

# WESTERN (ALLOPATHIC) MEDICINE

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## SECTION

## 4

## FUTURE OF ALLOPATHIC HEPATITIS C TREATMENT

### Introduction

Despite ongoing advances in treatments for *chronic hepatitis C*, more effective and safer treatments are still needed. About one-half of people infected with the hepatitis C virus (HCV) worldwide will not have a long-term response to the best current western therapy or to any treatments on the immediate horizon.

Progress has been made determining how HCV infects human cells. Cell culture models are now available to determine what medications work to stop HCV *replication*. These models have also advanced our understanding of how receptor sites allow HCV to enter cells and the processes in liver cells that allow HCV to thrive.

Despite these advances, we need to learn more about the hepatitis C virus itself. We need to know more about the virus *proteins* and how they help the virus multiply and infect other cells. We need a better understanding of how the *immune system* responds to the virus. Finally, we need a better understanding of disease progression. What causes hepatitis C to progress in some people but not in others? All this information will lead to the development of new *antiviral* agents. New therapies may be used as single agents. However, it is more likely they will be used in combination with current agents such as *interferon* and *ribavirin*.

This section discusses western therapies currently being studied as potential treatments for hepatitis C. Although some of the concepts are technical and may be challenging to understand, try not to let that keep you from seeing what the future might hold for hepatitis C treatment. Many of the medical and technical terms are defined in the *Glossary*. These definitions should make it easier to understand the concepts presented in this section.

There are many references in this section to *clinical trials*. If you are unfamiliar with the clinical trial process, it may be helpful to review the definitions of the different phases of clinical trials in the *Glossary*. As you read about potential therapies currently in development, keep in mind that many new drugs or treatments that appear promising in the laboratory, or in clinical trials are withdrawn from development because of unexpected side effects and/or lack of effectiveness. At the time this book was published (August 2008), there were more than 40 drugs in clinical development for HCV. However, in general, for every 100 drugs taken through *phase I* testing, only one will eventually be approved by the Food and Drug Administration (FDA).

### Interferons

#### Pegylated Interferon

Interferon is an important, naturally occurring chemical produced in small quantities by many different cells of the body. Interferon helps regulate the body's *immune system*. Man-made versions of naturally occurring interferons are the mainstay of current treatment for hepatitis C. The first man-made interferons (standard interferons) were rapidly processed and eliminated from the body, making frequent dosing a necessity. These interferons were improved upon by attaching a molecule called polyethylene glycol (peg) to different sites on the interferon. The result is *pegylated interferon*.

or *peginterferon*. The kidneys do not clear pegylated interferon as quickly as standard interferon. Thus, pegylated interferon remains active in the body much longer than standard interferon does.<sup>1-9</sup> In theory, long-acting pegylated interferons deliver a more constant interferon dose than standard interferons. Because the drug is cleared from the body slowly, pegylated interferon can be given once a week. Although the activity of interferon is decreased by the attachment of peg molecules to it, the longer duration of action counteracts the reduction in immune activity. The effects of weekly pegylated interferon on the immune system and HCV are an enhanced version of those produced by standard interferon.

The FDA approved PegIntron® (pegylated interferon alfa-2b) as stand-alone for treatment of chronic hepatitis C in January 2001. It was approved for use in combination with ribavirin (Rebetol®) in August 2001. Pegasys® (pegylated interferon alfa-2a) has also been FDA-approved for use as stand-alone therapy or in combination with ribavirin. The overall *sustained response* rates with these two pegylated interferons in combination with ribavirin are approximately 53% to 55%.<sup>10,11</sup> Emerging data show overall response rates with pegylated interferon plus ribavirin in the 60% range if patients are adherent with optimal dosing of both medications. Among people with HCV *genotype* 1, response rates of approximately 50% have been observed in patients taking weight-based doses of PegIntron® plus ribavirin (at full dose) or Pegasys® with weight-based doses of ribavirin.<sup>12,13</sup>

The response rates to pegylated interferon plus ribavirin specifically among patients with *cirrhosis* or compensated *liver failure* are more modest than the overall response rates. One trial conducted exclusively among patients with cirrhosis reported a 29% sustained response rate with pegylated interferon alfa-2a compared to a 6% response rate with non-pegylated interferon alfa-2a. Another international, multi-center trial wherein 28% of the patients had cirrhosis reported that this group of patients had a overall sustained response rate of 39% with pegylated interferon alfa-2a compared to a 19% sustained response rate for non-pegylated interferon alfa-2a.<sup>14,15</sup> In a large, multicenter randomized trial known as HALT-C, among patients who had not responded to previous therapy and had either cirrhosis or advanced fibrosis, the overall sustained response rate to pegylated interferon plus ribavirin was 18%.<sup>16</sup> Among these populations of so-called difficult to treat patients, which include patients who have undergone liver transplantation, there is clearly a need for safe treatments that will be effective in greater numbers of patients.

