

# Therapy for Chronic Viral Hepatitis

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## ABSTRACT

*Chronic hepatitis due to hepatitis B virus (HBV) or hepatitis C virus (HCV) is still a major problem in terms of progressive liver damage, prevention and therapy in most parts of the world. Unfortunately, to date, there is still no specific and effective therapy for HBV. No therapy can be given to carrier, non-replicative and asymptomatic patients of chronic HBV infection. Lamivudine or alpha-interferon can be used for treatment of compensated, chronic hepatitis B infection with significant increase of aminotransferase. Approximately 40 % of patients can have seroconversion with this form of therapy. Chronic hepatitis D virus infection can be treated with alpha-interferon and in the final stage, may undergo liver transplantation. For chronic hepatitis C virus infection, alpha-interferon with ribavirin have been shown to have a better efficacy than alpha-interferon alone where the efficacy can reach 39 – 49 %.*

**Key words:** Hepatitis, interferon, lamivudin, ribavirin.

## INTRODUCTION

Chronic hepatitis is a liver disease in the form of continuous inflammation and necrosis for at least 6 months.<sup>1</sup>

There are many causes of chronic hepatitis, including genetic disorders, drugs, toxins, autoimmune, idiopathic; but the most common cause is viral. The virus that causes chronic viral hepatitis is the hepatitis B virus (HBV), hepatitis C virus (HCV), as well as hepatitis D virus (HDV) together with hepatitis B.<sup>2</sup>

Chronic viral hepatitis is the most common cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma in the world, and is currently the main reason for liver transplantation in adults.<sup>2</sup> There is not yet an ideal therapy for chronic viral hepatitis since there is still no specific medication that can produce satisfactory results.<sup>3</sup>

Management of chronic viral hepatitis is focused on HBV, HCV, and HDV, since these viruses most commonly cause chronic viral hepatitis. The use of interferon separately or in combination with ribavirin currently predominates therapy for chronic hepatitis due to hepatitis B, C and D virus, besides the use of Lamivudin for the therapy of chronic hepatitis due to hepatitis B virus. Several other anti-virus medications have been tested, but results so far have been unsatisfactory, for reasons discussed below.

## DISCUSSION

Antiviral therapy for chronic hepatitis is aimed at eradication of the virus and initiating remission.<sup>4</sup> To reach this aim, therapy must be administered as soon as possible before decompensated liver disorder ensues.

### Therapy for Chronic Hepatitis B Virus (HBV)

To date, there is still no specific and effective therapy for chronic HBV. Therapy of patients is mostly aimed at preventing further liver injury.<sup>2</sup>

Management of chronic hepatitis HBV depends on the replication rate of the virus. No therapy is given to carrier non-replicative and asymptomatic HBV.<sup>5</sup>

The form of therapy for HBV permitted by The Food and Drug Association of the United States is interferon alpha-2b or lamivudin, combined use of interferon and lamivudin is not recommended.<sup>4</sup> Based on clinical studies by Heatcote et al and Schiff et al in 1998, the use of combined interferon and lamivudin for chronic HBV was not significantly different in producing seroconversion of HbeAg and improvement of liver histology.<sup>6</sup>

### Alpha Interferon

Interferon is one of the body's protective mechanisms against foreign antigens such as virus, other infections, and tumor. Interferon has antiviral, anti-proliferative, and

Table 1. Indication and contraindication of antiviral therapy for chronic viral hepatitis.<sup>4</sup>

