Options When Initial Treatment Fails to Clear HCV

Introduction

Prior to May of 2011, the standard for initial treatment of chronic hepatitis C was the combination of peginterferon plus ribavirin for all genotypes. Despite the success of peginterferon/ribavirin treatment, approximately 20% of patients infected with HCV genotypes 2 or 3 and over 50% of patients infected with HCV genotype 1 did not clear HCV. Since sustained viral response (SVR) after interferon-based treatment is much lower in patients with genotype 1 HCV compared to genotypes 2 and 3, most patients remaining infected after an initial course of therapy are infected with genotype 1 HCV.

Options for Retreatment

Options for retreatment and management of patients who did not clear HCV with an initial course of peginterferon/ribavirin treatment are the key issues addressed in this chapter. In May 2011, two protease inhibitors, telaprevir and boceprevir, were FDA-approved, in combination with peginterferon/ribavirin (triple therapy), for retreatment of patients remaining infected with HCV genotype 1. These protease inhibitors also have some activity against HCV genotype 2, no activity against HCV genotype 3 and reduced activity against other HCV genotypes. Triple therapy is only approved for treatment or retreatment of HCV genotype 1. For these reasons, HCV genotype and type of prior treatment dictate your choices for retreatment. If you are infected with HCV genotype 1 and were initially treated with any interferon-based regimen, you should consider retreatment with a protease inhibitor plus peginterferon plus ribavirin. If you are infected with HCV genotype 2 or 3 and were initially treated with nonpegylated interferon with or without ribavirin, or peginterferon alone, you should consider retreatment with peginterferon plus ribavirin. If you are infected with HCV genotype 2 and were previously treated with peginterferon/ribavirin, then retreatment with triple therapy could be considered, but triple therapy is not FDA-approved for HCV genotype 2. If you are infected with HCV genotype 3 and were previously treated with peginterferon/ribavirin you will need to wait for future treatments or participate in a clinical trial.

<table>
<thead>
<tr>
<th>TABLE 1: OPTIONS FOR RETREATMENT</th>
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<tbody>
<tr>
<td>HCV GENOTYPE</td>
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<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td></td>
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<tr>
<td>3,4,5,6</td>
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IFN (interferon); RBV (ribavirin)

*NOT FDA-APPROVED FOR NON-1 GENOTYPES OF HCV.
Categories Of Response To Prior Treatment

A key issue, as you contemplate retreatment with triple therapy, is how well you responded virologically (drop in HCV RNA) and tolerated a prior course of treatment. More than 50% of people with chronic hepatitis C infected with HCV genotype 1 and 20% infected with HCV genotypes 2 or 3, who were treated with peginterferon/ribavirin, do not clear the hepatitis C virus (HCV) from their bodies. Virologic response during a prior course of therapy is assessed by the change in HCV RNA during the first 12 weeks of treatment. The likelihood that you will respond to retreatment is related to your virologic response to prior therapy (See Table 2) – relapse has the best chance for cure with retreatment while null response is least likely to be cured by retreatment with triple therapy.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION OF VIROLOGIC RESPONSE</th>
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<tbody>
<tr>
<td>RELAPSE</td>
<td>UNDETECTABLE HCV RNA DURING TREATMENT RECURRENCE OF POSITIVE HCV RNA AFTER TREATMENT</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>HCV RNA DROPPED AT LEAST 100-FOLD DURING TREATMENT</td>
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<td></td>
<td>HCV RNA ALWAYS POSITIVE DURING AND AFTER TREATMENT</td>
</tr>
<tr>
<td>NULL RESPONSE</td>
<td>HCV RNA DROPPED LESS THAN 100-FOLD DURING TREATMENT</td>
</tr>
<tr>
<td></td>
<td>HCV RNA ALWAYS POSITIVE DURING AND AFTER TREATMENT</td>
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Stage Of Fibrosis

Chronic hepatitis C induces an inflammatory response and accumulation of fibrosis in the liver, which ultimately lead to progression to cirrhosis. Fibrosis impairs hepatic function and alters the portal circulation, which then manifests as the classic clinical features of cirrhosis – varices, ascites, and encephalopathy.