## Other Interferons

Albinterferon alfa-2b (Albuferon™) is a long-acting interferon that has the potential for every 2 week or every 4 week dosing. The attachment of interferon alfa to the naturally occurring *protein albumin* keeps active interferon molecules circulating in the body for an extended period of time (a prolonged half-life). *Phase I/II clinical trial* data demonstrated albinterferon alfa-2b is well tolerated, has a prolonged half-life, and is biologically active in adults with chronic hepatitis C.<sup>17</sup> Albinterferon alfa-2b is in final, *phase III* development. Two large studies with this drug include treatment naïve patients with genotypes 1 and genotypes 2/3 using an every two week dosing schedule for albinterferon alfa-2b. Results are expected in early 2009.

Controlled-release recombinant interferon alfa-2b (Locteron™), omega interferon (being developed to be delivered by a continuous release device), and peginterferon lambda (interleukin 29) are in phase I-II clinical trials.

Possible treatment advances that may be possible with the successful development of longer acting interferons include:

- longer intervals between interferon dosing
- improved sustained viral response rates
- fewer treatment side effects

New delivery systems for interferons are also being explored including continuous release preparations, pumps, and depo preparations.

## Therapies That Modulate the Immune Response

### Vaccines

*Vaccine* research has historically focused on preventing infection. More recently, vaccine research has taken a new direction. Scientists are now attempting to develop vaccines to either protect people from developing chronic infection or to modify the course of chronic infection. A preliminary study conducted in chimpanzees found an experimental HCV vaccine led to the production of antibodies and inflammatory *T cells* (immune cells) against the virus. The experimental vaccine contained recombinant HCV envelope proteins (proteins found on the outside of the virus). The antibody and T cell responses observed in the chimpanzees prevented chronic HCV infection in the majority of the animals tested in this very small study.<sup>18</sup> A study reported in 2008 among hepatitis C patients who had not responded to prior therapy found that experiment vaccine IC41 resulted in T-cell proliferation in up to 67% who received the vaccine. However, significant reduction in *HCV RNA* was observed in only 3 of the 60 patients in the study.<sup>19</sup>

Recent advances in recombinant protein technology, novel vaccine *adjuvants*, and *DNA*-based vaccines are providing essential tools for the development of HCV vaccines. While several companies are working on developing therapeutic HCV vaccines, there has been no proven benefit to date. Although the preliminary research is encouraging, it will probably take many years to develop an effective HCV vaccine. Some of the many challenges of HCV vaccine research are described below.<sup>20-24</sup>

- HCV is difficult to grow in a laboratory setting.

Vaccine development begins in the research laboratory where potential vaccine components are studied in animals and living cells. In the past, HCV was found only in humans and chimpanzees. A breakthrough was realized when scientists at the University of Alberta, Canada developed a mouse model that supports HCV replication.<sup>25</sup> An additional animal model called the Trimer mouse has been developed by XTL Pharmaceuticals. Cell culture models have also been reported. The discovery of these culture systems and animal models is an important step in HCV vaccine research. In addition, they will aid in drug discovery and our understanding of how HCV behaves in humans.

- HCV is highly susceptible to *mutation*. This characteristic of the virus makes it difficult to provide long-term, antibody-based *immunity*. Thus, an effective vaccine must stimulate T cells, immune system partners to the antibody-producing *B cells*. T cells interact directly and indirectly with HCV-infected cells and other immune cells.

The underlying concept behind *vaccination* is that a vaccine will stimulate the immune system to respond to a specific infectious agent leading to elimination of the agent or limitation of its harmful activities. Immune system responses are highly specific. A specific antibody will react only with the agent that stimulated its production. This highly specific interaction is often described as being similar to a lock and key. HCV is known to mutate frequently, meaning the virus frequently makes small changes in its structure. These small changes may make the virus unrecognizable to specific antibodies against the virus. Therefore, developing a vaccine to stimulate the production of antibodies that will continue to recognize the virus long-term and provide protection is challenging.

