

HEPATITIS C TREATMENT

Options for Children with Hepatitis C

Updated 2007

Although chronic hepatitis C is usually a mild disease in children with few or no symptoms, significant liver damage, including severe hepatitis and cirrhosis, can occur. In such cases, medical intervention, including antiviral treatment, should be considered.

Doctors who treat children infected with the hepatitis C virus (HCV) are essentially starting from scratch. There are only a handful of drugs available to treat this infection, and they have not been extensively studied in children.

It is difficult to draw firm conclusions about the efficacy and safety of available antiviral therapy in young patients. There is currently only one treatment for chronic hepatitis C approved by the U.S. Food and Drug Administration (FDA) for this group.

In the absence of a “standard for care” for infected children, decisions about effective drug treatment are often based on adult clinical trial results because little authoritative pediatric data exists.

A study reported in *Hepatology* in 2005 indicates the FDA-approved drug therapy for children, an interferon/ribavirin combo, achieves about a 46 percent cure rate. As of late 2007, doctors are making treatment decisions on a case-by-case basis or by enrolling them in the few clinical trials that have been conducted. In cases where participation in clinical trials is not possible, some specialists choose to treat children with drugs that have been approved only for adults.

In an attempt to find a general consensus about the treatment of chronic hepatitis C in children, PKIDs interviewed leaders in the field of pediatric hepatology and reviewed the latest publications. What follows is a summary of the information collected on this important pediatric issue.

What’s Available for Treatment

As of December 2007 in the United States, there are three drugs approved for treating HCV+ adults:

- conventional alpha interferons
- pegylated alpha interferons, and
- ribavirin

Among conventional alpha interferons, alfa-2a, alfa-2b, and consensus interferon are available for treating hepatitis C. Among pegylated alpha interferons, peginterferon alfa-2b and peginterferon alfa-2a are available for treating hepatitis C. Additionally, there are two brands of ribavirin available for treating this virus.

One drug combination, pegylated interferon plus ribavirin, has become the “drug of choice” for treating adults, although others among the available drugs are still used as treatment in certain circumstances.

As of December 2007, the only FDA-approved drug therapy in the United States for children under the age of 18 who have chronic hepatitis C is the combination of conventional interferon plus ribavirin.

Because treatments that are researched for use in children typically evolve from what is known to work in adults, all of the hepatitis C treatments available are summarized here.

Conventional Alpha Interferon

Interferons are naturally occurring proteins that stimulate the immune system to fight viral infections and tumors. There are three types of interferon normally produced by the body in response to infection, of which alpha interferon has the most antiviral activity.

Several forms of synthetic alpha interferon using recombinant technology have been developed and approved for use in adults, including:

- interferon alfa-2a (known as Roferon®-A, by Roche)
- interferon alfa-2b (known as Intron® A, by Schering-Plough), and
- consensus interferon (known as INFERGEN®, by InterMune)

The recombinant process involves inserting the parts of human DNA that produce interferon into a host cell, often a cell taken from a virus or bacteria, thus enabling the host cell with the ability to produce interferon. This technology increases the efficient production and targeted use of interferon in the body.

Interferon is given by injection underneath the skin three times per week for 48 weeks.

Interferon has been the most studied drug for treatment of chronic hepatitis C for both adults and children. Although interferon is the only drug approved for use in children, most studies now focus on pegylated alpha interferon.

Pegylated Alpha Interferon

In the early 1990s, two pegylated alpha interferons were approved by the FDA to treat adults with hepatitis C:

- peginterferon alpha-2a (Pegasys® by Roche), and
- peginterferon alpha-2b (Pegintron® by Schering-Plough)

Peginterferon is a combination of interferon and polyethylene glycol, a substance that attaches to the interferon and helps it to stay active in the body for a longer period of time.

More importantly, pegylated products appear to more actively inhibit HCV replication than the “unmodified” interferons and have been associated with more sustained rates of viral eradication. Because they are easier to administer (once a week) and have better virus-fighting capabilities, pegylated interferons have replaced “unmodified” interferons for the treatment of chronic hepatitis C in adults.

The treatment period is usually 48 weeks, according to the *Chronic Hepatitis C: Current Disease Management* guidelines published by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 2006.

These two products are roughly equivalent in efficacy and safety but have slightly different dosing regimens.

Ribavirin

Ribavirin, a nucleoside analogue, was one of the first drugs shown to reduce the ability of viruses to reproduce. Ribavirin is effective against many different types of viruses, particularly “RNA” viruses such as HCV. The aerosolized form of ribavirin is FDA-approved for the treatment of severe viral pneumonia in infants and young children.