<table>
<thead>
<tr>
<th>STAGE OF FIBROSIS</th>
<th>LIKELIHOOD OF SVR</th>
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<tbody>
<tr>
<td>F0- F2</td>
<td>HIGH</td>
</tr>
<tr>
<td>F3 (BRIDGING)</td>
<td>INTERMEDIATE</td>
</tr>
<tr>
<td>F4</td>
<td>LOW</td>
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</table>
Severity of fibrosis (stage) is determined by liver biopsy. As shown in table 3 above, the stage of fibrosis on liver biopsy also defines your chances for success when retreated with triple therapy in the case of HCV genotype 1, or peginterferon/ribavirin in the case of HCV genotypes 2 or 3. Rates of SVR are highest in patients with minimal fibrosis (F0 – F2), and lowest in patients with cirrhosis (F4).

**Tolerability**

Another key issue is your ability to tolerate the side effects of the peginterferon/ribavirin backbone of triple therapy. After all, you have had previous experience with an interferon-based regimen; otherwise, you would not be reading this chapter! How well you can tolerate retreatment with triple therapy is related, at least in part, to how well you tolerated your prior course of interferon-based treatment. If you could not tolerate full doses of interferon, peginterferon, or ribavirin, in your prior course, you are not likely to tolerate full doses in retreatment. Dose reductions in peginterferon, or ribavirin during triple therapy may compromise your chance to be cured by retreatment with triple therapy.

To summarize, the five factors that determine retreatment are:

- HCV genotype
- Type of prior treatment
- Virologic response to prior treatment
- Stage of fibrosis
- Your ability to tolerate peginterferon/ribavirin

As a patient contemplating retreatment, your questions may be, “Should I be retreated? If I should be retreated, with what?” In addressing these questions, this chapter covers the following topics:

- The goals of retreatment
- Candidates for retreatment
- Success of retreatment
- Monitoring disease progression
- Reducing risk for liver cancer
- Screening for liver cancer
- Options if not retreated

**The Goals Of Retreatment**

The main goal of retreatment is to clear HCV from your body – remaining free of HCV, defined by undetectable HCV RNA, during and after completion of treatment, equates with cure! Clearing HCV from your body is the one sure way to reduce progression of liver disease and decrease your risk of complications including hepatocellular carcinoma (liver cancer).

Successful retreatment with achievement of SVR will:

- clear HCV from your body
- reduce your risk for progression to cirrhosis
- reduce your risk for clinical complications of liver disease
- reduce the risk of liver cancer (also known as hepatoma, hepatocellular carcinoma, and HCC)
SUSTAINED VIROLOGIC RESPONSE (SVR) is the primary goal of treatment. SVR is defined by undetectable levels of HCV RNA in your blood during treatment and for 12 weeks (SVR12) or more (SVR24) after completion of treatment. SVR 12 and SVR 24 are nearly identical – FDA now considers SVR12 when evaluating efficacy of new drugs and clinical trials for treatment of HCV. SVR equates with elimination of HCV from your body and cure of the infection. Clearing HCV is the only sure way to slow or halt disease progression in patients with chronic hepatitis C.

HCV RNA — The most common test used to measure viral load, HCV RNA, is the polymerase chain reaction (PCR) assay. Sustained viral clearance means HCV RNA is undetectable in the blood for three months or more after completing a course of antiviral therapy. Clearance of HCV RNA from the blood is usually accompanied by clearance of the virus from the liver. This is known as a virologic cure. A virologic cure is assumed to occur when a person maintains a sustained response for at least three months following completion of therapy. A small percentage of people (less than 1%) who have a sustained response may relapse, meaning the virus becomes detectable again. This usually occurs within a year of completion of therapy.13

Candidates For Retreatment

HCV Genotype 1: Retreatment With Triple Therapy

Four factors determine whether your doctor would recommend retreatment with triple therapy:

- Your category of response during a prior course of peginterferon/ribavirin (relapse, partial, null)
- Stage of fibrosis (no cirrhosis versus cirrhosis)
- Severity of liver disease (compensation versus decompensation)
- Your ability to tolerate peginterferon/ribavirin (side effects, adverse reactions)

PROTEASE INHIBITORS

Protease inhibitors (PI) target the HCV NS3/4a protease enzyme. The protease enzyme plays an important part in HCV reproduction. The virus uses it as a scissor, 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 scissor blades prevents cutting.

