

# 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. Historically, about one-half of people infected with the hepatitis C virus (HCV) worldwide did not have a long-term response to the best current western therapy. Progress has been made and we can now understand how HCV infects human cells. In addition, 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, package and export the virus.

Despite these advances, we need to learn more about the hepatitis C virus itself. We need to know more about the viral 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 to cancer and cirrhosis in some people but not in others? Refining our understanding of hepatitis C will greatly assist the development of new therapies as researchers overcome the obstacles that have made HCV research difficult.

Some of the many challenges of HCV drug research are the following:

- **HCV is difficult to grow in a laboratory setting.**

Drug development begins in the research laboratory where potential therapies 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>1</sup> A mouse model was developed for HCV viral replication, which can be used to test novel therapeutics for HCV.<sup>2</sup> Successful cell culture models have also been reported.<sup>3</sup> The discovery of these culture systems and animal models is an important step in our understanding of how HCV behaves in humans and, thus, in HCV vaccine research and drug discovery.

- **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 become resistant to drug treatments.**

Because HCV is prone to mutations, there is a likelihood that certain mutations will 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, become replication competent, and continue to multiply after an initial period of response while antiviral medications are continued. Drug resistance is caused by mutations in the genes of the virus that occur during viral replication. Many mutations occur daily as the virus replicates and some of these mutations can change the virus in a way that makes it resistant to the drugs currently being used. Then, as the virus continues to replicate, the mutated strains are able to flourish since the drug(s) being taken are not fully suppressing them. 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>4,5</sup> Studies with telaprevir and boceprevir have shown that resistant strains have poor replication efficiency and gradually fall to undetectable levels within 2-3 years after the therapy is stopped.<sup>6-9</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.

- **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 responses 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.

Because of the concern about treatment resistance, new therapies may never be used as single agents. It is more likely they will be used in combination regimens that will lessen the chance of resistance developing. Initially, the new oral drugs were tested in combination with the current standard of care, interferon and ribavirin, but current trials are testing the use of all-oral drug combinations, which will probably replace interferon-based therapy in the not distant future.

This section discusses western therapies currently being used and others that are 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 updated (May 2012), there were ~70 new drugs in clinical development for HCV.<sup>10</sup> The general expectation has long been that for every 100 drugs taken through phase I testing, the Food and Drug Administration (FDA) will eventually approve only one. Due to advances in drug selection and development, the authors of this chapter believe that 5-10 of the medications now in development will attain FDA approval.

## 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 and other body processes 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>11-17</sup> In theory, long-acting pegylated interferons deliver a more constant interferon blood and tissue level 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 therapy 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>18,19</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>20,21</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 alpha-2a compared to a 6% response rate with non-pegylated interferon alpha-2a. Another international, multi-center trial in which 28% of the patients had cirrhosis reported that this group of patients had an overall sustained response rate of 39% with pegylated interferon alpha-2a compared to a 19% sustained response rate for non-pegylated interferon alpha-2a.<sup>22,23</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>24</sup> Among these populations of so-called difficult-to-treat patients (which includes patients who have undergone liver transplantation) there is clearly a need for safe treatments that will be effective in greater numbers of patients.

Because of the side effects caused by interferon and the need for intravenous dosing, the future of HCV therapy is the move toward interferon-free regimens utilizing combinations of oral agents. As discussed below in the section on direct acting antivirals, multiple studies are now underway investigating interferon-free regimens. The goal at this time is to eliminate interferon therapy from the treatment regimen of most patients by 2015.

### Other Interferons

PEG-Interferon lambda is a type III interferon in Phase IIb development for the treatment of hepatitis C. Lambda interferon uses a different receptor than interferon alfa. This produces less side-effects than interferon alfa.<sup>25</sup> In clinical trial,<sup>26</sup> results were dose and genotype dependent with a range of 57 -83% SVR with 24 weeks of therapy in genotype 2/3.

Albinterferon alfa-2b (Albuferon™) is a long-acting interferon that has the potential for dosing every 2 weeks or every

4 weeks. The US FDA did not approve it when the risk-benefit profile was considered. Controlled-release recombinant interferon alfa-2b (Locteron™) has recently been shown to have dose-related reductions in interferon-induced flu-like symptoms and depression while achieving equal efficacy rates with half the number of required injections.<sup>27</sup>

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

Non-traditional interferon delivery mechanisms such as an external subcutaneous pump infusion system, depot preparations (forms of the drug that act over a period of time by controlled-release processes) and oral interferon formulations are also currently in development.<sup>10</sup> The current focus of drug development is to eliminate the need for interferon-based therapies from our tool kit. This new phase of HCV treatment for some patients is expected by 2015.