There are currently two licensed oral ribavirin preparations to treat chronic hepatitis C in adults:

- Copegus® (by Roche), and
- Rebetol® (by Schering-Plough)

Ribavirin alone is not effective against HCV, but when combined with interferon, rates of viral eradication are two to three times higher when compared to results achieved by

interferon alone in adults. Although little is known about how these medications work together, researchers suspect they either directly stop the virus from reproducing, or they stimulate the body's immune system to fight the virus.

Interferon Alpha and Ribavirin Combination

The interferon alpha and ribavirin combination is the only FDA-approved treatment for use in HCV+ children. FDA approval for pediatric use occurred in 2003.

Ribavirin is taken by mouth as a tablet, capsule, or oral solution twice daily in addition to the interferon, which is given by shot underneath the skin three times per week for 24-48 weeks.

Pegylated Interferon Alpha and Ribavirin Combination

Pegylated interferon and ribavirin combination treatment was approved for treatment of adults in 2002, and is the current standard of care for adults.

Ribavirin is taken by mouth as a tablet, capsule, or as an oral solution twice daily. The pegylated interferon is given by shot underneath the skin one time weekly for 24-48 weeks.

General Guidelines for Treating Children with HCV

Although evidence-based recommendations for managing and treating chronic hepatitis C are available, the majority of such recommendations are based on adult studies. Consequently, and perhaps unfortunately, pediatric guidelines are loosely based on what is known about treating adults.

For example, the American Gastroenterological Association's (AGA) *Medical Position Statement on the Management of Hepatitis C*, published in 2006, suggests that "for children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than three years."

In 2004, the American Association for the Study of Liver Diseases (AASLD) published guidelines that offer a bit more detail for managing hepatitis C treatment for children:

- Children who are suspected to have chronic HCV should be diagnosed and tested in the same way an adult is. This testing should include a liver biopsy.

- Testing of infants born to mothers who are infected with HCV should not occur until the infant is at least 18 months old. Many infants who acquire HCV at birth clear the virus within the first year without treatment. If early testing and diagnosis is desired, the infant can be tested with PCR (polymerase chain reaction assay) for HCV RNA at 1-2 months of age.
- Children who are 3-17 years of age who have hepatitis C can receive therapy with interferon alfa-2b and ribavirin if appropriate.
- Children who are less than 3 years old should not be treated.

The NIDDK guidelines published in November 2006 suggest adults should be considered for treatment with peginterferon and ribavirin when they have:

- anti-HCV
- HCV RNA
- elevated serum aminotransferase (ALT) levels
- evidence of chronic hepatitis on liver biopsy, and
- no contraindications to the treatment

The following factors are not relevant when determining whether or not to offer treatment to an adult:

- presence or absence of symptoms
- the way the disease was acquired
- the HCV genotype, or
- serum HCV RNA levels

Although much remains unknown about hepatitis C in children, a number of recently published pediatric studies attempt to understand the dynamics involved with spontaneous clearance of HCV infection, risk factors for progression of disease, and factors likely to affect treatment outcomes.

In 2007, the *Journal of Viral Hepatology* published the results of a retrospective study (a study that uses historical data gathered from chart review) that assessed rates of spontaneous HCV clearance in childhood. Spontaneous clearance was defined as having a history of positive HCV antibody tests plus a positive HCV RNA result, with two or more positive HCV antibody tests with negative HCV RNA occurring later.

In this study, a chart review was conducted among patients who received treatment at the Liver Clinic at the Hospital for Sick Children in Toronto, Canada, between 1990 and 2001. One hundred fifty-seven children who had hepatitis C confirmed by HCV RNA were included in the study cohort. Of these, 123 acquired HCV by blood transfusion; the remaining 34 acquired HCV as neonates (during the first month of life)—20 of those 34 were cases of mother-to-infant (vertical) transmission that occurred during birth.

The study found that the route of transmission did not affect the rate of clearance among those infected as neonates. In this group, results found there was a 25 percent chance of clearing the HCV infection after 7.3 years of infection.

The study also looked at clearance rates among patients who knew when they had become infected.

This group of 75 included the 20 cases of vertical transmission and 55 cases of transfusion-acquired HCV, many of whom acquired HCV at an older age. In this group, results found there was a 25 percent chance of clearing the HCV infection after 11.8 years of infection.

Overall, regardless of route of transmission and age of infection, 28 percent of the 157 HCV+ children spontaneously cleared the HCV virus. For those who did not have a known time of infection, it was assumed transmission occurred at age 0. In this group, results found there was a 25 percent chance of clearing the virus after 14.4 years.

This study also identified a better HCV clearance rate among children who had a lower proportion of abnormal ALT levels.

Authors Yeung and King summarize by suggesting that younger children with normal ALTs should be monitored and given an opportunity to clear the virus spontaneously before subjecting them to the demands of treatment.