- HCV can avoid detection by the human immune system.

The immune system has a highly developed surveillance system to detect the presence of any substance foreign to the body (such as viruses and bacteria). The detection of an “invader” leads to a complex series of immune response that are intended to eliminate the invader. Thus, the detection of a foreign substance is the first step in the immune response. HCV appears to have the ability to escape detection by the immune system allowing the virus to flourish with little disruption.

- HCV-neutralizing immune cells (specific *CD4* and *CD8 T cells*) are not efficiently produced in all persons.

As noted above, immune reactions are highly specific. Researchers have found that the cellular immune response to HCV varies from person to person. This may be partially responsible for the fact that some people

clear HCV on their own while others do not. This variability could also be a factor in potential treatments and vaccines.

- HCV can become resistant to drug treatments.

As noted earlier, HCV is prone to mutations. These mutations can result in the emergence of resistance to specific treatments for HCV. Resistance to drug therapy refers to the ability of the virus to “escape” the effects of a drug and continue to multiply after an initial period of response. Drug resistance is caused by mutations in the genes of the virus. The evolution of HCV strains that are resistant to certain treatments is problematic for both vaccine and new drug development. The ability of HCV to develop resistance to drug therapy has been documented for a number of *protease* inhibitors.<sup>26,27</sup> Studies with telaprevir and boceprevir have shown that resistant strains have poor replication efficiency and gradually fall to undetectable levels after the therapy is stopped.<sup>28-32</sup>

To date, there has been no documented evidence of the development of resistance to ribavirin or interferon in persons undergoing HCV treatment. However, the emergence of treatment resistance remains a serious concern as more therapies are developed.

## Immune Globulin Preparations

Approximately 22% to 29% of adults infected with HCV clear the virus through a naturally occurring immune process,<sup>33</sup> but approximately 70% to 80% do not. Studies suggest that children spontaneously clear HCV more often than adults do, especially those infected at a young age.<sup>34</sup>

While we do not yet know exactly how the immune system spontaneously clears HCV, we have discovered some of the mechanisms that allow HCV to persist in the body. HCV has the ability to rapidly change its structure (that is, to mutate). This helps the virus survive by allowing it to escape detection and recognition by the immune system’s B cells and T cells. B cells produce antibodies (also called globulins). T cells are immune cells that interact directly with infectious agents and infected cells. For additional information on this topic, see *Chapter 7.2 The Immune System and Hepatitis C*.

Researchers are exploring the possible uses of antibody preparations (*immune globulin*) to treat HCV. Current development is focused on liver transplantation. Investigators theorize that immune globulins may prevent transplanted livers from becoming infected with HCV when they are placed in HCV-positive persons. If the use of immune globulin preparations is successful in this setting, they may be tested for prevention of HCV infection after accidental exposure to blood or body secretions.

Civacir™ is an antibody preparation targeted specifically to HCV. The initial clinical trials for the prevention of hepatitis C infection of transplanted livers among HCV-infected transplant patients did not show any clinical benefit.<sup>35</sup> HCV-AB<sup>XTL</sup>-68 has also been studied for the prevention of reinfection in HCV-positive people undergoing liver transplantation. The study concluded HCV-AB<sup>XTL</sup>-68 may decrease viral load after transplantation, but further studies are needed.<sup>36</sup>

## Products Derived from Thymus Extracts

The *thymus gland* is a small structure located in the chest under the breastbone. It is an important part of the immune system. Immune cells called *lymphocytes* are formed in the bone marrow. Lymphocytes that travel to the thymus gland to mature become *T lymphocytes* or T cells. T cells are the primary actors involved in the cellular immune response, which is particularly important in battling viral infections.

Thymosin fraction 5 and thymalfasin (Zadaxin®, also known as thymosin alfa-1) are two special types of proteins called *cytokines* derived from the thymus gland. Cytokines are produced by many cell types in the body. They cause specific reactions, many of which are important for immune function. Thymosin fraction 5 and thymalfasin may be able to change a person’s response to HCV infection.<sup>37</sup> These compounds are being studied to determine if they are capable of preventing chronic HCV infection, or of slowing or halting disease progression.

