

# New treatment strategies against hepatitis C viral infection

Marc Bilodeau MD, Daniel Lamarre PhD

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Treatment of hepatitis C virus infection is currently based on a combination of pegylated interferon and ribavirin. Because efficacy of this therapy remains suboptimal and side effects sometimes problematic, major efforts have been put forward by scientists and the pharmaceutical industry to develop alternative treatments for this chronic infection. Over the past few years, clinical studies performed with some of these new agents have been presented at major international meetings. The present paper aims to review the rationale underlying the development of these new forms of treatment as well as the current available data concerning their clinical efficacy.

**Key Words:** Antivirals; Hepatitis C virus; Immunotherapy; Polymerase; Protease; Therapy

The treatment of hepatitis C virus (HCV) infection has significantly progressed over the past 10 years. The identification of the virus in 1989 represented a milestone in research efforts that had been put forward to understand the biology of the virus and to propose new therapies. The recognition that interferon (IFN) was efficacious against HCV dates back to 1987, a time when the virus was still a concept (1). The addition of ribavirin (RBV) to the usual IFN-based treatment led to an important improvement in the efficacy of the treatment (2). It is important to remember that the efficacy of treatment is essentially defined as the disappearance of HCV RNA in the blood of patients who have been off treatment for a period of at least six months. The modification of the IFN molecule to provide a more sustained level of this drug in the circulation, by the addition of a polyethylene glycol molecule, has further made a small improvement in the efficacy and in the ease of administration of the IFN molecule (3,4). However, the cornerstone of the treatment of HCV remains the administration of IFN, which has its limitations. First, significant amounts of HCV strains are resistant to the antiviral activity of IFN. Second, IFN has a number of side effects that either limit the administration of this drug to subgroups of patients or leads to significant disability, some of which are rarely permanent.

Because HCV infection is a major health problem affecting approximately 150,000,000 people worldwide and because current treatments have limitations, that have been briefly described above, it is not without surprise that a number of academic and industry-driven groups have invested a lot of time in the identification of new treatments for this infection.

## Les nouvelles stratégies de traitement contre l'infection virale à l'hépatite C

Le traitement de l'infection au virus de l'hépatite C se fonde sur une association d'interféron pégylé et de ribavirine. Puisque l'efficacité de ce traitement demeure sous-optimale et que ses effets secondaires sont parfois problématiques, les scientifiques et l'industrie pharmaceutique ont fait des efforts majeurs pour élaborer d'autres traitements contre cette infection chronique. Depuis quelques années, des études cliniques exécutées avec quelques-uns de ces nouveaux agents ont été présentées à de grands congrès internationaux. Le présent article vise à analyser la raison d'être sous-jacente à l'élaboration de ces nouvelles formes de traitement ainsi que les données disponibles et à jour au sujet de leur efficacité clinique.

The present review is aimed at defining the different approaches that have been developed to provide new anti-HCV treatments and at providing the current available data on the potential clinical utility of the compounds that have been investigated so far.

The actual ways to approach treatment of HCV are depicted in Table 1. Therapies can be divided into immunomodulatory therapies, nonspecific antiviral agents and specific HCV-targeted antiviral agents.

### IMMUNOMODULATORY THERAPIES

Immunomodulatory therapies are aimed at improving the efficiency of the immune response of the host infected by HCV. IFN is sometimes regarded as an immunomodulatory agent but it is also well known to have intrinsic antiviral activity (5). Modifications of the IFN molecule could therefore be placed in this category. For example, the addition of an albumin adduct to the IFN molecule significantly modifies the pharmacokinetic profile of IFN and has been shown to improve its antiviral efficacy (6). A number of other mechanisms are being targeted to improve the immune response to HCV. The identification of the importance of the innate immune response in controlling the acute HCV infection has led researchers to propose a therapeutic vaccine. The development of such a vaccine was put forward following the identification of antigenic determinants shown to be important for the clearance of HCV infection in individuals with spontaneous resolution of their infection. These antigens are then produced in the laboratory and administered to patients with active infection. Preliminary data from such a vaccine shows

**TABLE 1**  
**Ways to approach treatment of hepatitis C virus infection**

Immunomodulatory therapies
Modifications to the interferon molecule
Molecules that increase the innate immune response
Therapeutic vaccines
Nonspecific antiviral agents
Ribavirin analogues
Drugs with proven efficacy in other types of viral infection
Specific hepatitis C virus-targeted antiviral agents
Protease inhibitors
Polymerase inhibitors
Helicase inhibitors
Molecular targeting

improvements in the immune response against HCV antigens but so far has been associated with little impact on HCV viral load (7-10).