In an attempt to gain more knowledge about the natural course of hepatitis C disease in children, several observational studies were conducted and published in 2006 and 2007 to identify factors associated with positive treatment outcomes and to identify factors that are associated with progression of liver disease.

Risk factors for progression of liver disease in children were found to include:

- presence of other health conditions such as blood disorders, childhood cancer, or HIV

- longer duration of HCV infection in the presence of other health conditions
- older age at time of infection

Predictors for positive response to antiviral therapy in children were found to include:

- infection with viral genotype 2 or 3
- younger age at time of treatment
- absence of cirrhosis
- younger age at time of infection, and
- absence of other health conditions

Although statistical information is helpful, researchers acknowledge there is still much to learn. Clinicians will caution that it is important to consider each patient on an individual basis, weighing risks and benefits carefully when deciding whether to treat or to establish a “window of ‘watchful waiting’” (Yeung and King). “Watchful waiting” is a term that is used to describe regularly monitoring a patient’s lab values, liver enzymes, signs and symptoms for signs of improvement, stability or worsening as a way of postponing treatment, or avoiding treatment altogether.

Children who become infected at an early age usually have a mild course of disease during childhood. However, an article published in *Pediatric Transplantation* in 2004 addressed situations where complications can occur. For example, an association between childhood hepatitis C and adolescent and early-adult liver cancer has been identified in several case reports, and severe cirrhosis requiring liver transplantation in childhood has been examined in several retrospective studies.

These studies found hepatitis C infection was present in 4 to 6.5 percent of children undergoing liver transplantation. Because cirrhosis and liver cancer are potential results of childhood liver disease, children at risk for these complications should be closely monitored. Additionally, although it is known that most children with mild disease will have slow disease progression, what will happen in their later years still remains unknown.

In reality, since risk factors are not well-understood, doctors are making treatment determinations on a case-by-case basis, working with a limited number of drugs. Historically in adults, doctors have recommended treating only those who have abnormal liver tests or have evidence of liver damage on a liver biopsy.

Pediatric gastroenterologists and hepatologists have taken a similar approach with

children—primarily treating only those with signs of liver damage. However, there are some experts in the field who view HCV as an infection and believe that the virus should be eradicated, whether there is significant liver damage or not.

Given the current relatively low success rates and the side effects of the medications available, there is no agreement among the medical community about when to treat.

Ideally, the goal of drug therapy for chronic hepatitis C is to eradicate the virus from the body, which is usually measured by HCV RNA levels in the blood. It is unlikely that HCV RNA will reappear in the blood of patients who remain negative six months after completing antiviral therapy and thus, these persons are considered to be “cured.”

But because many patients do not achieve this “cure” with the drugs developed to date, a secondary treatment strategy is to find medications that reduce the reproduction of HCV RNA to minimize or halt liver damage, preventing the development of cirrhosis (scarring of the liver) and liver failure and cancer.

Who Should Not Be Treated?

According to the 2006 NIDDK recommendations, therapy is not recommended for those with:

- severe HCV-related cirrhosis
- a kidney, liver, heart or other solid-organ transplant
- age less than three years old, or
- specific contraindications to the medications

Contraindications or severe side effects from interferon can include marked irritability, anxiety, personality changes, depression, and even suicide or acute psychosis.

Contraindications to ribavirin include marked anemia, renal (kidney) dysfunction and coronary artery or cerebrovascular disease.

Ribavirin is also a teratogen—a drug that can cause fetal malformations and death. Therefore, women with child-bearing potential need to practice effective birth control during ribavirin treatment.

Some Important Factors To Consider For Treatment

HCV RNA

The presence of HCV RNA in the blood (serum) indicates an active infection with ongoing viral reproduction. HCV RNA must be present for a child to qualify for treatment. The best candidates for currently available treatments are those with low levels of HCV RNA. They have fewer viral “enemies” to overcome.

HCV Genotype

The HCV genotype or “viral strain” is determined by a blood test. Some HCV genotypes, such as types 2 and 3, are easier to eradicate than type 1, which is the prevalent genotype in the United States.

Knowing a child’s HCV genotype may influence the decision to treat or not. Because the progression and degree of liver damage are relatively similar between different HCV genotypes, most doctors will not test for a child’s genotype unless treatment is being considered.

Liver Enzymes

Doctors usually perform liver function tests on children who are infected with HCV. When liver cells are damaged or die, they release enzymes that are measured by these tests. The two most common liver enzymes tested for in HCV infection that indicate liver cell damage are the aspartate aminotransferases (AST) and alanine aminotransferases (ALT).