<b>INDICATION OF ANTIVIRAL THERAPY FOR CHRONIC VIRAL HEPATITIS</b>	
<b>Hepatitis virus B</b>	<b>Hepatitis virus C</b>
Positive HbsAg for more than 6 months Positive HbeAg Detectable serum HBV DNA Increased levels of alanine aminotransferase Compensated liver disease Interferon therapy	Positive Anti-HCV for more than 6 months Positive HCV RNA Increased levels of alanine aminotransferase Compensated liver disease
<b>CONTRAINDICATION FOR ANTIVIRAL THERAPY FOR CHRONIC VIRAL HEPATITIS</b>	
<b>Hepatitis virus B</b>	<b>Hepatitis virus C</b>
Negative HbeAg Decompensated cirrhosis Psychiatric disorder Severe illness Normal levels of alanine aminotransferase	Negative HCV RNA Decompensated cirrhosis Psychiatric disorder Severe illness Normal levels of alanine aminotransferase

immunomodulator effects.<sup>7</sup>

There are three types of interferon, alpha-interferon (IFN- $\alpha$ ), beta-interferon (IFN- $\beta$ ), and gamma-interferon (IFN- $\gamma$ ). The antiviral capacity of gamma-IFN is less than that of alpha or beta IFN.<sup>8</sup>

Several forms of recombinant alpha-IFN are recommended for therapy of viral hepatitis: alpha-IFN 2a, alpha-IFN 2b, and recombinant non-naturally occurring type 1 interferon (interferon alfacon-1).

Interferon eradicates virus by preventing viral penetration, synthesizing RNA messenger (m-RNA), translating viral protein and/or viral dissemination and assembly. IFN stimulates proteins such as 2'-5'-oligoadenylate (2-5(A)) synthetase and protein kinase that inhibits the synthesis of protein 2-5(A) synthetase responsible for

producing adenylyate oligomer, which in turn activates latent cellular endoribonuclease (RNase-L), which breaks down cellular and viral RNA. Protein kinase is a selective phosphorylase that non-activates proteins including the synthesis of eukaryotic initiation factor-2 (eIF-2). IFN also stimulates phosphodiesterase that breaks down transfer RNA, thus inhibiting peptide polymerization. Virus are inhibited through many steps. Such inhibitory effects differ for specific virus within a group of virus. Certain virus have the ability to avert IFN effects by inhibiting IFN production or certain IFN activity to stimulate proteins. IFN can change the immune response by stimulating the expression of the major histocompatible antigen that assists the antiviral activities of IFN by increasing the lytic effects of the cytotoxic T lympho-

Table 2. Side effects of alpha-Interferon

<b>Systemic effects</b> Fatigue, fever, headache, myalgia, arthralgia, anorexia, weight loss, nausea, vomiting, diarrhea, abdominal cramps, hair loss, hypersensitivity
<b>Neurologic effects</b> Difficulty concentrating, loss of motivation, sleep disturbance, delirium, disorientation, coma, seizure, changes in the EEG, hearing loss, tinnitus, dizziness, blurry vision, retinal bleeding
<b>Psychological effects</b> Anxiety, irritability, depression, self-isolation/social-withdrawal, reduced libido, paranoia or suicidal thoughts
<b>Haematologic effects</b> Thrombocytopenia, leukopenia, anaemic
<b>Immunologic effects</b> Increased susceptibility to bacterial infection, especially bronchitis, sinusitis, furuncle, urinary tract infection; rarely: pneumonia, lung abscess, brain abscess, septicemia, bacterial peritonitis
<b>Autoimmune effects</b> Development of autoantibodies and anti-interferon antibodies, hyperthyroid, hypothyroid, lichen planus, diabetes, hemolytic anemia, thrombocytopenic purpura, lupus-like syndromes
<b>Other effects</b> Rarely: pneumonitis, proteinuria, interstitial nephritis, nephritic syndrome, cardiac arrhythmia, congestive heart failure, acute exacerbation of liver disease

cyte.<sup>7</sup>

Patients in the active viral replication phase of chronic HBV, with a raised level of aminotransferase, liver biopsy demonstrating chronic hepatitis, and compensated liver disease should receive 5 million units of subcutaneous recombinant human alpha-IFN 2b daily, or 10 million units 3 times a week, for 4 months. Under such therapy, approximately 40% of patients will undergo seroconversion from the replicative phase to the non-replicative phase (detectable anti-HBc) and continuous improvement in histologic findings. Approximately 10% of patients will demonstrate loss of HbsAg.<sup>5,9</sup>

