

2010 Hepatitis C Treatment Updates

Summer 2010

Treatment Options

Conventional Interferon Alone (Monotherapy)

Studies in adults have demonstrated that monotherapy with conventional interferon is effective for adults 10-15% of the time.

Although children typically respond better than adults to this treatment (27% for genotype 1 and 71% for genotype 2 and 3), subsequent study has confirmed that using conventional interferon in combination with ribavirin produces better treatment outcomes for both adults and children. Thus, conventional interferon alone is no longer recommended for the majority of children requiring HCV therapy.

Conventional Interferon Alpha-2b in Combination with Ribavirin (Rebetron for Children)

Rebetron was the first drug to be FDA-approved to treat children with hepatitis C. It's approved for use in children between the ages of 5 and 16 years.

Rebetron is a combination drug that contains both Intron A (an interferon alfa-2b) and Rebetol (which is ribavirin). Rebetron is administered as a weight-based dose of oral Rebetol that is taken twice a day. (Rebetol should never be used alone to treat hepatitis C.) The Intron A portion of the treatment is a subcutaneous injection that is given three times weekly for 24 to 48 weeks.

Sometimes, problems with anemia or depression can develop with this treatment. When this occurs, doses should be reduced temporarily or permanently until the problem is reversed. Additionally, if uncontrollable thyroid abnormalities (such as hypothyroidism) occur, treatment should be discontinued.

Use of conventional interferon alpha-2b in combination with ribavirin has been shown to improve treatment outcomes in adults when compared to using conventional interferon alone. Improved treatment outcomes with use of this drug combination in children have also been demonstrated. For example, the *American Journal of Therapeutics*, in 2009, summarized studies that demonstrated treatment success rates of 36% for genotype 1 and 84% for genotype 2 and 3.

Subsequent study has confirmed, however, that using pegylated interferon in combination with ribavirin produces even better treatment outcomes for both adults and children and is now the treatment of choice for both adults and children.

Pegylated Interferon

For adults, there are two types of pegylated interferon available and both are considered to be equally effective for treating hepatitis C. Only one of these, pegylated interferon alfa-2b has been approved for use with hepatitis C in children to date. The other type, pegylated interferon

alfa-2a, has not yet been approved for use in children, although approval is expected in the near future.

Pegylated interferon has demonstrated superiority over conventional interferon because it has an increased half-life in comparison to conventional interferon. This increased half-life is beneficial for three reasons:

- it reduces the frequency of dosing from three times a week to one time per week
- it decreases the overall amount of medicine needed to provide effective therapy (thereby reducing the risk for unintended negative effects of the drug)
- it results in more evenly sustained levels of the drug in the blood, which improves the drug's action against its intended target

As pegylated interferon becomes more widely used, a better understanding of its side effects is developing. Some studies in adults have found that retinopathy is a rare but significant side effect when used in adults.

Retinopathy is a disease of the retina which is a layer of tissue within the eyeball that consists of the cones and rods that allow for vision. Retinopathy occurs when blood flow to the retina is decreased. Untreated retinopathy can eventually lead to blindness. Rates of retinopathy in adults using pegylated interferon to treat hepatitis C have ranged from 2-69%.

One study, reported in *Ophthalmologica* in 2010, discovered 5 of 10 patients showed early signs of retinopathy on exam, but had no changes in functional vision six months after completing treatment. One patient who experienced a more advanced sign of retinopathy—visual dimness—also had type 2 diabetes, a disease that can cause retinopathy in and of itself. This patient discontinued the pegylated interferon treatment and her vision did not improve.

Generally, retinopathy associated with pegylated interferon is asymptomatic and reversible. Regular eye screening for patients receiving pegylated interferon is recommended. Results of the study indicated retinopathy occurred in adults regardless of age, sex, preexisting hypertension, and diabetes.

Because retinopathy has been identified as a side effect of pegylated interferon use in adults, a group of researchers examined the occurrence of pegylated interferon-associated retinopathy in children. The study examined 114 children between the ages of 5-17 years who received pegylated interferon alfa-2a with or without ribavirin and found a low occurrence of retinopathy.

The study also confirmed lower pre-treatment rates of retinopathy supporting the well-known theory that retinopathy is more likely to occur in adults regardless of drug-associated factors. Typically adult diseases such as diabetes and hypertension also increase the likelihood of developing retinopathy; these diseases are less likely to occur in children.