In the past, pediatric specialists recommended treatment only when AST and ALT levels had been elevated for months, indicating chronic liver cell damage. However, this requirement is being reconsidered by experts in the field because of new information that indicates AST and ALT levels can be poor predictors of the actual health of the liver. As a result, it is the liver biopsy that provides the best information about the severity of disease. Additionally, research published in 2006 in the *Archives of Disease in Childhood* suggests that interferon in combination with ribavirin works well in children whether ALT levels are normal or not.

Liver Biopsy

A doctor may also recommend a liver biopsy, a relatively safe procedure used to obtain a very small piece of the liver for microscopic examination. Examining the liver sample under a microscope is the best way to assess the degree of liver inflammation and fibrosis (scarring). Many doctors will only do a biopsy on a child with chronic HCV infection if other tests, including the AST and ALT, indicate liver damage.

Dr. Philip Rosenthal, Professor of Pediatrics and Surgery and Medical Director of the Pediatric Liver Transplant Program and Director of Pediatric Hepatology at the University of California, San Francisco, explains the important information the liver biopsy provides in determining a treatment plan. “I routinely do a liver biopsy before I treat any child with HCV. I believe the biopsy guides whether or not to do therapy at this time or if [signs of liver damage are] mild, perhaps waiting is the prudent course.”

In summary, treatment should be considered when:

- anti-HCV and HCV RNA are present in the blood
- a liver biopsy indicates damage such as inflammation and fibrosis or scarring
- there are no contraindications to receiving treatment, and
- the child is three years of age or older

In addition to using these guidelines, Dr. Rosenthal explains that each patient deserves to be treated on an individual basis. A liver biopsy will help with determining the degree of inflammation and fibrosis, and genotype can help predict likelihood of response to therapy.

Dr. Kathleen Schwarz, Director of the Pediatric Liver Center and Professor of Pediatrics at Johns Hopkins University School of Medicine in Baltimore, Maryland, adds that while she generally agrees with the guidelines, she recommends that “children with genotype 2 or 3 should be treated since they have a high likelihood of getting rid of the virus.”

Dr. Regino P. González-Peralta from the Division of Pediatric Gastroenterology, Hepatology and Nutrition at the University of Florida, Gainesville, emphasizes that although adults with normal liver enzymes are not typically considered candidates for treatment, “children with normal liver tests should be considered candidates on an individual basis.”

The physician will also look at other factors, such as any side effects of a drug therapy and whether or not the liver is “compensated”—healthy enough to function well during

the drug therapy period. Any other medical issues will also be taken into consideration before a physician prescribes treatment.

Data suggest children receiving interferon may have diminished growth while taking this drug therapy, though growth improves once they stop taking the drug.

Interferon has also been associated with psychiatric disorders such as depression and suicidal behavior.

It's imperative to detect liver cancer early enough so it can be removed or treated to improve long-term survival, even if the risk of recurrence remains. Monitoring alpha-fetoprotein levels and abdominal ultrasounds that can identify liver tumors are two ways to detect development of liver cancer in its early stages.

Many doctors suggest that because liver cancer rarely develops in those without cirrhosis, screening should be limited to those chronically infected with HCV who do have cirrhosis.

Treatment Response

Response to treatment is determined by detection of HCV RNA and is assessed in the following ways:

- Sustained Response: HCV RNA becomes negative during treatment and remains undetectable for at least six months after therapy is stopped. It is unlikely that HCV RNA will reappear in the blood of patients who achieve a sustained response. These people are considered cured.
- Relapse: HCV RNA levels become negative by the end of treatment but reappear once treatment is stopped. Rarely, HCV RNA reappears and becomes positive during treatment, and this is called a “break-through” response.
- Non-Response: HCV RNA remains detectable during the treatment period. If serum HCV RNA levels do not significantly decrease within the first 12-24 weeks after starting therapy, there is very little chance to achieve a sustained virologic response.

Treatment Options

Conventional Interferon Alone (Monotherapy)

Conventional interferon monotherapy was the first medication used to effectively treat adults with chronic hepatitis C. However, even when high doses were given for long periods of time (up to 18 months), a sustained rate of viral eradication occurred in approximately 10 percent of adults, according to a 1997 report published in *Clinics in Liver Disease*.

Although similar lackluster results were seen in children treated with conventional interferon alpha, a recent published report suggests that when given alone, this drug may work better in children than in adults with hepatitis C.

Although conventional interferon alone has not been approved for use in treating children with hepatitis C, its use for children has been studied in several small, mostly uncontrolled clinical trials. In 2002, the *Journal of Pediatric Gastroenterology and Nutrition* published a report that analyzed the use of interferon monotherapy in children.

In this report, 19 trials were reviewed. These trials amounted to the study of 366 treated and 105 untreated children between the ages of 2 and 21. Treatment regimens varied. Treatment duration ranged from six months to one year; the trialed dosages and types of conventional interferon varied between studies as well. In the end, the analysis found no statistical differences on end results among the various conventional interferons, dosages and treatment durations used.