The therapeutic effects of IFN should be continuously monitored. The concentration of serum aminotransferase should be measured every 2 to 4 weeks, using serologic testing for HbsAg, HbeAg and HBV DNA, throughout the period of therapy and 6 months afterwards.<sup>2</sup>

After IFN therapy is terminated, the patient should be monitored to ascertain the disappearance of HbsAg, HbeAg and HBV DNA. The patient's response is considered satisfactory if, 6 months after therapy is terminated, HbeAg and HBV DNA are negative and the level serum aminotransferase is normal or close to normal. Liver biopsy is no longer necessary.<sup>2</sup>

The results for antiviral therapy for chronic HBV infection are as follows:<sup>4</sup>

1. Normal ALT levels.
2. Histologic findings demonstrate reduced necrosis and inflammation.
3. Permanent disappearance of HbeAg and HBV

DNA.

4. Appearance of anti-HbeAg.

Several criteria that could help predict satisfactory results using IFN therapy are as follows:<sup>10</sup>

1. Increased aminotransferase concentration (more than 100 IU/ml)
2. Low levels of HBV DNA (less than 200 mg/L)
3. Liver biopsy demonstrating moderate to severe inflammation
4. Less than 65 years of age.

New forms of therapy are needed for chronic HBV, since response towards the benefits of alpha-interferon is unsatisfactory and repeated therapy does not show much benefit.<sup>2</sup>

**Nucleoside Analog: Lamivudin (3-Thyacytidine)**

Lamivudin is a second-generation nucleoside analog that is more effective in fighting HBV in vivo and in vitro (in laboratory animals), and is safer than other nucleosides such as adenosine arabinose (ARA-A) due to lower cellular cytotoxic effects.<sup>2</sup>

Lamivudin competitively inhibits the activity of reverse transcriptase, the enzyme that changes the genome of viral RNA into double-stranded DNA that integrates into the cell genome during the replication phase.<sup>7,8</sup>

Patients with chronic hepatitis are given 100 mg of lamivudin daily for 52 weeks.<sup>11</sup>

A problem that occurs during lamivudin therapy is due to the fact that lamivudin only inhibits the enzyme reverse transcriptase. Unlike other DNA viruses, HBV

Table 3. The benefits and disadvantages of chronic HBV with alpha-2b-interferon and lamivudin<sup>4</sup>

Interferon-alpha 2b	Lamivudin
<p><b>Benefits</b></p> <p>Short-term therapy (4 months)</p> <p>Disappearance of HbeAg &gt;30%</p> <p>Better response if ALT levels are high and HBV DNA is low</p> <p>Disappearance of HbsAg &gt; 10%</p> <p>Not associated with mutation</p> <p>Availibility of long-term follow-up data</p>	<p>Few side effects</p> <p>Disappearance of HbeAg &gt;30%</p> <p>Histologic response in most patients</p> <p>Effective in those who failed after therapy with alpha-interferon</p> <p>Can be administered in immunosuppressed patients and those with decompensated liver disease</p>
<p><b>Disadvantages</b></p> <p>Uncomfortable method of administration (injection)</p> <p>Many side effects</p> <p>Head to head ratio is not better</p> <p>Limited benefit in immunosuppressed patients and those with decompensated liver disease</p>	<p>Unknown duration of therapy</p> <p>Virus mutation</p> <p>HBsAg remains positive</p>

is an RNA-like virus. The process of reverse transcription (from RNA into DNA in contrary to from DNA to RNA) catalyzed by the reverse transcriptase enzyme is only one of the replication pathways inside the hepatocyte. Lamivudin inhibits this process. There are 2 paths in which HBV replicates, the episomal path outside of the human genome that produces infectious virions that contain HBV DNA and DNA polymerase as well as produce excessive HbeAg, and the path in which HBV DNA integrates into the human genome. The process of reverse transcription occurs after the close circular DNA is formed, and immediately after the viral DNA enters the hepatocyte. Thus, lamivudin has little effect on the episomal path. Since such therapy partially inhibits but does not eliminate the source of replication, hepatitis B can recur after the therapy is terminated.