Retinopathy occurred in only 1% of the children in this study, indicating pegylated interferon-associated retinopathy is not as likely to occur in children. Among the 1% of children who

experienced retinopathy changes, treatment was discontinued, so it is unknown if the situation would have resolved with continued treatment.

In practice, if or when cases of retinopathy develop in children, it would be important for clinicians to consider the risks and benefits of continuing treatment until the issue is more clearly understood. Clinicians should be aware of the potential for this side effect, and monitoring for visual complications should occur for children during treatment with pegylated interferon.

These findings were reported in the *Journal of Pediatric Gastroenterology and Nutrition* in 2010.

Pegylated Interferon alfa-2b with Ribavirin (PegIntron plus Rebetol) for Children

PegIntron plus Rebetol was approved in 2008 by the US Food and Drug Administration for treating children with hepatitis C. It is approved for use in children over the age of 3 years who have compensated liver disease.

PegIntron plus Rebetol is a combination treatment that includes the pegylated interferon alfa-2b drug PegIntron and Rebetol which is ribavirin. Rebetol is administered as a weight-based dose of 15mg/kg/day that is taken twice a day orally. The PegIntron portion of the treatment is a subcutaneous injection that is administered only once per week.

Children who have HCV genotypes 2 and 3 should be treated for a total of 24 weeks. Treatment for children with genotype 1 should generally continue for a total of 48 weeks. However, if no early viral response is noted after 12 weeks of therapy, or if the HCV RNA is still detectable after 24 weeks, treatment should be discontinued. In these cases, research in adults has shown that a treatment response is not likely to occur. At that point, the benefits no longer outweigh the risks of treatment; therefore, treatment should be stopped.

Sometimes, undesirable adverse effects can occur with this type of treatment. Doses may need to be temporarily or permanently reduced if blood problems such as decreasing hemoglobin (indicating anemia), white blood cell count or platelet count occur. In clinical trials, dose modifications were required in 25% of pediatric patients, mostly due to anemia and neutropenia (decreased white blood cell count) and weight loss.

Other common side effects of pegylated interferon plus ribavirin therapy in pediatric patients include fever, headache, decreased white blood cell count, fatigue, anorexia, redness at the injection site, and vomiting. These side effects were most common, occurring in over 25% of cases.

Use of pegylated interferon alfa-2b in combination with ribavirin has been shown to improve treatment outcomes in adults when compared to using conventional interferon with ribavirin. Improved treatment outcomes for use of this drug combination in children have also been demonstrated. For example, the *American Journal of Therapeutics*, in 2009, summarized studies that demonstrate treatment success rates of 47.8% for genotype 1 and 100% for genotype 2 and 3.

Results of a study published in the *Journal of Hepatology* in 2010, evaluated the effectiveness and safety of pegylated interferon alfa-2b plus ribavirin and currently recommended doses in children ages 3-17 years. Children with genotypes 2 and 3 and low viral loads were treated for 24 weeks; children with genotypes 1, 3 and 4 with high viral loads were treated for 48 weeks.

The goal of treatment was to achieve undetectable HCV RNA at 24 weeks after therapy completion (considered a sustained viral response, or SVR). In this study, 65% of the 107 children enrolled achieved a sustained viral response. The two main predictors for successful treatment response included: genotype, and low baseline viral loads for genotype 1. Patients with genotype 1 achieved an SVR of 53%. Patients with genotypes 2 and 3 achieved an SVR of 93%; patients with genotype 4 achieved an SVR of 80%. These results are superior to those obtained using conventional interferon with ribavirin.

Study results suggest all children with genotype 2 and 3 should be considered for this treatment. Factors that suggest less favorable outcomes for children include having had a previous nonresponse to treatment, having had previous treatment with pegylated interferon, having significant fibrosis or cirrhosis, and having genotype 1.

Pegylated Interferon alfa-2a with Ribavirin (Pegasys and Copegus)

This type of pegylated interferon, alfa-2a, has not yet been approved for use in children, although approval is expected in the near future.

The *Journal of Hepatology* reported results of a multi-center study using pegylated interferon (alfa-2a) plus ribavirin in 2010. This study aimed to evaluate safety and response to this treatment by genotype.