Thymalfasin stimulates the immune system. Abnormally low levels of thymalfasin have been found in people chronically infected with the *hepatitis B* virus (HBV).<sup>38</sup> Initial studies in HBV-infected animals and humans suggested that thymalfasin and thymosin factor 5 increase the rate of *clearance* of HBV DNA (the genetic material of the virus).<sup>39-41</sup> However, another study showed no difference in HBV clearance when thymalfasin was compared to a *placebo* (an inactive substance). Therefore, the results from these studies were inconclusive. Small, preliminary studies suggested that the addition of thymalfasin to interferon-based therapy for HCV may enhance treatment response.<sup>42, 43</sup> However, two large phase III studies of thymalfasin in combination with Pegasys® (without ribavirin) were recently completed and showed no efficacy for the treatment of HCV-infected people who were non-responders to previous interferon plus ribavirin therapy. A phase III trial of thymalfasin in combination with pegylated interferon alfa and ribavirin is currently being conducted in Europe.

### Other Therapies That Modulate the Immune System

Interferon works by stimulating the immune system. Currently, noninterferon substances that also stimulate the immune system are being explored as possible HCV treatments.

Toll-like receptor (TLR) agonists are a class of small molecules that specifically stimulate the innate immune system. Research has shown that these molecules have antiviral activity, but none have yet proven both safe and effective. For more information on how this class of drugs works, see *Chapter 7.2 The Immune System and Hepatitis C*.

GI-5005 is another substance that is being evaluated for its potential to enhance the body's cellular immune response to HCV. A phase II study of combination therapy with GI-5005 in combination with pegylated interferon plus ribavirin in genotype 1 *nonresponders* is underway.

### STAT-C: Specifically Targeted Antiviral Therapy for HCV

Interferon-based therapy for hepatitis C is based on that notion that by enhancing the body's immune response to hepatitis C, it will be able to effectively clear the virus. In other words, interferon-based therapy boosts the immune system to that it can kill the virus.

Emerging therapies take a different, more direct approach. These agents are designed to interfere with the virus directly by targeting molecules essential to the lifecycle and replication of the hepatitis C virus. These agents are collectively referred to as STAT-C (specifically targeted antiviral therapy for HCV).

The total genetic blueprint of any living organism is called its genome. The genome contains the specific information that makes a tree a tree, a virus a virus, and a human a human. The genome is made up of individual genes. Each gene has the blueprint or code for a specific protein. The types of proteins made by an organism determine how it lives, functions, and survives.

The HCV genome contains the code for ten building blocks that make up the "house" the virus lives in and the machinery needed for the virus to make more copies of itself (replication). New virus particles infect other liver cells and can infect other people.<sup>44</sup> The machinery proteins of HCV act primarily as enzymes, which are needed for viral replication (reproduction) and processing other proteins. Enzymes are specialized proteins that are necessary for various chemical reactions.

Several HCV enzymes (called *proteases*, *helicases*, and *polymerases*) are the targets of STAT-C therapies currently in development. Researchers theorize that if the function of one or more of these enzymes can be interrupted, the replication and damage caused by HCV may also be interrupted. Several pharmaceutical companies are currently developing molecules that act as HCV enzyme inhibitors.

It is important to recognize there are many barriers to overcome in the development of effective HCV enzyme inhibitors. Such barriers include the need for inhibitors to have activity against a broad range of virus genotypes and *quasispecies*, and the potential development of resistance to the drugs. Due to the development of resistance with this class of drugs, it is unlikely in the near future that they will be considered for *monotherapy*.

## Protease Inhibitors

NS3 is a non-structural (NS) protein encoded by the HCV genome. The protein is a specific type of enzyme called a serine protease. This protein is one of the potential targets for HCV inhibitor research.

Two promising protease inhibitors are currently going into *phase III clinical trials*, telaprevir and boceprevir. These agents are taken by mouth, and are intended to be used in conjunction with interferon-based therapy.

The results of the first phase I clinical trial of telaprevir (VX-950) were presented in late 2005. Three phase II clinical trials, PROVE 1, 2, and 3, were subsequently launched. PROVE 1 (conducted in the U.S.) evaluated short-duration therapy with telaprevir (VX-950) in combination with pegylated interferon and ribavirin in treatment-naïve, genotype 1-infected patients. Sustained viral response was reported for 61% of those that received 24 weeks of treatment, and 67% for those receiving 48 weeks of treatment.<sup>45</sup>

PROVE 2 (conducted in Europe with a trial design like PROVE 1) researchers reported sustained viral response in 62% of those treated for 24 weeks and 68% in those that received 36 weeks of treatment. There was a greater incidence of rash in the telaprevir arms of these trials than in the control groups that were given pegylated interferon and ribavirin alone.<sup>46</sup>