Ultimately, the analysis found that for genotype 1 infections, 27 percent of the children treated with conventional interferon achieved a sustained viral response. For children with nongenotype 1 infections (in this study, other genotypes besides genotype 1 were not specified), 70 percent of the children treated with conventional interferon achieved a sustained viral response.

“The higher response rate observed in children might be the result of the earlier stage of the disease, the higher relative interferon dosage or lack of co-morbid [other medical complicating] conditions,” observed Dr. Rosenthal.

But even if children do better than adults with interferon, the results from interferon monotherapy are still poor, especially for genotype 1. That is why parents have been eagerly awaiting new drugs and drug combinations that have to date been approved for use only in adults.

Conventional Interferon Alpha in Combination with Ribavirin

In 2003, the combination treatment of conventional interferon plus ribavirin was approved by the FDA for use in children between the ages of 3-17. As of December 2007, it remains the only therapeutic treatment that has been FDA-approved for treatment in children.

Because of relatively successful results for adults, conventional interferon with ribavirin was studied in several pediatric trials.

In 2002, a large pediatric study was presented by Dr. González-Peralta at the annual meeting of the AASLD. This study assessed the safety and efficacy of interferon-alpha 2b plus ribavirin in 70 children with chronic hepatitis C.

The clinical features of the children studied are summarized here:

Average Age	10.5 years
Gender	
Boys	34
Girls	36
Ethnicity	
White	56
Hispanic	8
Asian	3
African-American	2
Other	1
Type of Infection	
Birth	43
Transfusion	25
Not known	2
Average Serum ALT	52 IU/ml
HCV Genotype	
Type 1	52
Type 2/3	17
Type 4	1

Nearly all children in the study had no symptoms of liver damage, about 30 percent had normal ALT levels, and none had cirrhosis (scarring of the liver).

Based on previous drug-concentration studies, the doctors administered ribavirin (15 mg/kg/d, maximum 1200 mg/d) as either syrup (n=55) or capsules (n=15).

Children who had at least a 100-fold decrease in HCV RNA by treatment week 24 completed the full 48 weeks of therapy. However, treatment was discontinued at week 24 in those who did not achieve an early virologic response.

Success (sustained virologic response) was defined as undetectable HCV RNA (<100 copies/ml) in the bloodstream 24 weeks after completion of therapy.

Ultimately, 34 of the 70 (49 percent) who began treatment experienced a sustained response. A sustained response occurred in 29 of 43 children (67 percent) who completed at least 38 weeks of treatment and received 80 percent of the interferon and ribavirin doses and in only 5 of 27 children (19 percent) who did not.

Surprisingly, children younger than 12 years of age responded significantly better to combination treatment (57 percent vs. 30 percent for those older than 12). As expected, children infected with HCV genotypes 2 or 3 responded far better to treatment (82 percent vs. 38 percent with genotype 1).

Children with genotype 1 who had lower levels of HCV RNA responded better than those with higher HCV RNA levels.

The response rate in the treated children was not affected by ethnicity, gender, type of infection, estimated duration of infection, ALT level or ribavirin formulation (syrup vs. pills).

Historically, doctors caring for adults have recommended treating only patients with elevated liver test levels or those with liver damage as revealed by a liver biopsy. Pediatric gastroenterologists and hepatologists have taken a similar approach with children, although evidence continues to show that children with normal liver test levels respond equally well to treatment.

“One of the important results of this study is the fact that the response rate to treatment was similar among children with normal and abnormal ALT levels,” observed Dr. González-Peralta.

Data from several adult clinical trials indicate the viral clearance success rates (the cure rates) are similar or better in patients with normal liver tests compared to those with elevated ones.

Based on these important observations, some adult specialists are suggesting that factors such as HCV genotype, viral levels in blood, and motivation for treatment should play a more important role than results of liver tests when considering treatment for chronic hepatitis C.

In a similar study from Germany published in the November 2002 issue of *Hepatology*, a group of investigators evaluated the safety and efficacy of interferon-alpha 2b in combination with ribavirin in 41 children with chronic hepatitis C.

All of the children had either vertical or transfusion-acquired HCV infection and were between the ages of 3 and 16 years. Sixteen of the children were infected through transfusions and 21 had been vertically infected at birth. In four children, the transmission mode was unknown.

The children received interferon-alpha 2b (3 or 5 MU/m² thrice weekly by shot) plus oral ribavirin (15 mg/kg/d) for 12 months.

Forty patients completed the study. Eleven children, who remained HCV RNA positive six months after the beginning, discontinued therapy. One boy stopped treatment because of side effects.

