WESTERN (ALLOPATHIC) MEDICINE

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SECTION

2 | INITIAL TREATMENT OPTIONS

Introduction

It has only been possible to diagnose hepatitis C since 1990. However, great progress has been made in the treatment of hepatitis C in this short period. Currently, all western therapy for hepatitis C is based on the use of alfa interferons. However, alpha interferons alone (monotherapy) provided only limited success. The allopathic standard of care as of this writing (August 2012) is combination therapy with pegylated interferon and ribavirin, plus boceprevir or telprevir for people with genotype 1. For genotype 2 the standard of care is combination therapy with pegylated interferon plus ribavirin. Hepatologists (liver doctors) generally agree that it is no longer advisable to treat hepatitis C with interferon alone unless the use of ribavirin is contraindicated.

Western Treatment: Who and Why

The discussion in this chapter is focused primarily on western treatment for chronic hepatitis C. A person is said to have chronic hepatitis C if he/she continues to have the virus for six or more months after the time of initial infection. (Note: A brief discussion on the treatment of acute hepatitis C appears later in this chapter section.)

This section discusses the treatment options available to those with chronic hepatitis C who have not previously received interferon-based therapy. The term used to describe this group of patients in western medicine is "treatment naïve." See Chapter 8.3 *Options When Initial Treatment Fails to Clear the Hepatitis C Virus,* if you have previously been treated with interferon.

Although each person <u>must</u> be evaluated on a case-by-case basis, there are some generally accepted characteristics of persons for whom *interferon-based therapy* is widely accepted.[1] These characteristics include:

- abnormal ALT
- chronic hepatitis with significant *fibrosis* on *liver biopsy*
- no evidence of liver *decompensation*
- no absolute contraindications to treatment
- willingness to undergo and commit to the requirements of treatment

The only way to know if you are a candidate for interferon-based therapy is to talk with your doctor. The criteria listed above only give a broad view. Each person with hepatitis C is different, and only you and your doctor can determine whether interferon-based therapy is appropriate for you, taking into consideration all the unique characteristics of your personal situation.

The five major goals of western treatment for chronic hepatitis C are:

- eliminate the virus from the body

- restore normal liver function (as shown by liver-specific blood tests)

- prevent further liver damage (shown by improvement or stabilization on the liver biopsy)

- improve overall health and well-being

- produce a response to therapy (a durable or *sustained response*) that will last for the rest of the patient's life

A *sustained response* is defined as continued undetectable *HCV* in the blood 6 months after the completion of treatment. At this point, a person is considered *cured* of chronic hepatitis C.[2]

IT IS YOUR GENES

Researchers at Duke have recently identified a polymorphism of Interleukin (IL)-28B (a specific sequence in your DNA) that predicts response to interferon therapy.[3] The IL-28B is genotyped as CC, CT or TT. Caucasians are primarily CC while African Americans are primarily TT. This genetic difference explains why African Americans have a lower response rate to interferon therapy. This genetic difference also appears to be important with the new DAA therapies. People with IL-28B CC genotype may be eligible for a shorter duration of treatment.[4] The IL-28B genetic test is commercially available and should be discussed with your doctor when discussing treatment options.

Interferon-Based Therapies

From Past to Present

Interferon monotherapy refers to hepatitis C treatment with interferon alone (that is, without ribavirin). Standard interferon was the first therapy approved by the U.S. Food and Drug Administration (FDA) for chronic hepatitis C in 1991. With overall durable response rates of 20% to 25%[5-10], hepatologists and patients were encouraged, but also determined to find other options that would lead to successful outcomes for a much greater proportion of those undergoing treatment.

The addition of ribavirin to interferon was a big breakthrough in the western treatment of hepatitis C, improving overall durable response rates to approximately 40%.[11-18] The improvement was encouraging, but insufficient.

Standard interferon is cleared from the body very quickly, within 6 to 7 hours. With thrice weekly dosing, there were long periods with no interferon circulating in the blood. This gives the virus time to recover from the effects of the interferon. The development of pegylated interferons came about from an effort to solve these problems and to keep interferon continuously circulating in the blood.[19, 20] It was hoped that a longer-acting form of interferon would provide a great improvement in the treatment success rate, and this has proven to be the case.

The attachment of polyethylene glycol (a long-chain sugar molecule known as "peg") to a protein such as interferon slows its absorption, and decreases its breakdown and clearance from the body. Based on this knowledge, pegylated interferons were developed and tested.[21-33] Treatment with pegylated interferon provides a relatively constant level of interferon in the blood when given only once a week. This makes it more convenient (one injection each week rather than three) and produces a continuous interferon level to combat the virus.

Landmark studies have shown that approximately 80% of people with genotypes 2 and 3 who receive pegylated interferon plus ribavirin achieve a durable response. Just under 50% of people with genotype 1 achieve a durable response with this treatment protocol.[25, 34-36] Side effects are similar to those seen with standard combination therapy.[24, 25, 34, 37-40]

The development of direct acting antivirals (DAAs) changed the landscape for genotype 1 patients. In 2011, the first two oral drugs, protease inhibitors, telaprevir (Incivek®) and boceprevir (Victrelis®) were approved by the FDA in 2011 for people with Genotype 1. In clinical trials, both agents used in conjunction with pegylated interferon and ribavirin resulted in substantially higher SVR rates.[41-44] Either boceprevir or telaprevir—but never both—are used with peginterferon and ribavirin to treat hepatitis C.

Management of hepatitis C therapy has also improved with the advent of response-guided therapy (RGT). Patients viral load (HCV RNA) is tested more frequently and therapy times are adjusted accordingly. This allows therapy to be shortened in some cases by 6 months. RGT may lead to early discontinuation of therapy that is not working, saving the patient many months of exposure to a toxic therapy and the development of drug resistant virus.