PROVE 3 is an ongoing phase IIb study evaluating telaprevir-based treatment in patients with genotype 1 chronic hepatitis C virus (HCV) infection who did not achieve sustained virologic response (SVR) with at least one prior pegylated interferon (peg-IFN) and ribavirin (RBV) regimen. Interim results were reported in June 2008. Fifty-two percent of patients randomized to receive treatment with a 24-week telaprevir-based regimen (12 weeks of telaprevir in combination with peg-IFN and RBV, followed by 12 weeks of peg-IFN and RBV alone) maintained undetectable HCV RNA 12 weeks post-treatment. PROVE 3 is ongoing, and an additional phase III trial to be conducted among prior nonresponders is planned.<sup>47</sup>

Telaprevir resistance has been observed, but the rate of resistance to the drug is substantially reduced when used together with pegylated interferon.<sup>48-51</sup>

Boceprevir (SCH 503034) is another oral NS3 protease inhibitor currently in development. A phase I study found the drug to be well-tolerated and reduced HCV viral loads were observed.<sup>52-54</sup> In August 2008, preliminary data from a phase II study were reported. The group treated with a lead-in phase of Peg-Intron<sup>®</sup> plus ribavirin (standard doses) for 4 weeks followed with triple therapy (boceprevir/ Peg-Intron<sup>®</sup>/ribavirin) for another 44 weeks achieved 74% SVR12 (continued undetectable viral load 12 weeks after treatment ends). Patients who received 48-weeks of triple therapy (boceprevir/ Peg-Intron<sup>®</sup>/ribavirin) but who did not have a lead-in phase achieved a 66% SVR 12 weeks after the end of treatment.<sup>55</sup>

As with telaprevir, boceprevir resistance has been reported but is reduced when the drug is used in combination with pegylated interferon.<sup>30,56</sup>

The clinical trial data for these protease inhibitors are promising. However, the upcoming phase III trial data will be important in determining how more diverse groups of patients respond to interferon and ribavirin therapy plus telaprevir or boceprevir.

TMC435350 is third oral NS3 protease inhibitor that will be evaluated in a phase II trial, genotype 1 known as OPERA 1. Whereas both telaprevir and boceprevir are taken three times daily, the developers of TMC435350 will be exploring a once daily dosing schedule in the OPERA 1 study. Phase I trial data indicate that TMC435350 is well-tolerated.<sup>57</sup>

## Polymerase Inhibitors

The HCV RNA-dependent RNA polymerase is a key viral enzyme responsible for HCV replication. Potential target sites in this protein for polymerase inhibition include the polymerase active site, the GTP-binding site, nucleotide binding sites, and the template RNA binding groove.<sup>58</sup> Several companies are also developing drugs to target other key sites of the HCV RNA-dependent RNA polymerase cascade. Nine companies currently have drugs in phase I or II clinical trials.<sup>59</sup>

The polymerase inhibitor furthest along in clinical development at the time of this writing (August 2008) is oral drug R1626. The drug has been shown to be effective in significantly reducing HCV viral load both alone<sup>60</sup> and in combination

with pegylated interferon plus ribavirin. Interim results from an ongoing phase II clinical trial indicated that 81% of patients receiving triple therapy (R1626/pegylated interferon/ribavirin) had undetectable HCV RNA at 4 weeks after the start of therapy<sup>61</sup> and 84% were virus-negative at the end of treatment.<sup>62</sup> No evidence of resistance to R1626 has been detected to date.<sup>63</sup> However, R1626 has been associated with high rates of significant leukopenia (a low white blood cell count), which could limit dosing and influence rates of effectiveness. Further study is needed into the appropriate balance between safety and effectiveness with this drug.

## Anti-sense Oligonucleotides

The genome of a living organism exists in the form of either RNA (*ribonucleic acid*) or DNA (*deoxyribonucleic acid*), depending upon the type of organism. The HCV genome is made of RNA; the human genome is made of DNA. Because HCV “borrows” the protein-making machinery of human cells during replication, the blueprint for HCV’s specific proteins must be “read” or translated into DNA before HCV proteins can be produced. Anti-sense oligonucleotides are small pieces of DNA or RNA molecules that are designed to block the “reading” (translation) of viral RNA.<sup>64</sup> ISIS 14803 (Isis Pharmaceuticals) is an antisense medication that inhibits HCV replication and protein production and release in cell cultures and animals. However, ISIS 14803 reduced HCV viral load only moderately in a small number of patients recently who experienced a high level of liver enzymes. This medication may possess direct antiviral effects or works through general immune stimulation. Development was discontinued, but it is unclear if other anti-sense oligonucleotides may have a role in HCV therapies of the future.