At the end of treatment, 25 patients (61 percent) of the 40 who completed treatment cleared the virus (HCV RNA). All individuals remained HCV RNA negative during the six-month follow-up period.

Nine of 15 children with transfusion-related infection (56.3 percent), 14 of 21 with vertical infection (66.6 percent), and two of the four with unknown route of infection, responded to the combination therapy.

Most importantly, sustained response rates were similar between children who had normal ALTs and those who did not in these clinical trials.

Side effects in these studies including fever, headache, fatigue, influenza-like symptoms, thyroid problems, anorexia, weight loss and depression were those which are commonly seen in adults.

In *Pediatric Transplantation* in 2004, González-Peralta summarized results of several pediatric conventional interferon plus ribavirin studies that were published between 2000 and 2002. In this report, results indicated that sustained viral response rates (undetectable HCV RNA) in serum were achieved in 50 percent of the pediatric participants who received conventional interferon plus ribavirin. This rate is an improvement over the rate of 36 percent that is achieved in children when using conventional interferon alone.

Results from a phase three clinical trial assessing use of conventional interferon plus ribavirin led by Dr. González-Peralta were described in *Hepatology* in 2005.

Results of this study confirmed what other studies have found. Children with genotype 2 or 3 and children with genotype 1 with lower levels of HCV RNA in their blood are more likely to respond favorably to treatment. In this study, 84 percent of children with genotype 2 or 3 demonstrated sustained virologic response after receiving interferon alfa-2b plus ribavirin for 48 weeks. Children with genotype 1 achieved a 35 percent sustained viral response after receiving the same treatment.

In summary, combination interferon alpha with ribavirin appears to be at least as safe and effective in children as in adults with chronic hepatitis C.

Pegylated Interferon Alpha

Several clinical studies have confirmed that pegylated interferon alpha is significantly more efficient than conventional interferon for treating adults with hepatitis C. According to data published in *Clinical Therapeutics* in 2002, rates of sustained viral response when adults were treated with pegylated alfa-2a were 39 percent.

Because of its improved efficacy and dosing efficiency, pegylated interferon became the interferon of choice for treating adults with hepatitis C in 2001. Clinicians are hopeful that pegylated interferon will prove to be equally useful for treating children.

As of late 2007, there have been few published reports on the efficacy and safety of pegylated interferons in children. One report in the 2006 *Journal of Pediatric Gastroenterology and Nutrition* reported results from a small pilot study conducted with 14 children between the ages of two to eight. This study demonstrated safe and effective use of peginterferon alfa-2a to treat hepatitis C in these children. Data results found that 43 percent of the participants achieved a sustained virologic response after 48 weeks. This compares to a 39 percent success rate when this treatment is used for adults. In this study, 21 percent of the children (3 of the 14) had to discontinue treatment due to

problems with adverse events. Neutropenia (decreased white blood cell count) was a common problem.

According to the study results, the success rate for pegylated interferon in children is similar to success rates found when using conventional interferon in combination with ribavirin. One of the advantages of pegylated interferon treatment includes an easier dosing schedule that involves one injection per week instead of three.

Future studies will focus on management of neutropenia and evaluate the effectiveness and safety of the drug in children, both as monotherapy and in combination with ribavirin.

Pegylated Interferon Alpha with Ribavirin

Use of pegylated interferon in combination with ribavirin replaced conventional interferon plus ribavirin as the “standard for care” for adults in 2002.

There are now several large adult studies that demonstrate significantly improved sustained response or cure rates by using pegylated interferons instead of conventional interferon in combination with ribavirin.

The duration of recommended treatment depends on viral genotype.

Rates of sustained response for adults range from 44 to 56 percent depending on genotype, according to results published in the *New England Journal of Medicine* in 2002.

Guidelines published by the NDDIC and the NIH in November of 2006 suggest that sustained response rates in adults infected with HCV genotypes 2 or 3 (about 70-80 percent) are similar between those treated for 24 or 48 weeks. As a result, the recommended treatment duration for these patients is 24 weeks.

In contrast, patients infected with HCV genotype 1 who are treated for 48 weeks have significantly higher sustained response than those given 24 weeks of therapy (about 60 percent vs. 40 percent respectively). Therefore, adults infected with HCV genotype 1 should receive a 48-week course of pegylated interferon with ribavirin.

While several large controlled trials of pegylated interferon and ribavirin in adults have demonstrated effective results for use of pegylated interferon with ribavirin, little is known about the effects of peginterferon and ribavirin in children. In 2004, Dr. Jay

Hoofnagle with the NIH announced the beginning of a large phase III trial of peginterferon with or without ribavirin in children with HCV called PEDS-C. This study began in December 2004.