TREATMENT CANDIDATES

The best candidate for retreatment with triple therapy is a patient who relapsed after peginterferon/ribavirin, has minimal fibrosis, and tolerated the side effects of interferon well during the prior treatment. When retreated with triple therapy, this individual would have an 80 to 90% chance for SVR and cure! The candidate least likely to benefit from retreatment with triple therapy is one who had a null response to prior peginterferon/ribavirin, has cirrhosis or clinical complications of advanced liver disease, and is poorly tolerant of peginterferon/ribavirin. When retreated with triple therapy, this individual would have less than a 15% chance for SVR!

If you have features intermediate between the two extreme examples describe above, you would have intermediate chances to achieve SVR and cure. In the REALIZE trial of telaprevir-based retreatment, SVR ranged from 84% to 87% for relapers regardless of stage of fibrosis! In contrast, in the same trial, rates of SVR in partial responders to a prior course of peginterferon/ribavirin were influenced by stage of fibrosis. SVRs were 77% in patients with F0-F2, 56% in F3, and 34% in F4 (cirrhosis) (Figure 1).14, 15
When you are retreated your doctor will monitor your HCV RNA levels to determine if you are responding to retreatment. Rapid and sustained declines in HCV RNA are the best indicator of whether you will be cured by retreatment. Table 4 lists some of the terms used to describe your virologic response to retreatment with triple therapy.

**TABLE 4: VIROLOGIC RESPONSES DURING RETREATMENT WITH TRIPLE THERAPY**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Viral Response (RVR)</td>
<td>Undetectable HCV viral load by week 4 of therapy</td>
</tr>
<tr>
<td>Extended RVR (eRVR)</td>
<td>Undetectable HCV RNA from weeks 4 through 12 of telaprevir-based triple therapy; or from weeks 8 through 24 of boceprevir-based triple therapy. With telaprevir, relapsers without cirrhosis who achieve eRVR may stop treatment at week 24. All other treatment-experienced patients with undetectable HCV RNA at week 24 receive a total of 48 weeks of treatment. With boceprevir, response-guided therapy is used. Patients with eRVR may stop triple therapy at week 36. All other responders receive a total of 48 weeks of treatment.</td>
</tr>
<tr>
<td>Early Viral Response (EVR)</td>
<td>100-fold or greater drop in HCV RNA by week 12 of therapy</td>
</tr>
<tr>
<td>Partial Early Virologic Response (pEVR)</td>
<td>Greater than 100-fold decline in HCV RNA by week 12 but HCV RNA is persistently positive throughout the course of treatment</td>
</tr>
<tr>
<td>Sustained Viral Response 12 (SVR12)</td>
<td>Undetectable HCV RNA at 12 weeks after the completion of treatment</td>
</tr>
<tr>
<td>Sustained Viral Response (SVR24)</td>
<td>Undetectable HCV RNA at 24 weeks after the completion of treatment</td>
</tr>
</tbody>
</table>
Treatment-naïve patients who achieve eRVR receive a shortened duration of triple therapy, either 24 weeks (telaprevir-based) or 28 weeks (boceprevir-based). However, in treatment-experienced patients other factors override the eRVR rule. (Figure 2)

**FIGURE 2: TELAPREVIR TREATMENT ALGORITHM – TREATMENT NAÏVE**

<table>
<thead>
<tr>
<th>Triple therapy with TPV+P+R for 12 weeks</th>
<th>eRVR HCV RNA negative at weeks 4 and 12</th>
<th>Additional 12 weeks of P+R treatment * (24 weeks total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA is quantified at weeks 4, 8, 12 while the patient is taking TPV — to evaluate for viral response and resistance</td>
<td>No eRVR Slow Responder</td>
<td>Additional 36 weeks P+R treatment (40 weeks total)</td>
</tr>
<tr>
<td>TPV is stopped if there is evidence of rebound in HCV RNA</td>
<td>All treatment is discontinued if HCV RNA &gt; 1000 IU mL at week 4 or 12 or detectable at week 24</td>
<td></td>
</tr>
</tbody>
</table>

"Consider extending P+R for an additional 36 weeks in patients with cirrhosis (FDA)"

With retreatment using telaprevir-based therapy, treatment duration is shortened to 24 weeks only in patients without cirrhosis who achieve eRVR and who had relapsed after a prior course of peginterferon/ribavirin. All other treatment-experienced patients, who are HCV RNA negative at week 24 receive a total of 12 weeks of telaprevir and 48 weeks of peginterferon/ribavirin. (Figure 3)
FIGURE 3: TELAPREVIR TREATMENT ALGORITHM – TREATMENT EXPERIENCED

