presidency. We are facing complex issues, including our involvement in Iraq and the economy. Health care issues are not going to be at the top of the list, but these are very important issues. Protecting the rights of patients seems like a comparatively tame issue compared to providing af-

fordable health care for everyone. Now is the time to become informed and involved. Find out how your elected officials stand on issues important to you. Examine their voting records. Then look at your voting record. Are you registered to vote? Do you know where to vote? Will you vote? Will you encourage others to vote? Voting is one way we can hold elected officials accountable for their acts. Let your elected officials know you are paying attention.

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