Pegylated Interferon with Ribavirin for Children

According to Dr. Hoofnagle in “This Month from the NIH” published in *Hepatology* in 2005, the purpose of the Peds-C study is “to determine the safety and efficacy of peginterferon alfa-2a in combination with ribavirin and peginterferon alfa-2a alone for the treatment of chronic hepatitis C infection in children. The purpose of this study is also to determine whether peginterferon alfa-2a alone will result in a longer response rate in children with chronic hepatitis.”

A group of investigators led by Dr. Kathleen Schwarz, Chief of Pediatric Gastroenterology at Johns Hopkins University in Baltimore are currently conducting this multicenter trial.

In this study, 112 children between the ages of 5 and 18 years are randomly assigned to receive either pegylated interferon alpha2a alone or with ribavirin. Therapy will be discontinued in nonresponders at 24 weeks. Responders will continue to receive therapy for an additional 24 weeks. Overall treatment duration for responders will be 48 weeks. All of the children who respond to therapy will be treated for 48 weeks and followed for an additional 24 weeks after stopping medications. The goal for treatment responders will be undetectable HCV RNA in serum for a minimum of 24 weeks after completing therapy.

In addition to assessing virologic response, growth and quality of life issues as well as important virologic and immunologic issues will be studied.

Dr. Schwarz, the principle investigator for this study, reports that results will likely be presented at the fall 2008 AASLD meeting.

While results from this major study have not yet been published, two smaller-scale studies assessing use of pegylated interferon in combination with ribavirin in children have reported encouraging results.

In 2005, the first results of peginterferon alfa-2b plus ribavirin use in children and adolescents were reported in *Hepatology*. In this uncontrolled pilot study, 62 children between the ages of 2 and 17 with chronic HCV received a recombinant peginterferon alfa-2b injection of 1.5 micrograms per kilogram of body weight one time weekly, and

ribavirin by mouth at 7.5 milligrams per kilogram of body weight twice a day for 48 weeks.

Participants who had not responded after receiving six months of treatment discontinued the drug therapy at that time. Participants infected with genotypes 2 and 3 were given an option of ending treatment after six months or continuing for the full 48 weeks. This was done because adults infected with genotypes 2 and 3 require only six months of therapy to achieve a sustained viral response. Given the choice, 8 of the 13 patients infected with genotypes 2 or 3 opted to continue treatment for 48 weeks while the other 5 opted to discontinue treatment at six months.

Monitoring and follow-up consisted of blood work and physical exam at 2, 4, and 8 weeks, and then every three months until treatment ended, and then at 3 and 6 months as follow-up. The goal of treatment was to achieve a sustained viral response for six months after ending treatment. A sustained viral response was defined as normalization of serum alanine aminotransferase (ALT) and undetectable HCV RNA during treatment and for six months after ending treatment.

Results of this study showed a sustained viral response rate of 59 percent. This compares to a success rate in adults of 44-80 percent depending on genotype. Of the 46 patients who had genotype 1, 47.8 percent achieved a sustained viral response. All of the patients with genotype 2 or 3 achieved a permanent sustained response whether they took treatment for 24 or 48 weeks. One of the 2 patients with genotype 4 achieved a sustained viral response

Another study, published in January of 2007 in the *Journal of Clinical Gastroenterology*, also described results of pegylated interferon alfa-2b and ribavirin use in children with chronic hepatitis C. In this small, uncontrolled study, ten children between the ages of 11-18 with chronic hepatitis C received a pegylated interferon alfa-2b injection of 1.5mcg/kg of body weight one time weekly, and ribavirin at 400mg by mouth twice a day for 48 weeks.

Monitoring and follow-up consisted of blood work prior to starting treatment, and then at 2 weeks, and then every 4 weeks until treatment ended, and then at 6 months as follow-up. The goal of treatment was to achieve undetectable levels of HCV RNA at any time during treatment. A sustained viral response was defined as undetectable HCV RNA and a decrease in ALT levels six months after ending treatment.

In this study, nine of the ten patients achieved undetectable HCV RNA for a period of time during the course of their treatment. Of these nine, a sustained viral response was

achieved in three patients. Of these three patients, one had genotype 3 and was expected to do well, one had had hemophilia and a history of previous treatment with conventional interferon, and the other contracted HCV from the mother at birth and had no prior history of treatment.

This sustained viral response rate of 30 percent was lower than expected; however, of the 10 participants, nine were infected with the more difficult-to-treat genotype 1. Another factor making a positive outcome difficult to achieve includes the fact that three of the participants had previously failed conventional interferon treatment. Additionally, this study used a lower dose of ribavirin in comparison to other studies.

Treatments on the Horizon: Interferons and Beyond

Although the combination of pegylated interferon with ribavirin is effective in more than half of treated adults and conventional interferon/ribavirin has been approved for use in children, better treatment options are clearly needed, especially for those infected with HCV genotype 1, the more difficult strain to treat.