With retreatment using boceprevir-based therapy, patients achieving eRVR receive a total of 36 weeks of treatment – 4 weeks of Lead-In with peginterferon/ribavirin and 32 weeks of triple therapy. Patients with cirrhosis or those who were prior null responders to peginterferon/ribavirin or poor responders during Lead-In should receive 48 weeks total, 44 weeks of triple therapy. Patients without eRVR but who have undetectable HCV RNA at treatment week 24 receive a total of 48 weeks of treatment – 4 weeks of Lead-In with peginterferon/ribavirin and 44 weeks of triple therapy.
**FIGURE 4: BOCEPREVIR TREATMENT ALGORITHM – TREATMENT NAIIVE**

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

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

<table>
<thead>
<tr>
<th>BOC</th>
<th>boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>pegylated interferon</td>
</tr>
<tr>
<td>R</td>
<td>ribavirin</td>
</tr>
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\( (eRVR) \) Extended RVR - Undetectable HCV RNA at week 4 and through week 12 of therapy
HCV RNA at weeks 4, 8, 12, 24 while the patient is taking BOC — to evaluate for viral response and resistance.

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

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

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

*Patients with cirrhosis, prior null response, or poor responders are considered for 44 weeks BOC+P+R, regardless of eRVR during Lead-in.

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<td>R</td>
<td>ribavirin</td>
</tr>
<tr>
<td>(eRVR)</td>
<td>Extended RVR - Undetectable HCV RNA at week 4 and through week 12 of therapy</td>
</tr>
</tbody>
</table>
HCV Genotypes 2,3,4,5, 6: Retreatment With Peginterferon/Ribavirin

PROTEASE INHIBITORS

There is no FDA-approved retreatment regimen for HCV genotypes 2,3,4,5,6. Some studies have suggested that HCV genotype 2 might be susceptible to telaprevir. So retreatment using telaprevir-based triple therapy might be considered – however, remember that the FDA has not approved triple therapy for this circumstance and use of triple therapy in this setting would be considered off-label. Genotype 3 is resistant, and genotypes 4, 5, and 6 are less responsive to telaprevir and boceprevir. Triple therapy should not be used to retreat genotypes 3 through 6.

PEGINTERFERON/RIBAVIRIN

You and your doctor might consider retreatment with peginterferon plus ribavirin if:
- you did not receive full doses of peginterferon plus ribavirin during the initial therapy, or
- you had side effects that led to discontinuation, which might now be better tolerated or manageable with supportive care and treatments, or
- you relapsed after a short duration of treatment and want to consider a longer duration of treatment, or
- you had decreases in blood counts that lead to decreases in peginterferon or ribavirin and no growth factors were used to support the blood counts

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</tr>
<tr>
<td>Complete Early Virologic Response (cEVR)</td>
<td>Undetectable HCV RNA at week 12 of therapy</td>
</tr>
<tr>
<td>End of Treatment Response (ETR)</td>
<td>Undetectable HCV RNA at the end of the therapy period</td>
</tr>
<tr>
<td>Sustained Viral Response 12 (SVR12)</td>
<td>Undetectable HCV RNA at 12 weeks after the completion of treatment</td>
</tr>
<tr>
<td>Sustained Viral Response (SVR24)</td>
<td>Undetectable HCV RNA at 24 weeks after the completion of treatment</td>
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</table>

Issues In The Retreatment Of HCV Genotype 1

As stated above, the probability that retreatment will clear HCV is affected by the type of prior treatment, your personal characteristics, stage of fibrosis, and viral characteristics. The impact of your response to prior peginterferon/ribavirin and stage of fibrosis on your chances to be cured by retreatment with triple therapy is shown in Figure 1. You are much more likely to be cured by retreatment with triple therapy if your prior treatment response was relapse or partial response and you have only F0 – F2 stage of fibrosis.
If you had a null response during a prior course with peginterferon/ribavirin your chance for SVR and cure when retreated with triple therapy is only about 30%. SVR in persons with prior null response is further influenced by severity of fibrosis. Patients with prior null response to peginterferon/ribavirin and F0-F3 fibrosis have over a 40% chance for SVR, but patients with F4 fibrosis (cirrhosis) and prior null response have only a 15% chance for SVR (Figure 1).