### **Corticosteroid**

Long-term glucocorticoid therapy is ineffective and potentially harmful. However, under certain conditions, there is a supposedly strong effect of glucocorticoid on HBV. Glucocorticoid increases HBV replication and expression in the hepatocyte, and represses the activity of cytolytic T cells. Theoretically, if this steroid is administered for a short term and is immediately terminated, the cytolytic T cells repressed during steroid-induced HBV replication are able to attack and destroy new HBV antigens expressed in the hepatocyte. Pioneering research demonstrates that administration of glucocorticoid for 6 weeks with a dose of 60 mg for 2 weeks, 40 mg for 2 weeks, and 20 mg for 2 weeks, and then terminated, is beneficial if combined with IFN therapy (5 ml subcutaneously for 4 months) in patients with chronic HBV, especially those with mildly increased or close to normal levels of aminotransferase. However, this approach is rarely used and does not receive much attention.<sup>5</sup>

### **Therapy for Chronic B Hepatitis in The Future**

Patients with HBV where infection could be eliminated develop a polyclonal, multispecific immune response effective for a long period of time. Such response is not found in patients with persistent HBV infection, where the response of the T helper against HBsAg is inadequate and the response of the cytotoxic T lymphocyte towards multiple epitopes of hepatitis B is weak or undetected. Such observation gave way to the concept of vaccine therapy to stimulate the response of the T cell. Based on several researches with the concept of vaccine therapy, it has been shown that the T cell immune response is not triggered in all patients with chronic HBV. Based on this study, the question came up, why does the

immune response towards vaccination vary among patients? How much immune response is needed? Do multiple viral antigens initiate a better immune response? Could other antiviral agents be combined with such a vaccine and is this therapy different among certain chronic HBV patients? Such questions must be answered before vaccination therapy is routinely used.<sup>12</sup>

In the future, chronic HBV patients may be managed using a combination of nucleoside and nucleotide analogs. In current clinical studies, adefovir dipivoxil, a nucleotide analog, demonstrates a strong activity against HBV and seems to be effective in combating mutant YMMD.<sup>4</sup> Other concepts of therapy are other immunomodulator therapies and the molecular approach.<sup>12</sup>

### **Chronic D Virus Hepatitis**

Chronic D virus hepatitis (HDV) is caused by the delta hepatitis virus or HDV, a defective RNA virus that requires the assistance of HBV. HDV was first identified in HBsAg carriers in Italy. Chronic HDV follows chronic viral hepatitis as the least frequent cause of cirrhosis but the most frequent cause of final stage liver disease. Acute HDV infection occurs by means of 2 patterns, the first occurring simultaneously with acute HBV infection, also called co-infection. The second, acute HDV could develop in chronic HBsAg carriers (superinfection).<sup>13</sup>

### **Therapy for Chronic Virus D Hepatitis (HDV)**

#### **Alpha-interferon**

The therapeutic response in patients with chronic HDV is less satisfactory compared to that in patients with HBV and the recommended alpha-IFN regimen for chronic HDV differs.<sup>13</sup> Patients with chronic HDV are considered for alpha-IFN therapy if they have suffered from compensated liver disease, with positive serum HBsAg and antiHDV and raised levels of serum aminotransferase. The dose of IFN is relatively higher, 5 million units daily or 9 million units three times a week. Therapy should be administered for at least 6 months. If the serum aminotransferase does not return to normal or does not improve within 6 months, the therapy is terminated. Relapse often occurs if IFN therapy is terminated, except in patients with negative serum HbeAg during therapy.<sup>13</sup>

#### **Other Agents**

There are no forms of therapy that demonstrate any benefit for the management of chronic HDV. Antiviral therapy for chronic HDV is still under trial.<sup>5</sup>