In this study, 18 children with genotypes 2 and 3 received treatment for 24 weeks; 47 children with genotypes 1, 4, 5 and 6 received treatment for 48 weeks. SVR was achieved in 94% of patients with genotypes 2 and 3; SVR was achieved in 57% of the patients with genotypes 1, 4, 5 and 6. These rates are higher than what adults have achieved in similar studies with similar treatment regimens and are similar to results obtained in children with pegylated interferon alfa-2b and ribavirin.

Ten patients stopped treatment early. Two of these occurred as a result of adverse events, including thyroid problems, eight of these occurred as a result of having no virologic response after 24 weeks of therapy.

Fifteen of the patients (23%) required dose adjustment for either neutropenia or anemia. Other side effects were fever and flu-like symptoms, mood changes such as depression and irritability, vomiting, abdominal pain and skin rash occurring in >25% of cases.

Treatments on the Horizon: Interferons and Beyond

While progress in developing effective treatments for hepatitis C has occurred, there is still room for improvement, particularly in the fight to effectively treat patients who have genotype 1.

Many drugs that treat hepatitis C in new ways are currently being studied for use. New pediatric drug treatments are usually developed once effective use has been proven in adults. To glimpse the future for pediatric treatments, we can examine what is occurring in adult studies.

In addition to finding better treatments for hepatitis C genotype 1, other goals include discovering treatments that are less toxic yet more effective, using new classes of drugs while avoiding problems with drug resistance, finding better treatments for people who relapse or fail to respond to initial treatments, and developing more convenient treatments that avoid the need for regular injections. Additionally, developing treatments that are cost-effective and affordable is another important priority.

Better Interferons

Some studies are focusing on using new or different types of interferon for treating hepatitis C. While treatment with pegylated interferon is the current standard of care, any type of interferon that would be considered superior to this would need to be at least as effective, but could also carry an added benefit of reducing problems with the troublesome side effects of depression or anemia that can result from pegylated interferon use. Other interferon research studies are examining comparatively effective interferons that require a less frequent injection schedule.

Albumin Interferon, (also known as Albinterferon or Zalbin, formerly known as Albuferon)

Albinterferon is a newer type of interferon that is in late stages of study for use in treating adults who have hepatitis C. Albinterferon combines standard interferon with human albumin (a protein found in blood). This combination results in an interferon that has a longer half-life compared to using standard interferon alone.

The longer half-life is potentially beneficial in two ways. First, it may allow for a less frequent dosing schedule. In fact, current studies are examining use of albumin at a dosing schedule of 1 to 2 times a month. (Dosing schedules for pegylated interferon require once weekly administration; dosing schedules for standard interferon require three times weekly administration.) Second, the increased half-life of the drug can potentially reduce the rate of side effect occurrence by producing a steadier level of drug presence in the blood.

In a small study published in *Hepatology* in 2007, albinterferon plus ribavirin was given to 115 adult patients who had no sustained viral response to previous HCV treatment. With this treatment, 19% of the patients were able to achieve a sustained viral response. Among those with genotype 1, the sustained viral response rate was 12%.

Results from other large trials do not show an increased sustained viral response rate over peginterferon; however, the reduced risk of side effects and reduced administration rate may result in an increased role for albinterferon in future treatments.

FDA approval for albinterferon treatment was expected to occur in 2010, but on June 14, 2010, the company that produces albumin interferon, Human Genome Sciences, announced that preliminary feedback from the FDA suggested that approval for albinterferon use at an administration rate of once every two weeks was unlikely to occur. The problem, as cited by the FDA, is that albinterferon, at the less frequent dosing rate of 900 mcg every two weeks, is not as

effective as the other interferons that are already available. Human Genome Sciences stated that future study may focus on development of a once-monthly dosing schedule.

Locteron

Locteron is standard interferon packaged in a controlled release formula. The controlled release formula has two potential benefits—it allows for a more convenient administration rate of once every two weeks, and reduces the risk for problems with drug side effects by avoiding the high levels of drug in the blood that occur with more frequent dosing.

Results from the SELECT-1 phase 2a clinical trial results were reported by Biolex and the *Journal of Interferon and Cytokine Research* in 2008. This trial was a dose-finding study that evaluated 32 adult patients with genotype 1 who had never received HCV treatment. Patients were divided into groups and treated with four different locteron doses plus ribavirin for 12 weeks.