**Side Effects Of Triple Therapy**
You may experience side effects from any or all of the drugs in the Triple Therapy regimen.

**WARNING:** The doses of telaprevir or boceprevir should never be reduced due to risk of emergence of viral resistance to these and related protease inhibitors. When side effects cannot be managed by other strategies, it may be necessary to discontinue telaprevir or boceprevir. In a patient with virologic response who discontinues telaprevir or boceprevir due to side effects, peginterferon/ribavirin may still be continued.

**Peginterferon and Ribavirin**
Peginterferon side effects include flu-like symptoms, mood disorder, depression, cytopenias (lowering of white blood cells, red blood cells (anemia), and platelets) and risk for infection. Ribavirin side effects include breakdown of red blood cells (hemolytic anemia), rash, and worsening of peginterferon side effects. Other rare reactions can include pulmonary, renal, cardiac, neurologic illnesses and exacerbation of underlying conditions such as autoimmune disease, thyroid disease, arthritic conditions and dermatologic conditions.

**Boceprevir**
**Anemia** — Anemia is common during boceprevir treatment – you are likely to need some type of treatment or intervention for anemia. There are three methods for managing anemia during treatment – reducing ribavirin dose, transfusion of red blood cells, or adding erythropoietin analogue (EPO) typically by weekly subcutaneous injections. In the clinical trials, nearly half of the patients who received boceprevir were treated with erythropoietin analogue (EPO). Although anemia sufficient for institution of therapy with erythropoietin analogue was common, discontinuation due to anemia was uncommon.

**Other** — While taking boceprevir, you may also experience dysgeusia, the medical term for “foul taste in mouth”. Although this symptom is annoying it rarely leads to discontinuation of therapy. Boceprevir is not associated with rash or anal pain.

**Telaprevir**
**Anemia** — Similar to boceprevir treatment, you are likely to experience anemia during telaprevir treatment. However, the period of anemia attributable to telaprevir is much shorter in duration since telaprevir is only given for 12 weeks. During the first 12 weeks of telaprevir-based Triple Therapy, anemia is more severe than the anemia that occurs when peginterferon/ribavirin is used without telaprevir. After the first 12 weeks, the incidence and severity of anemia due to telaprevir wears off - the subsequent anemia is that due to peginterferon/ribavirin. If you experience significant anemia during telaprevir treatment your doctor may choose to manage it primarily by dose reduction of ribavirin. This was the strategy used in the clinical trials of telaprevir. After the first 12 weeks, if anemia occurs during peginterferon/ribavirin, your doctor may choose ribavirin dose reduction, blood transfusion, or erythropoietin analogue. Rarely, you may require all three approaches to manage anemia during Triple Therapy.

**Rash** — You have about a 50% chance of developing skin rash during telaprevir-based treatment; the rash is mild in most cases but occasionally can be moderate or severe. In the clinical trials, telaprevir was discontinued in 5% to 7% of patients due to moderate to severe rash. In most cases, peginterferon/ribavirin was continued so that
only 0.5 to 1.4% of patients discontinued all treatment due to rash.\textsuperscript{5,18,19} Rash, when it occurs, typically occurs after at least 8 weeks of treatment. As shown in the ADVANCE trial, 8 weeks of telaprevir be a sufficient duration of treatment for most patients to achieve SVR. So, if you develop a rash, neither the rash nor its management reduces your chance to achieve SVR.

If your rash is mild your treating physician may recommend topical steroids, such as triamcinolone ointment, moisturizing lotions, and antihistaminics, such as hydroxyzine. If the rash involves your mouth, eyes, or internal surfaces or you have low blood pressure, swelling of tissues, or asthma-like findings on lung exam, telaprevir must be stopped immediately. A specific skin reaction, called DRESS (drug reaction with eosinophilia and systemic symptoms), is another indication to stop telaprevir. If you experience a severe rash, you may even need to be admitted to hospital and receive fluids and, potentially, high-dose oral or intravenous steroids.

**ANAL PAIN** — Anal pain, with a burning quality, is a peculiar and very annoying side effect of telaprevir. Although annoying, anal pain rarely leads to discontinuation of treatment. The cause is unknown. Treatment may require topical analgesics, suppositories, stool softeners, or medications.