### **Liver Transplantation**

Patients with final stage liver disease due to chronic HDV could undergo successful liver transplantation. The result of transplantation is better in patients with chronic HDV than in patients with chronic HBV.<sup>5</sup>

### **Therapy for Chronic Virus C Hepatitis (HCV)**

Antiviral therapy is administered in patients with chronic HCV with increased levels of ALT, seropositive for HCV and sustained inflammation in liver histology evaluation.<sup>4</sup> In the United States, regimens approved for chronic HCV therapy are monotherapy using alpha-IFN and ribavirin.<sup>14</sup>

#### **Alpha-interferon**

Based on prospective clinical trials, alpha-IFN is recommended for the management of chronic HCV. The dosage for administration is 2 to 5 million units, three times a week. This study demonstrated effective results, but the initial recommended dose is 3 million units of subcutaneous injection three times a week for 6 months or 24 weeks.<sup>5</sup> There are 3 kinds of alpha-IFN that could be administered to patients with chronic HCV: alpha-IFN 2a, alpha-IFN 2b, and alphacon-1 interferon. The recommended dose for alphacon-1 interferon is 9 micrograms by subcutaneous injection three times a week.<sup>4</sup>

The indications for therapy using alpha-IFN in patients with chronic HCV are elevated serum transaminase, anti-HCV and positive HCV RNA and liver biopsy findings showing chronic hepatitis.<sup>12</sup>

The contraindications for alpha-IFN therapy are severe depression or other neuropsychiatric syndromes, alcoholism, autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus or psoriasis, bone marrow disturbance and patients who are unable to undergo birth control.<sup>4</sup>

The expected results of IFN therapy in patients with chronic HCV are normal levels of ALT and disappearance of HCV RNA.<sup>4</sup>

Several retrospective analysis identified clinical and serologic findings that could predict the long-term response of alpha-IFN therapy, which are, aged under 45 years, duration of illness of less than 5 years, no cirrhosis or minimal histologic findings, low levels of iron in liver tissue prior to therapy, low levels of serum HCV prior to therapy (less than 2 million/ml), HCV genotype 2 or 3, and low levels of genetic variation of HCV.<sup>13</sup>

Even though alpha-IFN is most commonly used as a single agent, the success of this medicine in maintaining viral absence in the blood only amounts to about 15%, and thus better forms of therapy for chronic HCV are

needed.<sup>15</sup>

### **Ribavirin Nucleoside Analogs**

Another more promising antiviral agent is ribavirin, an oral antiviral high spectrum agent.<sup>13</sup> Ribavirin is a synthetic nucleoside analog that inhibits the DNA and RNA virus. Its mechanism of action has not been completely determined, and may differ for different virus groups. Ribavirin 5-monophosphate inhibits the change of inosine 5-monophosphate into xantosine 5-monophosphate by influencing the synthesis of the nucleotide guanine, that also inhibits the capping of specific messenger RNA virus in certain virus systems. Ribavirin is used in aerosol form for management of viral spirochaeta in the respiratory tract of infants.

The half-life of ribavirin varies among cells. It lasts for less than 2 hours in the fibroblast and 40 days in the erythrocyte. When administered orally, it has a bioavailability of 25-50%. Ribavirin could also pass through the blood-brain barrier, with a concentration of 70% of serum levels.<sup>7</sup>

The most common side effects of ribavirin are anemia, weakness and irritability, itching, skin rash, nasal obstruction, sinusitis and cough.<sup>4</sup>

The contraindications for long-term ribavirin are anemia, renal dysfunction, coronary artery disorders, and female patients who could not ensure birth control.<sup>4</sup>

Oral administration of ribavirin is capable of improving serum aminotransferase levels in more than one third of patients with HCV.<sup>13</sup>