Combination Therapy for Genotype 1:
Pegylated Interferon Plus Ribavirin Plus Protease Inhibitor
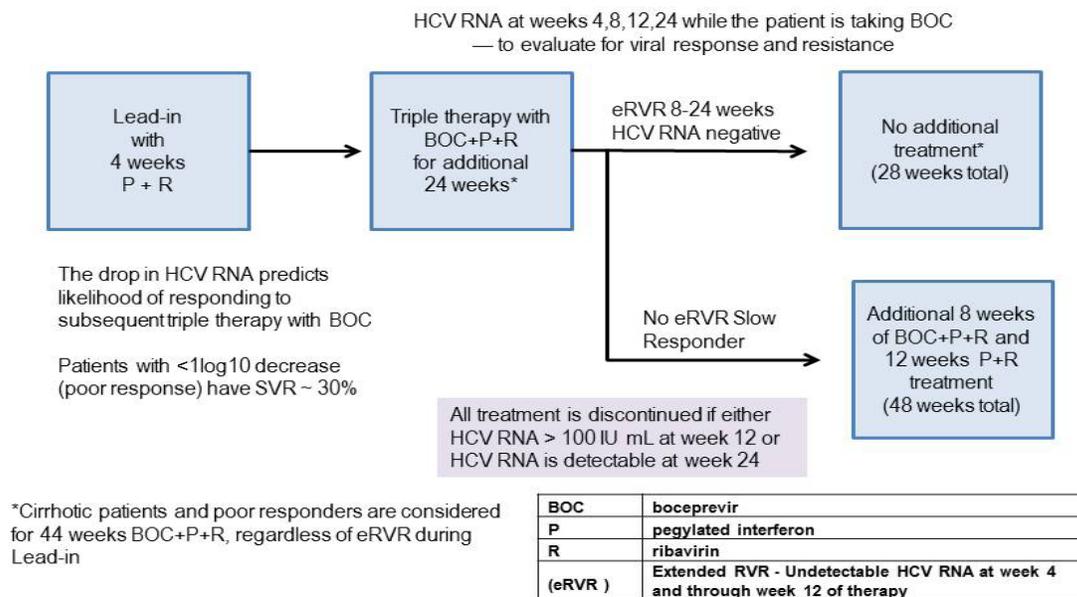
PROTEASE INHIBITORS

Protease inhibitors target the HCV protease enzyme. The protease enzyme plays an important part in HCV reproduction. The virus uses it as a scissors, to cut viral proteins into smaller pieces so that they can be put back together as individual HCV particles (called virions).   Protease inhibitors work by binding to the protease enzyme, so it cannot cut, the same way that inserting something between the blades of a scissors prevents cutting.

BOCEPREVIR

In the phase III clinical trials, the addition of boceprevir to pegylated interferon and ribavirin in people new to HCV therapy (treatment-naïve) almost doubled the number of people who achieved an SVR. Viral load levels remained undetectable for at least six months after treatment. Nearly 70 percent of those who added boceprevir to the standard therapy achieved an SVR, compared with only 38 percent of those who received only pegylated interferon with ribavirin.[44] Boceprevir resistance has been seen but is reduced when the drug is used in the recommended combination with pegylated interferon.[45]

Boceprevir is taken every eight hours. A lead-in period of standard therapy with pegylated interferon and ribavirin is first given alone for four weeks, after which boceprevir is added for a variable length of time depending on a person's previous use of HCV treatment and how much boceprevir suppresses HCV levels at early time points. Anemia and dysguesia (metallic or bad taste in mouth) are the only common side effect of standard therapy, which appears at even higher rates with the addition of boceprevir. In phase III trials, in those given boceprevir, anemia rates increased by about 65 percent in those new to therapy.[43,44] In those taking boceprevir, it will be important to monitor for anemia so that it can be addressed in a timely manner by ribavirin dose reduction. In a few patients, erythropoietin, a hormone that boosts production of more red blood cells, may be needed. (Figure 1)[46]

Figure 1: Boceprevir Treatment Algorithm – Treatment Naïve

HCV RNA at weeks 4,8,12,24 while the patient is taking BOC
— to evaluate for viral response and resistance

| Lead-in with 4 weeks P + R | → | Triple therapy with BOC+P+R for additional 24 weeks* |

eRVR 8-24 weeks HCV RNA negative → No additional treatment* (28 weeks total)

The drop in HCV RNA predicts likelihood of responding to subsequent triple therapy with BOC

Patients with <1log10 decrease (poor response) have SVR ~ 30%

No eRVR Slow Responder → Additional 8 weeks of BOC+P+R and 12 weeks P+R treatment (48 weeks total)

All treatment is discontinued if either HCV RNA > 100 IU mL at week 12 or HCV RNA is detectable at week 24

*Cirrhotic patients and poor responders are considered for 44 weeks BOC+P+R, regardless of eRVR during Lead-in

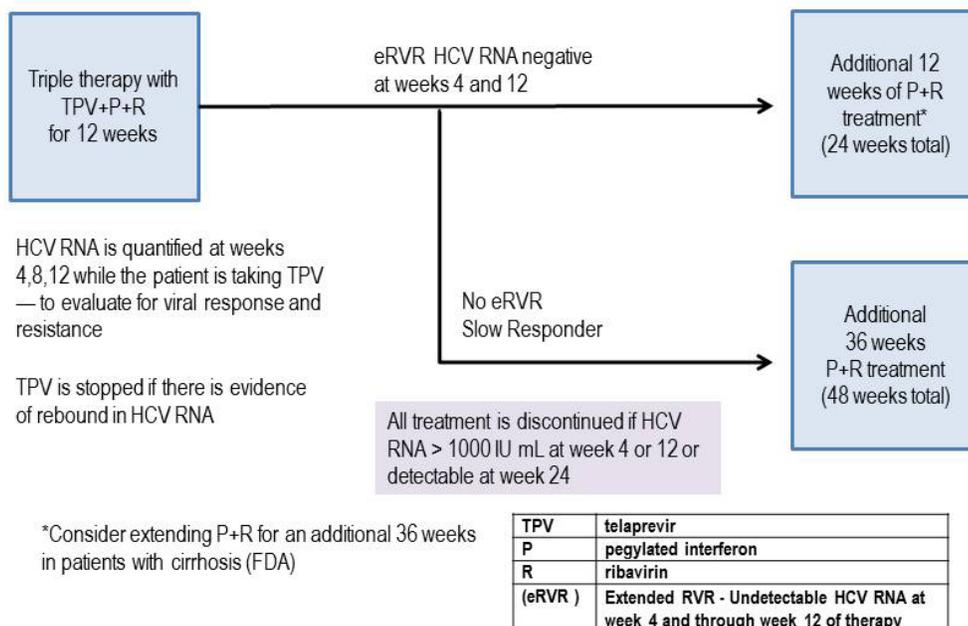| BOC	boceprevir
P	pegylated interferon
R	ribavirin
(eRVR)	Extended RVR - Undetectable HCV RNA at week 4 and through week 12 of therapy

TELAPREVIR

In the phase III clinical trials in people who were new to treatment, up to 79 percent achieved an SVR with telaprevir used in combination with the standard therapy of pegylated interferon and ribavirin, compared with 44 percent of people who received only the standard therapy.[47]

In addition, results seen with telaprevir in treatment-naive studies show that it may be possible to achieve an SVR with a shorter treatment period of only 24 weeks, compared to the 48 weeks required with the use of standard therapy alone. In one trial, combining telaprevir with standard therapy for the first 12 weeks of treatment increased the percentage of people with undetectable genotype 1 HCV levels after 4 and 12 weeks, compared with standard therapy alone.[48] In these patients, the so-called "extended rapid virologic responders" (eRVRs), stopping all drugs after only 24 weeks did not reduce the likelihood of an SVR. The overall number of people with genotype 1 who achieved an SVR, regardless of their early virologic response, was also relatively high at 72 percent.[49] The sustained virologic response rate for patients treated with telaprevir across all studies, and across all patient groups, was 20% to 45% higher than the current standard of care.