The study reported that 100% of the subjects receiving the highest doses showed an early virologic response to the treatment after 12 weeks. Of the groups receiving the two highest doses, 63% actually had undetectable HCV RNA levels after 12 weeks of treatment.

The treatment was generally well-tolerated at all doses, and only one adverse event, ear inflammation, occurred and eventually resolved.

These results suggest locteron is equally effective with the additional benefit of an improved side effect panel in comparison to the pegylated interferons and albuferon.

Gamma Interferon

Gamma interferon is a type II interferon. It is similar to standard interferon but acts on a different part of the body's immune system. Because it works differently, gamma interferon may be useful for treating patients who do not respond to standard hepatitis C treatments.

In 2005, the *Journal of Hepatology* reported pilot study results using gamma interferon. The study examined 14 adult patients with HCV genotype 1 who either did not respond or relapsed after receiving treatment with standard interferon plus ribavirin. This group of patients was treated with gamma interferon for 4 weeks. The results of the pilot study showed no statistically significant decreases in HCV RNA blood levels.

In spite of these discouraging results, future study will focus on appropriate and effective dosing levels and length of treatment. Additionally, it is possible that use of gamma and standard interferon together may produce effective results when used together.

Consensus Interferon (also known as IFN-alphacon-1 or CINF)

Consensus interferon is another type of interferon that is being studied for use in treating patients with hepatitis C. CINF was developed by recombining and reordering the protein sequences that exist in standard interferon. The result of this recombination is a drug that has the potential to work better than natural, standard interferon.

A potential role for CINF is for use as an alternative to pegylated interferon in adults who did not respond to standard hepatitis C therapies. A potential benefit is that it may have a better side effect profile when compared to pegylated interferon.

One disadvantage, compared to other available treatments, is that CINF likely will require daily administration and closer monitoring to ensure patients are able to follow the more-involved treatment.

Researchers hope CINF can play a role in improving outcomes for patients who did not respond or relapsed after receiving treatment with standard interferon plus ribavirin or pegylated interferon plus ribavirin. Study results so far have demonstrated two predictors for successful CINF treatment. First, patients who achieved significant viral suppression with interferon therapy but did not have a full response may have better outcomes with CINF treatment. Additionally, patients who do not have advanced fibrosis but require retreatment may benefit from treatment with CINF. Future study will examine the best uses for consensus and its target population.

Biologics: Targets & Therapy published results from the DIRECT study in 2009. The DIRECT study was a large, multicenter study that compared two doses of CINF plus ribavirin in adults who had not responded to previous standard therapies. Results discovered patients who had no cirrhosis and who had a previous partial (but incomplete) response to standard treatment achieved a 31.6% response rate using this new therapy.

Omega Interferon

Omega interferon is yet another type of interferon that is secreted by human white blood cells that are infected by viruses. Omega interferon demonstrates one of the many strategies the human immune system uses to fight diseases. Omega interferon may be beneficial for treating hepatitis C because of the way that it is able to specifically target the liver. This reduces the drug's presence in the blood stream and contributes to a decreased risk for side effects.

In 2005, *Hepatology* reported that one type of omega interferon, nonglycosylated, was well-tolerated and safe, demonstrating an efficacy rate against hepatitis C that was similar to standard interferon with and without ribavirin. Future studies will examine administration of omega interferon via an implantable device. The implantable device will release a steady dose of omega interferon over a period of nine days.

Multiferon (Viragin)

Multiferon is a highly purified natural human interferon taken from human white blood cells. It consists of several subtypes of natural interferons that facilitate interaction within the body in a variety of ways. Multiferon is already approved for use as an HCV treatment in other countries. Multiferon has been shown to improve interferon treatment function when artificial interferons have become ineffective.

Better Ribavirin

While ribavirin has played an important role in standard HCV treatment, its use is not without drawbacks. Specifically, ribavirin treatment can often cause problems with hemolytic anemia.

Hemolytic anemia occurs because ribavirin present in the blood stream will enter the red blood cell, causing it to break down and become non-functional. This often requires dosage reductions or even drug discontinuation that results in a compromise to treatment effectiveness.