#### **Combined Alpha-interferon and Ribavirin**

In 1998, the FDA permitted the use of combined therapy of alpha-IFN and ribavirin for chronic HCV.<sup>16</sup> Combined ribavirin and alpha-IFN is more effective than monotherapy using alpha-IFN alone, not only in patients with relapse but also in patients using it as an initial therapy.<sup>17</sup> Monotherapy using alpha-IFN produces continuous results at a rate of 5% if given to patients with relapse, and 6% to 13% if given as the initial therapy. Combination therapy produces a continuous result at a rate of 9% if administered in patients with relapse during IFN therapy, and more than 39% if used as the initial therapy.<sup>4</sup>

Side effects that could occur when alpha-IFN is combined with ribavirin are autoimmune disease, severe bacterial infection, thrombocytopenia, neutropenia, seizure, depression, suicidal thoughts, tinnitus and hair loss.<sup>14</sup>

Even though the cost of therapy is quite high, combined alpha-IFN and ribavirin is currently the therapy of choice for chronic HCV. The recommended regimen is

3 million international units of subcutaneous alpha-IFN 2b 3 times a week with 400 mg of oral ribavirin in the morning and 600 mg in the afternoon in patients with a body weight of less than 75 kg or 600 mg in the mornings and afternoons in patients weighing more than 75 kg.<sup>4</sup>

### Therapy in The Future

A new approach is long-acting IFN, which is alpha-IFN modified with polyethylen glycol (PEG) administered once a week with a longer half-life and steady level of IFN.<sup>14</sup> Initial studies demonstrate that such

pegylated formulation has a significantly higher concentration of alpha-IFN and a higher response rate compared to standard regimens administered 3 times per week.<sup>4</sup>

Another approach is using other cytokines, new antiviral such as RNA-polymerase, helicase, or protease inhibitors. Other medications that inhibit other steps of HCV replication also help cure this disease, by inhibiting the production of the HCV antigen from RNA (IRES inhibitor), protecting the normal process from protein inhibitors (glycosylation inhibitors) or inhibiting HCV pen-