Telaprevir resistance has been seen, but the rate of resistance to the drug is substantially reduced when used in the recommended combination with pegylated interferon.[50,51] Telaprevir should never be used alone and if there are adverse events from the drug, it should be discontinued rather than reducing the dose. (Figure 2)[46]

Figure 2: Telaprevir Treatment Algorithm – Treatment Naïve

The optimal therapy for genotype 1, chronic HCV infection is
the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin.

Combination Therapy for Genotype 2/3: Pegylated Interferon Plus Ribavirin

The current treatment of choice for genotype 2 or 3 chronic hepatitis C among western doctors is pegylated interferon plus ribavirin. The hepatitis C treatment guidelines from the American Association for the Study of Liver Diseases include the following recommendations regarding the dose and duration of therapy (see Table 1).

Table 1. AASLD Guidelines on Pegylated Interferon Plus Ribavirin Therapy[1]

	Genotype 2 or 3
Duration of Therapy	24 weeks
Ribavirin Dose	800 mg
Early Viral Response Check	Week 12
Sustained Viral Response Check	24 weeks after completion of therapy

Important: Research on dosing, when to test for response to therapy, and duration of therapy is ongoing, and new studies are reported each week. Your doctor will customize your treatment protocol based on not only standard guidelines, but also the unique circumstances of your situation, and the latest medical research data.

The optimal therapy for genotype 2 or 3, chronic HCV infection is
the use of peginterferon alfa and ribavirin.

Response to Interferon-Based Therapy

Western medicine's key measurement of successful treatment of hepatitis C is undetectable virus in the blood. Among those for whom therapy is successful, this usually occurs very early during the treatment course. If therapy fails to produce an undetectable or very low viral load test after 12 weeks of treatment, it is highly unlikely that the therapy will be successful.[25, 34]

Most doctors discontinue treatment if HCV is not undetectable by week 12 after the initiation of interferon-based therapy. However, the decision to continue therapy for another 12 weeks is sometimes made if the viral load has dropped by at least 100-fold (for example from 1,000,000 to 10,000). It is a rare and unusual occurrence for a doctor to continue therapy for an additional 12 weeks if there is no viral response to treatment within the first 12 weeks.

If a durable response is to occur, HCV should be undetectable after 24 weeks of therapy. It is important to recognize that measurement of viral levels can vary greatly from one laboratory to another. Therefore, you should try to have the same laboratory perform your HCV viral load tests before and during your treatment.

Also, be aware that small changes in viral load are not significant. Recall that viral levels must fall at least 100-fold to be considered significant. For example, even a seemingly large drop from 800,000 to 200,000 would not be considered significant because it is not a 100-fold decrease and would not be an indication of successful therapy.

Boceprevir and telaprevir have set discontinuation rules. It is important that these rules are followed to avoid resistance.

There are several different phrases your doctor may use when talking about your response to treatment. The terms are changing with the evolution of therapy. Table 2 below summarizes some of the most common of these terms at this time.

Table 2. Terms Used to Describe Response to Therapy

Term	Definition
Rapid Viral Response (RVR)	undetectable HCV RNA by week 4 of therapy
Extended RVR (eRVR)	Undetectable HCV RNA at week 4 and through week 12 of therapy
Early Viral Response (EVR)	100-fold or greater drop in HCV RNA by week 12 of therapy
Complete Early Virologic Response (cEVR)	undetectable HCV RNA at week 12 of therapy
End of Treatment Response (ETR)	Undetectable HCV RNA (by PCR testing) at the end of the therapy period
Sustained Viral Response 12 (SVR12)	Undetectable HCV RNA (by PCR testing) 12 weeks after the completion of treatment
Sustained Viral Response (SVR)	Undetectable HCV RNA (by PCR testing) 24 weeks after the completion of treatment

Relapse	Return of detectable HCV RNA (by PCR testing) after a documented end of treatment response
Non-Response or Null-Responder	Treatment fails to produce a 100-fold or greater drop in HCV RNA by week 12 of treatment

A relapse is defined as having no detectable virus during treatment, but the return of detectable virus after treatment ends. If the virus becomes detectable after treatment, there are usually no symptoms but ALT levels often rise. A relapse typically occurs within 4 to 24 weeks after completing therapy. Developing detectable virus more than 12 to 24 weeks after completing treatment is rare and occurs in less than 5% of those treated.[7, 52, 53] Relapse beyond two years after completing therapy is exceedingly rare. Retreatment for people who have a relapse is discussed in Section 3 of this chapter.

> **Although a negative test for HCV RNA by PCR testing is the critical measurement that is followed throughout treatment and afterwards to determine cure, it is important to recognize that the test results carefully state that the virus was "not detected". The PCR test for HCV RNA has a lower limit of sensitivity below which it is unable to detect the virus, even if it is still present in minute quantities. This is why patients who have had negative tests throughout treatment may still relapse and why treatment is continued for many weeks after the PCR test has already become negative.**

It is notable that a study that followed sustained viral responders for up to seven years after the successful completion of interferon-based therapy found that 99% remained free of detectable hepatitis C virus. This study, conducted at nearly 40 sites worldwide, has given both doctors and patients the news they have long awaited: hepatitis C is a curable disease.