## Ribozymes

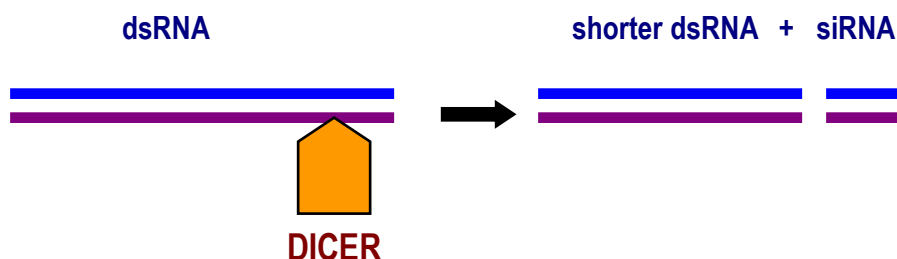
At one time, scientists believed all enzymes were proteins. However approximately 20 years ago, researchers discovered that certain RNA molecules can act as enzymes. These specialized RNA molecules are called *ribozymes*. They act by binding to and cutting (cleaving) specific sites of larger RNA molecules.<sup>65</sup> *Anti-HCV* ribozymes have been developed in the laboratory. However, there were serious side effects when these molecules were administered to animals. Because of the toxicity of the anti-HCV ribozymes developed to date, further development has been halted for the time being. It is unclear whether ribozymes may have a role in therapy for chronic hepatitis C at some time in the future.

Ribozymes are RNA molecules that bind to and break specific RNA messages. Hepatzyme is an IRES-specific ribozyme that has also been investigated in phase II trials. However, development of this agent was halted because of heart problems in monkey. Whether other ribozymes may be developed as potential HCV therapies is yet to be determined.

## Short Interfering RNAs

During the replication process of many viruses, including HCV, two strands of RNA come together to form a double-stranded RNA molecule (dsRNA). An enzyme called DICER binds to and cuts (cleaves) dsRNA. *siRNA* molecules are small pieces of dsRNA produced when larger lengths of dsRNA are cleaved (see Figure 1).

Figure 1. Formation of siRNA



siRNA molecules bind with proteins to form a unit called the RNA-induced silencing complex (RISC). Through a series of complex interactions, RISC suppresses the expression of the gene it corresponds to in the viral genome. In other words, the gene from which the siRNA is derived is silenced. In theory, the ability to silence specific genes in the HCV viral genome could prevent viral replication. Recent studies have confirmed this theory. HCV-specific siRNAs have been shown to block HCV replication and protein expression.<sup>66</sup> These early findings suggest that RNA interference may have a role in treating people with chronic hepatitis C. It is yet to be determined whether siRNA molecules, which are relatively large compared to other molecules used to treat HCV, can be delivered in such a way that they are able to reach the site of viral replication inside infected cells.

Companies are currently conducting research to determine if products that work by this mechanism may be useful in the treatment of hepatitis C.

## Therapies Targeting Host Factors

Another tack being taken in developing new therapies for HCV is to target molecular sites in the host (the patient) that may help in viral clearance.

### Cyclophilin B Inhibitors

Cyclophilin B is a naturally occurring substance in the body that acts as a regulator of not only the immune system but also the HCV RNA-dependent RNA polymerase. In theory, inhibitors of cyclophilin B may well inhibit the activity of the HCV viral polymerase thereby halting viral replication.

DEBIO-025 has been evaluated in a phase Ib study of HIV/HCV coinfecting patients. In this study, DEBIO-025 was found to be associated with significant reductions in both cyclophilin B and HCV viral load.<sup>67, 68</sup> Interim results from a phase II study of DEBIO-025 conducted in HCV mono-infected patients have been reported indicating that 66% of genotype 1/4 patients treated with 1,000 mg of DEBIO-025 daily plus pegylated interferon were virus negative at day 29.<sup>69</sup> Another phase II trial with DEBIO-025 is underway in interferon nonresponders.