Currently, large efforts are being put forward to identify potential deficiencies in the innate immune response during HCV infection. The innate immune response is the reaction that can be observed quickly after the administration of an antigen; it is the result of highly specialized sentinel cells that have the capacity to recognize the specific shapes of molecules not present in the host (11). Some of the cells responsible for this response are dendritic cells, natural killer cells and macrophages. Furthermore, receptors present at the surface of these cells or at the surface of the target cells (the hepatocytes in the case of HCV infection) have also been shown to be important for the innate immune response; the toll-like receptors are part of this group of receptors. Therefore, therapies aimed at improving the innate immune response, such as increasing the toll-like receptor response, have been proposed for the treatment of HCV infection. One of these molecules is isatoribine, which has been shown to induce hepatic 2', 5'-oligoadenylate synthetase, to stimulate natural killer cells and macrophages, and to induce the expression of cytokines leading to increased production of IFN. A recent clinical trial has revealed small, albeit significant antiviral activity of this compound in HCV-infected individuals (12). Another molecule aimed at stimulating toll-like receptor 9 activity has been studied in infected patients. At the highest dose, CPG 10101 was found to induce a 1.4 log reduction in viral load after four weeks of treatment (13,14).

Thymosin-alpha 1 is an immune stimulator that has undergone clinical evaluation in HCV infection. Unfortunately, the addition of this molecule to an IFN-based regimen has not led to any significant increases in the antiviral efficacy of IFN itself (15).

### NONSPECIFIC ANTIVIRAL AGENTS

RBV is an antiviral agent that is devoid of significant antiviral activity when used alone in HCV infection (16). It significantly increases the antiviral effect of IFN when used in combination treatment (17). RBV is associated with hemolytic anemia which can sometimes significantly limit the dosage of this drug in patients. Therefore, efforts have been made to develop RBV analogues that would have at least the same synergistic effect on IFN but would lack its toxicology profile. Viramidine, a prodrug of RBV, has been put forward as one of

these agents. Viramidine is converted to RBV by an enzyme named adenosine deaminase, which is expressed significantly more in the liver than in any other organ (18). Therefore, viramidine is expected to yield lower levels of RBV in red blood cells and higher concentrations in the liver, thereby reducing its hematological toxicity profile. A recent study released at the 2005 European Association for the Study of Liver meeting revealed that doses up to 800 mg twice a day of viramidine were associated with a 11% rate of anemia (defined as hemoglobin level less than 100 g/L) in comparison with 27% in the RBV controls. The levels of sustained virological response observed in the viramidine-treated group were 23%, 37% and 29%, in the 400 mg twice a day, 600 mg twice a day and 800 mg twice a day viramidine treatment arms, respectively. Sustained virological response was 44% in the RBV controls (19).

Merimepodib is an inosine monophosphate dehydrogenase inhibitor. RBV is known to have this activity as well. The administration of merimepodib to genotype 1 HCV-infected patients who were nonresponders to regular treatment of IFN and RBV is currently under analysis. Results suggest that the combination of merimepodib with pegylated (PEG)-IFN and RBV might be superior to the administration of PEG-IFN and RBV in these difficult-to-treat patients (20).