> **Although a patient may be cured of hepatitis C by successful therapy, that DOES NOT mean that the patient is immune from future infection by the hepatitis C virus. Should the patient be re-exposed to the virus, whether via return to high risk behaviors (as defined in Chapter 1) or inadvertent , accidental exposure, they CAN BE reinfected so vigilance in avoiding high risk behaviors must be maintained.**

The best measure of treatment success is improvement on liver biopsy. However, a follow-up liver biopsy after successful treatment is rarely performed outside of research studies. Liver biopsy is an invasive procedure with potential complications such as bleeding and infection. It is also much more costly and time-consuming to do than simple blood tests for liver enzyme levels and viral load. If the virus is undetectable and ALT levels have returned to normal, it is assumed that the biopsy will show improvement based on a large amount of information obtained from carefully controlled research studies.[54, 55]

Drug Resistance

While HCV circulates in the blood of an infected person, the virus spends most of its life inside liver cells. Once inside, HCV "hijacks" the liver cell's production equipment in order to produce more copies of itself. The rate at which a virus is able to make copies of itself is called its replication rate. HCV has an extremely high replication rate with 10^{12} (that is 1,000,000,000,000 or one trillion) virus particles produced each day in an infected person.[56, 57] With so many copies of the virus being made each day, there is some variation in the virus particles produced. Think of the replication process as a very rapid assembly line of HCV production. With the assembly line running at such a high rate of speed, mistakes are

inevitably made and the viruses produced are not perfect copies of the original. Therefore, as an HCV infection persists, several slightly different versions of the virus emerge. The process leading to these slight variations is called mutation. Mutations can prevent drugs from being effective by making the virus drug resistant. (For more information on HCV mutation see Chapter 7.1 and 7.2 *The Immune System and the Hepatitis C Virus*.)

People who are treatment-naïve have HCV mutations that are already drug resistant to current therapies. Because of the high rate of mutation and the emergence of antiviral resistant variants, hepatitis C therapy is more effective when using a combination of drugs.[45, 50 - 51] Adherence to therapy can reduce the risk for drug resistance. Emergence of antiviral resistant variants during therapy has been observed during all trials for boceprevir and telaprevir and is associated with virological failure and relapse. Because of the rapid development of resistance to DAA drugs, it is optimal to avoid missing even a single dose and to take the DAA drug on a strict schedule of every 8 hours (maximum variation of 7-9 hours). If treatment is not working, following all stopping rules for therapy is important to reduce further drug resistance.

The clinical significance of antiviral resistant variants that emerge during therapy is uncertain at this time.[58] It is not clear if viral resistance will impact future treatment options or how long they will last. Further data are needed to determine whether resistance affects future treatment choices for those with virologic failure.

Special Situations

Treatment of Acute HCV Infection

The initial phase of hepatitis C infection is called acute hepatitis C. This acute phase describes the first 6 months after HCV enters the body. Acute hepatitis C is rarely diagnosed because there are either no symptoms, or they are so mild that no medical care is sought.

The acute phase of hepatitis C infection is when most cases of spontaneous clearance occur. Spontaneous clearance refers to the immune system successfully getting rid of the virus without medical intervention. We do not know the true rate of spontaneous clearance of HCV. Many experts think it is in the range of 15% to 30%, but it may vary by age, gender, genotype, immune status, and other factors yet to be identified.

Because acute hepatitis C is so rarely encountered, large scale controlled trials to study its treatment have not been feasible. As a result, there is no currently approved therapy for acute hepatitis C. Nonetheless, both standard interferon monotherapy and pegylated interferon monotherapy have been reported to produced durable viral clearance in more than 85% of patients treated for 24 weeks.[59-61] Most experts believe that if interferon treatment is a consideration, it is advisable to wait until 8 to 12 weeks after the exposure to allow time for possible spontaneous clearance.

The role of combination therapy for the treatment of acute hepatitis C is presently unknown. Clinical trials must be conducted to determine if combination therapy is a valuable option to reduce the frequency of chronic hepatitis C.

Treatment of Chronic Hepatitis C with Normal Liver Enzymes

The treatment of people with chronic hepatitis C who have persistently normal liver enzyme levels is controversial. The question is one of risk versus benefit. If one believes that the majority of people with normal liver enzymes are (overall) not at significant risk for the development of debilitating liver disease in their lifetime, the scale tips in favor of not treating. This is because the inherent medical risks, cost, and personal toll of treatment seem unjustified in the face of a treatment that seems unlikely to benefit the patient in any substantive way. On the other hand, studies have shown that up to 10% of people with persistently normal liver enzymes have significant fibrosis on liver biopsy.[62-65] This calls into the

doubt the assumption of little risk of harm just because the liver enzyme levels are normal, and begins to tip the scale back in favor of treatment.

As one might expect, this leads one back to the gold standard of liver evaluation in people living the hepatitis C: the liver biopsy. AASLD hepatitis C treatment guidelines state that, "Regardless of the serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of comorbid conditions."[1]

Research must be conducted to look at the natural course of hepatitis C disease when ALT levels remain normal. Clinical trials are also needed to determine whether combination therapy or alternative therapeutic approaches are helpful in this situation. It is hoped that a more standardized approach will be developed for defining what normal liver enzyme levels are. This should include correction for body weight or body mass, and gender.

Treatment of Chronic Hepatitis C in Patients with Cirrhosis

Overall, there is an inverse trend between the degree of fibrosis and the probability of response to interferon-based therapy. In other words, the greater the degree of fibrosis, the lower the chance for sustained viral response. Thus, it is known that people who have developed cirrhosis are somewhat less likely to respond to pegylated interferon + ribavirin than those who have not. However, <u>many</u> people with cirrhosis are successfully treated even with cirrhosis.

In two studies using combined pegylated interferon plus ribavirin, 43% and 44% of patients with cirrhosis achieved a durable response. The studies in genotype 1 when a DAA is added to therapy have shown that up to 62% of people with advanced fibrosis/cirrhosis achieve a durable response. These study data demonstrate that patients with cirrhosis can and do benefit from state-of-the-art interferon-based therapy.[25, 34, 35, 66] This holds true even for patients who have had previous unsuccessful treatment.[67]

POTENTIAL THERAPY-RELATED COMPLICATIONS FOR PATIENTS WITH CIRRHOSIS

Patients with cirrhosis require somewhat more intensive medical supervision during treatment than those without cirrhosis. People with cirrhosis have an increased risk during treatment of developing serious bacterial infections and other liver disease complications because the liver has been damaged and may not be functioning properly. People with cirrhosis are also more likely to develop low neutrophil, platelet, or hemoglobin levels than someone without cirrhosis. Neutrophils are a type of white blood cell, and a low level makes you more susceptible to bacterial infections. A low platelet count makes it more difficult for your blood to clot normally, and may cause you to bleed and/or bruise easily. Anemia is present when the hemoglobin gets low, which can cause fatigue.

If you have cirrhosis and are undergoing treatment, it is very important that you tell your healthcare provider about any problems you experience. Your healthcare provider should check your blood counts frequently to identify potential problems and treat them early.