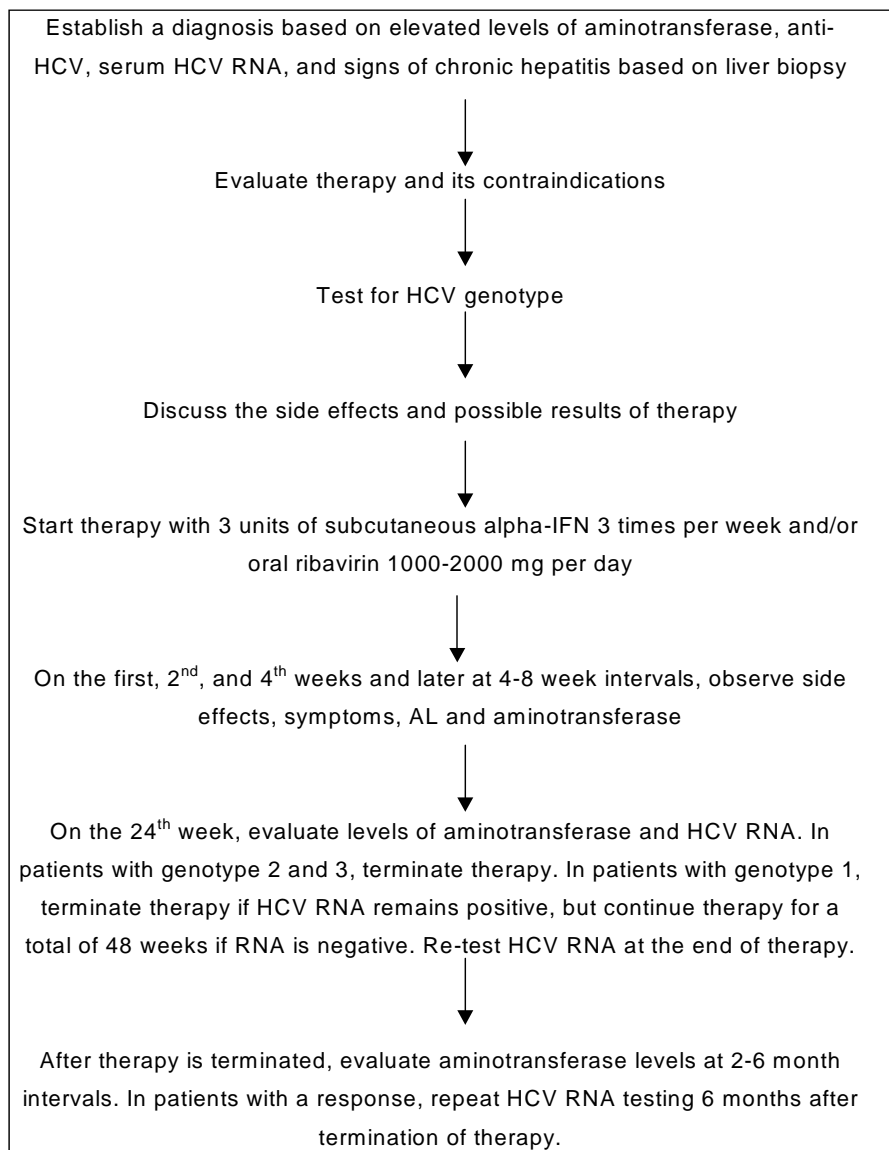


Figure 1. The algorithm of therapy<sup>14</sup>

### Prior to therapy

- Conduct liver biopsy to ensure the diagnosis of HCV, evaluate degree and stage of disease, rule out other diagnoses. If there are contraindications such as clotting disorders, combination therapy may be administered without prior liver biopsy
- Measure serum HCV RNA using PCR to determine viremia
- Test for HCV genotype or serotype to determine the duration of therapy
- Measure AL and aminotransferase to determine the baseline prior to therapy
- Advise patient on relative risks and the benefits of therapy, always discuss side effects

### During therapy

- Measure AL aminotransferase at the first, 2<sup>nd</sup>, and 4<sup>th</sup> weeks and then at every 4-8 week intervals. Adjust ribavirin dosage (by 200 mg every decrease) if there is significant anemia (Hb<10 g/dl or Ht <30%) and discontinue ribavirin in the presence of severe anemia (Hb<8,5 g/dl or Ht<26%)
- Measure HCV RNA using PCR on the 24<sup>th</sup> week. If HCV RNA is still positive, discontinue therapy. If HCV RNA is negative and the patient's genotype is 1 (1a or 1b), continue therapy for 24 more weeks.
- Increase the need for birth control during therapy and for the consecutive 6 months
- Measure TSH level every 3-6 months during therapy
- At the end of therapy, measure HCV RNA using PCR to determine a response at the end of therapy

### After Therapy

- Measure aminotransferase every 2 months for 6 months
- Six months after termination of therapy, test HCV RNA using PCR. If HCV RNA remains negative, there is a high hope of cure; relapse rarely occurs at this point

etration into the cell (receptor inhibition). Non-specific cytoprotective agents, such as rybozim, an enzyme that destroys the molecule of viral RNA, and antisense oligonucleotide, a DNA portion that binds with RNA and inhibits viral replication, are also useful for the management of HCV. All of these approaches are still under trial.

### CONCLUSION

The method of therapy that has been proven beneficial for chronic BVH is alpha-IFN 2b and lamivudin. With these medications, only approximately 40% of patients undergo seroconversion.

Up to date, the therapeutic response for chronic HDV is still unsatisfactory. The recommended therapy is alpha-IFN 2b administered for at least 6 months.

The best therapy for chronic HCV is alpha-IFN and combined alpha-IFN and ribavirin. Continuous response with alpha-IFN is found in 5% of patients with relapse, and in 6-13% of initial patients. Continuous therapy using combination therapy reaches 49% in patients with relapse and more than 39% if administered as initial therapy.

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