Here is a summary of some options that are currently being trialed for adults. This summary was published in *Future Virology* in 2007.

Better Interferons

Researchers are developing different compounds of interferon and different methods to deliver longer-acting interferons that might be more effective in combating the virus when combined with ribavirin or other agents. For example, researchers are developing a device that would be implanted under the skin. This system would provide a continuous dose of omega interferon without the need of daily injections. Dose-finding studies of omega interferon in adults have shown a rate of 35 percent effectiveness in adults when combined with ribavirin.

In 2007, *World Journal of Gastroenterology* reported that another form of interferon, albinterferon (interferon-alfa2b that has been fused to human albumin), was in phase III trials. The albumin provides a prolonged half-life, allowing albinterferon to be administered less often—only once every two weeks. In clinical trials, albinterferon has demonstrated effectiveness and side effect occurrences comparable to pegylated interferon alpha-2a.

Specific Inhibitors of HCV Proteins

There are a number of viral enzymes (proteins) that are critically important for viral reproduction. There are several agents in development to work against some of these viral proteins, including HCV protease and RNA polymerase inhibitors.

Protease Inhibitors

Protease inhibitors are a class of drugs that aim to block or inhibit a cell's ability to replicate. In hepatitis C, the protease that gives the hepatitis C virus the ability to reproduce is known as NS3 serine protease. Protease inhibitors are beneficial because they can target viral protease without affecting human protease.

Telaprevir (VX-950) is a protease inhibitor currently in phase II trials and is used as an addition to pegylated interferon and ribavirin therapy.

Boceprevir (SCH 503034) is another protease inhibitor in phase II trials and is used as an addition to pegylated interferon and ribavirin therapy to treat genotype 1 hepatitis C.

BILN-2061 was the first HCV-specific protease inhibitor to be trialed in humans. Because it was found to be toxic in animals, it is no longer being developed for human use.

Polymerase Inhibitors

Polymerase inhibitors are another class of drugs which attempt to block or inhibit a cell's ability to replicate, but they inhibit polymerase rather than protease. Polymerase is also involved in helping a cell to reproduce. In hepatitis C, this polymerase is known as RNA-dependant RNA polymerase (RdRp). Polymerase inhibitors are beneficial because they can target viral polymerase without affecting human polymerase.

Researchers were hopeful that the polymerase inhibitor valopicitabine (NM283), combined with pegylated interferon in a phase IIb trial would prove promising. Despite the optimism, no sustained viral responses occurred after 24 weeks of treatment. Future studies will focus on use of valopicitabine as triple therapy combined with peginterferon and ribavirin.

Other Approaches

Drugs that block other steps in the HCV replication process will become an important focus for drug development in the future. These drugs will work by attacking the HCV replication process from a variety of angles. Perhaps treatment in the future will be a cocktail of these drugs that will impair viral replication from enough different angles to result in a complete cure.

Dr. Hoofnagle, in *New Therapies for Hepatitis C* explains that for every 10 drugs that enter clinical trials for humans, only 1 or 2 actually survive the trial process by gaining FDA approval for treatment use. While telaprevir is a drug that may hold promise for the future, pegylated interferon and ribavirin are likely to remain the treatment of choice (for adults) for the next 3-5 years.

Barriers to New HCV Treatments

The life cycle of HCV is not clearly understood at this time. Scientists do not know the functions of all its proteins, nor do they understand the nature of the genetic elements that control its reproduction, which makes it difficult to develop effective antiviral medications.

An article published in 2007 by the U.S. National Academy of Sciences outlines the steps researchers have taken to develop a cell-culture system that would allow researchers to study HCV outside of the human body.

In 2005, several labs reported success in developing a tissue culture system using genotype 2. Current research is focusing on improving use of these systems so that the HCV virus can be studied more closely. Important questions that still need to be answered include how the virus infects cells, how the virus injures cells, and if antibodies and antiviral drugs can stop its spread.

The presence of multiple HCV genotypes and subtypes demands that effective antiviral agents be effective against a variety of viral strains. The genetic variability of the virus also hampers efforts to develop an effective vaccine against HCV.

HCV-related Liver Cancer

Chronic hepatitis C is a major risk for liver cancer in adults in the United States and worldwide. However, liver cancer has been reported in only a few children with HCV infection.

HEPATITIS C TREATMENT

Children and adolescents with HCV-related cirrhosis should be screened for liver cancer. Although there are no foolproof strategies to screen for liver tumors, most specialists recommend checking blood levels of alpha-fetoprotein (a protein which is usually elevated in liver cancer) every six months and yearly abdominal (liver) ultrasound examinations (to look for tumors).

Any suspicious or abnormal result should prompt more extensive evaluation.

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