## 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 therapeutic vaccines, which will either protect people from developing chronic infection or will modify the course of chronic infection. As discussed above, there have been many challenges that have faced researchers working to develop vaccines. However, at least one therapeutic vaccine has now been shown to offer some benefit, and research on other vaccine approaches continues. Recent advances in recombinant protein technology, novel vaccine adjuvants, and DNA-based vaccines are providing essential tools for the development of HCV vaccines.

The first successful use of a therapeutic HCV vaccine was demonstrated with a phase 2b study in genotype 1 patients who were given the combination of pegylated interferon and ribavirin with GlobelImmune's GI-5005 vaccine, a product that contains conserved HCV structural proteins and is designed to generate an HCV-specific T-cell response.<sup>28</sup> In treatment-naïve patients given the GI-5005 combination there was a sustained virologic response<sup>29</sup> (SVR) of 58 percent, compared to 48 percent for patients receiving only the pegylated interferon plus ribavirin.<sup>29</sup> The study also demonstrated that the addition of GI-5005 resulted in an improvement in normalization of alanine aminotransferase (ALT).

Transgene's TG4040 reported encouraging preliminary results in a abstract at EASL 2012.<sup>30</sup>

Another therapeutic vaccine currently in phase II development is Inovio's ChronVac-C. Intercell and AG recently joined efforts to continue research on the Intercell vaccine.

### Immune Globulin /Antibody Therapies

Approximately 22% to 29% of adults infected with HCV clear the virus through a naturally occurring immune process<sup>31</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>32</sup> More recently, we have learned that patients who spontaneously clear the virus are more likely to have polymorphisms near the IL-28B gene which codes for interferon λ-3, a component of the host's natural immunity.<sup>33</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.

A 2011 phase 2 trial is investigating the possibility that MassBiologics' MBL-HCV1, a human monoclonal antibody preparation, could clear HCV from a patient's bloodstream and protect the transplanted liver from infection.<sup>34</sup> Infusions of MBL-HCV1 are given just before the transplantation procedure, during the surgery just after the diseased liver is removed but before the donor liver is implanted, immediately after the surgery is completed, daily for a week post-surgery, and finally on day 14 after the surgery. Preliminary studies with antibody preparations have not shown any protection from infection or reinfection. Due to the lack of antibody-mediated immunity to HCV, these authors do not see a significant role for antibody therapy to treat or prevent HCV.

### **Other Therapies That Modulate the Immune System**

Interferon works by stimulating the immune system. Currently, non-interferon 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*.

## **Direct acting antivirals (DAA)**

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 so 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. Previously termed Specifically Targeted Antiviral Therapy for HCV (STAT-C), these agents are now collectively referred to as direct acting antivirals (DAA).

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>35</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, NS5A proteins, and polymerases) are the targets of antiviral therapies currently in development. Researchers theorize that if the function of one or more of these enzymes can be interrupted this will result in decreased replication and less damage caused by HCV, with resulting immune reconstitution and viral clearance. Several pharmaceutical companies are currently developing molecules that act as HCV enzyme inhibitors.

There have been 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. However, considerable success is now being seen with a number of these antiviral agents.

The future of HCV therapy is the move toward interferon-free regimens utilizing combinations of these oral agents. Multiple studies are now underway investigating interferon-free regimens. Recently, as discussed further below, an exciting advance was described in which four prior null responder patients receiving an all-oral regimen of BMS-790052 combined with BMS-650032 for 24 weeks achieved an SVR.<sup>36</sup> This was the first report of patients achieving an SVR without interferon.

Viral kinetic modeling suggests that three to four oral agents may be needed to achieve optimal SVR rates without interferon and ribavirin.<sup>39</sup> Ribavirin, which reduces viral breakthrough and enhances antiviral activity, will likely also continue to be an important part of many combination therapy approaches.