Cyclosporine has previously been shown to be active against HIV (21). However, the development of various powerful and specific antiviral agents to treat this infection has put aside this aspect of cyclosporine activity. In 2003, Watashi et al (22) convincingly showed that cyclosporine possessed antiviral activity against HCV *in vitro*. Furthermore, Inoue et al (23) published results of a small study showing that the combination of IFN and cyclosporine is superior to the treatment with IFN alone in a difficult-to-treat population. Watashi et al (22) further demonstrated that the antiviral effect of cyclosporine on HCV was independent of its immunosuppressive function. Because a number of cyclosporine analogues, devoid of immunosuppressive activity, have already been developed, interest in these molecules has increased significantly over the past few years (24). This is particularly true in the liver transplantation setting, where systematic reinfection of the graft by HCV can lead to significant graft injury sometimes leading to cirrhosis and graft failure.

Other targets of the therapeutic artillery against HCV are centred on the importance of the endoplasmic reticulum in the formation and maturation of the virus. Inhibitors of alpha-1-glucosidase activity, which is essential for the addition of sugar branches to some of the viral proteins, have been developed and are being tested *in vitro* and *in vivo*. It is too early to conclude if these agents will have an impact in the treatment of HCV infection.

### SPECIFIC HCV ANTIVIRAL AGENTS

The determination of the RNA sequence, the amino acid composition and the structure of HCV has enabled researchers to better understand the biological behaviour of this virus. Figure 1 shows the classical schematic representation of the HCV polyprotein. To understand how the virus works, it is important to know that the genetic material of the virus is made up of RNA. The RNA is translated into a long single protein in the endoplasmic reticulum of the host cell (the hepatocyte). This long protein contains all that is necessary for the virus to make another copy of itself (viral replication) and

to form a complete virion. A complete virion is formed of a structural envelope that contains the genetic material (the RNA), which is considered the only possible way that the virus can infect the cells and other organisms. The so called structural parts of the virus therefore represent the framework that will form the shell of the virion. On the other hand, the nonstructural proteins will not be embedded in the virion. However, these so called nonstructural proteins are essential for the production of the virion itself or for the replication of the genomic material. The role of each of these nonstructural proteins has not yet been fully identified. However, by analogy with other similar viruses and by reconstituting the activity of some of the nonstructural proteins, researchers have been able to identify the essence of the activity of the nonstructural (NS)-3, NS4 and NS5B proteins.

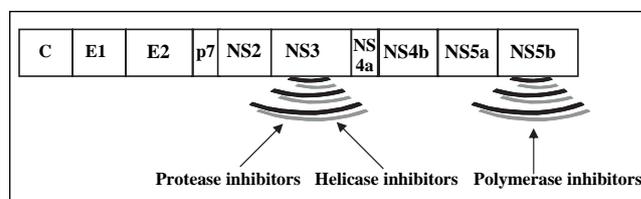
The NS3 protein possesses protease activity that is highly specific for sequences present in the amino acid chain of the HCV virus. The importance of this enzymatic activity can be understood by recognizing that the full-length protein is not present in the virion exported out of the liver; therefore, it is essential to cut this polyprotein at precise sites. If the proteolytic activity of the NS3 protein is lost, the virus will not be efficiently produced and the other enzymatic activities will not be able to take place because these activities are not present when the long protein remains intact. The first cut in this protein occurs through the activity of cellular proteases. NS3 activity is required for the cut between the NS3 and NS4A, NS4A and NS4B, NS4B and NS5A, and NS5A and NS5B (25). The NS3 protein also possesses helicase activity. This helicase activity is essential for the untwisting of the RNA molecule during replication. Little is known of the NS4 protein except that it works as a cofactor for the NS3 protease.

The NS5 protein possesses RNA polymerase activity. This is essential for the reproduction of the RNA molecule. For the virus to replicate itself, it needs to make another stretch of RNA identical or very close to the genetic material of the virus. This is made possible by the NS5B enzyme. Its role is to make a mirror image of the RNA molecule. The cardinal importance of the HCV protease is again underscored by the recognition that the NS5B protein cannot be active if it has not been released first by the NS3 protease.

Several laboratories have therefore tried to develop drugs that inhibit the enzymatic activity of the NS3 protease and of the NS5B polymerase in particular.