Taribavirin

Taribavirin is a ribavirin prodrug. This means the ribavirin molecule has been chemically modified in an attempt to improve the function of ribavirin and remove the risk of side effects. Specifically, taribavirin was developed in an attempt to avoid the problem of anemia that can occur with ribavirin treatment. Taribavirin works in the liver the same way ribavirin does, but its difference is the fact that it does not easily enter the red blood cells; therefore it avoids the problem of anemia as a side effect.

Phase III study results examining use of taribavirin with both pegylated and standard interferon were reported in the Journal of Hepatology in 2006 and 2007. The study found that flat doses of 0.6g twice a day were not as effective as weight-based doses of ribavirin in treating hepatitis C.

Future studies will compare weight-based doses of taribavirin to weight-based doses of ribavirin.

Specifically targeted antiviral therapies against HCV (STAT-C)

While the goal of more traditional interferon and ribavirin therapies is to improve the body's own immune response against the hepatitis C virus, newer strategies target the virus itself in an attempt to impair the virus at different points along its life cycle.

Recently, scientific advances have improved our understanding of cell function and the science of the hepatitis C virus, its replication process, and how the virus works in the human cell to cause disease. Additionally, advances in using chemistry to make medications that can interfere with the viral replication process are leading to possibilities for new and effective drug treatment strategies against hepatitis C.

As understanding of the HCV lifecycle emerges, scientists have documented the presence of two enzymes that the hepatitis C virus makes and uses in order to make copies of itself once inside a human cell. These two enzymes, known as NS5B polymerase and NS3 protease, have emerged as potentially good targets for new HCV drug therapies. Current research is developing a variety of drugs to target these two enzymes. Specifically, a variety of nucleoside and non-nucleoside polymerase inhibitors are in development for use against NS5B polymerase; a variety of protease inhibitors are in development for use against NS3 protease.

Many of these types of drugs have already been studied and used extensively as treatments for HIV and hepatitis B. More recently, scientists are discovering a new role for these drugs in treating HCV, particularly against the genotype 1 viruses that are more resistant to current therapies.

While current drug development advances are focusing primarily on the NS5B polymerase and NS3 protease inhibitors, it is likely that other specific enzymes the hepatitis C virus uses to replicate itself will be discovered and the potential exists for the development of new drugs to

target these aspects of virus reproduction as well. As developments continue, it is possible that interferon and ribavirin may no longer be major players in treating HCV.

Future HCV drug regimens will build on the successes achieved with pegylated interferon and ribavirin by adding to it other drugs that directly impede the virus's ability to invade and multiply.

These drugs will likely become available over the next 5-8 years.

Nucleoside Polymerase Inhibitors (NIs)

NIs act on various binding sites to prevent the hepatitis C virus from emitting an enzyme called polymerase that the hepatitis C virus uses to copy its viral genetic material. Copying its viral genetic material is an important step in the process the virus uses to replicate, or make copies of, itself once it has entered a human cell. Drugs, such as NIs, that are able to block or stop the replication process will result in a decreased load of the virus within the body because the virus will not be able to replicate itself to take over other cells. NI drugs are likely to be equally effective against all HCV genotypes. Early studies suggest NIs demonstrate a lower risk for mutation development when compared to the NNIs and PIs which will be discussed later.

One NI drug, R7128, was described in the *Journal of Hepatology* in 2008. It is currently in phase 2 trials. In early studies, R7128 demonstrated a rapid virologic response rate (undetectable HCV RNA at 4 weeks) in a group of adult HCV genotype 1 patients who had never received treatment for HCV. For this study, patients were divided into two groups; each group received either 500 or 1,500 mg of R7128 twice a day in combination with pegylated interferon and ribavirin for four weeks. Results found that 85% of patients receiving the higher dose of R7128, and 30% of patients receiving the lower R7128 dose achieved undetectable HCV RNA after 4 weeks of treatment. Only 10% of patients receiving just the pegylated interferon plus ribavirin demonstrated that same result. No viral resistance was noted after the four weeks of treatment.

R7128 was also studied in adult patients with HCV genotype 2 and 3 patients who previously received pegylated interferon and ribavirin therapy but did not respond to treatment. For this study, various doses were administered with pegylated interferon for 4 weeks and continued to use pegylated interferon with ribavirin for at least 20 weeks more. Results obtained after four weeks of therapy demonstrated undetectable HCV RNA in 86% of the patients. This result is comparable to the result obtained in the genotype 1 treatment-naïve study.