## 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 protease inhibitors, Vertex's telaprevir (Incivek) and Merck's boceprevir (Victrelis) were approved by the FDA in 2011. In clinical trials, both agents used in conjunction with pegylated interferon and ribavirin resulted in substantially higher SVR rates.<sup>38-40</sup>

In the phase III clinical trials that led to approval of boceprevir, the addition of the drug to a standard regimen of pegylated interferon and ribavirin in people new to HCV therapy almost doubled the number of people who achieved an SVR with HCV levels remaining undetectable for at least six months after treatment. Nearly 70 percent of those who added boceprevir to the standard therapy achieved an SVR, compared with only 38 percent of those who received only pegylated interferon with ribavirin. In people who had previously failed standard therapy, SVR's were achieved in up to 66 percent of patients who added boceprevir to the standard regimen, compared with only 23 percent of those who received only the standard therapy.<sup>41</sup> Boceprevir resistance has been reported but is reduced when the drug is used in the recommended combination with pegylated interferon.<sup>9</sup>

Boceprevir is taken every eight hours. It is recommended, due to the study design, that for those beginning the drug, a lead-in dose of standard therapy with pegylated interferon and ribavirin is first given alone for four weeks, after which boceprevir is added for a variable length of time depending on a person's previous use of HCV treatment and how much boceprevir suppresses HCV levels at early time points. Anemia is the only common side effect of standard therapy, which appears at even higher rates with the addition of boceprevir. In phase III trials, in those given boceprevir, anemia rates increased by about 65 percent in those new to therapy and more than doubled in those who had failed previous HCV therapy.<sup>40,41</sup> In those taking boceprevir, it will be important to monitor for anemia so that it can be addressed in a timely manner by ribavirin dose reduction. In a few patients, erythropoietin, a hormone that boosts production of more red blood cells, may be needed.

In the phase III clinical trials that led to approval of telaprevir, in people who were new to treatment, up to 79 percent achieved an SVR with telaprevir used in combination with the standard therapy of pegylated interferon and ribavirin, compared with 44 percent of people who received only the standard therapy.<sup>42</sup> The trials also showed that telaprevir works well for patients with HCV genotype 1, the most common yet difficult-to-treat form of HCV in the United States.

In addition, results seen with telaprevir in the treatment-naïve studies (ADVANCE and ILLUMINATE) indicate that it may be possible to achieve an SVR with a shorter treatment period of only 24 weeks, compared to the 48 weeks required with the use of standard therapy alone. In the ADVANCE trial, combining telaprevir with standard therapy for the first 12 weeks of treatment increased the percentage<sup>43</sup> of people with undetectable genotype 1 HCV levels after 4 and 12 weeks, compared with standard therapy alone. In these patients, the so-called “extended rapid virologic responders” (eRVRs), stopping all drugs after only 24 weeks did not reduce the likelihood of an SVR. Similar results were seen in the ILLUMINATE trial in which the standard therapy of pegylated interferon with ribavirin was combined with telaprevir for the first 12 weeks, followed by another 12 weeks of treatment with only pegylated interferon and ribavirin (24 weeks of treatment in all). Patients who achieved an eRVR, defined as undetectable HCV levels after 4 and 12 weeks of therapy, were then randomized to either discontinue all therapy after 24 weeks or to continue standard therapy for a total of 48 weeks. Patients who did not achieve an eRVR were also continued on standard therapy for 48 weeks. In eRVRs who did only 24 weeks of therapy, 92 percent achieved an SVR, compared with 88 percent of those who continued treatment for 48 weeks. The overall number of people with genotype 1 who achieved an SVR, regardless of their early virologic response, was also relatively high at 72 percent.<sup>44</sup> The sustained virologic response rate for patients treated with telaprevir across all studies, and across all patient groups, was 20% to 45% higher than the current standard of care. Telaprevir resistance has been observed<sup>6,7,45</sup> but the rate of resistance to the drug is substantially reduced when used in the recommended combination with pegylated interferon. Telaprevir should never be used alone and if there are adverse events from the drug, it should be discontinued rather than attempting dose reduction. For more information on treatment with FDA approved DAA's, see Chapters 8.1, 8.2 and 8.3 of *Western (Allopathic) Therapy for Hepatitis C*.

TMC435 is a potent second-generation oral once daily NS3 protease inhibitor that in July 2011 was given “fast track” status by the FDA for the treatment of chronic hepatitis C genotype-1 infection. Three global clinical phase 3 trials were initiated in early 2011: QUEST-1 and QUEST-2, each of which has approximately 375 treatment-naïve patients, and PROMISE which includes approximately 375 patients who have relapsed after prior interferon-based treatment. Phase II data in genotype 1 treatment naïve patients demonstrated increased SVR rates with shorter duration of therapy required.<sup>46</sup> The ASPIRE trial has shown 51% - 85% response rates in treatment experienced patients who have previously failed therapy.<sup>47</sup>

Trials are now assessing the use of TMC435 in combination with pegylated interferon plus ribavirin, as well as in combination with other DAA agents without pegylated interferon. In June 2011, the combination study of TMC435 with TMC647055, a non-nucleoside NS5B polymerase inhibitor being developed by Tibotec Pharmaceuticals, was initiated. A second interferon-free phase II trial is investigating the combination of TMC435 with Pharmasset's PSI-7977, a once daily nucleotide NS5B polymerase inhibitor, with or without ribavirin, for the treatment of patients who have previously failed standard therapy.