Treatment of Patients with HCV-Related Diseases Outside the Liver

HCV has been associated with a wide variety of diseases outside the liver including cryoglobulinemia, lichen planus, and porphyria cutanea tarda.[68, 69] All of these cause disfiguring skin problems. Cryoglobulinemia can also cause kidney, nerve, blood vessel, and other tissue damage that, in the most severe cases, may be life threatening.

If you have an immune complex disease, you may still be a candidate for interferon-based therapy. Successful treatment often results in not only HCV clearance, but also the resolution of HCV-related immune complex syndromes.

Treatment of Coinfection (Hepatitis B Virus or Human Immunodeficiency Virus)

HEPATITIS B VIRUS

Coinfection with HCV and the hepatitis B virus (HBV) increases your risk of developing cirrhosis and other liver complications compared to infection with either virus alone. There is no standard of care treatment recommendation for patients coinfection with both hepatitis B and hepatitis C. Treatment is individualized and is based on many factors, including which virus appears to be "dominant" in the liver disease process. A number of different therapies have been tried in clinical trials, including standard interferon (with and without ribavirin) and pegylated interferon (with and without ribavirin). Flares have been reported while on treatment, so close medical supervision is a must. Working with a hepatologist who has experience in the management and treatment of HBV/HCV is encouraged. In the end, you and your doctor will need to make decisions about what is best in your specific circumstance. All of the clinical trials investigating new drugs to-date have excluded people co-infected with hepatitis B.

HUMAN IMMUNODEFICIENCY VIRUS

People infected with both HCV and the human immunodeficiency virus (HIV) have more rapidly progressive liver disease compared to people infected with HCV alone.[70-73] End-stage liver disease is now a leading cause of death in the HIV+ population.[74]

As in monoinfected patients, the standard treatment choice for hepatitis C in HCV/HIV coinfected patients is combination therapy with pegylated interferon plus ribavirin. Overall, the response rate among coinfected patients is lower than among HCV-monoinfected patients.[75-77] Studies are under way with the new DAAs in combination with SOC that look promising. However, as of August 2012, neither of the new DAAs approved for HCV therapy is approved for coinfection with HIV. A low CD4 count (less than 200), high alcohol consumption (more than 1.75 ounces per day), and older age at the time of HCV infection are associated with an increased rate of progression to liver fibrosis.[69, 74, 78]

If you are living with HIV and HCV, discuss your treatment options with both a liver specialist and your HIV health care provider. While treatment is more complex and requires more intensive medical monitoring than in HCV monoinfected individuals, successful treatment has been shown to lead to significant stabilization or regression of fibrosis.[79] The new DAAs may have potential drug-drug interactions with a patient's current HIV treatment regimen. Treatment considerations will need to be discussed and evaluated with your doctors. There is also evidence that even in the absence of a sustained viral response, interferon-based treatment may lead to improvements in liver histology (fibrosis).[80] See Chapters 20.1 and 20.2, *HIV/HCV Coinfection*, for additional information about western treatment of HCV/HIV coinfection.

Possible Side Effects of Combination Therapy and Successful Management

Strong medicines such as interferon and ribavirin carry with them the possibility of some side effects. Not everyone experiences side effects. In those that do, they range from barely noticeable to severe. Many of these side effects can be managed, especially if caught early. Nonetheless, side effects are unpredictable and quite variable. With severe side effects, your doctor may need to reduce the dose of your medications. In rare cases, therapy is discontinued, but this is quite uncommon.

A few thoughts to keep in mind before you read the rest of this section:
- Because "bad news travels fast" and "no news" travels – nowhere – you are much more likely to hear about the worst case scenarios than you are the experiences of those who underwent treatment without any significant

difficulty.

- "Attending" is a psychological term that refers to how much attention or focus we devote to something. How much we "attend" to something affects how we experience it. We attend to or don't attend to literally hundreds of different thoughts, feelings, and experiences every day. For example, if you are watching an engrossing television program at the same time you are eating your dinner, you may well find that you finish your meal without even tasting it much. That is because you were attending to the television program, and not attending to the taste of your food. The same holds true for other physical experiences. If we've heard that a certain food is likely to make people feel ill, we attend to any feelings that may arise in our gut after having eaten the food with much more attention and vigor than we normally give our gut after a meal. Similarly, if we have heard horror stories about certain medications, we are more likely to experience anything remotely related to what we've heard about with greater intensity. This is not a weakness, it's just part of being human. But we are not helpless in these situations. If we are aware of how attending affects our experiences, we can often willfully damp down the attending response. This is not to say that we should not "listen" to our bodies – of course we should! But we can listen to our bodies and also be aware of the power of our attentions on our experiences.

- Thousands of people have successfully made it through interferon-based therapy.

- Adherence to therapy will influence treatment outcomes.

- The decision to undergo treatment is highly personal, and the experiences you have will be as well. A good rule of thumb is to be aware of the possibilities so that you're prepared, but to take each day as it comes.

Interferon Side Effects

Interferons all have similar side effects. The most common side effects are fever and flu-like symptoms. Other potential side effects include injection site reactions, decreased blood cell counts, hair loss, depression, and thyroid abnormalities. One of the most serious side effects of interferon is depression or the worsening of other psychiatric disorders. With the exception of hypothyroidism, virtually of all of these side effects go away after treatment has ended. Following are brief discussions of these potential side effects of interferon therapy.

FEVER AND FLU-LIKE SYMPTOMS

Up to 66% of people taking interferon experience some form of flu-like symptoms including fever, chills, fatigue, myalgia (muscle pains), arthralgia (joint pains), and weight loss. These symptoms wax and wane and usually decrease after the first two or three treatments. Taking acetaminophen or a nonsteroidal analgesic (pain medicine) such as ibuprofen or naproxen 30 to 60 minutes before your dose can further reduce these symptoms. However, you should discuss using these or any other medicines with your doctor before taking them.

Most patients prefer taking their interferon in the late afternoon or early evening so that the worst side effects occur while they are asleep. However, this must be individualized as some patients feel better taking their injections early in the morning. People have also reported that drinking at least eight 8-ounce glasses of non-caffeinated or decaffeinated beverages per day markedly reduces their flu-like symptoms. Those who have tried this approach swear by the value of increasing their fluid intake. A good rule of thumb to determine how much water you should be drinking each day is to divide your weight in pounds in half, and drink that many ounces of fluid per day. For example, a 120 pound female should drink at least 60 ounces of fluid, preferably water, per day. Good indicators that you are drinking enough fluids are clear to very pale yellow urine, and having to get up at least once during the night to urinate.