Another cyclophilin B inhibitor in early clinical development is NIM811, which has shown antiviral activity against HCV that is enhanced in the presence of pegylated interferon.<sup>70, 71</sup>

### Nitazoxanide

Nitazoxanide is a drug that is already on the market to treat protozoal infections such as giardiasis and cryptosporidiosis. Recently, researchers have found that nitazoxanide inhibits HCV replication, which has led to clinical studies to examine the use of this drug to treat hepatitis C.<sup>72</sup> In a study of Egyptian patients with genotype 4 infection, 79% of patients who received triple drug therapy (nitazoxanide/pegylated interferon/ribavirin) had a sustained viral response compared to 50% in those receiving only pegylated interferon plus ribavirin.<sup>73</sup> A phase II U.S. study among genotype 1 nonresponders is underway, and a phase II trial among genotype 1 patients who have not previously been treated is planned.<sup>74</sup>

## Anti-Fibrotic Therapy

The liver damage caused by HCV is largely the result of an inflammatory response that leads to fibrosis. For people who do not respond to therapy it is important to find another way to mitigate the damage caused by HCV in the liver. To this end, companies are currently investigating therapies to slow down or prevent liver damage caused by the hepatitis C virus.

## Ribavirin Analogues

Ribavirin is one component of current standard therapy. It is described as a nucleoside-like antiviral drug. Its structure resembles that of nucleosides, the building blocks of the gene-carrying molecules DNA and RNA. Ribavirin is minimally effective against HCV when used as monotherapy and has a troublesome side-effect profile. Several pharmaceutical companies are currently involved in developing improved versions of ribavirin. The new compounds are chemically altered versions of ribavirin and are known collectively as ribavirin analogues.

### Taribavirin (also known as Viramidine)

Taribavirin is a liver-targeting prodrug of ribavirin. Taribavirin is converted to ribavirin by an enzyme called adenosine deaminase (ADA). The liver is rich in ADA, which leads to a higher concentration of ribavirin in the liver compared to other tissues when taribavirin is taken by mouth.

Two phase III clinical trials of taribavirin in combination with pegylated interferon alfa-2b (VISER1 and VISER2) lower rates of anemia but also lower SVRs compared to pegylated interferon alfa-2b plus ribavirin.<sup>75, 76</sup> A subsequent phase IIb study using pegylated interferon alfa-2b plus weight-base dosing of either taribavirin or ribavirin revealed equivalent rates of HCV RNA clearance with the two drugs but significantly less anemia associated with taribavirin.<sup>77</sup> The study is expected to continue through to end of treatment (48 weeks) and posttreatment (72 weeks) endpoints.

## Future of Non-Western Treatments

One goal of researchers and practitioners of *complementary and alternative medicine (CAM)* is to determine the role of CAM therapies in the management of hepatitis C. This is important for both people living with HCV and their healthcare providers.

The role of herbal and other therapies in controlling *arthralgia*, *myalgia*, mental foginess, and *fatigue* is clear to individual patients. However, research data are needed to support broad usage of these agents in symptom management across diverse populations. The possible anti-inflammatory role of herbal therapies to prevent or slow disease progression must also be explored. Carefully designed clinical trials may determine which therapies are most beneficial to specific subgroups of people with HCV. For instance, herbal therapy and acupuncture may benefit people with joint pain. Large-scale clinical studies are needed to obtain conclusive information about the efficacy of CAM therapies for these and other signs and symptoms of HCV. A series of anecdotes is not sufficient. NCCAM is currently sponsoring clinical trials using milk thistle in people with chronic liver disease.

Clinical research may clarify whether the use of CAM approaches is safe and beneficial in combination with western therapies. Such studies may also determine if CAM therapies are useful to control side effects of western therapies. Safety is an important issue since many CAM therapies have been anecdotally reported to cause side effects that may be serious. We need to determine the actual incidence of these reported side effects and document their severity with carefully designed clinical studies.

Proving the presence or absence of antiviral effects of nonwestern therapy is important. Some CAM practitioners claim to be able to cure HCV with a variety of therapies. But these claims are poorly documented. Scientifically sound studies are needed to discover which, if any, CAM agents have clinical benefit. Herbal remedies may actually decrease liver inflammation, the early component of liver disease that can lead to fibrosis and cirrhosis. Prevention of the development of cirrhosis would be of great benefit to people with chronic HCV who cannot be cured with interferon-based therapy. Integrative medicine utilizes both western and CAM therapies. For information on the integrative medicine approach to hepatitis C management, see *Chapter 9*.

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