BI 201335, a potent NS3/4A protease inhibitor given once daily, has shown high efficacy and tolerability in genotype 1 patients in phase II data.<sup>48</sup> Phase III trials are now evaluating the combination of BI 201335 with pegylated interferon and ribavirin in both treatment-naïve and -experienced patients with chronic genotype-1 HCV. Results from the phase III studies are expected in the first half of 2013. BI 201335 has been given fast track status by the FDA.

Numerous other second generation protease inhibitors have entered phase II development including Achillion's ACH-1625, Abbott and Enanta's ABT-450/r, Bristol-Myers Squibb's BMS-650032, Gilead's GS-9256,<sup>10</sup> Intermune and Roche's ITMN-191/R7227, Roche and Intermune's danoprevir, and Merck's vaniprevir.

Many of these agents are given once daily and are being investigated in combination with pegylated interferon and ribavirin, as well as in interferon-free regimens.

## 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. Several companies are also developing drugs to target other key sites of the HCV RNA-dependent RNA polymerase cascade. As of this writing there are eighteen drugs in phase I or II clinical trials.<sup>10</sup>

A novel uridine nucleotide analogue polymerase inhibitor, Pharmasset's PSI-7977, has demonstrated antiviral activity across all HCV genotypes in preliminary phase II data. Research to date has shown that it has rapid and consistent antiviral effects and a high barrier to resistance. In the PROTON study, PSI-7977 when given in combination with pegylated interferon and ribavirin resulted in rapid virologic response (undetectable HCV RNA at week 4 of treatment) in 98% of genotype 1 treatment naïve patients.<sup>49</sup> Similar findings were shown among HCV genotype 2 and 3 patients with rapid virologic response rate of 95%.<sup>50</sup>

Based on the promising results seen to date, trials are now ongoing with patients with genotypes 2 or 3 to assess the use of PSI-7977 as monotherapy (without either pegylated interferon or ribavirin), and in combination with ribavirin, with and without interferon, for varying lengths of time. It is also being studied with genotype 1 patients who had previously failed standard therapy in combination with pegylated interferon and ribavirin. In addition, it is being studied as part of an all-oral combination therapy using PSI-7977 with BMS-790052, Bristol-Myers Squibb's NS5A replication complex inhibitor.<sup>51</sup> This combination is being studied in treatment-naïve patients with genotypes 1, 2, or 3.

The nucleoside analogue polymerase inhibitor mericitabine (Roche and Pharmasset, RG7128) has been studied in combination with standard of care with an SVR achieved in 91% of treatment-naïve patients (genotypes 1 and 4) by 24 weeks of treatment.<sup>52</sup> Mericitabine continues in two phase 2b trials and one interferon-free trial being conducted through collaboration with Roche.

As mentioned above, a trial of an interferon-free combination of Tibotec's TMC647055, a non-nucleoside NS5B polymerase inhibitor, and TMC435, a protease inhibitor, was initiated in June 2011. A second interferon-free phase 2 trial is investigating the combination of TMC435 with Pharmasset's PSI-7977, a once daily nucleotide NS5B polymerase inhibitor, with or without ribavirin, for the treatment of patients who have previously failed standard therapy.

Another ongoing interferon-free phase 2 trial combines Gilead Sciences' GS-9256 (an HCV NS3 protease inhibitor) with GS-9190 (a non-nucleoside HCV NS5B polymerase inhibitor).

Multiple other polymerase inhibitors are in phase II development, including Vertex's VX-222 non-nucleoside polymerase inhibitor, Pfizer's PF-868554 non-nucleoside polymerase inhibitor, Anadys' setrobuvir (ANA598), Idenix's IDX184 nucleoside polymerase inhibitor, Gilead's GS 9190 non-nucleoside polymerase inhibitor, and Abbott's ABT-072 and ABT-333 non-nucleoside polymerase inhibitors.<sup>10</sup>

## NS5A Inhibitors

NS5A is a multifunctional protein that plays a central role in viral replication. Its exact mechanism of action is not known but is postulated to be related to viral packaging for liver cell export. It has been associated with interferon resistance and it modulates cellular functions.