**Monitoring Disease Progression**

If viral clearance cannot be achieved, the secondary goals of treatment are to reduce the extent of liver damage, slow disease progression, and reduce the risk of complications.

If you are still infected with HCV despite courses of treatment, you are at risk for disease progression and should be monitored. If you experience deterioration in liver function tests (bilirubin, albumin, INR, platelet count) you should consider evaluation by specialists in digestive (Gastroenterologists) and liver (Hepatologists) diseases – if the deterioration is severe you may need referral to a center specializing in liver diseases and transplantation. Clinical information, laboratory tests, and/or liver biopsy results define the progression of liver disease. See Chapter 5, *Signs & Symptoms that May be Associated with Hepatitis C* and Chapter 6, *Laboratory Tests and Procedures* for further explanation of the following criteria that point toward disease progression.

**Clinical Criteria**

- ankle edema
- ascites
- encephalopathy
- gastrointestinal bleeding from varices
- skin manifestations (spider telangiectasia, palmar erythema)
- varices

**Blood Tests**

- increased bilirubin
- increased prothrombin time
- reduced albumin
- reduced platelet and/or neutrophil count
Liver Biopsy Findings
- increased fibrosis
- development of cirrhosis

Despite increased awareness of the potentially serious consequences of hepatitis C, many people ignore warning signs and see their healthcare provider only when they already have late stage disease. Unfortunately, it is more difficult to treat people with late stage disease using interferon-based therapy. Patients who present to their doctor late in the course of the disease may progress to liver failure and may ultimately need a liver transplant.

SVR Slows Disease Progression
Achieving SVR halts disease progression. Numerous studies have looked at the changes in fibrosis and inflammation of the liver following a course of antiviral therapy with interferon monotherapy, peginterferon monotherapy, or peginterferon plus ribavirin combination therapy. Overall, they show an improvement in inflammation and fibrosis in those that achieve an SVR, a smaller benefit to patients who relapse following a course of therapy, and an uncertain benefit to those who are null responders. The HALT-C trial showed in patients with advanced fibrosis who had achieved an SVR a reduction in death/liver transplant and liver-related morbidity/mortality. However, those patients remained at risk for HCC. In people with cirrhosis, a long-term follow-up study shows that achievement of SVR prevents the development of esophageal varices (0% in SVR vs 32% in untreated patients over 12 years of follow-up).

Maintenance therapy with low-dose peginterferon is ineffective in slowing disease progression. The primary goal of the NIH-sponsored HALT C trial was to determine if maintenance therapy with pegylated interferon alfa-2a could halt disease progression in people with chronic hepatitis C. All HALT C participants (1,050 patients) experienced prior treatment failure with peginterferon/ribavirin and had biopsy proven advanced fibrosis (F3 to F6, Ishak staging). Approximately 60% had bridging fibrosis and 40% had cirrhosis. Ninety-four percent had HCV genotype 1.

This treatment also had no effect on clinical outcome in the HALT C trial. In other words, there was no significant difference in the rate of death, liver transplantation, liver cancer, or liver failure between the maintenance therapy group and the control group. Although there was a trend toward reduced adverse clinical outcomes in patients with marked reduction in HCV RNA during initial treatment with peginterferon/ribavirin, overall, there was no significant relationship between viral reduction and clinical outcome.

The results do not support a recommendation for maintenance therapy with low-dose peginterferon for treatment-experienced patients.

Reducing The Risk Of Liver Cancer
Achieving SVR may reduce your risk for future development of liver cancer. Among people with chronic hepatitis C, the risk of liver cancer is greatest in those with cirrhosis. Screening tests for liver cancer often include twice-yearly blood tests for alpha-fetoprotein and radiologic imaging of the liver (usually ultrasonography or ultrasonography alternating with CT).

Despite aggressive screening efforts, at least one-third of liver cancers are not detected in the early stages of the disease. Later stage tumors cannot be cured, but palliative procedures (TACE, RFA) may provide some extension of survival.

A recent review of 20 studies with (4700 patients with cirrhosis) was done to look at the effect of antiviral therapy on the risk of developing liver cancer. Fourteen (n=3310) of the studies showed a reduced risk of liver cancer in patients...
who achieved an SVR compared to nonresponders. Four studies found that maintenance interferon in previous nonresponders failed to reduce risk. Cancer risk is also related to stage of liver fibrosis. The risk is lowest but not eliminated in patients with minimal or no fibrosis. Risk is highest in patients with cirrhosis.