DECREASED BLOOD CELL COUNTS

Mild bone marrow suppression, especially leukopenia (a low white cell count) and thrombocytopenia (a low platelet count) can occur with interferon-based treatment. This can be easily monitored and managed.

THYROID ABNORMALITIES

Hypothyroidism among people taking interferon is usually due to stimulation of an unsuspected autoimmune thyroid disorder. This side effect of treatment can occur in 3% to 5% of patients. Hypothyroidism is managed with thyroid hormone replacement therapy. Patients may require continued thyroid hormone replacement after treatment has ended.

INJECTION SITE REACTIONS

The development of redness and warmth with or without itchiness at the injection site is a common side effect of interferon treatment. This often does not occur until 24 to 48 hours after the injection. This is a common and does not lead to complications. However, it is important to rotate injection sites in order to avoid injecting the same spot over and over again. This is particularly true with the pegylated interferons, which are absorbed more slowly and may stay in the skin for a prolonged period. Injection site reactions can take 2 to 3 weeks to clear. It is important not to inject interferon into an area that is still red from a prior injection. Repeated injections into the same area can lead to severe skin reactions including deep skin ulcers that take many weeks or months to heal.

HAIR LOSS

Limited hair loss occurs in about 20% of patients taking interferon. When it occurs, this side effect lasts only during treatment.

DEPRESSION AND PSYCHIATRIC DISORDERS

Interferon can worsen existing depression (and possibly other psychiatric disorders), and can lead to new depression among people who have not previously suffered from this condition. Studies show that about 1/3 of those on interferon therapy experience depression. Suicidal thoughts or attempts occur in less than 1% of those taking interferon.

It is very important to tell your healthcare provider if you have had any psychiatric counseling or have been dealing with depression before you consider treatment. If you have ever attempted or seriously considered suicide, you must tell your doctor. You should not be treated with interferon if you have recently struggled with thoughts of or have attempted suicide because interferon could intensify these thoughts and feelings. Once you and your healthcare provider are confident your depression is under control, you may reconsider therapy. Depression can usually be managed with counseling and/or antidepressant medications.

ANECDOTAL STORY OF SUCCESS WITH INTERFERON THERAPY DESPITE PSYCHIATRIC COMPLICATIONS

A 44-year-old female was found to have elevated liver enzymes when she donated blood in 1990. She tested positive for hepatitis C (genotype 1b) in 1992. Enzyme levels remained 1 to 2 times normal until 1998 when they were noted to be 4 to 6 times above normal. The patient had abused alcohol and used multiple oral and IV drugs until 1994. She was asymptomatic, and her physical exam was

unremarkable. She had a history of depression while actively using drugs, but no suicide attempts. A liver biopsy showed moderate activity and moderate fibrosis.

The patient was treated with pegylated interferon alfa 2b plus ribavirin for 48 weeks. Fever, decreased appetite, "weird dreams," and increased moodiness complicated the patient's therapy during the first few weeks. These symptoms resolved except for worsening mood swings. Three months into therapy, the patient was referred for psychiatric help due to decreased ability to concentrate, insomnia, excessive crying, anxiety, feelings of loss of control, and hopelessness. She was diagnosed with a mood disturbance related to interferon and started taking Xanax® and Effexor.® Because of intolerance to Effexor®, she was switched to Prozac® with occasional Xanax®. Xanax® was changed to Klonopin® to manage residual anxiety. This was later switched to Ativan® due to oversedation with the Klonopin®. The patient was also started on intensive psychotherapy to address her personal problems. She remained on Prozac® and a variety of anti-anxiety drugs throughout therapy with no more active depression. She has continued with psychotherapy since completing her hepatitis C treatment

The patient remains virus-free with normal liver enzymes for more than one year after completing therapy. Follow-up liver biopsy showed a definite decrease in activity and fibrosis.

This patient's experience demonstrates the importance of close follow-up for early recognition of the development of psychological problems. It also shows that the majority of such problems can be successfully overcome and therapy completed with the cooperation of a psychiatrist experienced in the management of interferon-related depression. This patient's experience stresses the concept that there is no simple "one drug fits all" approach to interferon-related psychiatric problems. Therapy must be individualized.

Ribavirin Side Effects

Ribavirin can lead to side effects such as cough, dyspnea (difficulty breathing), insomnia, pruritus (itching), rash, and reduced appetite (anorexia). These side effects are generally mild and usually do not require discontinuation of therapy or dose reduction. Most side effects go away over several weeks to months after stopping therapy.

Ribavirin can cause two serious side effects, hemolytic anemia and birth defects, which are discussed below.

HEMOLYTIC ANEMIA

The most common side effect of ribavirin is hemolytic anemia, which occurs in up to 54% of patients on the medication.[33] The severity of this type of anemia depends on the amount of ribavirin you are taking. Hemolytic anemia means your red blood cells are breaking down at an abnormally high rate. Red blood cells are necessary to carry oxygen from your lungs to all the tissues of the body. Anemia causes a generalized feeling of tiredness as the number of red blood cells decreases. Your blood will be checked frequently during the first few months of therapy with ribavirin to test for hemolytic anemia. Your hemoglobin should be checked at 2, 4, 8, and 12 weeks after starting therapy (at a minimum). After 12 weeks of treatment, your hemoglobin should be checked every 4 to 8 weeks. This is especially important if you are taking protease inhibitors, have coronary artery disease, or have suffered a stroke or transient ischemic attacks (TIAs) in the past.

Hemoglobin levels typically decrease by 2 to 3 grams/dL during the first 4 to 8 weeks of therapy. If your hemoglobin falls below 10 grams/dL, your healthcare provider will probably reduce your ribavirin dosage. Hemolytic anemia is the most common reason for reducing the dose of ribavirin; however, it rarely causes therapy to be stopped. Hemoglobin levels usually increase within 4 to 8 weeks of completing therapy.

If you already have severe anemia, active coronary artery disease, peripheral vascular disease, or if you cannot tolerate anemia for any other reason, you are not a suitable candidate for combination therapy.

Your healthcare provider may suggest treatment with pegylated interferon monotherapy or may advise no treatment. An injectable form of erythropoietin, a hormone produced by the body to stimulate red blood cell production, is sometimes used to counteract the effects of hemolytic anemia and enable you to complete therapy.[81-91]

ANECDOTAL STORY OF PEGYLATED INTERFERON AND USE OF ERYTHROPOIETIN TO

MANAGE ANEMIA DUE TO RIBAVIRIN

A 49 year old nurse was diagnosed with hepatitis C in 1993, two years after an accidental needle stick from a known hepatitis C patient. She also had a remote history of IV drug use in 1969. She was asymptomatic and had a normal physical exam. A liver biopsy revealed minimal nonspecific changes with no fibrosis. She had genotype 2b virus. The patient's ALT remained mildly elevated over the next six years. A repeat liver biopsy in 1999 showed the development of mild activity and moderate fibrosis.