BMS-790052 is a first in class NS5A replication complex inhibitor with potent antiviral activity across multiple genotypes. The drug has demonstrated efficacy and safety when combined with pegylated interferon and ribavirin with SVR12

(undetectable viral load 12 weeks after treatment completion) rates as high as 92%.<sup>53</sup>

In a groundbreaking phase 2a study that used an all-oral drug combination of BMS-790052 (60 mg once-daily) and the protease inhibitor BMS-650032 (600 mg twice-daily) in genotype 1 prior null-responders (patients who had previously failed to achieve a 2 log<sub>10</sub> drop in HCV RNA at 12 weeks of treatment with pegylated interferon and ribavirin, generally considered the most difficult patients to re-treat), 4 out of 11 patients achieved an SVR12. In patients given the two oral drugs combined with pegylated interferon and ribavirin, 10 out of 10 patients achieved an SVR12, and 9 out of 10 patients achieved an SVR 24.<sup>36</sup>

As mentioned above, BMS-790052 is also being studied as part of an all-oral combination therapy with PSI-7977, a nucleotide analogue polymerase inhibitor. This combination is being studied in treatment-naïve patients with genotypes 1, 2, or 3.

Other NS5A inhibitors are currently in phase II development, including Achillion's ACH-2928, Bristol-Myers Squibb's BMS-824393, AstraZeneca's AZD7295, and Can-Fite's CF102.<sup>51</sup>

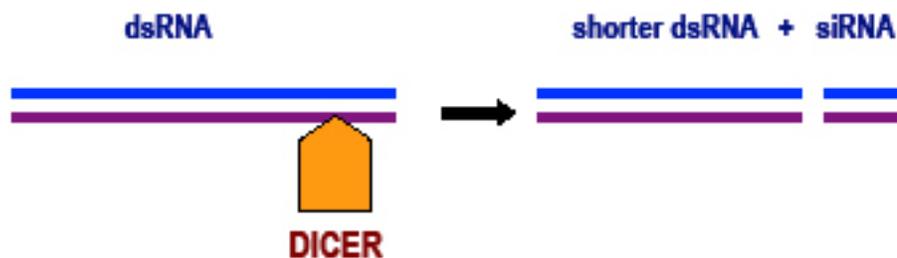
### Anti-sense Oligonucleotides

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>54</sup> To date, no antisense or interfering RNA medications have been able to proceed through clinical development.

### 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. Short interfering RNA (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>55</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 (Alisporivir) 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>56,57</sup> Interim results from a phase II study of DEBIO-025 conducted in HCV monoinfected 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>58</sup> Results from a Phase II study of HCV genotype 1 treatment-naïve patients who were treated with DEBIO-025 plus pegylated interferon and ribavirin reported a 76% SVR rate in the group that was treated for 48 weeks compared to 55% in the group that received pegylated interferon plus ribavirin alone.<sup>59</sup> The agent has shown pan-genotypic activity. Unfortunately due to safety concerns all trials are currently on hold.

Another cyclophilin B inhibitor in early clinical development is NIM811, which has shown enhanced antiviral activity against HCV when used with pegylated interferon.<sup>60,61</sup>

SCY-635 is a cyclophilin B inhibitor that in pre-clinical study showed both antiviral activity against HCV and synergistic effects when used with interferon and ribavirin in vitro.<sup>62</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>63</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>64</sup> Response rates among genotype 1 patients were lower at 44% in phase II study.<sup>65</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. However, with potent direct acting antivirals now available, the role for nitazoxanide is not clear.

## 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. The mitochondria targeted antioxidant mitoquinone has been evaluated in a phase II study and was shown to significantly decrease plasma ALT and AST levels in patients with chronic hepatitis C. This finding suggests that mitoquinone may reduce necroinflammation thus slowing liver fibrosis progression.<sup>66</sup>

## 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

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.

In two phase III clinical trials of taribavirin in combination with pegylated interferon alfa-2b (VISER1 and VISER2) there were lower rates of anemia but also lower SVRs compared to pegylated interferon alfa-2b plus ribavirin.<sup>67,68</sup> A phase IIb study using pegylated interferon alfa-2b plus weight-based dosing of either taribavirin or ribavirin revealed equivalent rates of HCV RNA clearance with the two drugs but significantly less anemia associated with taribavirin. The study reported SVR rates of 27-28%.<sup>69</sup> While the SVR rates were low, it should be noted that the study incorporated a large number of African Americans and patients with more advanced fibrosis, both considered difficult-to-treat populations. With the near term elimination of interferon from the HCV treatment algorithm, ribavirin alternatives have been halted in the development pipeline.

## 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. Antioxidants, natural anti-inflammatories, and some 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, *Integrative Medicine*.

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