Two other NI drugs are in development for possible use in treating HCV. IDX184 entered clinical testing in 2009, and PSI-7851 was in late preclinical development in 2009. These drugs are both designed to act mainly in the liver, which will minimize risk for developing systemic toxicities.

Non-Nucleoside Polymerase Inhibitors (NNIs)

NNIs are drug treatments that also act to inhibit polymerase, but they target other aspects of polymerase activity than the NIs. Specifically, NNIs bind to multiple sites on the virus that exist so that the polymerase enzyme can function correctly. When NNIs block these sites, polymerase can't work like it is supposed to; therefore, replication of the virus can't occur. Early studies

suggest the potential for mutation development is a greater concern for NNIs in comparison to the NIs.

Protease Inhibitors (PIs)

Protease is another enzyme, like polymerase, that is secreted by the hepatitis C virus. Protease, plays a role in helping the virus replicate itself. Specifically, protease helps the virus order proteins into new virus particles. PIs function by inhibiting, or blocking, the effect of protease so that new virus particles cannot be made.

More than NIs and NNIs, resistance development is a significant concern with use of protease inhibitors. Therefore, it is important that protease inhibitors be used in combination with other drugs and other treatment strategies in order to sustain treatment effectiveness. Additionally, it is important to monitor for mutation development throughout the course of treatment.

PI drugs that are currently available have been developed specifically to target the more treatment-resistant HCV genotype 1. Consequently, it is not likely that they would be very effective against other HCV genotypes. Two of these drugs, telaprevir and boceprevir, are nearing end stages of clinical trials. Hopefully they will be available by 2011 or 2010 as long as phase III trials are successful.

Telaprevir

Telaprevir is an NS3/4A protease inhibitor that has been studied in the PROVE1 and PROVE2 trials. Results of the study were published in the *New England Journal of Medicine* in 2009. In these studies, adults with HCV genotype 1 used telaprevir for 12 weeks, in addition to using pegylated interferon and ribavirin for 24 weeks. Treatment results demonstrated a sustained viral response at treatment end of 61% and 69% in patients receiving all three drugs. This compares to a sustained viral response rate of just 41% and 46% of HCV genotype 1 patients who received only the standard combination of pegylated interferon plus ribavirin.

Boceprevir

Boceprevir is an NS3 protease inhibitor that was studied in the SPRINT-I trial. Results of the study were published in *Hepatology* in 2008. In the study, adults with genotype 1 used boceprevir in addition to standard therapy with pegylated interferon and ribavirin. Treatment results demonstrated undetectable HCV RNA in 55%-57% of patients 12 weeks after treatment ended. This compares to a sustained viral response rate of just 41% and 46% of genotype 1 patients who received only the standard combination of pegylated interferon plus ribavirin.

Study results show a clear benefit of adding either telaprevir or boceprevir to the standard therapy of pegylated interferon and ribavirin when treating HCV genotype 1 in adults. Perhaps these study results also suggest that for children who have genotype 1 with minimal fibrosis, it might be prudent to delay treatment until these drugs are available for pediatric use.

ITMN-191

ITMN-191 is a protease inhibitor that is phase II clinical trials. Results from its preclinical study were reported in *Antimicrobial Agents and Chemotherapy* in 2008. The preclinical results suggested ITMN-191 is more effective against HCV genotype 1, and is less effective against

genotype 3. ITMN-191 also appeared to have a potentially low risk for side effects. The preclinical results also demonstrated the drug would work well with both peginterferon alfa-2a and standard interferon and acknowledged the important benefit of combination use to prevent development of virus mutations.

A subsequent early clinical study examined use of ITMN-191 in adult patients who had never received treatment for their chronic hepatitis C. These patients received ITMN-191 for 14 days. Results showed that patients did experience an early decrease in HCV RNA. The drug is now being studied in combination with peginterferon alfa-2 and ribavirin and in combination with polymerase inhibitors.