The patient was treated with pegylated interferon alfa 2b plus ribavirin, and her hemoglobin dropped to 8.7 grams/dL. She had severe fatigue and was unable to carry out her normal work. Ribavirin was initially stopped, allowing her hemoglobin to recover to 10.4 grams/dL. Ribavirin was restarted at half dose, but her hemoglobin again fell to 8.7 grams/dL. Erythropoietin therapy was added to stimulate red blood cell production. This allowed the patient to continue ribavirin therapy and to return to work with a hemoglobin of 11.0 to 12.1 grams/dL. Three years after completion of therapy, the patient has undetectable virus and her liver enzymes remain normal.

This patient's experience demonstrates the value of working through side effects to complete treatment if early viral tests indicate that therapy is likely to be successful. It also demonstrates the usefulness of the red blood cell growth factor, erythropoietin, in increasing the hemoglobin level so that the patient was able to complete therapy.

BIRTH DEFECTS

A major concern with ribavirin therapy is its ability to cause birth defects or miscarriage. If you are a woman of childbearing age and have not had a hysterectomy, you must have a pregnancy test prior to starting therapy, and periodically thereafter. Reliable birth control is essential during therapy with ribavirin. Neither the male nor the female in a partnership can take ribavirin if the female is pregnant or could become pregnant. Ribavirin cannot be given to pregnant women, or to men or women who cannot comply with the requirement for adequate birth control for the duration of treatment and six months following the conclusion of treatment. If you are planning to have children, it is important to discuss this with your healthcare provider.

Protease Inhibitor Side Effects

Side effects occurred more frequently in patients treated with protease inhibitors (DAAs or PIs) than in those treated with pegylated interferon and ribavirin therapy alone. In the boceprevir trials, anemia and dysgeusia (metallic or bad taste in mouth) were the most common adverse events. In the telaprevir trials, rash, anemia, pruritus (itching), nausea and diarrhea developed more commonly among those who received telaprevir than SOC therapy.[43, 47] While on protease inhibitors, it is important to be closely monitored for anemia and for rash. Talk to your doctor about any symptoms so they may be addressed immediately. See more about hemolytic anemia under ribavirin side effects.

Another critical factor in the use of the new DAAs is their major interaction with many common medications which you may already be taking, either increasing or decreasing the effect of your medication or of the DAA itself. Thus is it is essential that you inform your physician of any and all medications, herbal remedies, supplements and other over the counter agents you may be taking before starting therapy and before adding

any new treatment while on triple therapy for hepatitis C.

Making Therapy Work

As discussed elsewhere in Hepatitis C Choices, the most important risk factors contributing to rapid progression of hepatitis C are being over age 40 years, being male, and drinking alcohol. Of course, you cannot change your age or sex. Therefore, the single most important thing you <u>can</u> do to slow the progression of hepatitis C is to eliminate <u>all</u> alcohol. This includes hard liquor, beer, and wine, and any products that may contain alcohol such as certain over-the-counter cough remedies, mouthwashes, and other products. Remember, even so-called nonalcoholic beer contains some alcohol.

Your liver is damaged by infection with the hepatitis C virus. It has to both fight the virus and repair itself. As discussed in other chapters in this book, a well-balanced diet will give your liver the building blocks and energy it needs to repair itself. Adequate exercise and sleep can also help the repair process and improve your immune function.

Alternative approaches to managing the symptoms of hepatitis C and the side effects associated with interferon and ribavirin treatment are discussed elsewhere in this book. It is critical to make sure your western doctor is aware of everything you are taking so that he or she can coordinate all of your medicines, including both prescription and over-the-counter medicines. This includes supplements you may be taking such as Chinese and Ayurvedic herbs, amino acids, nutritional supplements, minerals, and any other substances you are taking. In other words, to avoid drug-drug interactions you should tell your doctor about <u>anything</u> you ingest, put on your skin, inject, or in any other way introduce into your body. Your doctor must have the full picture in order to best advise you and evaluate the results of your treatment.

ADHERENCE

Adherence to interferon-based therapy can be challenging. Hepatitis C treatment requires serious commitments from both you and your healthcare provider. With interferon and ribavirin combination therapy studies have shown that if you do not take at least 80% of the prescribed interferon and ribavirin doses at least 80% of the time, your chances of long-term success are dramatically reduced.[71] Thus, the phrase "the 80-80-80 goal" was coined. Achieving the 80-80-80 goal increases the likelihood of a durable response rate. With the addition of DAAs adherence becomes even more critical and the 80-80-80 goal is no longer good enough. Anytime doses are missed or stopped, especially of the DAA, the virus can start multiplying again, and producing resistant viruses Careful attention from you and your healthcare provider to prevent and treat side effects, anticipate complications, and support one another's efforts will produce a high likelihood of success. Failure to make every effort to achieve at least the 80-80-80 goal plus the entire protease inhibitor dose described above is likely to be a fruitless exercise, wasting your effort and causing discomfort.

While this goal may sound formidable, remember, you are initially committing to only a 12-week trial of therapy. At the end of that period, it should be clear if therapy is not working and should be stopped.[25, 34, 35, 87] However, if you are responding at week 4 and/or week12, it is critical that you make every effort to complete a full course of therapy.

Studies suggest that taking full dose therapy, especially of ribavirin, during the first 12 weeks of treatment is the single most important factor in achieving a durable response.[35, 87-90] The use of substances called growth factors to stimulate the body's production of red and white blood cells is sometimes necessary to enable a person to complete a full course of adequate dose therapy.[81-84]

Reasons for Using the Allopathic Treatment Approach and Who Might Benefit

Chronic hepatitis C is often silent in the early years of infection, but eventually progresses to liver cirrhosis, liver failure, and/or liver cancer in 20% to 30% of those infected. Now that successful therapy is available, these serious consequences can be avoided in over 70% of patients. Most people infected with HCV remain asymptomatic until the disease is quite advanced. However, during this time, infected people can pass HCV on to others.

You are urged to consider combination therapy if one or more of the following circumstances applies to you.

- If you have HCV genotype 1, combination therapy should be considered because the durable response rate is greater than 70%[58] with a protease inhibitor plus pegylated interferon plus ribavirin.