### Protease inhibitors

The first clinical evidence that this type of approach is efficient to treat HCV infection came from the discovery of BILN 2061 (Boehringer Ingelheim, Canada). This specific HCV protease inhibitor was discovered by Lamarre et al (26). This small peptide inhibitor was shown to efficiently inhibit HCV replication in *in vitro* models before being used in a phase 1 proof-of-principle trial in HCV-infected patients. When administered to HCV genotype 1-infected patients, BILN 2061 was shown to have very potent antiviral activity, decreasing the viral load by more than 2 logs after the administration of only four doses (27). Viral load slowly came back toward baseline levels after stopping the drug. Unfortunately, further clinical studies were halted because of possible cardiotoxicity. Other reports of the preclinical use of this drug have shown that its efficacy was slightly less in HCV genotype 2- and genotype 3-infected patients (28). This lower efficacy was not



**Figure 1)** Schematic representation of hepatitis C virus polyprotein and specific enzymatic targets for drug design. C Core; E Envelope; NS Nonstructural

due to changes in the pharmacokinetic profile of the drug but due to a lower affinity of this compound for the HCV protease of HCV genotype 2- or genotype 3-infected patients (29). This result underscores the importance of the capacity of the virus to present different shapes of all these proteins. This suggests that it is possible that resistance to all of these HCV highly specific compounds will eventually occur.

Other protease inhibitors have been developed and recent results have revealed interesting antiviral activity. VX-950 (Vertex Pharmaceuticals, USA) is one of these inhibitors; it has been shown to be a potent HCV protease inhibitor against HCV genotype 1 as well as HCV genotypes 2 and 3, in enzymatic assays. A phase 1B clinical trial has revealed very potent antiviral activity with a median decrease of 4.4 logs in HCV viral load after only 14 days of therapy (30). This was associated with normalization in serum transaminases. Results of clinical trials with another protease inhibitor, SCH 503034 (Schering-Plough, USA), revealed a dose-related reduction in viral loads with a mean decline of more than 2 logs in viral load after two weeks of therapy with the highest dose studied (31). Combination therapy with SCH 503034 and PEG-IFN is also undergoing clinical evaluation (32). Mutation in the targeting domain of these compounds is achievable *in vitro* (33-34) and has been observed after a short exposure in humans (35).

### Polymerase inhibitors

Valopicitabin (Idenix Pharmaceuticals Ltd, USA) is a nucleoside analogue that possesses a specific HCV RNA polymerase inhibitory activity. Clinical data recently released have shown that a daily dose of 800 mg of valopicitabin in combination with PEG-IFN in HCV genotype 1-infected patients leads to a significant decrease in HCV viral load after 12 weeks of treatment (36-39). The decrease in viral load with valopicitabin alone was of 0.87 log.

Many other polymerase inhibitors have been developed by a number of drug companies. No clinical data have been published in scientific journals so far.

### Molecular targeting

The evolution of molecular biology techniques has enabled researchers to specifically target proteins or RNA molecules with the help of enzymes which possess the activity to inhibit or to cleave the target molecule. Examples of these tools are ribozymes, silencing RNA and peptides aptamers. Different parts of HCV have been targeted with these agents. Clinical studies have been performed with ribozymes and antisense molecules. Results have been disappointing probably because of the rapid development of resistance through molecular adaptation of the RNA during viral replication (40,41). Even if these tools are efficient *in vitro*, the future of the

administration of these molecules in humans seems to be far away.

### CONCLUSION

When all the different potential targets that are being evaluated to treat HCV infection are considered, it seems probable that we will be in a situation where we will have access to novel and powerful tools to treat this infection in the future. The efforts made in understanding the structure of the virus and the activity of the different parts of its protein has increased tremendously despite the difficulty in working with this agent *in vitro*. The dramatic decrease in viral load observed after the administration of a potent HCV protease inhibitor gives strong hope that despite the capacity of the virus to mutate, our efficiency to block viral replication will be able to overcome the mechanisms the virus has developed to evade immune surveillance and to adapt to the host environment. The future is considered full of promises.

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