MK-7009

MK-7009 is a protease inhibitor that is currently in phase I clinical trials. Results from its preclinical study were reported in *Antimicrobial Agents and Chemotherapy* in 2010. The preclinical results suggest MK-7009 will work well in treating HCV genotypes 1 and 2. The drug appears to work well in combination with interferon alfa-2b.

Early phase I trials are currently examining MK-7009 use in healthy volunteers and in HCV-infected patients.

Other Approaches

Targeting Host Factors

Where experimental drugs such as the NIs, NNIs and PIs target specific factors on the virus itself, other treatments could target the specific factors on the human cell that are used by the virus. Although this strategy has the potential to increase the risk of adverse effects to the patient, targeting human factors (rather than viral factors) could provide a higher threshold against viral mutation development.

Drugs targeting host factors could work in a variety of ways. Blocking the virus's entry into human cells could be the first strategy. Three receptors on the human cell, CLDN1, SR-BI and CD81, are known to be used by the virus to gain entry into the human cell. Therapies that block the virus's ability to attach to the cell would inhibit the virus's ability to infect patients.

Interfering with the metabolism of the human cell might be another way to prevent HCV infection. Metabolism refers to the ways cells use nutrients to produce energy so that important cell functions can be performed. When HCV enters the cell, it causes the cell to break down nutrients and produce energy to perform cell functions that are vital to making new hepatitis C viruses. Therapies that make it impossible for the human cell to perform these unnecessary, abnormal functions would inhibit the virus's ability to function in the human body.

Recently, the *Journal of Pediatric Gastroenterology and Nutrition* reported an association between higher BMI (body mass index) and unfavorable response to HCV treatment. This report suggests that being overweight plays a role in reducing positive treatment outcomes. Scientists first discovered the correlation in adults; subsequent pediatric STUDY 1 and STUDY 2 trials reported similar findings.

Often, obesity is associated with insulin resistance. Insulin resistance occurs when cells in the body lose their ability to respond to insulin. Insulin allows cells to use the glucose that is present in the blood. Glucose is an important source of energy for cells; the presence of energy allows the cell to perform specific cell functions.

The presence of insulin resistance appears to affect HCV treatment responses negatively in two ways. First, insulin resistance appears to inhibit the normal antiviral effect of interferon. Second, insulin resistance may also contribute to an environment that strengthens the health of the virus.

Treatments that restore the cell's sensitivity to insulin may improve HCV treatment outcomes. One study reported in the *World Journal of Gastroenterology* in 2009 demonstrated improved HCV treatment outcomes for women who used metformin (a drug that is used to improve insulin sensitivity for diabetic patients) in addition to standard pegylated interferon plus ribavirin. These women had HCV genotype 1 and known insulin resistance at baseline.

Nitazoxanide

Nitazoxanide comes from the thiazolide class of drugs that are sometimes used as anti-infectives. It is also classified as a protein kinase inducer. Nitazoxanide is currently used to treat the parasitic infectious diseases of cryptosporidium and *Giardia*. In hepatitis C, it has been shown to improve the body's ability to block the hepatitis C virus from entering a host cell.

Results from a study using nitazoxanide in various combinations with standard therapy were published in *Gastroenterology* in 2009. In this study, adults with HCV genotype 4 who had never received treatment for HCV, received standard therapy with pegylated interferon and ribavirin for 48 weeks, nitazoxanide for 12 weeks followed by nitazoxanide plus pegylated interferon for 36 weeks, or nitazoxanide alone for 12 weeks followed by nitazoxanide plus pegylated interferon plus ribavirin for 36 weeks. The best outcomes occurred in the group of patients who received all three drugs. Sixty-four% of these patients demonstrated undetectable HCV RNA at 4 weeks and 79% of these demonstrated sustained viral response at the end of treatment. Additionally, this group experienced no increase in adverse effects. Future studies will examine the effectiveness of nitazoxanide against HCV genotype 1.

Hepatitis C vaccine

Hepatitis C vaccine development has been difficult for several reasons. First, the various genotypes of HCV make it difficult to develop something that would be effective against all types. Additionally, the hepatitis C virus has a high mutation rate which makes it difficult to develop a vaccine that would maintain effectiveness against mutations. Finally, to date, scientists have not been able to develop a good model or medium for testing vaccines. In spite of the barriers, the search for an effective vaccine continues. A successful vaccine would likely include several components that stimulate the development of immunity in several ways.

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