- If you have HCV genotype 2 or 3, combination therapy should be considered because the durable response rate is greater than 70-80%[91] with 24 weeks of therapy with pegylated interferon plus ribavirin.

- If your liver biopsy shows stage 2 to 3 fibrosis and/or grade 2 to 4 necrosis/inflammation (see Chapter 4.1 *Liver Disease Progression*), you should consider therapy regardless of your genotype. Without treatment, you will eventually progress to cirrhosis. Almost all serious complications and deaths due to hepatitis C are related to the development of cirrhosis.

- If you have active disease, stage 4 fibrosis (cirrhosis), and your liver disease is compensated, you should consider combination therapy because if your disease cannot be stabilized, the next step is liver transplantation. Hepatitis C is currently the leading reason for liver transplantation in the United States and throughout the western world.

Reasons for Not Using the Allopathic Treatment Approach

You may wish to delay therapy if you are asymptomatic, have minimal disease on liver biopsy (stage 0-1, grade 0-1), and have no manifestations of hepatitis C outside the liver. This is particularly true if you have had the disease for over 20 years, are over 60 years of age, and/or have HCV genotype 1 or 6 (the most difficult genotypes to treat). However, even if you decide not to pursue treatment at this time, you still need regular medical follow-up and a repeat liver biopsy in 3 to 5 years to look for evidence of disease progression.

You cannot safely take interferon if you:

- have an uncontrolled psychiatric condition
- are actively using drugs or alcohol
- have severe heart disease, very low white blood cell or platelet counts, organ transplantation (except liver), and/or uncontrolled seizures

If you have decompensated cirrhosis (liver failure), you should be evaluated at a transplant center promptly to determine whether you are a candidate for liver transplantation. You may be put on carefully monitored therapy in an attempt to reduce HCV viral load prior to transplant. Because of the increased dangers of treating hepatitis C in the face of advanced liver disease, this should only be done by a very experienced hepatologist and after you have been accepted for liver transplantation should you develop liver deterioration while on therapy.

Other conditions such as uncontrolled diabetes or hypertension, moderately decreased white blood cells or platelets, uncontrolled autoimmune disease, psoriasis, and rheumatoid arthritis may make interferon treatment unsafe. Your doctor will advise you of the relative safety of interferon treatment if you have one or more of these conditions.

Pregnant women and women of childbearing age who do not use a reliable form of birth control cannot take ribavirin due to the risk of birth defects. Because ribavirin is cleared from the blood by the kidneys, patients on hemodialysis or

with end-stage renal failure cannot take ribavirin. Severe anemia (hemoglobin less than 11gm/dL), hemoglobinopathies, or other conditions in which anemia can be dangerous may make it unsafe to take ribavirin.

Marked obesity (BMI >35) will also decrease your chances of responding to therapy. If your evaluation indicates you are in the early stages of hepatitis C (stages 0-2, grades 0-2) you may benefit by first attempting to lose 5-10% of your body weight in order to increase the likelihood of a positive response to therapy. This should be discussed with your physician before initiating treatment.

What You Need to Know Regarding Therapy

There are a number of things you and your doctor need to know about your situation before you decide to begin interferon-based therapy and at various stages of treatment once it has begun. Most of this information can only be gained through testing.

Before Starting Therapy

Before therapy begins, you will need to have the following tests, and discuss these aspects of your medical history.

- HCV genotype and HCV RNA
- liver biopsy grade (inflammation/necrosis) and stage (fibrosis)
- hemoglobin level
- white blood cell count with neutrophil count
- platelet count
- cryoglobulin level
- thyroid stimulating hormone (TSH) level to check thyroid status
- electrocardiogram (EKG) if you are over 50 years of age
- presence or absence of other liver diseases (for example, hepatitis B, HIV, alcoholic liver disease, etc.), autoimmune diseases, heart or kidney disease, seizure disorder, diabetes, and/or severe lung disease
- presence or history of any psychiatric disorder, especially depression or suicidal thoughts; psychiatric consultation may be required if one of these is present
- pregnancy or ability to become pregnant and the use of appropriate means to prevent pregnancy

During Therapy

During therapy, the following tests need to be done.
- complete blood count (CBC) and differential cell count (neutrophils) at 2, 4, 8, and 12 weeks, and then every 4 to 8 weeks until therapy is completed
- ALT levels are usually checked at the same time points as your CBC
- HCV RNA at week 4, 8 (when taking boceprevir),12, 24 and end of treatment
- TSH (thyroid stimulating hormone) at 12, 24, and 48 weeks
- a standardized test for depression (for example, Beck's Inventory or the Hospital Anxiety/Depression Index) as well as a clinical evaluation for depression at the time of each visit to screen for the development of psychological problems

You must eliminate <u>all</u> alcohol and strive to take more than 80% of your prescribed protease inhibitor, interferon and ribavirin doses more than 80% of the time in order to have the best chance of achieving a durable response.

After Therapy

If your HCV viral load is negative at the end of treatment, the following tests need be done after therapy is completed.

- ALT at 4, 12, 24, and 48 weeks
- HCV viral load at 12, 24, and 48 weeks, or at any time your ALT becomes elevated
- yearly tests after these time points

If you have detectable virus at the end of treatment, or if the virus becomes detectable again after the completion of treatment, see Chapter 8.3 , *Options When Initial Treatment Fails to Clear the Hepatitis C Virus,* for additional treatment options.

Summary

Many people are candidates for interferon-based treatment of chronic hepatitis C. You may be a candidate for therapy if you have an elevated ALT, other conditions related to your HCV infection, a detectable HCV viral load, and/or chronic inflammation or fibrosis on liver biopsy. Currently, the best initial treatment for chronic hepatitis C, genotype 1, is boceprevir or telaprevir plus pegylated interferon plus ribavirin. This combination has resulted in a sustained response in 63% to 75% of patients studied in clinical trials. The best initial treatment for chronic hepatitis C, genotype 2 or 3, is pegylated interferon plus ribavirin. This combination has resulted in a sustained response in 70%-80%of patients studied in clinical trials.[43, 44]

Therapy for hepatitis C is rapidly changing but the primary goals of eliminating the virus, improving quality of life, and alleviating the effects of HCV infection on the liver and other organs remain the same. In this rapidly changing environment, the recommendations for therapy will probably change every few years. If you are not a candidate for combination therapy, you may be a candidate for new therapies in development. It is expected that new approaches will provide more effective therapy for the majority of people infected with hepatitis C. See Chapter 8.4 *The Future of Allopathic Treatment of Chronic Hepatitis C.*

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