A study from Japan examined the recurrence of HCC and SVR. SVR failed to reduce the incidence of an initial or first recurrence, but did lower rates for subsequent HCC recurrence. In addition, SVR was associated with better survival. Other studies have suggested, but not proven, that interferon may slow the growth or metastatic spread of existing liver cancer. Detection of slow-growing cancers at an early stage of disease can allow for effective and possibly curative therapies such as liver transplantation. Since urgent transplantation may be required for cure, living donor liver transplantation may be of particular benefit for people with liver cancer – this type of liver transplantation can be performed within a short period of time from the diagnosis of cancer.

**Screening For Liver Cancer**

Because chronic hepatitis C increases your risk for liver cancer, screening is recommended for people with advanced fibrosis or cirrhosis. However, there are no screening guidelines with which everyone agrees. A recently published large study out of Japan has shown that achieving an SVR does not eliminate the risk for liver cancer, even in those with mild fibrosis. This study recommends patients with and SVR be monitored for more than 10 years after completion of therapy for HCC.

Liver cancer can be effectively treated if detected early. For this reason, I recommend that people with bridging fibrosis or cirrhosis have ultrasonography (or ultrasonography alternating with CT) of the liver and an alpha-fetoprotein blood test every six months. A persistent, progressive rise in alpha-fetoprotein levels or the development of a new liver mass indicates the need for additional tests. These tests might include special radiologic studies. Rarely is a biopsy of the mass required. If liver cancer is diagnosed, it may be treated with nonsurgical approaches (TACE, RFA), surgery, or liver transplantation. Sorafenib is FDA-approved for the treatment of liver cancer not treatable by other modalities.

**Options If You Are Not A Candidate For Retreatment**

Despite many advances in antiviral treatment for HCV, some people decide against retreatment with currently available combination therapies. They may choose different therapies or decide not to wait for future treatment options. Alternatives to interferon-based retreatment protocols include:

- clinical trials
  - protease, helicase, NS5a, or polymerase inhibitors
  - new interferons (Albuferon®, continuous infusion pumps, others)
  - therapeutic vaccines
- wait for future treatment options

Factors such as religious beliefs, lifestyle, lack of financial resources or health insurance coverage, and/or health conditions that might make undergoing existing interferon-based treatment difficult can affect the decision each person makes.

**Clinical Trials** — If you are being treated at a major teaching hospital and/or by a hepatitis C specialist, you may have access to any of a number of clinical trials. Some of these trials will study new formulations of standard interferon and other antiviral agents. Others will be looking at completely new drugs or approaches to the treatment of hepatitis C. Talk with your doctor about which of these trials might be available and appropriate for you. The Internet is a good source of information about clinical trials. Check the Resource Directory at the back of this book for Internet addresses.
Future Treatments — Many new drugs are under development and preliminary evaluation suggests that they may have a therapeutic role in the management of those who do not respond to current therapies. These options may include new interferons, new methods for administering interferons, second generation protease inhibitors, polymerase inhibitors, additional agents targeting other molecular sites of HCV, therapeutic vaccines, and others. See Chapter 8.4, Western (Allopathic) Medicine: The Future of Allopathic Treatment for Hepatitis C for additional information about emerging therapies.

Summary
This chapter addresses several important clinical issues for an increasingly large population of patients with chronic hepatitis C — those in whom treatment failed to clear HCV. For people with genotype 1, there are two new treatment options — boceprevir-based triple therapy and telaprevir-based triple therapy. For those with genotype 2 or 3 you have been provided with information to help you determine if you should consider retreatment with pegylated interferon plus ribavirin. The goals of retreatment are to clear virus, slow disease progression, and reduce the risk of liver cancer. This chapter identifies criteria for selection of patients for retreatment and provides definitions for response. Studies are summarized that provide information on expected response rates should you elect to undergo retreatment with interferon-based therapy with or without a protease inhibitor.

New drugs, such as second generation protease- or polymerase-inhibitors, may improve the chances for treatment-experienced patients to clear HCV. Many clinical trials are ongoing at the time of this writing.

If you have advanced fibrosis or cirrhosis, even if you clear HCV with retreatment, you must have regular clinical follow-up to monitor for liver decompensation, liver failure, and the development of liver cancer.

References


